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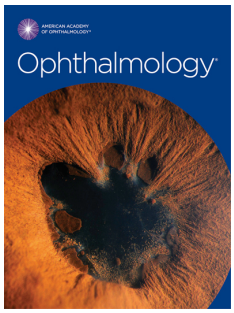

Evaluation of a new model of care for people with complications of diabetic retinopathy: The EMERALD Study

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Evaluation of a new model of care for people with complications of diabetic retinopathy: The EMERALD Study

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Key words: Diabetes, diabetic macular oedema, proliferative diabetic retinopathy, ophthalmic graders, follow-up, ophthalmic photographers, ultra-wide field images, spectral domain optical coherence tomography, SD-OCT, 7 field ETDRS images, Early Treatment Diabetic Retinopathy Study, images, photographs, pathway.

Declared competing interests of authors:

Noemi Lois: none. Jonathan Cook: none. Ariel Wang: none. Stephen Aldington: none. Hema Mistry: none. Mandy Maredza: none. Danny McAuley: none. Tariq Aslam: Advisory boards, Grants, Lecture fees from Novartis, Bayer, Thea Pharmaceuticals, Allergan, Alimera Sciences. Clare Bailey: Sat on advisory boards for Novartis, Bayer, Roche & lecture fees from Bayer, Novartis, Roche, Allergan, Alimera Sciences. Victor Chong: VC is an employee of Boehringer Ingelheim International GmBH, the study was performed outwith Boehringer Ingelheim, and Boehringer Ingelheim did not endorse the study or its result. Faruque Ganchi: consulting fees or paid advisory: Alimera, Allergan, Bayer, Novartis, Roche; lecture fees or honoraria: Alimera, Allergan, Bayer, Novartis; research funds (to institute): Allergan, Bayer, Boehringer Ingleheim, Chengdu pharma, Novartis, Pan-optica, Roche. Peter Scanlon: attended Advisory Boards for Allergan, Roche, Boehringer and Bayer; received Educational, Research and Audit Grants from Allergan, Boehringer, Novartis and Bayer in the last 5 years. Sobha Sivaprasad: received research grants and attended advisory boards of Novartis, Bayer, Allergan, Gyroscope, Roche, Oxurion, Apellis, Boehringer Ingelheim, Heidelberg and Optos.

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EMERALD Study Group

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Clinical sites participating in recruitment

The Belfast Health and Social Care Trust, Belfast, Northern Ireland; Bradford Royal Infirmary, Bradford Teaching Hospitals NHS Foundation Trust; Bristol Eye Hospital, University Hospitals Bristol NHS Foundation Trust; Frimley Park Hospital NHS Foundation Trust; Gloucestershire Royal Hospital, Gloucestershire Hospitals NHSF Trust; James Cook University Hospital, South Tees Hospitals NHS Foundation Trust; Kings College Hospital NHS Foundation Trust; Manchester Royal Eye Hospital, Central Manchester University Hospitals NHS Foundation Trust; Moorfields Eye Hospital NHS Foundation Trust; John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; Queen Margaret Hospital, Fife; Sheffield Teaching Hospitals NHS Foundation Trust; Sunderland Eye Infirmary, City Hospitals Sunderland NHS Foundation Trust.

Trial Management Group

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Trial Steering Committee

Prof John Norrie (Chair); Dr David Owens; Mrs Florence Findlay-White; Dr Winfried Amoaku; Dr Yemisi Takwoingi.

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Abstract

Objectives: The increasing diabetes prevalence and advent of new treatments for its major visual-threatening complications (diabetic macular edema [DME] and proliferative diabetic retinopathy [PDR]), which require frequent and life-long follow-up, have markedly increased hospital demands. Resulting delays in the evaluation/treatment of patients are leading to sight loss. Strategies to increase capacity of medical retina clinics are urgently needed. EMERALD tested diagnostic accuracy, acceptability and costs of a new health care pathway for people with previously treated DME/PDR.

Design: Prospective, multicentric, case-referent, cross-sectional, diagnostic accuracy study, undertaken in 13 hospitals in the United Kingdom.

