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# BMJ Open

## A short online course successfully trains non-ophthalmic diabetic retinopathy graders to recognize glaucomatous optic nerves in Vietnam

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3 **Title: A short online course successfully trains non-ophthalmic diabetic retinopathy**  
4 **graders to recognize glaucomatous optic nerves in Vietnam**  
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38  
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43  
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51 **Keywords:** Glaucoma, screening, online course, diabetic retinopathy grading, non-ophthalmic  
52 graders, training  
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## Abstract

**Purpose:** To test an online training course for non-ophthalmic diabetic retinopathy (DR) graders for recognition of glaucomatous optic nerves in Vietnam.

**Methods:** This was an uncontrolled, experimental, before-and-after study in which 43 non-ophthalmic DR graders underwent baseline testing on a standard image set, completed a self-paced, online training course and were retested using the same photographs presented randomly. 29 local ophthalmologists completed the same test without the training course. DR graders then underwent additional one-one training by a glaucoma specialist and were re-tested. Test performance (% correct, compared to consensus grades from 4 fellowship-trained glaucoma experts), sensitivity, specificity, positive and negative predictive value, and area under the receiver operating (AUC) curve, were computed.

**Results:** Mean age of DR graders ( $32.6 \pm 5.5$  years) did not differ from ophthalmologists ( $32.3 \pm 7.3$  years,  $p=0.13$ ). Online training required a mean of 297.9 (SD 144.6) minutes. Graders' mean baseline score ( $33.3\% \pm 14.3\%$ ) improved significantly after training ( $55.8\% \pm 12.6\%$ ,  $P < 0.001$ ), and post-training score did not differ from ophthalmologists ( $58.7 \pm 15.4\%$ ,  $P=0.384$ ). Grader sensitivity did not differ before [ $85.5\%$  (95% CI 83.5 – 87.3)] vs after [ $80.4\%$  (78.3 – 82.4)] training, while specificity improved significantly [ $47.8$  (44.9 – 50.7) vs  $79.8$  (77.3 – 82.0),  $p < 0.001$ ]. Grader AUC also improved after training [ $66.6$  (64.9 – 68.3) to  $80.1$  (78.5 – 81.6),  $p < 0.001$ ]. Additional one-one grader training by a glaucoma specialist did not further improve grader scores.

**Conclusion:** Non-ophthalmic DR graders can be trained to recognise glaucoma using a short online course in this setting, with no additional benefit from more expensive one-one training.

## Strengths and Limitations of this study

### Strengths

- Strengths of this study include an approach to assessing the impact of training which included both a before-after comparison and external validation against the performance of local ophthalmologists.
- Both the course and the assessment test reflected input from clinical experts, specialists in image-based screening and those engaged professionally in capacity-building for the recognition of glaucomatous optic nerves.
- A number of widely-used indices of screening accuracy were computed, allowing us to elucidate specific benefits of training in improving specificity.

### Limitations

- The generalizability of our results to other cadres of trainees and other settings is uncertain.
- Further research is needed to better understand the practicality of this training model within the context of a full glaucoma screening program.

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**Synopsis:**

After 5-hour online training in recognizing glaucomatous discs, scores of non-ophthalmic diabetic retinopathy graders doubled, and did not differ from local ophthalmologists. Intensive one-to-one training did not further improve performance.

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## Key Message

**What is already known on this topic:** Little is known about the efficacy of interventions to train existing non-ophthalmic diabetic retinopathy (DR) graders to deliver accurate glaucoma screening on available retinal images.

**What this study adds:** Our study found that after a 5-hour, self-paced online training course in recognizing glaucomatous optic nerves, scores of non-ophthalmic DR graders doubled, and did not differ from local ophthalmologists. More resource-intensive one-to-one training by specialists did not further improve performance.

**How this study might affect research, practice or policy:** This training model may leverage existing DR screening capacity to improve glaucoma detection in low resource settings



## Introduction

Glaucoma is the leading cause of irreversible blindness globally.<sup>1,2</sup> The number of persons living with glaucoma has increased from 64.3 million in 2013 to 76.0 million in 2020,<sup>3</sup> and is projected to rise a further 74% by 2040 due to an ageing and growing global population. Asia accounts for 60% of the world's total glaucoma cases, followed by Africa at 13%.<sup>3</sup> The number of persons blind due to glaucoma increased by 0.8 million between 1990 and 2010, with most of this rise occurring in low and middle-income countries (LMICs).<sup>4</sup> This trend is likely to continue without new and more effective screening strategies appropriate for low-resource settings.

Glaucoma often progresses unnoticed until central visual acuity is permanently compromised, therefore early detection of the disease, before symptoms develop is key in reducing the impact of visual loss in these patients. The rate of undiagnosed glaucoma is high, especially in LMICs, where approximately 95% of those affected are not aware of having the disease.<sup>5,6</sup>

Screening of any disease is a form of secondary prevention, with the goal of preventing undesirable outcomes. In the context of glaucoma, screening is designed to promote diagnosis, and treatment if necessary, during the asymptomatic stage in order to prevent further vision loss and blindness. So far, glaucoma screening has not been found to be cost effective in high income countries.<sup>7,8</sup>

Recently, however, a decision-analytic Markov model has been used to show that population screening for both primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) was cost effective in both rural and urban China.<sup>9</sup> John et al<sup>10</sup> reported that community screening for glaucoma in India would prevent 2,190 person years of blindness over a 10-year period. They concluded that community population screening might be cost effective if targeted at persons aged 40-69-years, and if implemented in urban areas.

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3 Unlike screening programs for glaucoma, diabetic retinopathy (DR) screening is well established  
4 in many high-income countries, and increasingly in LMICs as well. It would seem logical that  
5 screening for two major blinding eye diseases, glaucoma and DR, using the same equipment  
6 and personnel would be more cost effective. It may be possible to train non-ophthalmic graders  
7 who are currently screening for DR to recognize glaucoma using the colour fundus images,  
8 reducing the diagnostic burden on scarce, highly trained health care providers in low-resource  
9 settings.

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11 The aim of the current study is to develop and test an online course to train nurses, technicians,  
12 and non-ophthalmologist physicians working as DR graders in a non-governmental organization  
13 (NGO) program in Vietnam to recognize glaucomatous optic nerves from ophthalmic images.

14 The pre- and post-training performance of graders are assessed on a standard test set of optic  
15 nerve images drawn from a variety of sources, and compared with the performance of local  
16 ophthalmologists not undergoing the same training.

## 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 **Methods**

36 Approval for the study was obtained from the Ethical Review Board of the Queen's University  
37 Belfast in the United Kingdom, and the Ethics Committee of the Hanoi Medical College in  
38 Vietnam before the commencement of the study. Participating DR graders and ophthalmologists  
39 in Vietnam all provided written informed consent before recruitment into the study.

40 This is an uncontrolled, experimental, before-and-after study in which 43 non-ophthalmic DR  
41 graders were trained to screen for glaucoma using optic nerve photos. The online training  
42 course was developed specifically for the study and focused on a standardized approach to the  
43 pattern recognition of glaucomatous damage to the optic nerve. The study flow was as follows:  
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- Non-ophthalmic graders in an NGO DR program (DR graders) were consented, enrolled and underwent testing on the standard image set at baseline.
- The DR graders then completed the self-paced, online training course. Participants were encouraged to attempt practice questions placed at the end of each module of the course, and those failing to answer these correctly were asked to review the course again.
- DR graders then repeated the test on the standard image set. Images were identical to those at baseline, but were presented in random order. DR grader test scores were compared to baseline and also to those of 29 local ophthalmologists taking part in the NGO DR program, but who did not take the optic nerve grading course.
- Finally, to determine whether further improvement was practical, the non-graders each underwent approximately 20-30 minutes of individually-focused, one-to-one training by a glaucoma specialist (LN), and were tested a third time on the standard image set.

## Participants

We enrolled 43 graders currently working in the Orbis and Fred Hollow Foundation (FHF) DR screening project in Vietnam, excluding any ophthalmologists or optometrists. These included nurses, technicians and non-ophthalmic physicians (Table 1). Twenty-nine ophthalmologists in Vietnam from 20 eye hospitals and general hospitals in cities such as Hanoi, Da Nang and Ho Chi Minh City taking part in the project were also recruited for comparison.

The DR graders had already been trained to grade images for DR through the Orbis and FHF DR projects. Participants were informed that if they chose not to participate in the study, their jobs would not be affected in any way.

