British Journal of Ophthalmology

Comparison of True-colour Wide-field Confocal Scanner Imaging (EIDON™) with Standard 2-field Fundus Photography for Diabetic Retinopathy Screening

Journal:	*British Journal of Ophthalmology*
Manuscript ID	bjophthalmol-2019-315269.R1
Article Type:	Clinical science
Date Submitted by the Author:	n/a
Complete List of Authors:	Olvera-Barrios, Abraham; Moorfields Eye Hospital; University College London Institute of Ophthalmology Heeren, Tjebo; Moorfields Eye Hospital; University College London Institute of Ophthalmology Balaskas, Konstantinos; Moorfields Eye Hospital NHS Foundation Trust Chambers, Ryan; Homerton University Hospital NHS Trust, Diabetes Bolter, Louis; Homerton University Hospital NHS Trust Tufail, Adnan; Moorfields Eye Hospital; University College London Institute of Ophthalmology Egan, Catherine; Moorfields Eye Hospital; University College London Institute of Ophthalmology Anderson, John; Homerton University Hospital NHS Trust, Diabetes
Keywords:	Retina, Public health, Neovascularisation, Epidemiology, Diagnostic tests/Investigation

Comparison of True-colour Wide-field Confocal Scanner Imaging (EIDON™) with Standard 2-field Fundus Photography for Diabetic Retinopathy Screening

Abraham Olvera-Barrios,[1-2,4] Tjebo Heeren,[1-2] Konstantinos Balaskas,[1] Ryan Chambers,[3] Louis Bolter,[3] Adnan Tufail,[1-2] Catherine Egan,[1-2] John Anderson.[3]

1. NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom
2. University College London Institute of Ophthalmology, London, United Kingdom
3. Homerton University NHS Foundation Trust, London, United Kingdom
4. Universidad Autónoma de Nuevo León, University Hospital "Dr. José Eleuterio González", Ophthalmology Department, Monterrey, México.

Word count: 3,071

Corresponding Author

Abraham Olvera-Barrios

Moorfields Eye Hospital

162 City Road

London EC1V 2PD

United Kingdom

a.olvera@nhs.net

Synopsis:

Vision-threatening diabetic retinopathy features which are missed with standard fundus cameras, can be evidenced with the true-colour, wide-field EIDON confocal scanner. Clinically relevant differences in grading result in more referrals for vision-threatening disease when using the EIDON.

Abstract

BACKGROUND: Screening of Diabetic retinopathy(DR) reduces blindness by early identification of retinopathy. This study compares DR grades derived from a 2-field imaging protocol from two imaging platforms, one providing a single 60-degree horizontal field of view(FOV), and the other, a standard 45-degree FOV.

METHODS: Cross-sectional study which included 1257 diabetic patients ≥18 years attending their DR screening visit in the English National Diabetic Eye Screening Programme(NDESP). Patients with maculopathy(M1), pre-proliferative(R2), or proliferative DR(R3) are referred to an ophthalmologist. Patients with ungradable images(U) are examined in a slit-lamp biomicroscopy clinic. Image acquisition under mydriasis of two images per eye was carried out with the EIDON and with standard fundus cameras. Evaluation was performed by masked graders.

RESULTS: Agreement after consensus with kappa statistic was 0.89(quadratic weights[95%CI,0.87-0.92]) for NDESP severity grade, 0.88(quadratic weights[95%CI,0.82-0.94]) for referable disease, and 0.92(linear weights[95%CI,0.88-0.95]) for maculopathy. The EIDON detected clinically relevant DR features outside the 45-degree fields in 2 patients(0.16%): one with intrarretinal microvascular abnormalities(IRMA) and one with neovascularisation. In 8 patients(0.64%), the EIDON allowed DR feature visualisation inside the 45-degree fields that were not identified in the NDESP images: 3(0.24%) patients with IRMA and 5(0.40%) with maculopathy. The rate of ungradable encounters was 12(0.95%) and 13(1.03%) with the EIDON and NDESP images, respectively.

CONCLUSION: The EIDON identifies a small number of additional patients with referable disease which are not detected with standard imaging. This is due to the EIDON finding disease outside the standard FOV, and greater clarity finding disease within the standard FOV.

INTRODUCTION

Diabetic retinopathy (DR) is a common neurovascular complication of diabetes and the leading cause of visual loss in the working age population in many countries.[1–4] There are 451 million people with diabetes worldwide, a number projected to rise to 693 million in 2045.[1] Thirty five percent of these patients will develop DR and around 12% will progress to vision-threatening DR (VTDR).[1] Early diagnosis through regular clinical examination or grading of retinal photographs is essential to identify vision-threatening disease and prevent diabetes-related visual impairment.[5] National photography-based DR screening programmes, including the English National Diabetic Eye Screening Programme (NDESP) are effective.[6] The steadily rising prevalence of diabetes poses significant organisational and financial challenges to screening programmes.

In England, annual screening with two (macula- and disc-centred) 45-degree fundus photographs is offered to every person with diabetes aged 12 years and older. The Early Treatment Diabetic Retinopathy Study (ETDRS) group (a 'gold standard' in the definition of retinopathy severity) used a 30-degree 7-field stereoscopic colour fundus photographs grading system.[7] This technique provided a wide view of the retina but is an unsuitable approach for screening due to its time consuming nature, and its need of skilled retinal photographers and cooperative patients. Even a 4-field protocol per eye poses practical problems in screening due to the acquisition time, image storage considerations, and the photographic skill needed in a high-volume screening service.[8] Nonetheless, DR is a disease with significant peripheral retinal pathology. There is a concern that disease will be missed in this subgroup of patients due to limitation in the field of view (FOV). The trade-off for a wider FOV of some imaging platforms is a reduced resolution, semi-realistic colour images, and a small degree of distortion of the posterior pole.[9,10] The EIDON confocal scanner (CenterVue, Padua, Italy) is the first commercially available wide-field platform to obtain 60-degree true-colour high-resolution fundus photographs by means of white light illumination (440–650nm).[11] Potential advantages of this platform may include better or similar acquisition time, reduced rates of

ungradable images in eyes with poor mydriasis[12] and more detailed visualisation of high-risk DR features, such as, intraretinal microvascular abnormalities (IRMA), or neovascularisation (NV) peripheral to or within the standard 2-field 45-degree photographs for screening.