Participants: Adults with type 1 or 2 diabetes and previously successfully treated DME/PDR who, at the time of enrolment, had active or inactive disease.

Methods: A new health care pathway entailing multimodal imaging (spectral domain optical coherence tomography [SD-OCT] for DME, and 7-field Early Treatment Diabetic Retinopathy Study [ETDRS] and ultra-wide-field fundus images [UWF] for PDR) interpreted by trained non-medical staff (ophthalmic graders) to detect re-activation of disease was compared with the current standard care (ophthalmologists face-to-face examination).

Main outcome measures: Primary outcome: sensitivity of the new pathway. Secondary outcomes: specificity; agreement between pathways; costs; acceptability; proportions requiring subsequent ophthalmologist assessment, unable to undergo imaging, with inadequate images/indeterminate findings.

Results: The new pathway had sensitivity of 97% (95% confidence interval [CI] 92-99%) and specificity of 31% (95% CI 23-40%) to detect DME. For PDR, sensitivity and specificity using 7-field ETDRS (85%, 95% CI 77-91%; 48%; 95% CI 41-56%, respectively) or UWF (83%, 95% CI 75-89%; 54%; 95% CI 46-61%, respectively) were comparable. For detection

of high risk PDR sensitivity and specificity were higher when using UWF images (87%, 95% CI 78-93%; 49% 95% CI 42-56%, respectively for UWF, versus 80%, 95% CI 69-88%; 40% CI 34-47%, respectively, for 7-field ETDRS). Participants preferred ophthalmologist's assessments; in their absence, wished immediate feedback by graders, maintaining periodic ophthalmologist evaluations. When compared with the current standard care, the new pathway could save £1,390/100 DME visits and between £461-£1,189/100 PDR visits.

Conclusion: The new ophthalmic grader pathway has acceptable sensitivity and would release resources. Users' suggestions should guide implementation.

Diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) are the major sight threatening complications of diabetic retinopathy which, in its turn, is the most common microvascular complication of diabetes.[1] DME and PDR are leading causes of sight impairment and blindness worldwide.[2-4]

Treatment for DME includes macular laser, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies, and intravitreal steroids.[5-14] Macular laser is delivered in a single session; retreatments may be required and, if so, are usually given at 3-4 month intervals. Anti-VEGFs are administered monthly until the macula is dry; for the great majority of patients this is not achieved during the first year of treatment.[15] Once DME has resolved, patients are followed every 3–4 months following macular laser, and monthly initially, and every 1–4 months thereafter, following anti-VEGFs.[16,17] Intravitreal steroids are given at less frequent intervals than anti-VEGFs but patients receiving them still require close follow-up as they can lead to an increase in intraocular pressure.[10] Independently of the treatment received, follow-up continues for the rest of the patient's life as DME may recur and further treatment required to prevent sight loss.

Laser panretinal photocoagulation (PRP) remains the mainstay therapy for PDR.[18] Laser PRP is most often completed in two sessions. Recent trials have shown anti-VEGFs to be non-inferior to PRP for the treatment of PDR.[19,20] Anti-VEGFs, however, do not appear to be cost-effective when compared with laser, except in patients with concomitant DME.[21] Once regression of PDR is noted, patients are followed every 6-12 months for life, as PDR may also recur. [16]

At follow-up appointments, ophthalmologists with expertise in retinal diseases examine the retina by slit-lamp biomicroscopy and determine whether recurrence of DME and/or PDR is present. Spectral domain optical coherence tomography (SD-OCT) is routinely used to aid the diagnosis of DME. Although the prevalence of DME and PDR is not very

high (~7% of all people with diabetes),[22,23] given the very high prevalence of diabetes in the population,[24,25] with ~463 million adults worldwide living with diabetes, and the requirement for patients to be reviewed frequently and for life, as underlined above, diabetic eye disease is posing major problems of capacity to ophthalmic clinics in many countries, especially due to shortage of ophthalmologists.[26] As a result, patients' appointments are often delayed, and treatments are not given timely. Delays in follow-up appointments in secondary care have been shown to lead to sight loss, even blindness in people with diabetic retinopathy.[27] The challenge that diabetes poses to health care systems in developed, and specially, developing countries has been recently highlighted.[16] Retinal clinics are further stretched as anti-VEGFs are used also to treat other diseases, including age-related macular degeneration and retinal vein occlusion. Recent cancellations of all routine appointments worldwide during the COVID19 pandemic have exacerbated this problem to unprecedented levels. Thus, it is imperative that new ways to increase efficiency and capacity of ophthalmic clinics are identified and, if safe and acceptable, implemented.

