

The Influence of Age, Duration of Diabetes, Cataract, and Pupil Size on Image Quality in Digital Photographic Retinal Screening

PETER HENRY SCANLON, MRCP¹
CHRIS FOY, MSC²

RAMAN MALHOTRA, FRCO, PHTH³
STEPHEN J. ALDINGTON, DMS⁴

OBJECTIVE — To evaluate the effect of age, duration of diabetes, cataract, and pupil size on the image quality in digital photographic screening.

RESEARCH DESIGN AND METHODS — Randomized groups of 3,650 patients had one-field, nonmydriatic, 45° digital retinal imaging photography before mydriatic two-field photography. A total of 1,549 patients were then examined by an experienced ophthalmologist. Outcome measures were ungradable image rates, age, duration of diabetes, detection of referable diabetic retinopathy, presence of early or obvious central cataract, pupil diameter, and iris color.

RESULTS — The ungradable image rate for nonmydriatic photography was 19.7% (95% CI 18.4–21.0) and for mydriatic photography was 3.7% (3.1–4.3). The odds of having one eye ungradable increased by 2.6% (1.6–3.7) for each extra year since diagnosis for nonmydriatic, by 4.1% (2.7–5.7) for mydriatic photography irrespective of age, by 5.8% (5.0–6.7) for nonmydriatic, and by 8.4% (6.5–10.4) for mydriatic photography for every extra year of age, irrespective of years since diagnosis. Obvious central cataract was present in 57% of ungradable mydriatic photographs, early cataract in 21%, no cataract in 9%, and 13% had other pathologies. The pupil diameter in the ungradable eyes showed a significant trend ($P < 0.001$) in the three groups (obvious cataract 4.434, early cataract 3.379, and no cataract 2.750).

CONCLUSIONS — The strongest predictor of ungradable image rates, both for nonmydriatic and mydriatic digital photography, is the age of the person with diabetes. The most common cause of ungradable images was obvious central cataract.

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The use of nonmydriatic photography has been reported from the U.S. (1–4), Japan (5), Australia (6,7), France (8), and the U.K. (9–13). Reports of ungradable image rates for nonmydriatic photography vary between 4% reported by Leese et al. (10) and 34% reported by Higgs et al. (13).

In the U.K., national screening programs for detection of sight-threatening diabetic retinopathy are being implemented in England (14), Scotland (15), Wales, and Northern Ireland. England and Wales are using two 45° field mydri-

atic digital photography as their preferred method. Scotland is using a three-stage screening procedure, in which the first stage is one-field nonmydriatic digital photography with mydriatic photography used for failures of nonmydriatic photography and slit-lamp biomicroscopy for failures of both photographic methods. Northern Ireland is performing nonmydriatic photography in those aged <50 years and mydriatic photography in those aged ≥50 years.

The Gloucestershire Diabetic Eye Study (9) was designed to formally eval-

uate the community-based nonmydriatic and mydriatic digital photographic screening program that was introduced in October 1998. The current study was designed to evaluate the effect of age, duration of diabetes, cataract, and pupil size on the image quality in nonmydriatic and mydriatic digital photographic screening.

RESEARCH DESIGN AND METHODS

For the comparison of mydriatic photography and nonmydriatic photography in those patients with gradable images, the Gloucestershire Diabetic Eye Study (9) was designed to detect a difference of 2% in the detection of referable diabetic retinopathy between the methods (9% for mydriatic and 7% for nonmydriatic photography). To detect this difference with 80% power and 5% significance level, 3,650 patients had to be examined, allowing for an estimated ungradable image rate of 15% with nonmydriatic photography. Eighty groups of 50 patients from within individual general practices were randomly selected for inclusion as potential study patients. This number allowed for lower rates of screening uptake within some of the study practices.

The patient's history (including diabetes type) was taken and signed consent obtained. Patients classified as type 1 had commenced insulin within 4 months of diagnosis, while patients classified type 2 were not requiring insulin or commenced insulin after 4 months of diagnosis.