### Test set of optic nerve images

A total of 60 digital photographic images was used, 33 from eyes with glaucoma and 27 healthy eyes. Among these, 19 images were obtained from the Orbis Vietnam program, 11 from the population-based NICOLA (Northern Ireland Cohort for the Longitudinal Study of Ageing) study and 23 from the Glaucomatous Optic Neuropathy Evaluation (GONE, <https://gone-project.com/newgone/>) training website. All images were of gradable quality in the opinion of the standard panel of glaucoma specialists, though clarity was not always optimal in order to mimic real world conditions. Images from the GONE website were categorized into difficult, intermediate and easy (Table 1) on the basis of the prior performance of several thousand website users in characterizing them as normal or glaucomatous.<sup>11</sup> The GONE images were graded into normal and abnormal by investigators (NC, AAB, MC, OO, all fellowship-trained glaucoma experts, and TP, a medical retina specialist with a clinical and research focus on image-based screening for eye disease). The images from NICOLA and the Orbis Vietnam program were also sorted into normal and abnormal based on characteristic glaucomatous features of the images by the same group of investigators. When there was internal disagreement between the investigators, the image was replaced with another on which all five agreed.

Although optic nerve images are considered personal data, all images in the test set were fully anonymized and de-identified. Blanket permission for research use of images was obtained through the NICOLA study, Orbis Vietnam DR program and the GONE website, all of which have received prior ethics approval.

### Online training course

The online training course was delivered on the Orbis Cybersight website, ([cybersight.org](http://cybersight.org)) and consisted of three modules (217 Vietnamese-language PowerPoint slides with voice-over narration in Vietnamese) describing a standardized, step-by-step process of evaluating the

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3 healthy and glaucomatous optic nerve head. Module 1 provided a simple introduction to  
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5 glaucoma. Module 2 introduced the normal optic nerve head and a systematic description of its  
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7 features, with some reference to images depicting glaucomatous damage. Module 3 described  
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9 a systematic method for assessing optic nerve head photos to screen for glaucomatous features  
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11 using “the 5 Cs”: Cup to disc ratio, color of the neuro-retinal rim, comparison between the optic  
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13 nerve heads in a single patient’s two eyes, contour of the nerve, and “concerns” (this includes  
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15 optic disc haemorrhage, and papilledema, or optic nerve oedema with blurred nerve head  
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17 margins). At the end of modules 2 and 3, trainees were provided 50 normal optic nerve images  
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19 and 50 images of glaucomatous nerves for practice, all drawn from the same three sources as  
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21 the test set (the Orbis Vietnam DR program, the NICOLA study and the GONE website).  
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25 Optic nerve photos suggestive of other ocular diseases besides glaucoma were excluded from  
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27 the course, with the exception of potentially fatal conditions affecting the optic nerve, including  
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29 optic nerve edema as above. All modules were independently assessed and validated by the  
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31 five investigators listed above (AAB, MC, TP, NC, OO) for content and appropriateness for  
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33 these cadres of health workers.  
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### 36 37 38 39 **Evaluation with the test set**

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41 As above, the set consisted of 60 images, which were presented without stereo on the Orbis  
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43 Cybersight website, and were each graded as “refer” (likely glaucoma) or “do not refer” (normal)  
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45 by the test-taker. For images graded as “refer,” the correct reason had to be selected from a list.  
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47 A score of five marks was given for a correct ‘no refer’ decision. For a correct ‘refer’ decision,  
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49 the participant received a score of 5 marks, and an additional 5 marks for every correct reason  
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51 given for the referral, ranging from one to six reasons. No marks were deducted for incorrect  
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53 responses. Each of the 60 questions was worth between 5 and 30 marks (depending on the  
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number of correct reasons for referral), and a total of 470 marks were available on the test. A percentage score was calculated for each grader as the number of marks received divided by 470.

Correct answers were not revealed to the graders. The questions were presented in a random order, which differed between pre-test and post-test, and also from one test-taker to the other. None of the optic nerve images used in the practice test were included in the quiz.

### **Additional focused one-to-one training**

In order to determine if additional, measurable performance improvements could be realized with further, more intensive training, the DR graders each underwent 20-30 minutes of one-to-one training in optic nerve recognition by a glaucoma specialist (LN) to better distinguish presence of glaucomatous optic nerve damage. The training focused on individual areas of deficiency identified by the post-course training and was conducted online due to Covid-related restrictions on face-to-face gatherings in Vietnam at the time. All 43 (100%) DR graders completed the additional training, and all underwent a final round of testing on the standard image set.

### **Sample size and statistical methods**

The minimum sample size of 42 participants (graders) was calculated using the paired sample size formula for qualitative outcome data reported by Hulley et al.<sup>12</sup> with confidence level of 95% and statistical power of 80%. Using the statistics from the GONE website, we estimated that the mean for our study participants at baseline (pre-training) would be at the 5<sup>th</sup> percentile in grading performance, while at the end of the course (post-training), they would be at the 50<sup>th</sup> percentile. Thus, our study was powered to detect an improvement from a score of 29% to 60% correct answers between baseline and post-training performance on the test set.

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3 True positives (TP) were images correctly graded as glaucomatous optic neuropathy while true  
4 negatives (TN) were those correctly graded as 'no glaucoma'. False positive (FP) were images  
5 that did not have any features suggestive of glaucomatous optic neuropathy but were incorrectly  
6 graded as glaucomatous, while false negatives (FN) were images with glaucomatous features  
7 that were incorrectly graded as normal by the test-taker. Sensitivity was then calculated as TP  
8 divided by the sum of TP and FN, specificity as TN divided by the sum of TN and FP, positive  
9 predictive value (PPV) as TP divided by the sum of TP and FP, and negative predictive value  
10 (NPV) as TN divided by the sum of TN and FN. Additionally, area under the receiver operating  
11 characteristic (AUC) curve and kappa statistic were computed, with their 95% confidence  
12 intervals (95% CI). The performance of DR graders after training was compared to that before  
13 training, and also to that of ophthalmologists who had not taken the course.

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27 Since this was a study involving diabetic retinopathy graders and ophthalmologists, we did not  
28 involve patients and public in the design or conduct or reporting or dissemination of the study  
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## 34 **Results**

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37 In total, 43 DR graders participated in the training course and completed both pre and-post  
38 training tests, and the additional test after the one-to-one training, while 29 Vietnamese  
39 ophthalmologists underwent a single test and did not take part in the training. All DR graders  
40 undergoing training completed three rounds of testing.  
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46 The mean age ( $32.6 \pm 5.5$  years) did not differ from that of the ophthalmologists ( $32.3 \pm 7.3$  years,  
47  $p=0.893$ , Table 1). There was also no statistically significant difference between the age, sex  
48 distribution and work experience of DR graders vs ophthalmologists. The DR graders required a  
49 mean of 297.8 minutes (144.6), to complete the course according to measurements carried out  
50 automatically by the Orbis Cybersight website.  
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3 DR graders improved significantly between their mean pre-training percent scores (33.3% ±  
4 14.3%) and their post-training performance score [(55.8% ±12.6%),  $P < 0.001$ ]. (Table 2) The  
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6 mean post-training score for DR graders did not differ significantly from that for local  
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8 ophthalmologists (58.7±15.4%,  $P=0.384$ ). These findings, significant improvement between pre  
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10 and post-training tests and the lack of a significant difference between post-training tests by DR  
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12 graders and the performance of ophthalmologists, were consistent across optic nerve images  
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14 from all sources. (Table 2)

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18 With respect to other indices of grading accuracy (Table 3), there was no significant change  
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20 between DR graders' pre-training [85.5% (83.5 – 87.3)] and post-training sensitivity [80.4%  
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22 (78.3 – 82.4), while specificity improved significantly [47.8 (44.9 – 50.7) to 79.8 (77.3 – 82.0),  
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24  $p < 0.001$ ]. The positive and negative predictive values also improved significantly between pre-  
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26 and post-training tests, as did the area under the ROC curve [66.6 (64.9 – 68.3) to 80.1 (78.5 –  
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28 81.6),  $p < 0.001$ ]. (Table 3) When compared to the 29 ophthalmologists, the 43 DR graders after  
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30 training had worse sensitivity, better specificity, worse negative predictive value and worse  
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32 kappa. The positive predictive value and the area under the ROC curve (our pre-specified  
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34 indicator of overall grading accuracy) did not differ between post-training DR graders and  
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36 ophthalmologists. (Table 3)

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40 Table 4 shows the predictors of the percentage of correct responses among study participants.  
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42 In the univariate analysis, age  $< 30$  years ( $p=0.005$ ) and experience  $< 5$  years ( $p < 0.001$ )  
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44 predicted higher scores. However, in the multivariate analysis, only experience  $< 5$  years  
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46 remained significant ( $p=0.006$ ). The difference between post-training graders and local  
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48 ophthalmologists remained non-significant when adjusting for other factors.

