An ensemble of deep convolutional neural networks is more accurate and reliable than board-certified ophthalmologists at detecting multiple diseases in retinal fundus photographs

Prashant U Pandey, Brian G Ballios, Panos G Christakis, Alexander J Kaplan, David J Mathew, Stephan Ong Tone, Michael J Wan, Jonathan A Micieli, Jovi C Y Wong

INTRODUCTION

Retinal imaging plays a key role in the diagnosis of retinal pathologies. In current clinical practices, retinal imaging is manually interpreted by ophthalmologists and this workflow is limited by human and initial weights were pretrained on the ImageNet dataset. We used 43,055 fundus images from 12 public datasets. Five trained ensembles were then tested on an ‘unseen’ set of 100 images. Seven board-certified ophthalmologists were asked to classify these test images.

Results

Board-certified ophthalmologists achieved a mean accuracy of 72.7% over all classes, while the DCE achieved a mean accuracy of 79.2% (p<0.03). The DCE had a statistically significant higher mean F1-score for DR classification compared with the ophthalmologists (76.8% vs 57.5%; p=0.01) and greater but statistically non-significant mean F1-scores for glaucoma (83.9% vs 75.7%; p=0.10), AMD (85.9% vs 85.2%; p=0.69) and normal eyes (73.0% vs 70.5%; p=0.39). The DCE had a greater mean agreement between accuracy and confidence of 81.6% vs 70.3% (p<0.001).

Discussion

We developed a deep learning model and found that it could more accurately and reliably classify four categories of fundus images compared with board-certified ophthalmologists. This work provides proof-of-principle that an algorithm is capable of accurate and reliable recognition of multiple retinal diseases using only fundus photographs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Artificial intelligence (AI) algorithms have demonstrated excellent accuracy in classifying pathologies from retinal fundus photographs.

WHAT THIS STUDY ADDS

⇒ Our AI algorithm demonstrates not only superior accuracy to board-certified ophthalmologists, in a balanced test containing four image categories, but also superior reliability as the confidence output by our model more closely matches its accuracy compared with ophthalmologists.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This model could be used a blueprint for future decision-making support systems to assist pathology detection both in specialist ophthalmology clinics and in generic healthcare settings such as family practices and emergency rooms.

In particular, several machine learning approaches based on convolutional neural networks (CNNs) have already been developed to recognise pathologies in fundus images.

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临床科学

目的

开发一个算法来分类多类视网膜疾病，并根据其性能对抗人类专家。

方法

我们训练了一个包含五个卷积神经网络（CNNs）的深度卷积集合（DCE），以分类视网膜疾病图像，将视网膜疾病图像转换为糖尿病视网膜病变（DR）、青光眼、年龄相关性黄斑变性（AMD）和正常图像。该CNN架构基于InceptionV3模型，初始权重在ImageNet数据集上进行预训练。我们使用了12个公共数据集的43055张图像。五个训练的集合模型分别在四种图像类别上进行了测试。七个具有执业资格的视网膜病学家被要求对这些测试图像进行分类。

结果

执业视网膜病学家在所有类别的平均准确率为72.7%，而DCE在所有类别的平均准确率为79.2%（p<0.03）。DCE具有显著较高的F1分数，DR分类比执业视网膜病学家（76.8% vs 57.5%；p=0.01）和非统计学上但显著较高的F1分数，分别为：青光眼（83.9% vs 75.7%；p=0.10）、AMD（85.9% vs 85.2%；p=0.69）和正常眼睛（73.0% vs 70.5%；p=0.39）。DCE具有更大且统计学上显著的准确性和可信度，分别为81.6% vs 70.3%（p<0.001）。

讨论

我们开发了一个深度学习模型，并发现它可以在更准确和可靠地识别四种视网膜疾病图像方面，与执业视网膜病学家相比，具有板上的优势。这项工作提供了证明原理，即算法可以准确可靠地识别多种视网膜疾病，仅使用视网膜图像。