Visual acuity was measured using retroilluminated LogMAR charts modified from those used in the Early Treatment Diabetic Retinopathy Study (16). One 45° nonmydriatic digital photograph was taken of each eye using a Topcon NRW5S camera with Sony 950 video camera centered on the macula, repeated once only if necessary. After mydriasis with Tropicamide 1%, two 45° photographs, macular and nasal, were taken of each eye according to the EURODIAB protocol (17). Direct ophthalmoscopy was performed, the results of which were recorded. The screener was at liberty to take additional retinal or anterior segment views if he

From the ¹Department of Ophthalmology, Cheltenham General Hospital, Cheltenham, U.K.; the ²R&D Support Unit, Gloucester Hospitals National Health Service Trust, Gloucester, U.K.; the ³Oxford Eye Hospital, Oxford, U.K.; and the ⁴Retinopathy Grading Centre, Imperial College, London, U.K.

Address correspondence and reprint requests to Dr. Peter Scanlon, Gloucestershire Eye Unit, Cheltenham General Hospital, Sandford Road, Cheltenham, GL53 7AN, U.K. E-mail: peter.scanlon@glos.nhs.uk.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1

Description	Grade right eye	Grade left eye	Outcome
No diabetic retinopathy	0	0	12/12
Minimal nonproliferative diabetic retinopathy	1	1	12/12
Mild nonproliferative diabetic retinopathy	2	2	12/12
Maculopathy	3	3	Refer
Hemorrhage <1 DD from foveal center	3a	3a	Routine
Exudates <1 DD from foveal center	3b	3b	Soon
Groups of exudates (including circinate and plaque) within the temporal arcades >1 DD from foveal center	3c	3c	Soon
Reduced VA not corrected by a pinhole likely to be caused by a diabetic macular problem and/or suspected clinically significant macular edema.	3d	3d	Soon
Moderate to severe nonproliferative diabetic retinopathy	4	4	Refer
Multiple cotton wool spots (>5) and/or multiple hemorrhages	4a	4a	Soon
and/or intraretinal microvascular abnormalities	4a	4a	Soon
and/or venous irregularities (beading, reduplication, or loops)	4b	4b	Soon
and/or venous irregularities (beading, reduplication, or loops)	4b	4b	Soon
Proliferative diabetic retinopathy	5	5	Refer
New vessels on the disc, new vessels elsewhere, preretinal hemorrhage, and/or fibrous tissue			Urgent
Advanced diabetic retinopathy	6	6	Refer
Vitreous hemorrhage, traction/traction detachment, and/or rubeosis iridis			Immediate

DD, disc diameter; VA, visual acuity.

considered this to be appropriate and was specifically requested to take an anterior segment view of an eye with a poor quality image.

Grading

Patients for the reference standard examination ($n = 1,549$) using 78D lens slit-lamp biomicroscopy and direct ophthalmoscopy were recruited from those attending for photographic screening on days when an experienced ophthalmologist (P.H.S.) was able to attend. A separate study was performed to validate the ophthalmologist's reference standard against seven-field stereophotography (18).

A specialist registrar in ophthalmology (R.M.) interpreted the images from the study patients who received the reference standard examination ($n = 1,549$). P.H.S. interpreted the images of all patients who did not receive his reference standard examination ($n = 2,062$). Graders had a history sheet, including the patient's age, diabetes and ophthalmological history, visual acuity, screener's ophthalmoscopy findings, and reasons for extra views.

Nonmydriatic and mydriatic images were graded using Orion software (Cwmbran, U.K.) with time of grading separated by at least 1 month to prevent bias from a memory effect. It was not possible to mask the grader between methods because one image of each eye was captured without mydriasis and two images with mydriasis. For grading, 19-inch Sony Trinitron monitors were used with a screen resolution of $1,024 \times 768$ and 32-bit color (although we recognize that the camera system was limited to 24 bit). The Topcon fundus camera with Sony digital camera produced an image of resolution 768×568 pixels.

Image grading and the reference standard examination used the Gloucestershire adaptation of the European Working Party guidelines (19) for referable diabetic retinopathy (previously used in the Gloucestershire Diabetic Eye Study [9] and validated against seven-field stereophotography in a separate study [18]), as shown in Table 1. Referable retinopathy was classified as grades three to six on this form. The International Classification (20) was not used be-

cause the current study was undertaken before this was introduced and, even if this was available, referral to an ophthalmologist in the U.K. is at a level between level 3 and level 4 of the International Classification.

The ungradable image rate was classified as the number of patients with an ungradable image in one or both eyes unless referable diabetic retinopathy was detected in either eye. Image quality was judged with reference to each eye on the macular view and an eye was considered ungradable when the large vessels of the temporal arcades were blurred or more than one-third of the picture was blurred unless referable retinopathy was detected in the remainder. The nasal view was regarded as providing supplementary information and was not used for image quality assessments.