EMERALD (Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesseLs in Diabetic retinopathy) was conceived with the above purpose. It tested whether patients with DME and/or PDR previously successfully treated (i.e. DME cleared and PDR became inactive) could be followed through a new care pathway involving multimodal retinal imaging assessed by trained non-medical staff (ophthalmic graders). Diagnostic accuracy, cost-consequences, and acceptability of this new pathway to patients and healthcare professionals were evaluated against the current standard of care (face-to-face evaluation of patients by ophthalmologists).

Methods

Institutional Review Board and ethical approvals were obtained for this study prior to its initiation (reference 17/NI/0124); the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. EMERALD was funded by the Health Technology Assessment of the National Institute for Health Research (NIHR-HTA) in the United Kingdom (13/142/04).

Patient and Public Involvement

At study conception, a patient and public involvement (PPI) group was established, with the help of Diabetes UK, Northern Ireland. Meetings and discussions between EMERALD researchers and the EMERALD PPI group took place early on, at the planning stages of the project, to confirm the research question was important and the tests proposed adequate and feasible to patients. The PPI group provided, in addition, help and input to the elaboration of participant-related materials for the study and will provide support with the dissemination of findings.

Study design, setting, participants and recruitment period

EMERALD was designed as a case-referent, cross-sectional, multicentre, diagnostic study with sampling of patients and data collection carried out prospectively,[28] providing a cost-efficient design with low risk of bias in terms of diagnostic accuracy.[29]

The study was conducted in ophthalmic clinics of 13 National Health Service (NHS) hospitals across the UK, with sites in England (n=11), Scotland (n=1) and Northern Ireland (n=1). Eligible participants were adults with diabetes (type 1 or 2) with previously successfully treated DME/PDR in one/both eyes. Participants were considered to have been successfully treated if at their last visit in clinic, no further treatment had been indicated by the treating ophthalmologists due to lack of activity of PDR/DME. Only participants unable to speak/understand English and those unable to provide informed consent were excluded. Participants were identified through clinical records, electronic databases or while in clinic.

At the time of enrolment, DME/PDR could be active or inactive. An ophthalmologist confirmed eligibility; for those willing to participate, informed consent was obtained prior to enrolment. Participants were recruited between October 26th 2017 and June 7th 2019.

Clinical pathways assessed and training of ophthalmic graders

New pathway: Ophthalmic grader pathway

The new pathway tested consisted of the review of SD-OCT scans, to detect DME, and 7-field ETDRS and UWF images, to detect PDR, by trained and tested ophthalmic graders (see below). Ophthalmic graders determined whether there was active or inactive DME/PDR, or whether they were unsure or unable to grade images, in which case patients would be referred for an ophthalmologist assessment. If there was no DME/no active PDR, the grader would arrange a review appointment for the patient in the ophthalmic grader pathway at a pre-determined interval.

Standard of care pathway (reference standard)

The standard of care pathway for DME and PDR was the current standard of care: face-to-face evaluation of patients by ophthalmologists using slit-lamp biomicroscopy and SD-OCT scans. Active/Inactive DME/PDR were judged by ophthalmologists based on clinical examination and, in addition, for DME, findings on SD-OCT.

Enhanced reference standard for PDR

As it is possible that ophthalmologists miss new vessels when evaluating patients by slit-lamp biomicroscopy, EMERALD included an 'enhanced' reference standard for PDR. This consisted of the reference standard, as above, supplemented by the evaluation of 7-field ETDRS and UWF images, both reviewed by an ophthalmologist expert in DR. If active PDR was detected in one of these three evaluations (slit-lamp biomicroscopy, 7-field ETDRS or UWF fundus images) it was considered there was active PDR based on the enhanced reference standard.