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51 The test performance of DR graders ( $n=43$ ) did not improve significantly after additional  
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53 focused, one-to-one training, when compared to their performance after the online training.  
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3 (Table 5) Their mean scores still did not differ from the ophthalmologists after this additional  
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5 focused training. These patterns were the same for optic nerve images from all sources  
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## Discussion

This uncontrolled, experimental, before-and-after study found a significant improvement in the baseline mean scores of non-ophthalmic DR graders after undergoing a 5-hour training course.

The post course scores of the DR graders were almost double the baseline scores, and did not differ significantly from the scores of general ophthalmologists in Vietnam. This suggests that it is possible to train non ophthalmic DR graders to screen accurately for glaucoma using optic nerve photos using a short, self-paced online course. Additional, more intensive one-to-one training by an expert did not result in significant further improvement of grading performance, suggesting encouragingly that results obtained with a convenient and scalable tool like our course approach is what may be readily achievable with such cadres.

In many developing countries, half or more of glaucoma patients present with advanced disease.<sup>13–16</sup> Shortage of providers limits access to eye care and leads to delays in diagnosis and management of glaucoma until late in the disease process, often too late for effective, sight-saving treatment.<sup>17,18</sup> For example, a recent study reported > 60% prevalence of blindness in the operative eye among patients at the time of first glaucoma surgery in rural China<sup>19</sup>. Training non-ophthalmic graders to screen for glaucoma may be an initial step in promoting earlier glaucoma diagnosis in low resource settings. This has been described as task shifting, a model in which lower cadres of staff are trained to do simpler tasks so that scarcer and more highly-trained workers such as ophthalmologists can concentrate on high-level medical decision making and surgical management.<sup>20–23</sup>

The graders participating in this study were already trained to detect DR, the most frequent microvascular complication of diabetes and the leading cause of blindness in working-age adults. Studies<sup>24–26</sup> have demonstrated that > 90% of severe vision loss from DR can be prevented through regular screening and prompt referral and treatment. Diabetic screening is more cost-effective compared to no screening or opportunistic screening.<sup>27,28</sup> Glaucoma is the

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3 most common cause of irreversible blindness globally<sup>2,29</sup> and glaucoma blindness can similarly  
4 be prevented by regular screening of high-risk persons, prompt referral and treatment. Training  
5 the same cadres to screen for these two major causes of blindness may further improve cost  
6 effectiveness and cost-benefit of screening. This model is of particular interest in low-income  
7 settings, where traditional eye health services are mainly located in urban centres, often with  
8 poor accessibility to rural populations.  
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16 The model assessed in the current study differs from that described in previous reports in  
17 several ways. Non-expert health workers were trained to recognize glaucoma using an online  
18 course, and their performance was objectively measured and compared to their baseline, and to  
19 the scores of local ophthalmologists who had not taken the course. Previous studies have used  
20 telemedicine to send retinal images to reading centres for expert grading.<sup>30–32</sup> This can be  
21 challenging to sustain in low-resource settings, as it still depends on the time and availability of  
22 ophthalmologists or other relatively scarce trained experts to review retinal images for evidence  
23 of disease. Reading centres can also be logistically complex and expensive to establish and  
24 maintain in low resource settings, due to challenges such as the low bandwidth of available  
25 internet connections.  
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38 An advantage of training non experts as in our current model is that they are more likely to be  
39 able to review the images in real time due to lack of competing clinical duties. In delayed  
40 grading models, such as those using telemedicine, patients have to be contacted later to notify  
41 them of their screening results. Existing studies in LMICs have shown that this can lead to  
42 substantial loss to follow-up.<sup>33</sup> The RAIDERS study in Rwanda reported that patients receiving  
43 immediate feedback on the need for referral demonstrated higher adherence with  
44 recommended services compared to participants informed of the results of their screening  
45 several days later.<sup>33</sup>  
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3 Training with our course significantly improved graders' specificity and positive predictive value.  
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5 This effect of training is particularly relevant in low-resource settings, where the priority must be  
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7 to avoid over-burdening already weak health systems with large numbers of false positive  
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9 referrals. Ausayakhun et al<sup>34</sup> described a somewhat comparable model to ours, of training non-  
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11 ophthalmologists to deliver point-of-service screening for glaucoma, cataract and age-related  
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13 macular degeneration, and their reported specificity for glaucoma was approximately 80% using  
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15 fundus photographs, similar to that observed in the current study.  
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19 An important determinant of the positive predictive value of a screening program is the burden  
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21 of disease in the target population.<sup>35</sup> The heavy burden of glaucoma among Asians<sup>36–38</sup> and  
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23 Africans<sup>39–41</sup> has been well-documented. It is estimated that Asia has the highest number of  
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25 persons living with glaucoma globally, and that this figure will increase by 79.8% (primary open-  
26  
27 angle glaucoma) and 58.4% (primary angle closure glaucoma) by 2040.<sup>3</sup> In view of this high  
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29 glaucoma burden in Asia, and the growing gap between need and supply for ophthalmologists  
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31 globally,<sup>42</sup> it is clear that new screening models are needed which rely on non-experts. We were  
32  
33 able to train diabetic graders to perform at the level of local ophthalmologists, suggesting that  
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35 our training course can deliver successful and effective task shifting.  
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39 An important predictor of correct responses on the test set among study participants was  
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41 working experience of < 5 years. Lack of a positive effect of cumulative experience may seem  
42  
43 counter-intuitive, but we suggest this may reflect better performance among younger and more-  
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45 recently-trained cadres. Further studies are needed to replicate and better understand this  
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47 finding.  
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50 Although artificial intelligence (AI) has been used successfully for DR screening,<sup>43,44</sup> well trained  
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52 human graders are crucial in the validation of these AI systems, which must employ locally-  
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54 derived images and personnel to be most reliable. Moreover, there are substantial existing legal  
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3 and financial barriers to widespread sustainable use of AI for DR and glaucoma screening in  
4 many LMICs. Human systems are needed until these are overcome.  
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8 Strengths of this study include an approach to assessing the impact of training which included  
9 both a before-after comparison and external validation against the performance of local  
10 ophthalmologists. Success of the course against both of these criteria was consistent across  
11 images of varying difficulty and drawn from a wide variety of sources. Both the course and the  
12 assessment test reflected input from clinical experts, specialists in image-based screening and  
13 those engaged professionally in capacity-building for the recognition of glaucomatous optic  
14 nerves. A number of widely-used indices of screening accuracy were computed, allowing us to  
15 elucidate specific benefits of training in improving specificity.  
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25 This study has limitations as well. The generalizability of our results to other cadres of trainees  
26 and other settings is uncertain. Most importantly, further research is needed to better  
27 understand the practicality of this training model within the context of a full glaucoma screening  
28 program. Additional work is under way to test the model as part of delivering outreach screening  
29 for glaucoma in sub-Saharan Africa, aimed at a broad variety of patients at risk for glaucoma,  
30 and not solely those with DR.  
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39 In summary, our study shows that it is possible to train non ophthalmic DR graders quickly and  
40 at low cost to screen for glaucoma using optic nerve images. This model may improve  
41 glaucoma detection and ultimately reduce the prevalence of blindness from glaucoma in low  
42 resource settings.  
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**Table 1: Characteristics of DR graders and ophthalmologists participating in a study of glaucomatous optic nerve grading**