Reexamination of photographs

P.H.S. reexamined all the anterior segment photographs from eyes with ungradable images and any control eyes (i.e., if an anterior segment photograph had been taken of the patient's other eye) to determine whether cataract was present using the following classifications: 1) obvious central cataract: impaired central red reflex with obvious cataract almost certainly contributing to poor image quality; 2) early cataract: some impairment of central red reflex with cataract, which may or may not contribute to poor image quality; and 3) no cataract: good central red reflex and either no cataract or early peripheral lens changes not considered to contribute to poor image quality.

The horizontal pupil diameter of all the pupils in the central axis on the 19-inch monitor on which the anterior segment images were displayed was measured. The anterior segment images had been collected using a standardized methodology, so as to maintain near equivalence in image magnification between patients. Any other pathology that might have contributed to impaired quality of retinal images was recorded. Iris color of the ungradable eye was classified as blue, green (including blue with brown flecks or green), light brown, or dark brown.

Statistical methods

Data were entered into a customized database in the Medical Data Index (Patient Administration System) at Cheltenham General Hospital and downloaded into SPSS version 10 (SPSS, Chicago, IL) for

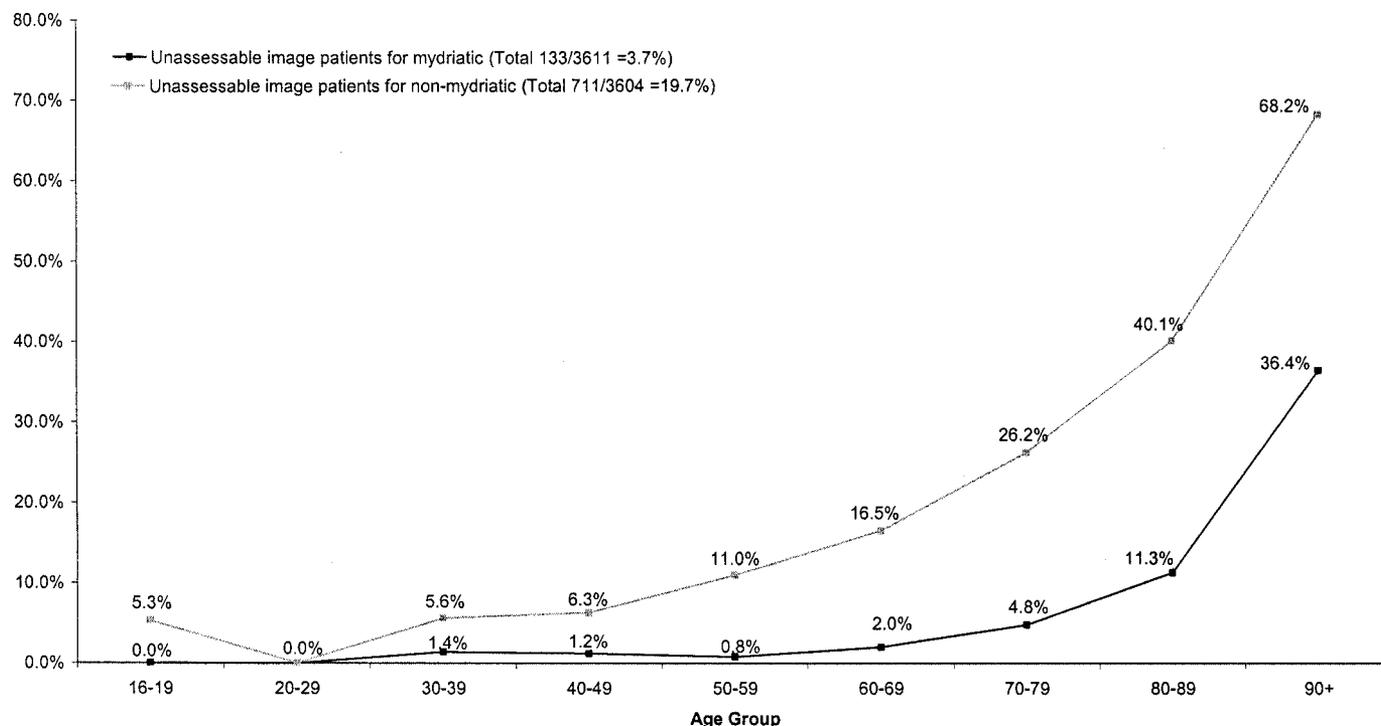


Figure 1—Unassessable image patients for mydriatic and nonmydriatic photographic screening.

data analysis as required. Percentages and 95% CIs were calculated. Multiple logistic regression was used to assess the impact of more than one predictive factor on the odds of poor image quality.