The purpose of our study is to compare the human grading of EIDON images with the English NDESP standard 2-field digital photographs in patients with diabetes attending a large-scale, community DR screening programme, assess potential advantages, and guide whether or not this supports its deployment in DR screening or surveillance programmes.

MATERIALS AND METHODS

We report a cross-sectional, comparative study with consecutive recruitment of adult patients (≥18 years) with diabetes attending their routine DR screening visit in the North East London Diabetes Eye Screening Programme (NELDESP), from 22nd January 2018 until 18th April 2018, which adhered to English NDESP guidelines.[13,14] This screening programme is based at and managed by Homerton University Hospital. The study protocol was registered and approved through the research governance process at this clinical centre and adhered to the tenets of the Declaration of Helsinki and the UK Data Protection Act 2018.

This was a service evaluation study of a new imaging platform (EIDON) which has not been evaluated in DR screening before. Assuming we needed to test an agreement for referable retinopathy with Cohen's Kappa of 0.7 with a precision of 0.2 on each side, a two-sided significance of 0.05 and a power of 0.8, a total of 87 subjects with referable retinopathy would be required.

During the study period 2,629 patients underwent routine photographic screening. All patients were asked if they were willing to have an additional set of images taken with a second camera. A total of 1,257 patients agreed to participate and had this additional imaging. Written informed consent was obtained from all patients who accepted to take part in the study.

Image acquisition

Figure 1 summarises the assessment pathway of this study. The English NDESP protocol was used in this study.[14,15] The protocol consists of retinal photography under mydriasis to capture four images per patient. For each eye, one image centred on the optic disc and one image centred on the macula. Additional images are often taken and stored on the screening software to ensure that enough images of sufficient quality for retinal grading are obtained and to document anterior segment pathology (NDESP images). A list of the approved fundus cameras can be found in the diabetes eye screening guidance on camera approval.[16] Two

further similarly centred images were then obtained with the EIDON (CenterVue, Padua, Italy). No images of the anterior segment were captured with the EIDON. The EIDON imaged a field of 60-degrees horizontal x 50-degrees vertically with a resolution of 4608x3288 pixels for each capture (EIDON images).[11] Image 1A shows a comparison between the FOV obtained with the EIDON, NDESP, and ETDRS fields.

Grading Protocol

Supplementary Figure 1 summarises the grading protocol used in this study. Standard photographic images were graded in accordance with the National Screening Committee UK (NSC-UK) classification for DR, and the current English NDESP pathway.[17] Up to three human graders who meet the NDESP quality assurance standards assessed the images to determine a disease severity grade and produce a "final grade" for each eye according to the highest level of severity observed. The grading classification in order of increasing severity are no retinopathy (R0), background retinopathy (R1), no maculopathy (M0), ungradable (U), maculopathy (M1), pre-proliferative retinopathy (R2) and proliferative retinopathy (R3).[17-18] Level 2 grading of images is carried out by more senior graders. Disagreements between level 1 and level 2 graders for episodes that are potentially M1 or R2 are sent to a level 3 grader for arbitration, whose assessment is final. After this, a final outcome grade was obtained for the NDESP images. Referral to hospital eye service ophthalmologists is carried out for patients with grades M1, R2 and R3. Patients with a U grade are re-examined by slit lamp biomicroscopy within the screening programme according to NDESP guidelines and referred to the hospital for the above grades or for other pathology.

EIDON images have a different colour cast to standard retinal photographic images. They require much greater magnification and resultant scrolling through the images, due to the higher pixel density. Because of these differences, it was not possible to introduce the EIDON images in the NDESP grading pathway. The EIDON images were graded by a level 3 grader with both wide experience grading in the NDESP, and wide experience of the manipulation techniques needed to grade EIDON images. This grader was masked to the outcome of grading the standard images. The resultant EIDON grades were compared with the final grade of the

NDESP images. All the patient encounters where there was a discrepancy between the EIDON grade and NDESP grade were re-examined by a different experienced level 3 grader within the screening programme and an ophthalmologist to obtain a consensus EIDON grade.

Anonymisation of images

Data extraction from a secure server running Digital Healthcare OptoMize diabetes eye screening software (version 4.5, Cambridge, UK) at Homerton University Hospital was carried out. Data for 1,257 patients was extracted using SQL searches and then anonymised to exclude personal identifying data. A unique identifier was created for each patient.

Statistical analysis

Statistical calculations were performed using R studio, version 1.1.463 (www.r-project.org). Levels of agreement for NDESP severity grade (grades R0M0, R1M0, U, R1M1, R2M0, R2M1, R3M0 and R3M1), retinopathy grade (R0, R1, R2 and R3), referable disease (grades U, M1, R2 or R3), and maculopathy (M1) were assessed by means of Gwet's first-order agreement coefficient (AC1),[19] Cohen's κ (linear and quadratic weights) and 95% confidence intervals (CI) for multilevel outcomes. Interpretation of κ statistics was according to Landis and Koch[20] ranges (<= 0.20: poor; 0.21-0.40: fair; 0.41-0.60: moderate; 0.61-0.80: substantial; 0.81-1.00: almost perfect agreement). The imaging platform selected as reference standard for sensitivity and specificity calculations in this study can be debatable because we compare two platforms with different optical properties and FOV. Since this is a NDESP protocol-based study and evidence of its accuracy for screening is available,[6,21] the final grades of the NDESP images were considered as reference standard to calculate sensitivity and specificity for any retinopathy, referable disease, and maculopathy.