Images were taken by trained ophthalmic photographers/imaging technicians at participating sites. 7-field ETDRS images were obtained using standard fundus cameras available at each participating site. The Optos system (Optos Inc., Dunfermline, Fife, UK) was used to obtain UWF images.

In EMERALD, all participants went through the standard of care pathway (i.e. were reviewed by an ophthalmologist who set the reference standard). SD-OCT scans were obtained as per standard of care. For the purpose of the study, 7-field ETDRS and UWF images were taken to detect PDR in the ophthalmic grader pathway and for the enhanced reference standard.

Anonymised images were transferred from participating sites to a central facility, then were randomly assigned to graders and ophthalmologists in the clinical sites. EMERALD used a commercially available platform (Ophthalsuite, BlueWorks, Coimbra, Portugal) for graders to see all images on computer screens.

Selection and training of ophthalmic graders was as follows. Firstly, local principal investigators suggested names of individuals at their sites with experience obtaining and/or grading images of patients with DME/PDR. These individuals were approached to confirm their interest/willingness to participate in EMERALD. They were asked to fill in a questionnaire detailing their experience recognising features of DME/PDR; those who stated they did not have experience and those unwilling to be part of the study were not invited to participate in EMERALD.

Candidates to be ophthalmic graders then received formal training. During training, which included a two-day face-to-face meeting and two additional half-day webinar sessions, features of active/inactive DME/PDR were reviewed and discussed, and extensive clinical examples were presented. A web-based teaching module with examples of DME/PDR was also provided so that graders could consolidate their knowledge. Graders received clear

guidelines on when patients would need referral to ophthalmologists. The following definitions for active and inactive DME and PDR were given:

- Active DME was defined as DME with central retinal thickness of > 300 microns on SD-OCT and/or presence of intraretinal and/or subretinal fluid on SD-OCT due to DME. Isolated or sparse small intraretinal cysts were not considered DME.
- Inactive DME was defined as no intraretinal/subretinal fluid.
- Active PDR was defined by the presence of sub-hyaloid or vitreous haemorrhage and/or active new vessels (new vessels with lack of fibrosis on them).
- Inactive PDR was defined by lack of sub-hyaloid or vitreous haemorrhage and lack of active new vessels.

Following training, ophthalmic graders were required to take a test involving the reading of SD-OCT, 7-field ETDRS, and UWF images, with and without DME and with and without active PDR. Those reaching a minimum of 80% of correct answers were invited to take part in EMERALD. If failing this first test, graders could undergo further training and take a new test but if the 80% minimum was not attained,[30] they were unable to be graders for EMERALD.

Masking

Ophthalmic graders were masked to the reference standard. To ensure this, they did not interpret images from patients recruited at their own centre and had no access to results of the reference standard. They did not read 7-field ETDRS, UWF, and SD-OCT images of the same eye, to ensure reading of one imaging technology would not influence the reading of the other.

Ophthalmologists doing the standard of care evaluation (i.e. setting the reference standard) were masked to findings/decisions made by ophthalmic graders (who reviewed images at a later date) and to the “enhanced” reference standard.

Outcome measures

Primary: Sensitivity of the new pathway to detect DME/active PDR.

Secondary: Specificity, concordance, costs, acceptability of the new pathway to patients and health care professionals, proportions of patients requiring subsequent assessment by ophthalmologists, unable to undergo imaging and with images of inadequate quality for interpretation.

Acceptability of the new pathway to patients and health care professionals

Focus group discussions were undertaken. Participants were approached and consent obtained from those willing to participate in focus group discussions at the same time they were approached to participate in the main diagnostic accuracy study. Ophthalmologists and ophthalmic photographers/graders were also invited to participate in separate focus group discussions. Detailed methodology and results of this qualitative part of EMERALD will be published separately.