Pupil diameters for ungradable eyes and the opposite gradable eyes (where anterior segment photographs of both eyes were available) were compared for the ungradable eyes with no cataract, early cataract, and obvious central cataract. To identify any trends, the diameters in ungradable and opposite eyes and the difference between them were compared between cataract groups using one-way ANOVA with a linear contrast. Age and duration of diabetes were compared between the no cataract and the obvious central cataract group using Mann-Whitney *U* tests.

RESULTS

Acceptance rate of screening invitation and nonattendance rate at screening appointment and identification of the study population

Of 11,909 people with diabetes in the county, 74% responded to the screening invitation and attended. Of those who responded to the screening invitation and booked an appointment, the attendance rate was 95%. The high response and at-

tendance rates enabled the target population of 3,650 patients from within 80 groups of 50 patients to be identified and examined.

Images of 39 patients from one practice were excluded from the study because the patient images were accidentally captured in JPEG format instead of TIFF format. Ungradable image rates were calculated for all remaining 3,611 patients in the study. Seven grading forms were absent from the nonmydriatic group, all of which were from the subgroup of 1,549 patients who had the reference standard examination.

Ungradable image rate and age

The ungradable image rate for nonmydriatic photography was 19.7% (95% CI 18.4–21.0) and for mydriatic photography was 3.7% (3.1–4.3). A total of 15 patients in the nonmydriatic group and 8 patients in the mydriatic group who were found to have an ungradable image in one eye were not included in the ungradable image rate because referable retinopathy was detected in the other eye (Fig. 1).

Detection of referable retinopathy in different age ranges

From the reference standard examination of 1,549 patients, 180 patients were found to have referable diabetic retinopathy. The grading form for one of these

patients (from the nonmydriatic group) was missing, making the maximum possible detection in that group 179. Levels of detection of referable diabetic retinopathy were 82.8% for mydriatic photography (149 of 180) and 57.5% for nonmydriatic photography (103 of 179). Analyzing the nonmydriatic figures in 10-year age-groups, the younger age-groups had better image quality results and better identification of referable diabetic retinopathy (Fig. 2).

Type of diabetes, sex of study patients, and duration of diabetes

Of 3,611 study patients, 16.5% had type 1 diabetes, 81.6% had type 2 diabetes, and 1.9% had unknown diabetes status. Participants were 55% male and 45% female. Duration of diabetes was 41.7% 0–4 years, 26.2% 5–9 years, 13.7% 10–14 years, 7.6% 15–19 years, 10.8% 20+ years, and 0.2% unknown duration. The 1,549 reference standard subgroup patients had very similar characteristics.

Ungradable image rate versus age and duration of diabetes

Because an association was found between ungradable image rate and both age and duration of diabetes and also between age and duration of diabetes, a logistic regression analysis was undertaken to see if