RESULTS

A total of 1,257 patients (2,508 eyes) were included in the study. A total of 5,061 and 6,735 images were obtained with the EIDON and standard fundus cameras, respectively. The file size for all the EIDON images was 24.82 GB, and 6.78 GB for the NDESP images. Table 1 summarises the grading differences between the EIDON and NDESP images per patient. With the EIDON images, the prevalence of R0, R1, M1, R2 and R3 was 57.68%, 39.14%, 7.08%, 1.67%, and 0.56%, respectively. With the NDESP images, the prevalence of R0, R1, M1, R2 and R3 was 65.39%, 32.06%, 6.92%, 1.03%, and 0.48%, respectively. The sample size calculation revealed that a minimum of 87 patients with referable retinopathy were required, and our sample included a total of 98 and 106 subjects with referable retinopathy according to NDESP and EIDON image grades, respectively. In relation to the prevalence of this sample, the number of patients needed to screen in order to detect one additional case of R2 and R3 with the EIDON would be 156 and 1250, respectively.

The sensitivity for referable retinopathy obtained with the EIDON (final NDESP images grade as reference standard) was 88.29% (95% CI, 82.03-92.93), specificity of 98.25% (95% CI, 97.47-98.84). For maculopathy, we found a sensitivity of 96.51% (95% CI, 91.23-99.04) and a specificity of 99.49% (95% CI, 98.99-99.78). For any type of retinopathy, a sensitivity of 98.16% (95% CI, 96.70-99.08) and specificity of 87.22% (95% CI, 85.15-89.10).

A comparison of the EIDON and NDESP images grade per eye, evidenced similar discrepancies, with the EIDON images detecting more VTDR (Supplementary table 1).

Table 1. Comparison of grades in the worst eye between EIDON wide-field confocal scanner and English National Diabetic Eye Screening Programme (NDESP) images after consensus. The highlighted patients represent clinically significant differences in the grades.

EIDON images grade, n (%)	*NDESP images grade, n (%)*								***Total***
	R0M0	R1M0	U	R1M1	R2M0	R2M1	R3M0	R3M1	
R0M0	717 57.04 %	2 0.16 %	6 0.48 %	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	725 57.68 %
R1M0	95 7.56 %	312 24.82 %	4 0.32 %	3 0.24 %	0 0 %	0 0 %	0 0 %	0 0 %	414 32.94 %
U	9 0.72 %	2 0.16 %	1 0.08 %	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	12 0.96 %
R1M1	1 0.08 %	4 0.32 %	1 0.08 %	72 5.73 %	0 0 %	0 0 %	0 0 %	0 0 %	78 6.21 %
R2M0	0 0 %	4 0.32 %	1 0.08 %	1 0.08 %	9 0.72 %	0 0 %	0 0 %	0 0 %	15 1.2 %
R2M1	0 0 %	0 0 %	0 0 %	3 0.24 %	0 0 %	3 0.24 %	0 0 %	0 0 %	6 0.48 %
R3M0	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	2 0.16 %	0 0 %	2 0.16 %
R3M1	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	1 0.08 %	0 0 %	4 0.32 %	5 0.4 %
Total	822 65.39 %	324 25.78 %	13 1.03 %	79 6.28 %	9 0.72 %	4 0.32 %	2 0.16 %	4 0.32 %	1257 100 %

Agreement

There were 157 (12.49%) patient encounters with grading discrepancies. Table 2 summarises the discrepant grades of clinical significance between the EIDON and NDESP images and whether the imaging platform allowed visualisation of retinopathy features inside or outside the 45-degree fields (see Image 1B,C). Referrals due to ungradable images were 12 (0.95%) with the EIDON, and 13 (0.95%) with the NDESP images. Table 3 summarizes the agreement coefficients obtained before and after consensus. Almost perfect agreement was found when evaluating the NDESP severity grade, retinopathy grade, referable disease and maculopathy.

Table 2. Clinically relevant differences in grades per patient encounter between EIDON true-colour confocal scanner and English National Diabetic Eye Screening Programme (NDESP) images after consensus.

	EIDON images	NDESP images
Features inside the 45-degree fields	3 (0.24%) routine referrals[¶] due to IRMAs 5 (0.40%) routine referrals due to M1	3 (0.24%) routine referrals due to M1 not detected as referable
Features outside 45-degree fields	1 (0.08%) urgent referral[§] due to NVE 1 (0.08%) routine referral due to IRMA	-----

[§] Refer within 2 weeks of the screen date

[¶] Refer within 3 weeks of the screen date

Table 3. Agreement analysis between EIDON wide-field confocal scanner and the English National Diabetic Eye Screening Programme (NDESP) standard images before and after consensus.

coefficient (95% Confidence Interval)	Before consensus	After consensus
NDESP severity grade		
Gwet AC1 agreement coefficient	0.97 (0.96-0.97)	0.98 (0.97-0.98)
Kappa coefficient		
linear weights	0.74 (0.71-0.77)	0.85 (0.83-0.87)
quadratic weights	0.81 (0.78-0.85)	0.89 (0.87-0.92)
Retinopathy grade		
Gwet AC1 agreement coefficient	0.99 (0.98-0.99)	0.97 (0.96 - 0.97)
Kappa coefficient		
linear weights	0.75 (0.72-0.78)	0.84 (0.82-0.86)
quadratic weights	0.78 (0.75-0.81)	0.86 (0.84-0.88)
Referable disease		
Gwet AC1 agreement coefficient	0.90 (0.89-0.90)	0.99 (0.993-0.997)
Kappa coefficient		
linear weights	0.20 (0.15-0.24)	0.86 (0.81-0.91)
quadratic weights	0.40 (0.30-0.49)	0.88 (0.82-0.94)
Maculopathy		
Gwet AC1 agreement coefficient	0.98 (0.97-0.98)	0.99 (0.988-0.995)
Kappa coefficient		
linear weights	0.79 (0.73-0.85)	0.92 (0.88-0.95)