Characteristics	Ophthalmologists (n=29)	DR graders (n=43)	T-test/Chi-Square (P-value)
<b>Age (Mean±SD) yrs</b>	32.6±5.5	32.3±7.3	0.13 (0.893)
<30 years	11 (37.9%)	21 (48.8%)	0.83 (0.361)
≥30 years	18 (62.1%)	22 (51.2%)	
<b>Sex</b>			1.99 (0.159)
Female (%)	17 (58.6%)	32 (74.4%)	
Male (%)	12 (41.4%)	11 (25.6%)	
<b>Job Title</b>			
Nurse (%)	0 (0.0%)	18 (41.9%)	
Ophthalmologist (%)	29 (100.0%)	0 (0.0%)	
Other physician* (%)	0 (0.0%)	22 (51.2%)	
Technician (%)	0 (0.0%)	3 (6.9%)	
<b>Work Experience (Mean±SD) yrs</b>	7.21±5.2	8.22±7.1	0.65 (0.516)
<5 (%)	11 (37.9%)	18 (41.9%)	0.11 (0.739)
≥5 (%)	18 (62.1%)	25 (58.1%)	

\*Endocrinologist (5); General Practitioner (14); Radiologist (2); Internist (1)

**Table 2: Accuracy (% Correct vs Gold Standard\*) in grading optic nerve images from different sources, comparing DR graders and ophthalmologists**

Source of Images	Number of images	% Pre-training Score of graders (A) Mean±SD	% Post-training Score of graders (B) Mean±SD	P-value (A vs B)	% Scores of Ophthalmologists (C) Mean±SD	P-value (B vs C)
GONE Website						
Easy	8	31.9±17.6	59.2±17.6	<0.001	65.1±21.9	0.216
Moderate	8	25.6±13.3	44.2±19.4	<0.001	48.1±17.8	0.392
Hard	7	22.7±15.9	47.7±22.5	<0.001	46.2±21.8	0.780
Orbis Vietnam DR program	19	47.0±22.7	70.3±12.0	<0.001	70.3±18.2	0.991
NICOLA population-based study in Northern Ireland	11	31.4±20.0	58.7±16.9	<0.001	55.2±22.1	0.443
Other images illustrating specific findings	4	31.0±19.8	51.9±24.1	<0.001	57.5±23.4	0.337
<b>**Total</b>	60	33.3± 14.3	55.8±12.6	<0.001	58.7±15.4	0.384

\*A panel of four fellowship-trained glaucoma specialist ophthalmologists and one medical retina specialist with a clinical and research focus on image-based screening for eye disease (AAB, MC, TP, NC, OO) \*\*The remaining 3 images came from a variety of other sources.

**Table 3: Accuracy in grading optic nerve images, comparing DR graders and ophthalmologists, and calculated against a panel of specialist ophthalmologists (the “gold standard”).**

Participant Type	Sensitivity (95%CI)	Specificity (95%CI)	Positive Predictive Value (95%CI)	Negative Predictive Value (95%CI)	Kappa (95%CI)	Area under the Receiver-Operator Curve (95%CI)
DR graders, Pre-Training	85.5 (83.5 – 87.3)	47.8 (44.9 – 50.7)	66.7 (65.4 – 68.0)	72.9 (70.1 – 75.6)	34.4 (30.9 – 37.9)	66.6 (64.9 – 68.3)
DR graders, Post-training	80.4 (78.3 – 82.4)	79.8 (77.3 – 82.0)	82.9 (81.2 – 84.5)	76.9 (74.9 – 78.8)	60.0 (56.9 – 63.1)	80.1 (78.5 – 81.6)
P-value Comparing Graders Pre and Post-training	<0.05	<0.05	<0.05	<0.05	<0.05	<0.001
Ophthalmologists (No Training Given)	92.9 (91.1 – 94.4)	73.8 (70.6 – 76.9)	81.3 (79.4 – 83.0)	89.5 (87.1 – 91.5)	67.8 (64.3 – 71.3)	83.4 (81.6 – 85.1)
P-value comparing Post-training graders and Ophthalmologists	<0.05	<0.05	Not significant	<0.05	<0.05	Not significant



**Table 4: Predictors of the percentage of correct responses on the test set among study participants**

Potential Predictor	Univariate Analysis			Multivariate Analysis		
	Beta	95% Confidence Interval	P-value	Beta	95% Confidence Interval	P-value
Age <30 years	9.0	2.8 – 15.2	0.005	0.4	-8.7 – 9.4	0.938
Male sex	0.4	-6.5 – 7.4	0.899	1.8	-4.7 – 8.3	0.585
Post-training non-ophthalmic grader (Vs ophthalmologist)	-2.9	-9.5 – 3.7	0.384	-3.1	-9.2 – 3.1	0.319
<5 years of work experience	12.5	6.6 – 18.4	<0.001	13.1	3.9 – 22.3	0.006
Nurse (vs “Other physicians,” non-ophthalmic grader group only)	-4.5	12.3 – 3.3	0.251			
Pre vs post-training (DR graders only)	0.4	0.1 – 0.6	0.007			

**Table 5: Accuracy (% Correct vs Gold Standard\*) in grading optic nerve images from different sources: the effect of additional one-one training for DR graders after the online course**

Source of Images	Number of images	% Post-training score of graders after online course Mean±SD (A) (n=43)	% Post training score of graders after additional focused one-one training, Mean±SD (B) (n=43)	P-value) (A vs B)	% Scores of Ophthalmologists Mean±SD (C) (n=29)	P-value (B vs C)
GONE Website						
Easy	8	59.2±17.6	60.0±21.6	0.9364	65.1±21.9	0.6463
Moderate	8	44.2±19.4	48.7±21.9	0.6702	48.1±17.8	0.9529
Hard	7	47.7±22.5	49.7±25.8	0.8797	46.2±21.8	0.7886
Orbis Vietnam DR program	19	70.3±12.0	69.8±14.8	0.9096	70.3±18.2	0.9265
NICOLA population-based study in Northern Ireland	11	58.7±16.9	66.7±14.8	0.2514	55.2±22.1	0.1670
Other images illustrating specific findings	4	51.9±24.1	56.1±26.4	0.8220	57.5±23.4	0.9393
<b>**Total</b>	<b>60</b>	<b>55.8±12.6</b>	<b>60.3±16.4</b>	<b>0.1573</b>	<b>58.7±15.4</b>	<b>0.6422</b>

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3 **Ethics statement**  
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5 Approval for the study was obtained from the Ethical Review Board of the Queen's University  
6 Belfast United Kingdom (MHLS 20\_98), and the Ethics Committee of the Hanoi Medical College  
7 in Vietnam (IRB-VN01.001/IRB 00003121/ FWA 00004148, Approval number 587)  
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## STARD Checklist

Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Page 2
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Page 2
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Page 5 and 6
	4	Study objectives and hypotheses	Page 6
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Page 6 and 7
<i>Participants</i>	6	Eligibility criteria	Page 7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Page 7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Page 7
	9	Whether participants formed a consecutive, random or convenience series	Page 7
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	Pages 8-10
	10b	Reference standard, in sufficient detail to allow replication	Pages 9-10
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Page 10-11
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	NA
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	9-11
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	10-11
	15	How indeterminate index test or reference standard results were handled	NA
	16	How missing data on the index test and reference standard were handled	NA
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	10-11
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	No diagram but well described on page 7
	20	Baseline demographic and clinical characteristics of participants	Page 11, table 1
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	Table 4
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3
	25	Any adverse events from performing the index test or the reference standard	NA
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Page 17

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1		<b>27</b>	Implications for practice, including the intended use and clinical role of the index test	Pages 16 -17
2	<b>OTHER INFORMATION</b>			
3				
4		<b>28</b>	Registration number and name of registry	NCT05151757 ClinicalTrials.gov
5				
6		<b>29</b>	Where the full study protocol can be accessed	
7		<b>30</b>	Sources of funding and other support; role of funders	eXcellence in Ophthalmology and Vision Awards (XOVA Novartis)
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# BMJ Open

## Impact of a short online course on the accuracy of non-ophthalmic diabetic retinopathy graders in recognizing glaucomatous optic nerves in Vietnam

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3 **Title: Impact of a short online course on the accuracy of non-ophthalmic diabetic**  
4 **retinopathy graders in recognizing glaucomatous optic nerves in Vietnam**  
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35 **Running Title:** Online training for non-ophthalmologists to recognize glaucoma

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43 **Keywords:** Glaucoma, screening, online course, diabetic retinopathy grading, non-ophthalmic  
44 graders, training  
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## Abstract

### Purpose:

To test an online training course for non-ophthalmic diabetic retinopathy (DR) graders for recognition of glaucomatous optic nerves in Vietnam.