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Clinical science
to five retinal specialists. Similarly, Son et al trained 12 independent networks to detect 12 retinal findings in fundus images and found this technique performed equivalently to three retinal specialists in identifying haemorrhages and hard exudates. Li et al developed an ensemble of CNNs to classify DR and diabetic macular oedema and demonstrated that it performed either as well or better than eight expert raters. To compare the reliability of the DCE to that of board-certified ophthalmologists, we also estimated the confidence of the ensemble models by taking the softmax of the mean logit output per image, and thresholding this value above 50% as ‘confident’ and

Deep convolutional ensemble
We implemented a DCE: a CNN-based ensemble classifier trained to predict the disease class in fundus images. The ensemble consisted of five InceptionV3 networks that were pretrained on the ImageNet dataset (figure 1). Each InceptionV3 model was independently trained on bootstrap aggregated samples from the training set, consistent with the deep ensembling methodology to improve uncertainty estimation and confidence calibration. We trained using a weighted cross-entropy loss where the weights for each class were inversely proportional to the count of images in that class. We used the rectified Adam for optimisation and a fixed batch size of 68 images. Input images were resized to 299×299 pixels, and random horizontal flipping and random scaling between 0% and 10% were used for data augmentation during training. The final predicted class per image was generated by taking the majority vote of the five networks, such that the model could only predict one class per image. In the case there was no majority vote, we randomly assigned the predicted class from one of the categories with the most votes so as not to favour one class over the others. The network architecture and optimisation process were implemented in PyTorch and executed on a single Nvidia V100 GPU.

Confidence

Table 1: Number of images in the training and validation set and in the test set, and the corresponding source datasets

<table>
<thead>
<tr>
<th>Source dataset</th>
<th>Training and validation set</th>
<th>Test set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>DR</td>
</tr>
<tr>
<td>DiareDB14</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>Drishti-GS15</td>
<td>31</td>
<td>0</td>
</tr>
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<td>DRIVE16</td>
<td>33</td>
<td>7</td>
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<tr>
<td>HRF17</td>
<td>15</td>
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<tr>
<td>IDRiD18</td>
<td>167</td>
<td>348</td>
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<tr>
<td>Kaggle-39</td>
<td>38</td>
<td>105</td>
</tr>
<tr>
<td>Kaggle-Dr19</td>
<td>25 769</td>
<td>9278</td>
</tr>
<tr>
<td>ODIR20</td>
<td>2276</td>
<td>1187</td>
</tr>
<tr>
<td>MESSidor21</td>
<td>546</td>
<td>651</td>
</tr>
<tr>
<td>ORIGA-light22</td>
<td>482</td>
<td>0</td>
</tr>
<tr>
<td>REFUGE23</td>
<td>1079</td>
<td>0</td>
</tr>
<tr>
<td>STARE24</td>
<td>39</td>
<td>134</td>
</tr>
<tr>
<td>Total</td>
<td>30 475</td>
<td>11 814</td>
</tr>
</tbody>
</table>

AMD, age-related macular degeneration; DR, diabetic retinopathy.

below 50% as ‘not confident’. This confidence estimation was not used during training.

**Experiment on test data**

Figure 2 illustrates the overall experiment process.

**Deep convolutional ensemble**

We trained the DCE for 20 epochs on the training set, as we found that the weighted cross-entropy loss did not further improve on the validation with more training. We then evaluated the model once on the test set. We independently repeated this process five times, using random seeds for the bootstrap sampling, training/validation splits and network weight initialisations. This allowed us to generate a distribution of performance of the DCE, such that we could report a mean and SD of metrics and conduct statistical tests to compare its performance against the board-certified ophthalmologists. We ensured that the model was not given any information about the test set, such as how many samples of each class to expect.

**Human expert classification**

We asked seven board-certified staff ophthalmologists (mean practice duration: 2.4 years, range: 1–7 years) to independently classify each image in the test set into one of the four predetermined classes (normal, DR, glaucoma, AMD), using only information from the image. We also asked each ophthalmologist whether they were ‘confident’ or ‘not confident’ in their classification of each image. The ophthalmologists were not informed about the underlying split of the classes (ie, how many images per class were included in the test set) and were only able to select one of the four classes per image. The task was administered remotely over Google Forms.