DISCUSSION

Adequate fundus imaging is a keystone in the photographic screening of DR. In our study, we demonstrate that the EIDON is comparable to the standard images obtained with NDESP approved fundus cameras for human grading in a large-scale, community-based DR screening programme. The EIDON images demonstrated almost perfect agreement for NDESP severity grade, retinopathy grade, referable disease, and maculopathy. However, the EIDON images allow detection of a small number of additional clinically relevant DR cases not only by identifying disease features outside the 45-degree fields, but also by cause of retinopathy feature visualisation within the 45-degree fields which were not evidenced in the NDESP images. Though small, the differences in the overall prevalence of referable retinopathy between the grading of EIDON and NDESP images is relevant in terms of screening. For instance, in 2015-2016 a total of 2,144,007 people with diabetes were screened in the English NDESP.[6] If the number of patients needed to screen obtained in our study would be consistent and the EIDON deployed in such a sample, an additional 13,746 cases of R2, and 1,715 cases of R3, could be detected. Moreover, with the difference rate of ungradable cases in this sample (0.08%), there would be 1,715 less referrals due to ungradable images if using the EIDON. It is likely that the slightly higher ungradable rate with the NDESP images, is explained by the confocal scanning imaging of the EIDON. However, this small difference in the context of DR screening should be evaluated in further studies. When considering the NDESP images as reference standard for screening in this sample, the EIDON images have met the Exeter Standards for DR detection (minimum sensitivity of 80% and minimum specificity of 95%).These were first agreed upon at a British Diabetic Association (now Diabetes UK) meeting in 1995.[6] The specificity for the detection of any retinopathy with the EIDON (87.22% [95% CI, 85.15-89.10]) using the NDESP images grade as standard, does not meet the minimum 95% recommended by the British Diabetic Association. This is explained by the fact that the EIDON images allowed detection of 106 patients (8.43%) with diabetic eye disease which were graded as R0 with the NDESP images. Conversely, if the EIDON images grade is considered as the reference standard, then the NDESP images have a sensitivity for any retinopathy of 80.08%

(95% CI, 77.01-82.89) and a specificity of 98.62% (95% CI, 97.67-99.25); and for referable retinopathy of 83% (95% CI, 76.33-88.48) and a specificity of 98.77% (95% CI, 98.09-99.26).

Previous studies comparing different imaging modalities have implemented Cohen's κ to analyse the agreement between different imaging systems/protocols.[21–29] However, κ coefficient can be affected by prevalence and marginal probability.[30,31] Gwet[19] addressed this variability and proposed the AC1, a more stable coefficient that adjusts the overall probability based on the chance that evaluators may agree on a grading, despite the fact that one or all of them may have given a random value. We implemented the Gwet's AC1 statistic in our analysis to support the reliability of κ statistics, evidencing stable coefficients (see Table 3).

The FOV of the two 60-degree EIDON images cover an estimate of 75-degree horizontally and 50-degree vertically (80% of the entire FOV of the ETDRS 7-field images). Areas between fields 3-4, 3-5 and 6-7 not imaged with the ETDRS fields are covered with this approach; however, the crescent of fields 4, 5, 6 and 7 are left out of the FOV (Image 1A). The ETDRS 7-field images cover a 75-degree FOV,[32] and the standard two-field 45-degree imaging approach used in the NDESP covers 60 degrees horizontally and 45 degrees vertically.[6] A wider FOV has importance because of the association between predominant peripheral lesions and DR progression.[8,12,27] The wide-field angle capture, the confocal scanning system (possibility to image through small pupils and media opacities), as well as the white light illumination system (acquisition of true-colour images) of the EIDON may benefit detection of DR features and be responsible for the detection of the small subset of patients with referable disease not picked up by the NDESP images, and for the discretely lower rate of referrals due to ungradable images. Nevertheless, the file size of the EIDON images was almost four times as big as the one from the NDESP images, a fact to consider because of its impact on image management and storage. We found an almost perfect agreement for maculopathy after consensus (κ 0.92; CI 0.88-0.95) using the DR severity scale approved by the NSC-UK.[17] Agreement coefficients with κ statistics ranging from 0.68 to 0.79 for the ETDRS definition of Clinically Significant Macular Oedema have been previously reported in the literature.[33–35] When the International Clinical Diabetic Retinopathy severity scale is used for grading diabetic macular

oedema, evidence of agreement values of 0.39 to 0.69 exists.[25,28] We performed a follow-up of the final outcome of the 3 cases of potentially VTDR (R1M1) missed with the EIDON images. One patient was returned to the digital surveillance pathway of the programme after evaluation in a hospital eye service, and the remaining two cases were maintained in the programme's digital surveillance pathway due to good visual acuity (6/6 Snellen fraction).

A feature of posterior segment imaging with confocal scanning is the possibility to acquire nonmydriatic images with pupils of even 2.5mm of diameter. Increasing duration of diabetes can cause pupillary autonomic denervation and result in poor mydriasis in this population.[36] It has been demonstrated that a pupil diameter of 2.7mm even in the absence of anterior segment alterations can be responsible for obtaining ungradable images with standard digital fundus photography.[37] Similarly, the presence of different grades of cataract related with pupillary diameters ranging from 3.4 to 4.4mm is also related to the presence of ungradable images.[37] Avoidance of mydriasis could make a screening programme more cost-effective. However, this may be offset by the need to dilate those patients who fail nonmydriatic photography.[29]

This study has several limitations. Due to the process of anonymisation demography (age, gender, ethnicity and duration of diabetes) of this dataset was not possible to analyse. Since the majority of the population who undergoes DR screening are older than 60 years, and because this study was carried out in a large-scale, community-based setting for the recruitment of patients, the rate of ungradable images might still be representative, though low for the previously 1.5 to 3.7% reported with standard digital photographs.[21,37] The acquisition time was not recorded in our study and it is not available for comparison with previous literature reports, this being important to assess if the platform can perform similarly or better when compared with standard fundus cameras in a high-volume screening centre. Pupillary diameter was not measured, and it is therefore not possible to determine if the differences in the ungradable images are due to poor mydriasis.

The present study provides valuable comparative information on the use of this new imaging technique in a routine screening programme. These results warrant further work to quantify the image acquisition time, pupillary diameter and the possibility of non-mydriatic imaging. An analysis of the stability of ungradable images and their impact in large population screening programmes should be addressed in order to estimate the overall cost-effectiveness of the platform.

CONCLUSION

The human grading of EIDON wide-field confocal scanner images is comparable with the grading of images obtained with NDESP approved cameras. However, the EIDON images allow detection of a small subset of patients with proliferative or pre-proliferative disease which are not identified with the standard NDESP image protocol. Key retinopathy features, not visualised in the NDESP images, are identified outside or within the standard 45-degree fields when using the EIDON.