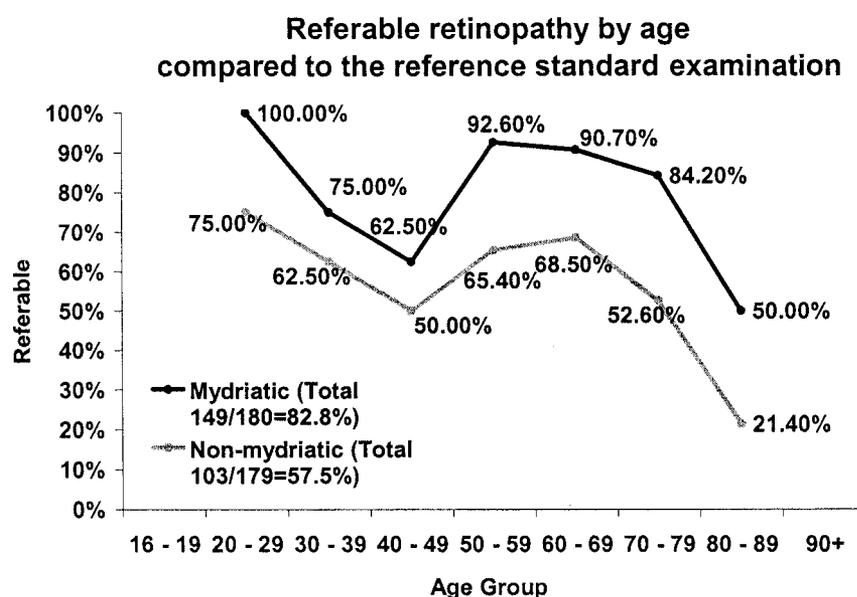


Figure 2—Referable retinopathy by age compared to the reference standard examination.

the associations were independent of each other.

For nonmydriatic photography, the odds of having one eye ungradable increased by 2.6% (95% CI 1.6–3.7) for each extra year since diagnosis, irrespective of age, and by 5.8% (5.0–6.7) for every extra year of age, irrespective of years since diagnosis. For mydriatic photography, the odds of having one eye ungradable increased by 4.1% (2.7–5.7) for each extra year since diagnosis, irrespective of age, and by 8.4% (6.5–10.4) for each extra year of age, irrespective of years since diagnosis. The analysis showed that both age and years since diagnosis contributed to the odds of having an ungradable image in one eye.

Influence of cataract and other pathology

Of the 169 ungradable eyes from 133 patients, 8 eyes had no anterior segment image. Of the 161 eyes with an anterior segment image, 92 eyes (57%) had obvious central cataract, 34 eyes (21%) had early cataract, and 15 eyes (9%) had no cataract. The study of other pathology showed 10 eyes (6%) had a corneal scar, 9 eyes (6%) had asteroid hyalosis, and 1 eye (1%) had a history of hemorrhage, glaucoma, and blindness (not from diabetic retinopathy).

Influence of pupil diameter

There were 97 patients in whom one eye was not assessable. In 12 cases, there was a nondiabetic, noncataract pathological

reason detected that would explain why imaging was unsuccessful (e.g., corneal scarring), and in 5 cases no anterior segment image was taken of the ungradable eye. In the remaining 80 cases, no obvious other pathology was detected that could explain poor image quality, suggesting a relationship with pupil size. To test this hypothesis, we examined the pupil diameter in those 54 cases in which an anterior segment view was available of both the ungradable eye and the gradable fellow eye. The following comparisons were made between the two eyes. In eight eyes with no cataract seen in the ungradable eye, the mean pupil diameter in the ungradable eye was 2.7 cm and in the gradable control eye was 3.6 cm (difference: 0.9 cm). In 14 eyes with early cataract seen, the mean pupil diameter in the ungradable eye was 3.4 cm and in the gradable control eye was 3.9 cm (difference: 0.5 cm). In 32 eyes with obvious cataract seen, the mean pupil diameter in the ungradable eye was 4.4 cm and in the gradable control eye was 4.3 cm (difference: +0.1 cm). The pupil diameter in the ungradable eye and the difference in pupil diameters between the two eyes both showed significant trends ($P < 0.001$ and $P = 0.008$, respectively) in the three groups. However, the pupil diameter in the gradable eye did not show a significant trend ($P = 0.072$) in any group.

The eight people in the no cataract group with poor pupillary dilation (mean 2.7 cm) had a mean age of 72.7 years and a mean duration of 20.4 years with diabe-

tes. The 32 people with obvious central cataract and good pupillary dilation (mean 4.4 cm) had a mean age of 78.5 years and a mean duration of 8.7 years with diabetes. The Mann-Whitney U test showed no significant difference for the ages between these two groups but a significant difference for duration of diabetes ($P = 0.003$).

Iris color in ungradable eyes

Of the 124 patients in whom anterior views enabled color determination, there were 68 blue (55%), 24 green (19%), 21 light brown (17%) and 11 dark brown (9%) eyes. The iris color is in keeping with Gloucestershire's predominant proportional white Caucasian population, the main ethnic minority groups being Indian/British Indian (0.7%) and Black/Black British (0.8%).