### Methods:

This was an uncontrolled, experimental, before-and-after study in which 43 non-ophthalmic DR graders underwent baseline testing on a standard image set, completed a self-paced, online training course and were retested using the same photographs presented randomly. 29 local ophthalmologists completed the same test without the training course. DR graders then underwent additional one-one training by a glaucoma specialist and were re-tested. Test performance (% correct, compared to consensus grades from 4 fellowship-trained glaucoma experts), sensitivity, specificity, positive and negative predictive value, and area under the receiver operating (AUC) curve, were computed.

### Results:

Mean age of DR graders (32.6±5.5 years) did not differ from ophthalmologists (32.3±7.3 years,  $p=0.13$ ). Online training required a mean of 297.9 (SD 144.6) minutes. Graders' mean baseline score (33.3% ± 14.3%) improved significantly after training (55.8% ±12.6%,  $P < 0.001$ ), and post-training score did not differ from ophthalmologists (58.7±15.4%,  $P=0.384$ ). Grader sensitivity did not differ before [85.5% (95% CI 83.5 – 87.3)] vs after [80.4% (78.3 – 82.4)] training, while specificity improved significantly [47.8 (44.9 – 50.7) vs 79.8 (77.3 – 82.0),  $p < 0.001$ ]. Grader AUC also improved after training [66.6 (64.9 – 68.3) to 80.1 (78.5 – 81.6),  $p < 0.001$ ]. Additional one-one grader training by a glaucoma specialist did not further improve grader scores.

**Conclusion:**

Non-ophthalmic DR graders can be trained to recognise glaucoma using a short online course in this setting, with no additional benefit from more expensive one-one training. After 5-hour online training in recognizing glaucomatous discs, scores of non-ophthalmic diabetic retinopathy graders doubled, and did not differ from local ophthalmologists. Intensive one-to-one training did not further improve performance

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## Strengths and Limitations of this study

### Strengths

- Use of an approach to assess the impact of training which included both a before-after comparison and external validation against the performance of local ophthalmologists.
- Both the course and the assessment test reflected input from clinical experts, specialists in image-based screening and those engaged professionally in capacity-building for the recognition of glaucomatous optic nerves.
- A number of widely-used indices of screening accuracy were computed, allowing the identification of specific benefits of training in improving specificity.

### Limitations

- The generalizability of our results to other cadres of trainees and other settings is uncertain.
- Further research is needed to better understand the practicality of this training model within the context of a full glaucoma screening program.



## Introduction

Glaucoma is the leading cause of irreversible blindness globally. [1,2] The number of persons living with glaucoma has increased from 64.3 million in 2013 to 76.0 million in 2020, [3] and is projected to rise a further 74% by 2040 due to an ageing and growing global population. Asia accounts for 60% of the world's total glaucoma cases, followed by Africa at 13%. [3] The number of persons blind due to glaucoma increased by 0.8 million between 1990 and 2010, with most of this rise occurring in low and middle-income countries (LMICs).[4] This trend is likely to continue without new and more effective screening strategies appropriate for low-resource settings.

Glaucoma often progresses unnoticed until central visual acuity is permanently compromised, therefore early detection of the disease, before symptoms develop is key in reducing the impact of visual loss in these patients. The rate of undiagnosed glaucoma is high, especially in LMICs, where approximately 95% of those affected are not aware of having the disease. [5,6]

Screening of any disease is a form of secondary prevention, with the goal of preventing undesirable outcomes. In the context of glaucoma, screening is designed to promote diagnosis, and treatment if necessary, during the asymptomatic stage in order to prevent further vision loss and blindness. So far, glaucoma screening has not been found to be cost effective in high income countries. [7,8]

Recently, however, a decision-analytic Markov model has been used to show that population screening for both primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) was cost effective in both rural and urban China. [9] John et al [10] reported that community screening for glaucoma in India would prevent 2,190 person years of blindness over a 10-year period. They concluded that community population screening might be cost effective if targeted at persons aged 40-69-years, and if implemented in urban areas.

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3 Unlike screening programs for glaucoma, diabetic retinopathy (DR) screening is well established  
4 in many high-income countries, and increasingly in LMICs as well. It would seem logical that  
5 screening for two major blinding eye diseases, glaucoma and DR, using the same equipment  
6 and personnel would be more cost effective. It may be possible to train non-ophthalmic graders  
7 who are currently screening for DR to recognize glaucoma using the colour fundus images,  
8 reducing the diagnostic burden on scarce, highly trained health care providers in low-resource  
9 settings.

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11 The aim of the current study is to develop and test an online course to train nurses, technicians,  
12 and non-ophthalmologist physicians working as DR graders in a non-governmental organization  
13 (NGO) program in Vietnam to recognize glaucomatous optic nerves from ophthalmic images.

14 The pre- and post-training performance of graders are assessed on a standard test set of optic  
15 nerve images drawn from a variety of sources, and compared with the performance of local  
16 ophthalmologists not undergoing the same training.

## 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 **Methods**

36 Approval for the study was obtained from the Ethical Review Board of the Queen's University  
37 Belfast in the United Kingdom, and the Ethics Committee of the Hanoi Medical College in  
38 Vietnam before the commencement of the study. Participating DR graders and ophthalmologists  
39 in Vietnam all provided written informed consent before recruitment into the study.

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47 Patient and Public Involvement statement: None

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49 This is an uncontrolled, experimental, before-and-after study in which 43 non-ophthalmic DR  
50 graders were trained to screen for glaucoma using optic nerve photos. The online training  
51 course was developed specifically for the study and focused on a standardized approach to the  
52 pattern recognition of glaucomatous damage to the optic nerve. The study flow was as follows:  
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- Non-ophthalmic graders in a non-governmental (NGO) DR program (DR graders) were consented, enrolled and underwent testing on the standard image set at baseline.
- The DR graders then completed the self-paced, online training course. Participants were encouraged to attempt practice questions placed at the end of each module of the course, and those failing to answer these correctly were asked to review the course again.
- DR graders then repeated the test on the standard image set. Images were identical to those at baseline, but were presented in random order. DR grader test scores were compared to baseline and also to those of 29 local ophthalmologists taking part in the NGO DR program, but who did not take the optic nerve grading course.
- Finally, to determine whether further improvement was practical, the non-graders each underwent approximately 20-30 minutes of individually-focused, one-to-one training by a glaucoma specialist (LN), and were tested a third time on the standard image set.

## Participants

We enrolled 43 graders currently working in the Orbis and Fred Hollow Foundation (FHF) DR screening project in Vietnam, excluding any ophthalmologists or optometrists. These included nurses, technicians and non-ophthalmic physicians (Table 1). Graders had a previous 3-day training course on grading diabetic retinopathy (DR). After the training, they were encouraged to continue practicing on their own until they were proficient in taking photos and grading these photos for DR. Twenty-nine ophthalmologists in Vietnam from 20 eye hospitals and general hospitals in cities such as Hanoi, Da Nang and Ho Chi Minh City taking part in the project were also recruited for comparison.

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3 The DR graders had already been trained to grade images for DR through the Orbis and FHF  
4 DR projects. Participants were informed that if they chose not to participate in the study, their  
5 jobs would not be affected in any way.  
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### 10 11 12 13 **Test set of optic nerve images** 14

15 A total of 60 digital photographic images was used, 33 from eyes with glaucoma and 27 healthy  
16 eyes. Among these, 19 images were obtained from the Orbis Vietnam program, 11 from the  
17 population-based NICOLA (Northern Ireland Cohort for the Longitudinal Study of Ageing) study  
18 and 23 from the Glaucomatous Optic Neuropathy Evaluation (GONE, [https://gone-project.com/  
19 newgone/](https://gone-project.com/newgone/)) training website. All images were of gradable quality in the opinion of the standard  
20 panel of glaucoma specialists, though clarity was not always optimal in order to mimic real world  
21 conditions. Images from the GONE website were categorized into difficult, intermediate and  
22 easy (Table 1) on the basis of the prior performance of several thousand website users in  
23 characterizing them as normal or glaucomatous. [11] The GONE images were graded into  
24 normal and abnormal by investigators (NC, AAB, MC, OO, all fellowship-trained glaucoma  
25 experts, and TP, a medical retina specialist with a clinical and research focus on image-based  
26 screening for eye disease). The images from NICOLA and the Orbis Vietnam program were  
27 also sorted into normal and abnormal based on characteristic glaucomatous features of the  
28 images by the same group of investigators. When there was internal disagreement between the  
29 investigators, the image was replaced with another on which all five agreed.  
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48 Although optic nerve images are considered personal data, all images in the test set were fully  
49 anonymized and de-identified. Blanket permission for research use of images was obtained  
50 through the NICOLA study, Orbis Vietnam DR program and the GONE website, all of which  
51 have received prior ethics approval.  
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## Online training course