FUNDING

This work was funded by the North East London Diabetes Eye Screening Programme (R.C., L.B. and J.A.). This research has received a proportion of its funding (salary support for A.T. and C.E.) from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology, the Lowy Medical Research Institute (T.H.), and from the Department of Ophthalmology of the University Hospital, *Universidad Autónoma de Nuevo León* (A.O.B.).

COMPETING INTEREST

There are no competing interests to declare for any author.

ACKNOWLEDGEMENTS

The authors wish to thank the substantial contributions to this study made by Grant Duncan (logistics, planning), Karla Costo-Cruz (patient recruitment and EIDON imaging) and Adeel Kassam (site management, patient recruitment and EIDON Imaging).

CONTRIBUTORSHIP STATEMENT

As per ICMJE guidelines all the authors agree to be accountable for all aspects of the work done on this study. In addition, each individual author's contributions are:

A Olvera-Barrios. – Statistical analysis, interpretation of data, manuscript preparation and manuscript approval.

T Heeren. – Statistical analysis, interpretation of data, manuscript preparation and manuscript approval.

Konstantinos Balaskas. – Acquisition of data, manuscript preparation and manuscript approval.

Ryan Chambers. – Acquisition of data, manuscript preparation and manuscript approval.

Louis Bolter. – Acquisition of data, manuscript preparation and manuscript approval.

Adnan Tufail. – Study conception and design, interpretation of data, manuscript preparation and manuscript approval.

Catherine Egan. – Study conception and design, interpretation of data, manuscript preparation and manuscript approval.

John Anderson. – Study conception and design, interpretation of data, manuscript preparation and manuscript approval.

REFERENCES

1 Cho NH, Shaw JE, Karuranga S, *et al.* IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;**138**:271–81. doi:10.1016/j.diabres.2018.02.023

2 International Diabetes F. *IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation*. 2017. doi:10.1289/image.ehp.v119.i03

3 Guariguata L, Whiting DR, Hambleton I, *et al.* Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014;**103**:137–49. doi:10.1016/j.diabres.2013.11.002

4 Klein BEK. Overview of epidemiologic studies of diabetic retinopathy. In: *Ophthalmic Epidemiology*. 2007. doi:10.1080/09286580701396720

5 Ferris FL. How Effective Are Treatments for Diabetic Retinopathy? *JAMA J Am Med Assoc* Published Online First: 1993. doi:10.1111/j.1600-079X.1987.tb00846.x

6 Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003–2016. Acta Diabetol. 2017. doi:10.1007/s00592-017-0974-1

7 Early Treatment Diabetic Retinopathy Study Research Group. Grading Diabetic Retinopathy from Stereoscopic Color Fundus Photographs—An Extension of the Modified Airlie House Classification: ETDRS Report Number 10. *Ophthalmology* 1991;**98**:786–806. doi:10.1016/S0161-6420(13)38012-9

8 Silva PS, Cavallerano JD, Haddad NMN, *et al.* Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. *Ophthalmology* 2015;**122**:949–56. doi:10.1016/j.ophtha.2015.01.008

9 Witmer MT, Kiss S. Wide-field Imaging of the Retina. *Surv Ophthalmol* 2013;**58**:143–54. doi:10.1016/j.survophthal.2012.07.003

10 Nicholson L, Goh LY, Marshall E, *et al.* Posterior Segment Distortion in Ultra-Widefield Imaging Compared to Conventional Modalities. *Ophthalmic Surgery, Lasers Imaging Retin* 2016;**47**:644–51. doi:10.3928/23258160-20160707-06

11 EIDON-Brochure. The First True-Color Wide-Field Confocal Scanner. https://www.centervue.com/wp-content/uploads/2016/05/EIDON-Brochure_REV02-160307_US.pdf (accessed 8 May 2019).

12 Silva PS, Horton MB, Clary D, *et al.* Identification of Diabetic Retinopathy and Ungradable Image Rate with Ultrawide Field Imaging in a National Teleophthalmology Program. *Ophthalmology* 2016;**123**:1360–7. doi:10.1016/j.ophtha.2016.01.043

13 Core National Diabetic Eye Screening Programme team. Diabetic Eye Screening Feature Based Grading Forms, Version 1.4. 2012. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/402295/Feature_Based_Grading_Forms_V1_4_1Nov12_SSG.pdf (accessed 21 May 2019).

14 Taylor D. Diabetic Eye Screening Programme Grading definitions for referable disease Public Health England leads the NHS Screening Programmes. 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/582710/Grading_definitions_for_referrable_disease_2017_new_110117.pdf (accessed 21 May 2019).

15 NHS Diabetic Screening Programme. Operational Guidance. 2015.https://www.gov.uk/government/collections/diabetic-eye-screening-commission-and-provide (accessed 21 May 2019).

16 NHS Diabetic Screening Programme. Diabetic eye screening: guidance on camera approval - GOV.UK. https://www.gov.uk/government/publications/diabetic-eye-screening-approved-cameras-and-settings/diabetic-eye-screening-guidance-on-camera-approval (accessed 4 Nov 2019).

17 Harding S, Greenwood R, Aldington S, *et al.* Grading and disease management in national screening for diabetic retinopathy in England and Wales. *Diabet Med* 2003;**20**:965–71. doi:10.1111/j.1464-5491.2003.01077.x

18 Taylor D, Widdowson S. Diabetic eye screening: assuring the quality of grading - GOV.UK. https://www.gov.uk/government/publications/diabetic-eye-screening-assuring-the-quality-of-grading (accessed 17 Jul 2019).

19 Gwet KL. *Handbook of Inter-Rater Reliability: the definitive guide to measuring the extent of agreement among raters*. 4th editio. Gaithersburg, MD 20886–2696, USA: : Advanced Analytics, LLC 2014.