Sample size and statistical analysis

The sample size was determined on the basis of setting a target of the number of people with reactivated (active) DME and PDR required to enable sensitivity to be tested against a pre-specified target level of 80%. The required sample size was calculated using formula T1 from Obuschowski 1998[31] in Microsoft Excel – it was a Wald-test based calculation. This level was considered the minimum acceptable for the new pathway to be clinically viable. A lower specificity was considered acceptable; a target of 65% was used to confirm sufficiency of sample size to assess specificity. Eighty-nine participants with DME/ PDR which had reactivated (active DME/PDR) was sufficient to detect if the sensitivity of the new pathway is 10% and 12% higher than the 80% minimal target set with 80% and 90% power, respectively at the 2-sided 5% significance level.[32] Ninety-three participants who have not reactivated would enable to detect a specificity 15% higher than the 65% target with 90% power. A 95%

confidence interval for the ophthalmic grader pathway sensitivity and specificity would have a confidence interval (Wilson method) with a width of 10-20% depending on the observed level.[33] Allowing for 10% missing/indeterminate results, 104 individuals who had re-activated and 104 who had not, were required (208 for each, DMEand PDR), leading to a maximum of 416 participants in the study overall. Because participants could have both DME and PDR and contribute to both targets, the number of participants required could be lower than 416.

Separate analyses were planned for DME and PDR. Participants were categorised as having active or inactive DME/PDR according to the reference standard, at the person level. Those with previously successfully treated DME/PDR constituted 'eligible' participants for each analysis (DME/PDR) for the new pathway. This person-based assessment reflects the consequences of the clinical decision in clinical practice. The diagnostic performance of the new pathway was quantified against the reference standard. Reflecting how the new pathway would function in practice, 'unsure', 'ungradable' and 'active' classifications required 'referral' and examination by an ophthalmologist under the main analyses. The impact of using 7-field ETDRS versus UWF images on the diagnostic performance of the new pathway was assessed under the principal analyses for PDR using both reference standard and enhanced reference standard. Agreement between PDR assessment methods was quantified. Planned sensitivity analyses included 1) assessment of the impact of 'unsure' and 'ungradable' on the diagnostic performance of the ophthalmic grader; 2) using the ophthalmologist's decision that further treatment was required, rather than presence of active disease; 3) detection of severe disease (central-involving in DME; sub-hyaloid/vitreous haemorrhage in PDR); 4) diagnostic performance within routine NHS clinics versus 'research' clinics, and; 5) for PDR only, diagnostic performance of the ophthalmic grader against the 'enhanced' reference standard (see supplementary Table 4).

Secondary analyses included evaluation of eye level data; analysis including all patients (with/without DME/PDR); assessment of the overall referral (for DME and PDR); and use of visual acuity as a proxy to detect active disease. Additional, post-hoc analyses were carried out in the PDR group only to aid understanding findings of pre-planned analyses (see supplementary Table 4).

The main analysis and sensitivity analysis included only eligible participants for the particular pathway (for the new DME pathway, people with at least one eye with previously successfully treated DME; for the new PDR pathway, people with at least one eye with previously successfully treated PDR). These participants may have had an "ineligible" eye but, as these analyses were based on a person level (as this is what will happen in real life if the pathway is introduced) each of the two eyes would have been taken into consideration for the analysis. For example, if a participant had a right eye with previously treated and inactive DME, this participant would have entered the DME pathway. If there was a "recurrence" of DME in the right eye at the time of the EMERALD evaluation, the patient would have said to have "active DME". Equally, if this same participant had "persistence" (i.e. never successfully treated prior to the EMERALD evaluation but active at the time of the visit) or "de novo" disease (active disease at the time of the EMERALD evaluation but never present before) in the left eye, the participant would have been considered also to have "active" DME. If this same participant did not have PDR in the right eye or left eye before (i.e. not eligible for the PDR pathway) but, at the time of the EMERALD study had "de novo" PDR in one eye, this participant would not have been included in main or sensitivity analyses for PDR but would have been included in the secondary analysis. The vice versa was also true for the DME main and sensitivity analyses, and correspondingly inclusion of "de novo" DME in the secondary analysis.