The online training course was delivered on the Orbis Cybersight website,(cybersight.org) and consisted of three modules (217 Vietnamese-language PowerPoint slides with voice-over narration in Vietnamese) describing a standardized, step-by-step process of evaluating the healthy and glaucomatous optic nerve head. Module 1 provided a simple introduction to glaucoma. Module 2 introduced the normal optic nerve head and a systematic description of its features, with some reference to images depicting glaucomatous damage. Module 3 described a systematic method for assessing optic nerve head photos to screen for glaucomatous features using “the 5 Cs”: Cup to disc ratio, color of the neuro-retinal rim, comparison between the optic nerve heads in a single patient’s two eyes, contour of the nerve, and “concerns” (this includes optic disc haemorrhage, and papilledema, or optic nerve oedema with blurred nerve head margins). At the end of modules 2 and 3, trainees were provided 50 normal optic nerve images and 50 images of glaucomatous nerves for practice, all drawn from the same three sources as the test set (the Orbis Vietnam DR program, the NICOLA study and the GONE website).

Optic nerve photos suggestive of other ocular diseases besides glaucoma were excluded from the course, with the exception of potentially fatal conditions affecting the optic nerve, including optic nerve edema as above. All modules were independently assessed and validated by the five investigators listed above (AAB, MC, TP, NC, OO) for content and appropriateness for these cadres of health workers.

## Evaluation with the test set

As above, the set consisted of 60 images, which were presented without stereo on the Orbis Cybersight website, and were each graded as “refer” (likely glaucoma) or “do not refer” (normal) by the test-taker. For images graded as “refer,” the correct reason had to be selected from a list.

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3 A score of five marks was given for a correct 'no refer' decision. For a correct 'refer' decision,  
4 the participant received a score of 5 marks, and an additional 5 marks for every correct reason  
5 given for the referral, ranging from one to six reasons. No marks were deducted for incorrect  
6 responses. Each of the 60 questions was worth between 5 and 30 marks (depending on the  
7 number of correct reasons for referral), and a total of 470 marks were available on the test. A  
8 percentage score was calculated for each grader as the number of marks received divided by  
9 470.  
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18 Correct answers were not revealed to the graders. The questions were presented in a random  
19 order, which differed between pre-test and post-test, and also from one test-taker to the other.  
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21 None of the optic nerve images used in the practice test were included in the quiz.  
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### 25 **Additional focused one-to-one training**

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28 In order to determine if additional, measurable performance improvements could be realized  
29 with further, more intensive training, the DR graders each underwent 20-30 minutes of one-to-  
30 one training in optic nerve recognition by a glaucoma specialist (LN) to better distinguish  
31 presence of glaucomatous optic nerve damage. The training focused on individual areas of  
32 deficiency identified by the post-course training and was conducted online due to Covid-related  
33 restrictions on face-to-face gatherings in Vietnam at the time. All 43 (100%) DR graders  
34 completed the additional training, and all underwent a final round of testing on the standard  
35 image set.  
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### 46 **Sample size and statistical methods**

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48 The minimum sample size of 42 participants (graders) was calculated using the paired sample  
49 size formula for qualitative outcome data reported by Hulley et al. [12] with confidence level of  
50 95% and statistical power of 80%. Using the statistics from the GONE website, we estimated  
51 that the mean for our study participants at baseline (pre-training) would be at the 5<sup>th</sup> percentile  
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3 in grading performance, while at the end of the course (post-training), they would be at the 50<sup>th</sup>  
4 percentile. Thus, our study was powered to detect an improvement from a score of 29% to 60%  
5 correct answers between baseline and post-training performance on the test set.  
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10 True positives (TP) were images correctly graded as glaucomatous optic neuropathy while true  
11 negatives (TN) were those correctly graded as 'no glaucoma'. False positive (FP) were images  
12 that did not have any features suggestive of glaucomatous optic neuropathy but were incorrectly  
13 graded as glaucomatous, while false negatives (FN) were images with glaucomatous features  
14 that were incorrectly graded as normal by the test-taker. Sensitivity was then calculated as TP  
15 divided by the sum of TP and FN, specificity as TN divided by the sum of TN and FP, positive  
16 predictive value (PPV) as TP divided by the sum of TP and FP, and negative predictive value  
17 (NPV) as TN divided by the sum of TN and FN. Additionally, area under the receiver operating  
18 characteristic (AUC) curve and kappa statistic were computed, with their 95% confidence  
19 intervals (95% CI). The performance of DR graders after training was compared to that before  
20 training, and also to that of ophthalmologists who had not taken the course.  
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34 Since this was a study involving diabetic retinopathy graders and ophthalmologists, we did not  
35 involve patients and public in the design or conduct or reporting or dissemination of the study  
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## 41 **Results**

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43 In total, 43 DR graders participated in the training course and completed both pre and-post  
44 training tests, and the additional test after the one-to-one training, while 29 Vietnamese  
45 ophthalmologists underwent a single test and did not take part in the training. All DR graders  
46 undergoing training completed three rounds of testing.  
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53 The mean age ( $32.6 \pm 5.5$  years) did not differ from that of the ophthalmologists ( $32.3 \pm 7.3$  years,  
54  $p=0.893$ , Table 1). There was also no statistically significant difference between the age, sex  
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3 distribution and work experience of DR graders vs ophthalmologists. The DR graders required a  
4 mean of 297.8 minutes (144.6), to complete the course according to measurements carried out  
5 automatically by the Orbis Cybersight website.  
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10 DR graders improved significantly between their mean pre-training percent scores (33.3% ±  
11 14.3%) and their post-training performance score [(55.8% ±12.6%), P <0.001]. (Table 2) The  
12 mean post-training score for DR graders did not differ significantly from that for local  
13 ophthalmologists (58.7±15.4%, P=0.384). These findings, significant improvement between pre  
14 and post-training tests and the lack of a significant difference between post-training tests by DR  
15 graders and the performance of ophthalmologists, were consistent across optic nerve images  
16 from all sources. (Table 2)  
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25 With respect to other indices of grading accuracy (Table 3), there was no significant change  
26 between DR graders' pre-training [85.5% (83.5 – 87.3)] and post-training sensitivity [80.4%  
27 (78.3 – 82.4), p<0.001], while specificity improved significantly [47.8 (44.9 – 50.7) to 79.8 (77.3  
28 – 82.0), p<0.001]. The positive and negative predictive values also improved significantly  
29 between pre- and post-training tests, as did the area under the ROC curve [66.6 (64.9 – 68.3) to  
30 80.1 (78.5 – 81.6), p<0.001]. (Table 3). Compared to the 29 ophthalmologists, the 43 DR  
31 graders had worse sensitivity, better specificity, worse negative predictive value and worse  
32 kappa after training. The positive predictive value and the area under the ROC curve (our pre-  
33 specified indicator of overall grading accuracy) did not differ between post-training DR graders  
34 and ophthalmologists. (Table 3)  
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47 Table 4 shows the predictors of the percentage of correct responses among study participants.  
48 In the univariate analysis, age <30 years (p=0.005) and experience < 5 years (p<0.001)  
49 predicted higher scores. However, in the multivariate analysis, only experience < 5 years  
50 remained significant (p=0.006). The difference between post-training graders and local  
51 ophthalmologists remained non-significant when adjusting for other factors.  
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3 The test performance of DR graders (n=43) did not improve significantly after additional  
4 focused, one-to-one training, when compared to their performance after the online training.  
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6 (Table 5) Their mean scores still did not differ from the ophthalmologists after this additional  
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8 focused training. These patterns were the same for optic nerve images from all sources  
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## 14 **Discussion**