20 Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics* 1977;**33**:159–74. doi:10.2307/2529310

21 Scanlon PH, Malhotra R, Greenwood RH, *et al.* Comparison of two reference standards in validating two field mydriatic digital photography as a method of screening for diabetic retinopathy. *Br J Ophthalmol* 2003;**87**:1258–63. doi:10.1136/bjo.87.10.1258

22 Purbrick RMJ, Izadi S, Gupta A, *et al.* Comparison of Optomap ultrawide-field imaging versus slit-lamp biomicroscopy for assessment of diabetic retinopathy in a real-life clinic. *Clin Ophthalmol* 2014;**8**:1413–7. doi:10.2147/OPTH.S66700

23 Aiello LP, Odia I, Glassman AR, *et al.* Comparison of Early Treatment Diabetic Retinopathy Study Standard 7-Field Imaging With Ultrawide-Field Imaging for Determining Severity of Diabetic Retinopathy. *JAMA Ophthalmol* 2018;**33647**:1–9. doi:10.1001/jamaophthalmol.2018.4982

24 Rasmussen ML, Broe R, Frydkjaer-Olsen U, *et al.* Comparison between Early Treatment Diabetic Retinopathy Study 7-field retinal photos and non-mydriatic, mydriatic and mydriatic steered widefield scanning laser ophthalmoscopy for assessment of diabetic retinopathy. *J Diabetes Complications* 2015;**29**:99–104. doi:10.1016/j.jdiacomp.2014.08.009

25 Liegl R, Liegl K, Ceklic L, *et al.* Nonmydriatic ultra-wide-field scanning laser ophthalmoscopy (optomap) versus two-field fundus photography in diabetic retinopathy. *Ophthalmologica* 2013;**231**:31–6. doi:10.1159/000355092

26 Silva PS, El-Rami H, Barham R, *et al.* Hemorrhage and/or Microaneurysm Severity and Count in Ultrawide Field Images and Early Treatment Diabetic Retinopathy Study Photography. *Ophthalmology* 2017;**124**:970–6. doi:10.1016/j.ophtha.2017.02.012

27 Silva PS, Cavallerano JD, Sun JK, *et al.* Peripheral lesions identified by mydriatic ultrawide field imaging: Distribution and potential impact on diabetic retinopathy severity. *Ophthalmology* 2013;**120**:2587–95. doi:10.1016/j.ophtha.2013.05.004

28 Szeto SKH, Wong R, Lok J, *et al.* Non-mydriatic ultrawide field scanning laser ophthalmoscopy compared with dilated fundal examination for assessment of diabetic retinopathy and diabetic macular oedema in Chinese individuals with diabetes mellitus. *Br J Ophthalmol* 2018;:1–5. doi:10.1136/bjophthalmol-2018-311924

29 Murgatroyd H, Ellingford A, Cox A, *et al.* Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. *Br J Ophthalmol* 2004;**88**:920–4. doi:10.1136/bjo.2003.026385

30 Feinstein AR, Cicchetti D V. High agreement but low kappa: II. Resolving the paradoxes. *J Clin Epidemiol* 1990;**43**:551–8. doi:DOI: 10.1016/0895-4356(90)90159-M

31 Di Eugenio B Di, Glass M. The Kappa Statistic: A Second Look. *Comput Linguist* 2004;**30**:95–101. doi:10.1162/089120104773633402

32 Von Wendt G, Rönnholm P, Heikkilä K, *et al.* A comparison between one- and two-field 60°fundus photography when screening for diabetic retinopathy. *Acta Ophthalmol Scand* 2000;**78**:14–20. doi:10.1034/j.1600-0420.2000.078001014.x

33 Silva PS, Cavallerano JD, Sun JK, *et al.* Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist

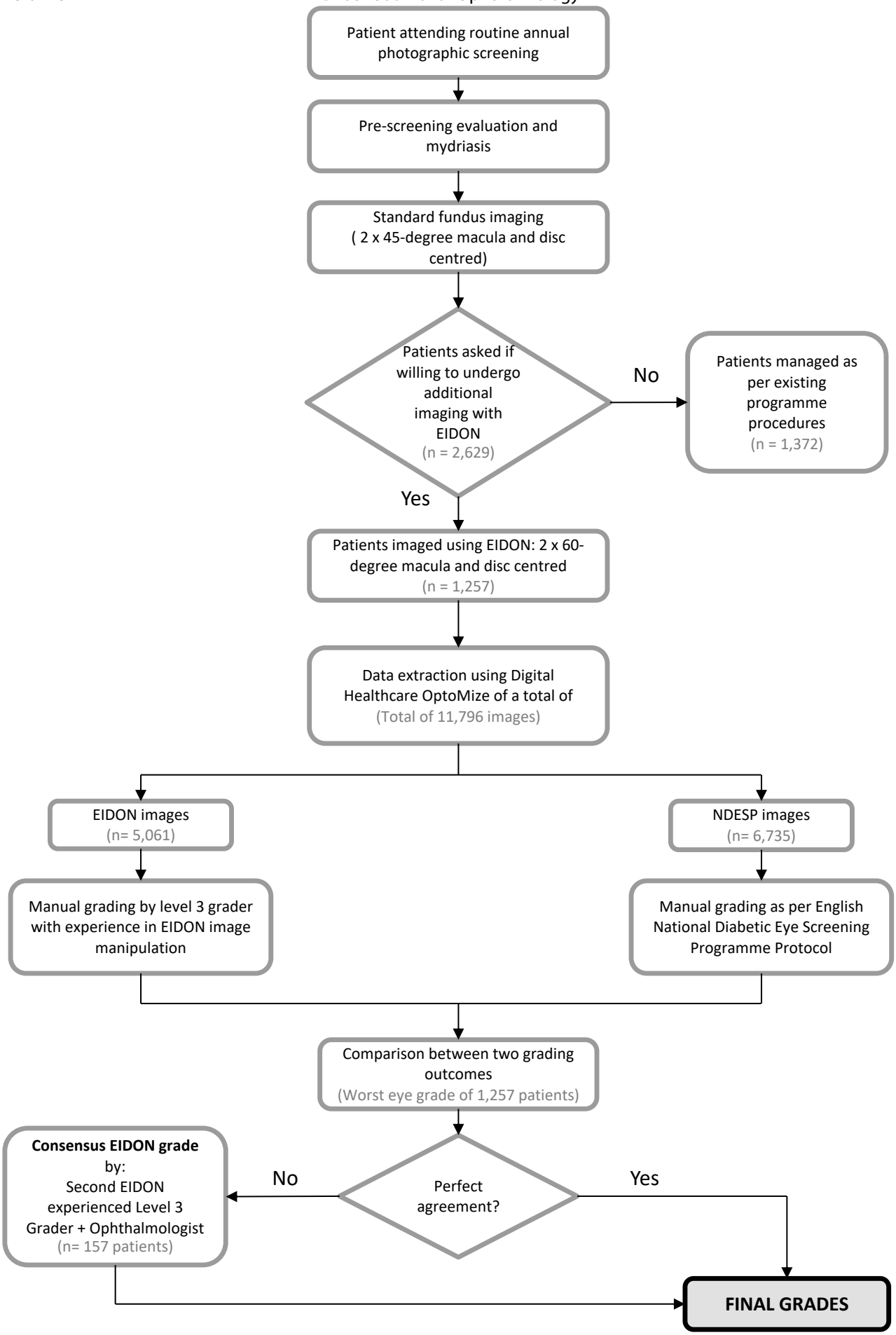
examination for evaluation of diabetic retinopathy. *Am J Ophthalmol* 2012;**154**:549-559.e2. doi:10.1016/j.ajo.2012.03.019