For all diagnostic accuracy analyses, the sensitivity, specificity, positive and negative likelihood ratios were calculated (with appropriate 95% confidence intervals (CIs) using Wilson's method and diagt command in Stata respectively). The difference in sensitivity and specificity between 7-field ETDRS and UWF images assessed by the ophthalmic graders was compared with corresponding 95% CIs produced using Newcombe's method for paired data[34] and McNemar's test for the main analysis and sensitivity analysis 1.[35]

All analyses were carried out using STATA V15 and without imputation of missing data.

Health economic evaluation

Resource use was captured on EMERALD case report forms (CRFs) at each participant's EMERALD clinic visit, in order to compare costs of delivering the standard care pathway, ophthalmic grader pathway and the enhanced reference standard. The cost analysis took the perspective of the NHS and personal social services and was estimated in UK pounds sterling using 2019/2020 prices. Costs included staff costs, based on the time and staff (including grade) required to obtain best-corrected visual acuity (BCVA), SD-OCT, 7-field and ultra-wide field fundus images. Costs included time and grade of the ophthalmologist evaluating the patient in the clinic, including undertaking slit-lamp biomicroscopy, review of the SD-OCT images to assess DMO as well as the time invested counselling the patient. Times taken by graders to grade SD-OCT, and by graders and ophthalmologists (for the purpose of the enhanced reference standard) to grade 7-field and ultra-wide field fundus photographs were also obtained and costed. Hourly wage rates for staff costs were obtained from the Unit Costs of Health and Social Care 2019. Other costs included the equipment required, overheads, and consumables. The equipment costs included acquisition and maintenance costs, considering the lifetime of the equipment and estimated throughput per year. Data were not collected on costs to patients.

It was hypothesised the new pathway would have similar sensitivity as the standard care pathway but at lower cost, making the analysis a cost-consequence one, including assessment of ophthalmologist time released by the new pathway. DME and PDR were assessed separately. Detailed methodology and results of the health economic evaluation will be published separately.

Statistical Analysis and Health Economic Plans were agreed and made accessible on the EMERALD website (http://www.nictu.hscni.net/emerald-trial/#) prior to commencement data analysis. Further methodological details of EMERALD can be found in the published protocol (https://bmjopen.bmj.com/content/9/6/e027795).[36] EMERALD was executed and reported following STARD guidelines,[37] and was prospectively registered (Clinicaltrials.gov-NCT03490318; ISRCTN-10856638.

Results

Diagnostic Accuracy

We recruited 397 participants of whom 272 were eligible with DME and 281 were eligible with PDR (Figure 1; supplemental tables 5 and 6). Participants were recruited consecutively, whether they had active or inactive DME or PDR at the time of the EMERALD visit, with no case selection.[34] We had planned to continue recruitment until we had achieved the minimum number of eligible participants for each group (104 individuals for each, active and inactive DME and PDR groups). As participants could contribute to both the DME or PDR pathways, by February 8th 2019, we had recruited enough participants for three groups (active and inactive DME, and inactive PDR). People with previously successfully treated and active PDR seemed to be less frequently seen in clinics and, thus, numbers recruited in this group had not reached the required number. Thus, from February 8th 2019, when we had 67 participants with active PDR (167 with inactive PDR, and 141 and 107 with active and

inactive DME, respectively), we decided to actively recruit people that had active PDR only and ask sites to actively pursue eligible participants for this group (e.g. recruiting from casualty, where these patients could present). Consecutive potentially eligible participants with active PDR were then approached until recruitment for this group was also completed (and surpassed, as recruitment was not halted until all potentially eligible participants identified and approached for the active PDR group had been assessed). As participants could contribute for all other groups, as mentioned above, then the number of eligible participants in all groups increased and was higher by the end of the study than that required based on sample size calculations.

Demographics of participants are shown in Table 1. In total, 157 (40%) of 397 presented with severe disease (central-involving DME) in the DME group, 132 were eligible to the new pathway. In the PDR group, severe disease (PDR with pre-retinal or vitreous haemorrhage) was present in 77 (19%) of 397 participants, 75 were eligible to the new pathway.