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16 This uncontrolled, experimental, before-and-after study found a significant improvement in the  
17 baseline mean scores of non-ophthalmic DR graders after undergoing a 5-hour training course.  
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19 The post-course scores of the DR graders were almost double the baseline scores, and did not  
20 differ significantly from the scores of general ophthalmologists in Vietnam. This suggests that it  
21 is possible to train non-ophthalmic DR graders to screen accurately for glaucoma using optic  
22 nerve photos using a short, self-paced online course. Additionally, more intensive one-to-one  
23 training by an expert did not result in significant further improvement of grading performance,  
24 suggesting encouragingly that results obtained with a convenient and scalable tool like our  
25 course approach is what may be readily achievable with such cadres.  
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36 In many developing countries, half or more of glaucoma patients present with advanced  
37 disease. [13-16] Shortage of providers limits access to eye care and leads to delays in  
38 diagnosis and management of glaucoma until late in the disease process, often too late for  
39 effective, sight-saving treatment. [17,18] For example, a recent study reported > 60%  
40 prevalence of blindness in the operative eye among patients at the time of first glaucoma  
41 surgery in rural China.[19] Training non-ophthalmic graders to screen for glaucoma may be an  
42 initial step in promoting earlier glaucoma diagnosis in low-resource settings. This has been  
43 described as task shifting, a model in which lower cadres of staff are trained to do simpler tasks  
44 so that scarcer and more highly-trained workers such as ophthalmologists can concentrate on  
45 high-level medical decision making and surgical management. [20-23]  
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3 The graders participating in this study were already trained to detect DR, the most frequent  
4 microvascular complication of diabetes and the leading cause of blindness in working-age  
5 adults. Studies [24-26] have demonstrated that > 90% of severe vision loss from DR can be  
6 prevented through regular screening and prompt referral and treatment. Diabetic screening is  
7 more cost-effective compared to no screening or opportunistic screening. [27-28] Glaucoma is  
8 the most common cause of irreversible blindness globally [2-29] and glaucoma blindness can  
9 similarly be prevented by regular screening of high-risk persons, prompt referral and treatment.  
10 Training the same cadres to screen for these two major causes of blindness may further  
11 improve the cost-effectiveness and cost-benefit of screening. This model is of particular interest  
12 in low-income settings, where traditional eye health services are mainly located in urban  
13 centres, often with poor accessibility to rural populations.  
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18 The model assessed in the current study differs from that described in previous reports in  
19 several ways. Non-expert health workers were trained to recognize glaucoma using an online  
20 course, and their performance was objectively measured and compared to their baseline, and to  
21 the scores of local ophthalmologists who had not taken the course. Previous studies have used  
22 telemedicine to send retinal images to reading centres for expert grading. [30-32] This can be  
23 challenging to sustain in low-resource settings, as it still depends on the time and availability of  
24 ophthalmologists or other relatively scarce trained experts to review retinal images for evidence  
25 of disease. Reading centres can also be logistically complex and expensive to establish and  
26 maintain in low resource settings, due to challenges such as the low bandwidth of available  
27 internet connections.  
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32 An advantage of training non experts as in our current model is that they are more likely to be  
33 able to review the images in real time due to lack of competing clinical duties. In delayed  
34 grading models, such as those using telemedicine, patients have to be contacted later to notify  
35 them of their screening results. Existing studies in LMICs have shown that this can lead to  
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3 substantial loss to follow-up. [33] The RAIDERS study in Rwanda reported that patients  
4 receiving immediate feedback on the need for referral demonstrated higher adherence with  
5 recommended services compared to participants informed of the results of their screening  
6 several days later. [33]  
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11 Training with our course significantly improved graders' specificity and positive predictive value.  
12 This effect of training is particularly relevant in low-resource settings, where the priority must be  
13 to avoid over-burdening already weak health systems with large numbers of false positive  
14 referrals. Ausayakhun et al [34] described a somewhat comparable model to ours, of training  
15 non-ophthalmologists to deliver point-of-service screening for glaucoma, cataract and age-  
16 related macular degeneration, and their reported specificity for glaucoma was approximately  
17 80% using fundus photographs, similar to that observed in the current study.  
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27 Although the sensitivity of DR graders decreased slightly after training, their specificity rose  
28 substantially. In screening programs for a relatively rare disease such as glaucoma, affecting  
29 roughly 2-4% of the population in most studies, avoiding false positives (good specificity) is  
30 most important for the cost-effectiveness of the program. For example, assuming a 3%  
31 prevalence of glaucoma, the increase in specificity from 47.8% to 79.8% observed after training  
32 would reduce the number of false positive referrals from 506 to 196 (61.3% more reduction) in a  
33 hypothetical population of 1000 persons, while the observed decline of sensitivity would result in  
34 only two more false negative cases." Although this is still a substantial number of false positives,  
35 it is fewer than the ophthalmologist would get, as the specificity of the graders post testing  
36 exceeds that of the ophthalmologists (79.8 vs 73.8%).  
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49 An important determinant of the positive predictive value of a screening program is the burden  
50 of disease in the target population. [35] The heavy burden of glaucoma among Asians [36-38]  
51 and Africans [39-41] has been well-documented. It is estimated that Asia has the highest  
52 number of persons living with glaucoma globally, and that this figure will increase by 79.8%  
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3 (primary open-angle glaucoma) and 58.4% (primary angle closure glaucoma) by 2040. [3] In  
4 view of this high glaucoma burden in Asia, and the growing gap between need and supply for  
5 ophthalmologists globally, [42] it is clear that new screening models are needed which rely on  
6 non-experts. We were able to train diabetic graders to perform at the level of local  
7 ophthalmologists, suggesting that our training course can deliver successful and effective task  
8 shifting.  
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11 An important predictor of correct responses on the test set among study participants was  
12 working experience of < 5 years. Lack of a positive effect of cumulative experience may seem  
13 counter-intuitive, but we suggest this may reflect better performance among younger and more-  
14 recently-trained cadres. Further studies are needed to replicate and better understand this  
15 finding.  
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18 Although artificial intelligence (AI) has been used successfully for DR screening, [43-44] well  
19 trained human graders are crucial in the validation of these AI systems, which must employ  
20 locally-derived images and personnel to be most reliable. Moreover, there are substantial  
21 existing legal and financial barriers to widespread sustainable use of AI for DR and glaucoma  
22 screening in many LMICs. Human systems are needed until these are overcome.  
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25 Strengths of this study include an approach to assessing the impact of training which included  
26 both a before-after comparison and external validation against the performance of local  
27 ophthalmologists. Success of the course against both of these criteria was consistent across  
28 images of varying difficulty and drawn from a wide variety of sources. Both the course and the  
29 assessment test reflected input from clinical experts, specialists in image-based screening and  
30 those engaged professionally in capacity-building for the recognition of glaucomatous optic  
31 nerves. A number of widely-used indices of screening accuracy were computed, allowing us to  
32 elucidate specific benefits of training in improving specificity.  
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3 This study has limitations as well. The generalizability of our results to other cadres of trainees  
4 and other settings is uncertain. Specifically, these results may not be directly applicable to  
5 novice graders without prior experience in interpreting fundus images.  
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10 Most importantly, further research is needed to better understand the practicality of this training  
11 model within the context of a full glaucoma screening program. Additional work is under way to  
12 test the model as part of delivering outreach screening for glaucoma in sub-Saharan Africa  
13 (SSA), aimed at a broad variety of patients at risk for glaucoma, and not solely those with DR.  
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17 In summary, our study shows that it is possible to train non-ophthalmic DR graders quickly and  
18 at low cost to screen for glaucoma using optic nerve images. This model may improve  
19 glaucoma detection and ultimately reduce the prevalence of blindness from glaucoma in low-  
20 resource settings.  
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**Table 1: Characteristics of DR graders and ophthalmologists participating in a study of glaucomatous optic nerve grading**

Characteristics	Ophthalmologists (n=29)	DR graders (n=43)	T-test/Chi-Square (P-value)
<b>Age (Mean±SD) yrs</b>	32.6±5.5	32.3±7.3	0.13 (0.893)
<30 years	11 (37.9%)	21 (48.8%)	0.83 (0.361)
≥30 years	18 (62.1%)	22 (51.2%)	
<b>Sex</b>			1.99 (0.159)
Female (%)	17 (58.6%)	32 (74.4%)	
Male (%)	12 (41.4%)	11 (25.6%)	
<b>Job Title</b>			0.65 (0.516)
Nurse (%)	0 (0.0%)	18 (41.9%)	
Ophthalmologist (%)	29 (100.0%)	0 (0.0%)	
Other physician* (%)	0 (0.0%)	22 (51.2%)	
Technician (%)	0 (0.0%)	3 (6.9%)	
<b>Work Experience (Mean±SD) yrs</b>	7.21±5.2	8.22±7.1	0.65 (0.516)
<5 (%)	11 (37.9%)	18 (41.9%)	0.11 (0.739)
≥5 (%)	18 (62.1%)	25 (58.1%)	