**Evaluation metrics**

Several metrics were measured to compare the performances of the DCE and ophthalmologists. We calculated the overall accuracy defined as the percentage of correct predictions over all test images, as well as the overall (macroaveraged over all four classes) F1-score, positive predictive value (PPV), sensitivity and specificity. We also measured these metrics per class in a one-versus-all manner. We use the conventional definition of F1-score as the harmonic mean of PPV and sensitivity with equal weighting:

$$F_1 = \frac{2 \times PPV \times Sensitivity}{PPV + Sensitivity}$$

We acknowledge that PPV is dependent on the true prevalence of each respective class, which will be different to the 25% in our test set. However, we report the PPV is solely a means of comparing relative performance between the DCE and ophthalmologists. For the DCE, we also report the AUROC averaged...
over all four classes. It was not possible to report the AUROC for the ophthalmologists as we did not ask the ophthalmologists to report their prediction decisions at multiple confidence levels.

To understand the reliability of predictions, we looked at the agreement between the confidence and accuracy in each prediction by the DCE and ophthalmologists. We would expect a truly reliable classifier to only be confident when it is accurate and not confident when it is inaccurate.\(^28\)

Statistical analyses
We conducted two-sample t-tests, assuming unknown and unequal variances, to determine statistically significant differences in metrics between the DCE and ophthalmologists.

RESULTS
We report the results of classification performance and reliability on the test set experiment. Unless stated otherwise, the order of numerical results below always leads with the DCE followed by the ophthalmologists.

Classification performance
Over all 100 test images and four classes, we found that the DCE had a mean higher overall accuracy than the ophthalmologists (79.2% vs 72.7%, \(p=0.03\)), as well as a higher mean overall F1-score (79.9% vs 72.2%, \(p=0.02\)), higher mean overall PPV (85.0% vs 77.4%, \(p=0.0005\)), higher mean overall sensitivity (79.2% vs 72.7%, \(p=0.03\)) and a higher mean overall specificity (93.1% vs 90.9%, \(p=0.03\)). Figure 3 illustrates these results as boxplots. The DCE classification performance corresponded to a mean class-averaged AUROC of 0.9424 (SD: 0.0014). A mean of 1.8% (range: 0.0%-3.0%) of response output by the DCE did not constitute a majority vote.

In classifying DR, the DCE had a statistically significant higher mean F1-score than the ophthalmologists (76.8% vs 57.5%, \(p=0.01\)), a statistically higher mean sensitivity (72.8% vs 49.7%, \(p=0.01\)), while achieving a similar mean PPV (81.8% vs 73.7%, \(p=0.18\)) and mean specificity (94.4% vs 93.7%, \(p=0.75\)).

For glaucoma classification, we found no statistically significant differences between the DCE and ophthalmologists. The DCE had a comparable mean F1-score (83.9% vs 75.7%, \(p=0.10\)), mean PPV (100% vs 88.9%, \(p=0.06\)), mean sensitivity (72.8% vs 68.6%, \(p=0.58\)) and mean specificity (100% vs 96.2%, \(p=0.10\)).

Lastly, in AMD classification, we found that the DCE had a comparable mean F1-score as the ophthalmologists (85.9% vs 85.2%, \(p=0.69\)), a statistically higher mean PPV (99.0% vs 85.6%, \(p=0.0006\)), a statistically lower mean sensitivity (76.0% vs 85.1%, \(p=0.01\)) and a statistically higher mean specificity (99.7% vs 95.0%, \(p=0.002\)). Figure 4 plots the classification performance per class, comparing the DCE and ophthalmologists.

Table 2 provides the confusion matrix for the DCE and the board-certified ophthalmologists, summarising the mean per cent agreement between the predicted class against the ground-truth labels.