34 Gangaputra S, Almukhtar T, Glassman AR, *et al.* Comparison of film and digital fundus photographs in eyes of individuals with diabetes mellitus. *Investig Ophthalmol Vis Sci* 2011;**52**:6168–73. doi:10.1167/iovs.11-7321

35 Kernt M, Neubauer AS, Hadi I, *et al.* Assessment of Diabetic Retinopathy Using Nonmydriatic Ultra-Widefield Scanning Laser Ophthalmoscopy (Optomap) Compared With ETDRS 7-Field Stereo Photography. *Diabetes Care* 2012;**35**:2459–63. doi:10.2337/dc12-0346

36 Cahill M, Eustace P, De Jesus V. Pupillary autonomic denervation with increasing duration of diabetes mellitus. *Br J Ophthalmol* 2001;**85**:1225–30. doi:10.1136/bjo.85.10.1225

37 Scanlon P, Foy C, Malhotra R, *et al.* The Influence of Age , Duration of Diabetes , Cataract, and Pupil Size on. 2005;**28**.


Patient attending routine annual photographic screening
Pre-screening evaluation and mydriasis
Standard fundus imaging (2 x 45-degree macula and disc centred)
Patients asked if willing to undergo additional imaging with EIDON (n = 2,629)
No
Patients managed as per existing programme procedures (n = 1,372)
Yes
Patients imaged using EIDON: 2 x 60-degree macula and disc centred (n = 1,257)
Data extraction using Digital Healthcare OptoMize of a total of (Total of 11,796 images)
EIDON images (n= 5,061)
NDESP images (n= 6,735)
Manual grading by level 3 grader with experience in EIDON image manipulation
Manual grading as per English National Diabetic Eye Screening Programme Protocol
Comparison between two grading outcomes (Worst eye grade of 1,257 patients)
Perfect agreement?
No
Yes
Consensus EIDON grade by: Second EIDON experienced Level 3 Grader + Ophthalmologist (n= 157 patients)
FINAL GRADES