\*Endocrinologist (5); General Practitioner (14); Radiologist (2); Internist (1)

**Table 2: Accuracy (% Correct vs Gold Standard\*) in grading optic nerve images from different sources, comparing DR graders and ophthalmologists**

Source of Images	Number of images	% Pre-training Score of graders (A) Mean±SD	% Post-training Score of graders (B) Mean±SD	P-value (A vs B)	% Scores of Ophthalmologists (C) Mean±SD	P-value (B vs C)
GONE Website						
Easy	8	31.9±17.6	59.2±17.6	<0.001	65.1±21.9	0.216
Moderate	8	25.6±13.3	44.2±19.4	<0.001	48.1±17.8	0.392
Hard	7	22.7±15.9	47.7±22.5	<0.001	46.2±21.8	0.780
Orbis Vietnam DR program	19	47.0±22.7	70.3±12.0	<0.001	70.3±18.2	0.991
NICOLA population-based study in Northern Ireland	11	31.4±20.0	58.7±16.9	<0.001	55.2±22.1	0.443
Other images illustrating specific findings	4	31.0±19.8	51.9±24.1	<0.001	57.5±23.4	0.337
<b>**Total</b>	60	33.3± 14.3	55.8±12.6	<0.001	58.7±15.4	0.384

\*A panel of four fellowship-trained glaucoma specialist ophthalmologists and one medical retina specialist with a clinical and research focus on image-based screening for eye disease (AAB, MC, TP, NC, OO) \*\*The remaining 3 images came from a variety of other sources.

**Table 3: Accuracy in grading optic nerve images, comparing DR graders and ophthalmologists, and calculated against a panel of specialist ophthalmologists (the “gold standard”).**

Participant Type	Sensitivity (95%CI)	Specificity (95%CI)	Positive Predictive Value (95%CI)	Negative Predictive Value (95%CI)	Kappa (95%CI)	Area under the Receiver-Operator Curve (95%CI)
DR graders, Pre-Training (%)	85.5 (83.5 – 87.3)	47.8 (44.9 – 50.7)	66.7 (65.4 – 68.0)	72.9 (70.1 – 75.6)	34.4 (30.9 – 37.9)	66.6 (64.9 – 68.3)
DR graders, Post-training(%)	80.4 (78.3 – 82.4)	79.8 (77.3 – 82.0)	82.9 (81.2 – 84.5)	76.9 (74.9 – 78.8)	60.0 (56.9 – 63.1)	80.1 (78.5 – 81.6)
P-value Comparing Graders Pre and Post-training	<0.001	<0.001	<0.001	<0.011	<0.001	<0.001
Ophthalmologists (No Training Given) (%)	92.9 (91.1 – 94.4)	73.8 (70.6 – 76.9)	81.3 (79.4 – 83.0)	89.5 (87.1 – 91.5)	67.8 (64.3 – 71.3)	83.4 (81.6 – 85.1)
P-value comparing Post-training graders and Ophthalmologists	<0.001	0.002	>0.05	<0.05	<0.05	>0.05



**Table 4: Predictors of the percentage of correct responses on the test set among study participants**

Potential Predictor	Univariate Analysis			Multivariate Analysis		
	Beta	95% Confidence Interval	P-value	Beta	95% Confidence Interval	P-value
Age <30 years	9.0	2.8 – 15.2	0.005	0.4	-8.7 – 9.4	0.938
Male sex	0.4	-6.5 – 7.4	0.899	1.8	-4.7 – 8.3	0.585
Post-training non-ophthalmic grader (Vs ophthalmologist)	-2.9	-9.5 – 3.7	0.384	-3.1	-9.2 – 3.1	0.319
<5 years of work experience	12.5	6.6 – 18.4	<0.001	13.1	3.9 – 22.3	0.006
Nurse (vs “Other physicians,” non-ophthalmic grader group only)	-4.5	12.3 – 3.3	0.251			
Pre vs post-training (DR graders only)	0.4	0.1 – 0.6	0.007			

**Table 5: Accuracy (% Correct vs Gold Standard\*) in grading optic nerve images from different sources: the effect of additional one-one training for DR graders after the online course**

Source of Images	Number of images	% Post-training score of graders after online course Mean±SD (A) (n=43)	% Post training score of graders after additional focused one-one training, Mean±SD (B) (n=43)	P-value (A vs B)	% Scores of Ophthalmologists Mean±SD (C) (n=29)	P-value (B vs C)
GONE Website						
Easy	8	59.2±17.6	60.0±21.6	0.9364	65.1±21.9	0.6463
Moderate	8	44.2±19.4	48.7±21.9	0.6702	48.1±17.8	0.9529
Hard	7	47.7±22.5	49.7±25.8	0.8797	46.2±21.8	0.7886
Orbis Vietnam DR program	19	70.3±12.0	69.8±14.8	0.9096	70.3±18.2	0.9265
NICOLA population-based study in Northern Ireland	11	58.7±16.9	66.7±14.8	0.2514	55.2±22.1	0.1670
Other images illustrating specific findings	4	51.9±24.1	56.1±26.4	0.8220	57.5±23.4	0.9393
<b>**Total</b>	<b>60</b>	<b>55.8±12.6</b>	<b>60.3±16.4</b>	<b>0.1573</b>	<b>58.7±15.4</b>	<b>0.6422</b>

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3 **Contributorship statement:** NC, OO, AB, VC, DC and NP conceived and designed the study.  
4 All authors made inputs into the final design of the study. OO drafted the initial course and the  
5 test for the graders and ophthalmologists. NC, AB, MK, MC, OO; VC, DC, LN and TP revised  
6 the course and test contents and ensured standardization for the study. OO, KF, NC, CR, TH  
7 conducted the analysis. OO drafted the initial manuscript. NC, AB, MK, DC, TP, MC, NP and VC  
8 made major contributions to the drafting of the manuscript. All authors reviewed it critically for  
9 important intellectual content; and approved the final version to be published.  
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15 **Competing interests:** Congdon serves as a paid consultant for Belkin Vision, a company  
16 selling devices for the treatment of glaucoma. Kahook has an equity interest in SpyGlass  
17 Pharma and receives royalties from New World Medical and Alcon. Olusola Olawoye is a  
18 Consortium for Advanced Research and Training in Africa (CARTA) Fellow.  
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25 Award grant Number: XOVA Novartis: N/A, Wellcome Trust: 222490/Z/21/Z  
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28 **Data sharing statement:** Data are available upon reasonable request  
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30 **Ethics Approval:** Approval for the study was obtained from the Ethical Review Board of the  
31 Queen's University Belfast United Kingdom (MHLS 20\_98), and the Ethics Committee of the  
32 Hanoi Medical College in Vietnam (IRB-VN01.001/IRB 00003121/ FWA 00004148, Approval  
33 number 587)  
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## STARD Checklist

Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Page 2
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Page 2
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Page 5 and 6
	4	Study objectives and hypotheses	Page 6
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Page 6 and 7
<i>Participants</i>	6	Eligibility criteria	Page 7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Page 7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Page 7
	9	Whether participants formed a consecutive, random or convenience series	Page 7
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	Pages 8-10
	10b	Reference standard, in sufficient detail to allow replication	Pages 9-10
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Page 10-11
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	NA
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	9-11
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	10-11
	15	How indeterminate index test or reference standard results were handled	NA
	16	How missing data on the index test and reference standard were handled	NA
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	10-11
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	No diagram but well described on page 7
	20	Baseline demographic and clinical characteristics of participants	Page 11, table 1
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	Table 4
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3
	25	Any adverse events from performing the index test or the reference standard	NA
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Page 17

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1		<b>27</b>	Implications for practice, including the intended use and clinical role of the index test	Pages 16 -17
2	<b>OTHER INFORMATION</b>			
3				
4		<b>28</b>	Registration number and name of registry	NCT05151757 ClinicalTrials.gov
5				
6		<b>29</b>	Where the full study protocol can be accessed	
7		<b>30</b>	Sources of funding and other support; role of funders	eXcellence in Ophthalmology and Vision Awards (XOVA Novartis)
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