Reliability
We found that the DCE had an overall higher mean agreement in confidence and accuracy, compared with the ophthalmologists (81.6% vs 70.3%, \(p<0.001\)). Specifically, the DCE was confident when accurate with a higher mean frequency compared with ophthalmologists (77.4% vs 58.7%, \(p<10^{-3}\)). The DCE was not confident while inaccurate with a lower mean frequency (4.2% vs 11.6%, \(p=0.001\)). Conversely, the ophthalmologists had a higher mean frequency of being not confident when inaccurate (16.6% vs 15.7%, \(p=0.80\)). Table 3 summarises these results. We observed that the DCE had a skewed, unimodal distribution of confidence values, with a mean of 94.0% confidences greater than 0.5 (table 3), and 50% of confidence values greater than 0.807. On the other hand, the board-certified ophthalmologists denoted a mean of 25.6% test images as ‘not confident’. Table 4 provides the confusion matrix of only the ‘confident’ predictions for both the DCE and board-certified ophthalmologists. This table illustrates the mean per cent agreement between the ‘confident’ predictions and the ground-truth labels. Figure 5A–C provide examples of fundus photographs that both DCE and ophthalmologists were completely confident in, and one each where the DCE and ophthalmologists were least confident in, as well as their respective diagnoses.

DISCUSSION AND CONCLUSION
We developed an ensemble of deep CNNs which we showed to be more accurate than seven board-certified ophthalmologists at classifying 100 fundus images, both in terms of overall mean accuracy and F1-score over the four image classes. The majority of this difference stems from the DCE’s superiority in classifying DR images compared with the ophthalmologists (figure 4), which is statistically significant. We believe this better performance is the result of the DCE’s ability to detect mild presentations of DR in fundus images compared with ophthalmologists, as the datasets the DCE was trained on contained a wide spectrum of DR presentations. On the other hand, ophthalmologists do not detect DR from images alone and would also use a dilated clinical fundus examination to make this diagnosis. We verified this
by manually reviewing the images which were incorrectly classified by the majority of ophthalmologists but correctly classified by the DCE and found that the majority of these (54.5%) fundi were classified by the ophthalmologists as ‘normal’ when they had mild DR. In contrast, the DCE did not exceed the ophthalmologists’ performance in classes where the number of training samples and original datasets were limited, such as for glaucoma and AMD. Nevertheless, we found that the DCE exhibited statistically equivalent or superior performance to ophthalmologists in all metrics over all classes, with the exception of sensitivity in AMD detection in which the ophthalmologists achieved a mean score of 85.1% compared with DCE’s mean of 76.0% (p=0.01; figure 4). Altogether, these results demonstrate that the DCE model has a higher accuracy in detecting and classifying disease from fundus images alone compared with ophthalmologists. To the best of our knowledge, this is the first study of its kind to show both superior classification performance and reliability compared with ophthalmologists for classifying multiple retinal diseases based on fundus photographs, although similar results have been demonstrated in lung lesion detection in radiographs and in skin lesion detection in photographs.

Our study also found that the DCE was more reliable in its predictions compared with ophthalmologists, as the DCE had a higher mean agreement between its stated confidence and accuracy compared with ophthalmologists. Our analysis showed that this was primarily due to the large proportion of underconfident responses (not confident yet accurate) given by the ophthalmologists compared with the DCE (table 3). As above, this could be explained by the fact ophthalmologists do not recognise pathology purely from fundus photographs but also rely on the dilated retinal examination and auxiliary testing (such as OCT and visual fields). Additionally, the test set included fundus photographs of variable quality, many of which would be considered suboptimal for the detection of retinal disease—as evident

![Figure 4](image_url)

**Figure 4**  Classification scores for both the DCE and ophthalmologists per class in the test set. Box plots include a horizontal solid line and solid cross indicating the median and mean, values, respectively for each score. P values less than 0.05 are indicated, as determined by a two-sample t-test. AMD, age-related macular degeneration; DCE, deep convolutional ensemble; DR, diabetic retinopathy; PPV, positive predictive value.