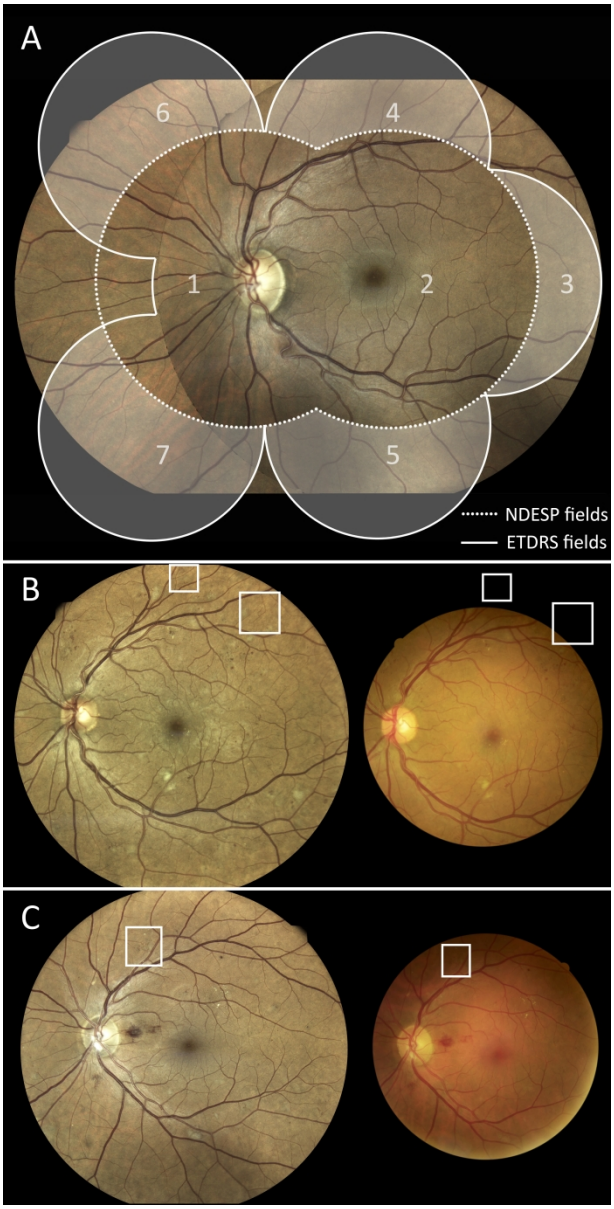
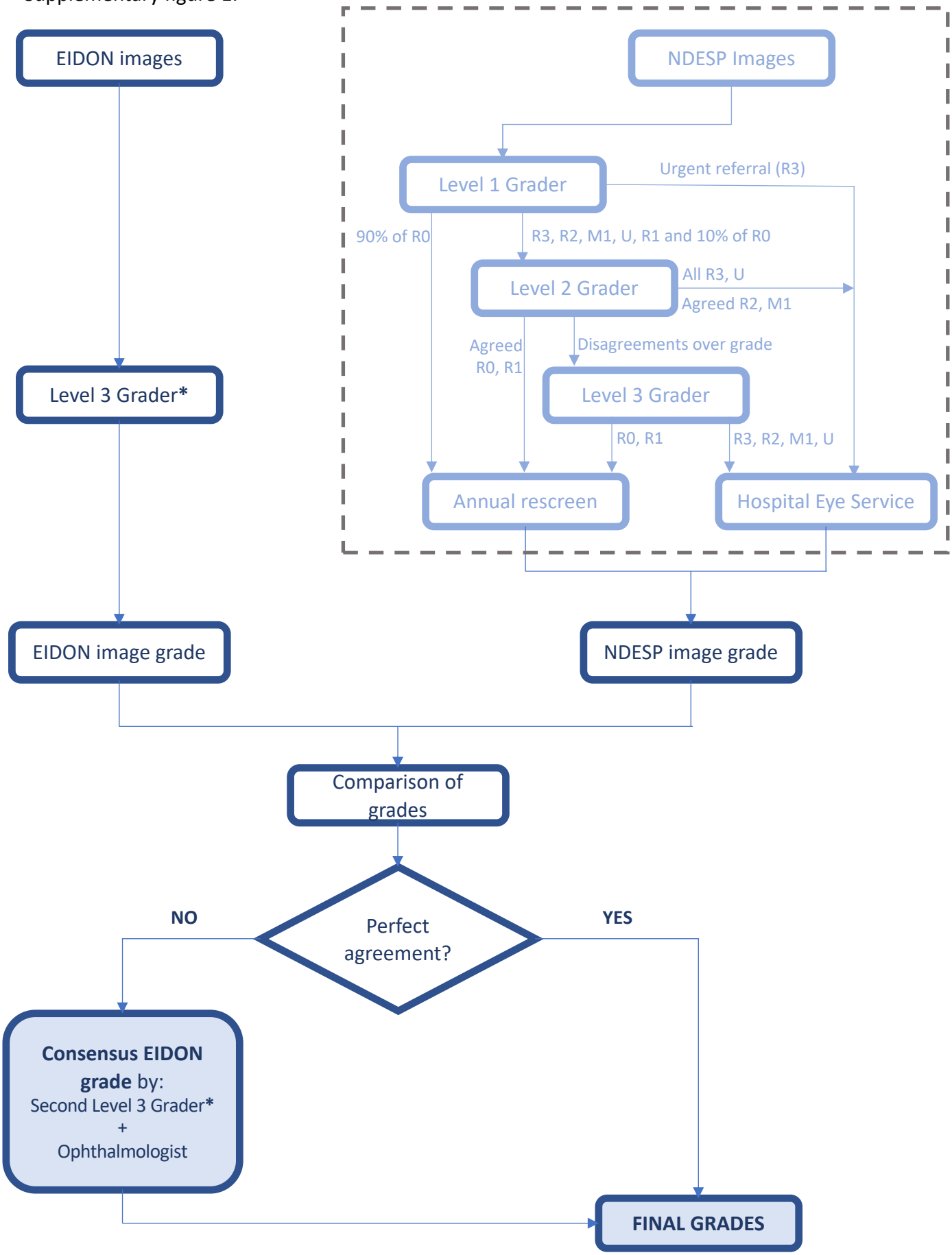


Figure 2. Comparison of field of view (FOV) and differences in diabetic retinopathy feature visualisation between the EIDON and NDESP images in left eyes. A: Overlap of macula and optic disc centred images of true-colour wide-field fundus image obtained with the EIDON; the FOV is compared with the standard ETDRS fields (solid white line) numbered 1 to 7, and the two 45-degree standard images of the NDESP (dotted white line). B: Colour EIDON (left) and NDESP (right) images of a case evidencing intraretinal microvascular abnormalities outside the NDESP image field (white boxes). C: Fundus colour images of another case illustrating intraretinal microvascular abnormalities, within the field of both imaging platforms (white boxes), which are easier to visualise with the EIDON image (left) when compared with the NDESP image (right).

349x690mm (300 x 300 DPI)

Supplementary figure 1.



– – – Delimitates the NDESP grading pathway

* Previous experience in EIDON image grading and manipulation

Supplementary Table 1. Comparison of grades per eye between EIDON wide-field confocal scanner and English National Diabetic Eye Screening Programme (NDESP) images after consensus. The highlighted patients represent clinically significant differences in the grades.

EIDON images grade, n (%)	*NDESP images grade, n (%)*								***Total***
	R0M0	R1M0	U	R1M1	R2M0	R2M1	R3M0	R3M1	
R0M0	1688 67.3 %	6 0.24 %	10 0.4 %	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	1704 67.94 %
R1M0	146 5.82 %	488 19.46 %	3 0.12 %	5 0.2 %	0 0 %	0 0 %	0 0 %	0 0 %	642 25.6 %
U	11 0.44 %	4 0.16 %	3 0.12 %	0 0 %	0 0 %	0 0 %	0 0 %	0 0 %	18 0.72 %
R1M1	4 0.16 %	7 0.28 %	0 0 %	88 3.51 %	0 0 %	0 0 %	0 0 %	0 0 %	99 3.95 %
R2M0	0 0 %	9 0.36 %	1 0.04 %	1 0.04 %	12 0.48 %	0 0 %	0 0 %	0 0 %	23 0.92 %
R2M1	0 0 %	0 0 %	1 0.04 %	4 0.16 %	0 0 %	5 0.2 %	0 0 %	0 0 %	10 0.4 %
R3M0	0 0 %	1 0.04 %	0 0 %	0 0 %	0 0 %	0 0 %	3 0.12 %	1 0.04 %	5 0.2 %
R3M1	0 0 %	0 0 %	0 0 %	1 0.04 %	0 0 %	1 0.04 %	0 0 %	5 0.2 %	7 0.28 %
Total	1849 73.72 %	515 20.53 %	18 0.72 %	99 3.95 %	12 0.48 %	6 0.24 %	3 0.12 %	6 0.24 %	2508 100 %