CONCLUSIONS— Several possible factors might have an influence on image quality in retinal photography. Age is suggested in the following studies. Higgs et al. (13) reported that 13% <50 years, 39% 50–70 years, and 54% >70 years had ungradable nonmydriatic images. Buxton et al. (21) reported that the ungradable image rate varied between 2% in the Exeter physician group and 9% in the Oxford general practitioner group. The difference between these two groups was principally related to age, duration of diabetes, and type of diabetes. Some studies (3,8) have reported nonmydriatic ungradable image rates <12%, but the average age of the study population was <55 years.

Duration of diabetes is suggested as a factor by Cahill et al. (22), who in 2001 reported that pupillary autonomic denervation increases with increasing duration of diabetes mellitus. Ethnicity is suggested by Klein et al. (23).

Flash intensity is suggested by Taylor et al. (24), who reported less patient discomfort with the lower flash power (10 W vs. 300 W) of the digital system. In nonmydriatic photography, there is a faster pupil recovery time with lower flash intensities, which may improve image quality in the fellow eye.

Age, duration of diabetes, and ethnicity were not reported in some studies (7,11,25), while others (1,6) have reported these variables but have not reported an association. The study by Lin et al. (4) excluded 197 patients (48.5%) for unusable seven-field reference standard photos and a further 12 patients (2.96%)

because of unusable ophthalmoscopy records, which made it difficult to interpret the ungradable image rate of 8.1%. Shiba et al. (5) excluded the >70 years age-group and remarkably attempted 9 × overlapping nonmydriatic 45° fields (5), whereas others have only attempted five fields (8), three fields (2,3), and the majority only one nonmydriatic field (1,6,9,10,13,21). Patient numbers varied from 40 eyes in the study by Lim et al. (2) to 3,611 patients in the current study.

The current study has suggested that, after excluding a small number of patients with other pathology, the causes of ungradable images in mydriatic photography are obvious central cataract (57%), a combination of early cataract and a small pupil (21%), and a small pupil alone (9%). There was a dip to 75% in the 30–39 age-group (two patients missed) and 62.5% in the 40–49 age-group (six patients missed) in detection of referable retinopathy using mydriatic photography. If ungradable images were test positive (i.e., referable), six patients in total would have been missed in the 30–49 age-group. On retrospective examination of the mydriatic images, the pathology was visible in five of six of these (two having received extensive laser treatment and being graded as stable treated diabetic retinopathy). There was only one person whose retinopathy visible within the two 45° fields was mild nonproliferative diabetic retinopathy (i.e., not referable), whereas small new vessels elsewhere were visible in the peripheral retina only on reference standard examination. This is the only patient in this age-group that should have been a definite false negative for the test.

While a 20% failure rate for nonmydriatic photography might be acceptable because patients could be reexamined by other means, there is a difference in detection of referable retinopathy between the two methods, as shown in Fig. 2. The Health Technology Board for Scotland used data from the current study in their report (15) and concluded that similar sensitivities and specificities could be achieved by dilating those patients with ungradable images. However, this relies on the ability of the screener to accurately determine an ungradable image at the time of screening and, in the Scottish system, relies on the assumption that the grading of one field will detect referable retinopathy with the same degree of accuracy as the grading of two fields (giving evidence from Olson et al.'s study [26]).

There have been differing views on the number of fields required for screening, Bresnick et al. (27) supporting Olson et al.'s view that one field may be sufficient. However, studies by Moss et al. (28), Shiba et al. (5), and von Wendt et al. (29) have suggested that higher numbers of fields give greater accuracy in detection of retinopathy levels.

Data from the current study indicates that there would potentially be very many occasions on which nonmydriatic imaging in patients aged ≥50 years would result in ungradable images. In the >80 years age-group, the failure rate is reduced from 41.6 to 16.9% by dilation with G Tropicamide 1%. It is possible that the failure rate of 16.9% following dilation with G Tropicamide 1% could be further reduced by the addition of G Phenylephrine 2.5% for this specific group. Routinely dilating the >50 years age-group with G Tropicamide 1% at outset could potentially reduce the failure rate by >80%. If screening programs are going to consider nonmydriatic photography to detect sight-threatening diabetic retinopathy, the findings of the current study largely support the use of this method for the group <50 years of age who are at lowest risk of ungradable images, and yet, this group contains a number of young regular nonattendees, who some authors suggest are at greatest risk of blindness (e.g., MacCuish et al. [30] and Jones [31]).

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P.H.S. is submitting this work for an MD thesis to University College London.

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