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Green cells indicate agreement between the ground-truth labels and predictions by the deep convolutional ensemble or ophthalmologists, and red cells similarly indicate disagreement.

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**Table 2** Confusion matrices for deep convolutional ensemble and board-certified ophthalmologists showing the mean (and SD) per cent agreement between the predicted labels against the ground-truth labels over the test set.

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in figure 5C which demonstrates the image rated least confidently by the ophthalmologists. Both the DCE and ophthalmologists had a similar rate of being overconfident (confident yet inaccurate), confirming that ensembling leads to well-calibrated classification in a manner that is equivalent to or better than human experts. A high agreement between confidence and accuracy is promising when considering an algorithm for clinical application, as the confidence values output by a model can be more meaningfully interpreted on newly acquired patient images when the ground-truth pathology is still unknown.

Our test set was limited to 100 fundus images, which is a relatively small sample size for evaluating modern machine learning methods. However, this sample size was chosen so that the ophthalmologists could perform image classification in one session without fatiguing. Another limitation of using previously published image sets for training and testing is the lack of access to clinical data in addition to the fundus photographs. As such, we have assumed that the ground-truth labels are accurate and that fundus photographs contain single diseases only. However, datasets used different criteria to grade retinopathies—for instance DiaretDB relied on ophthalmologists to manually detect visual findings in the fundus photographs to determine the presence of DR, whereas clinical diagnoses were used as ground-truth labels in the MESSIDOR dataset. It was not possible to standardise labels across the data sources, as each institution used different criteria for grading and clinical diagnoses for each eye were not available. It was not possible to guarantee images contained only single diseases for the same reason. This introduces a certain amount of noise, uncertainty and inconsistency in the training and test sets, which the DCE model learns but the board-certified ophthalmologists may not be aware of. Moreover, as our test set was proportionally sampled from the same data sources used in our training/validation pipeline, datasets were under-represented or over-represented in the test set based on the total number of images they contained for each disease category. Because the DCE was trained on the same distribution of data sources, and as some datasets contained a much greater number of certain conditions compared with others, this potentially biased the comparison with board-certified ophthalmologists who were not familiar with the data sets prior to grading the test set. Future work can address these limitations by collecting a prospective multidisease photographic database with associated clinical data.

We further explored the ophthalmologists’ responses on the test set to determine whether there were any images for which all ophthalmologists were in disagreement with the prescribed ground-truth label, but also had 100% consensus on the classification. There were two such images, both of which were labelled as DR in the original dataset but were rated as ‘normal’ and ‘AMD’, respectively, by all ophthalmologists. Given this consensus, we ran our statistical analysis after removing these two images. We found that the DCE maintained a higher mean accuracy than the ophthalmologists (80.4% vs 74.2%, \( p=0.04 \)), as well as a higher mean F1-score (81.0% vs 73.7%, \( p=0.03 \)), over all 98 test set images. The DCE also had statistically higher mean PPV, sensitivity and specificity than the ophthalmologists over all images.

In this study we showed that it is possible to train an ensemble of deep CNNs to accurately identify three retinal pathologies and normal retinas from colour fundus photographs alone. We
showed that this performance meets or exceeds the performance of human experts in the field, and further that the reliability (or confidence calibration) is better than that of the board-certified ophthalmologists. Although we use InceptionV3, a previously developed deep learning model, we showed that it is possible to use existing pretrained architectures in an ensemble configuration to meet, or even surpass, human expert medical image classification accuracy and confidence calibration. We expect future avenues of research to explore how technical advancements in model architecture and training algorithms might further advance classification accuracy and reliability of supervised learning algorithms. While clinicians typically have access to additional information such as clinical history, a clinical examination and auxiliary testing to assist with making these diagnoses, these tests are costly in both human and technical resources. Automated artificial intelligence (AI) classifiers could represent a method by which rapid population-based screening for retinal disease could be performed using fundus photographs alone. Future work should explore the potential deployment of multidisease AI classifiers to assist with community-based retinal screening, particularly in settings where access to ophthalmology diagnostics is limited.

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