All participants except 34 (9%) had all images (i.e. SD-OCT, 7-field ETDRS and UWF images) obtained for testing the ophthalmic grader pathway on the same day as the reference standard. The great majority of eyes (92-97% of eyes, depending on the imaging technology used) could be imaged and few images were ungradable (1% of SD-OCTs; 6% of 7-field ETDRS images; 5% of UWF images). Details for missing images are also summarised in supplementary Table 7).

Under the main analysis, ophthalmic graders had sensitivity of 97% (142/147; 95% CI, 92-99%) and specificity of 31% (35/113; 95% CI 23-40%) when compared with the reference standard, to detect DME (Table 2). Similar results were found when evaluating people with DME requiring further treatment, with central-involving DME, and when only referral for active DME was considered (i.e. excluding ‘unsure’ and ‘ungradable’) and when patients were assessed in NHS versus ‘research’ clinics (Table 2, supplementary table 8).

Under the main analysis, ophthalmic graders had lower sensitivity but higher specificity to detect PDR; both were similar (paired differences in sensitivity -3%, 95% CI (-14 – 8%), P=0·55; and specificity 5% (-5 to 16%), P=0·31) whether they used 7-field ETDRS (sensitivity 85%; 87/102, 95% CI 77-91%; specificity 48%; 77/160, 95% CI 41-56%) or UWF (sensitivity 83%; 87/105, 95% CI 75-89%; specificity 54%; 86/160, 95% CI 46-61%) images (Table 3). Results against the enhanced reference standard were similar to those against the reference standard (for 7-field ETDRS images, sensitivity of 82%; 111/135, 95% CI 75-88%; specificity 54%; 68/127, 95% CI 45-62%; for UWF images sensitivity 80%; 110/138, 95% CI 72-86%; specificity 60%; 76/127, 95% CI 51-68%). Diagnostic accuracy results were similar to those of the main analysis when grading patients requiring further treatment (Table 3, supplementary tables 9-11). Sensitivity and specificity to detect more severe disease (PDR with sub-hyaloid and/or vitreous haemorrhage) appear to be slightly higher (not formally compared) when using UWF imaging (sensitivity 87%; 62/71, 95% CI 78-93%; specificity 49%; 95/193, 95% CI 42-56%) instead of 7-field ETDRS (sensitivity 80%; 53/66, 95% CI 69-88%; specificity 40%; 79/196, 95% CI 34-47%). Findings were similar whether patients were assessed in NHS or research clinics. Sensitivity and specificity were lower when considering only referrals for active PDR (i.e. excluding 'unsure' and 'ungradable') (Table 3).

Results of post-hoc additional analyses for PDR and the secondary analyses are shown in Table 3 and supplementary Table 12. The additional analyses for PDR tended to have similar results or increased specificity with reduced sensitivity. Secondary analyses had very high sensitivity with low or very low specificity.

No adverse events were experienced by participants in either pathway.

Acceptability

Thirty-six participants attended focus groups organised in Northern Ireland (n=4), Scotland (n=2) and England (n=4). Participants voiced preference for face-to-face examinations by ophthalmologists, where information about their eye condition could be received and discussed, where they would have the opportunity to ask questions and have anxieties assuaged. In their absence, they wished immediate results from the grader's assessment and maintaining periodic evaluations by ophthalmologists, even if at longer intervals. Participants were uncertain of professional identity, training and performance of photographers and graders. Graders and ophthalmologists supported the new pathway, but graders expressed caution about their ability to answer questions from patients unrelated to the activity of their disease.

Cost-consequence analysis

For DME, the cost-difference (savings) for the grader's pathway would be £1390 per 100 follow-up visits. For PDR, the cost-difference (savings) for the grader's pathway would be £461 for 7-field ETDRS images and £1889 for ultra-wide field images per 100 follow-up visits. The main driver of the difference in costs of imaging modalities for PDR was the time to obtain and read images (Supplementary table 13).

Costs for the grader pathway take into account the specificity of the pathway (i.e. in each 100 patients, a proportion of "false positives" will still need to be referred to the ophthalmologist, with the reference standard cost for ophthalmologist follow-up applied).

Discussion

The new ophthalmic grader pathway had high sensitivity to detect DME, of over 90% in all analyses, suggesting it would be safe to implement in clinical practice. The pathway had lower sensitivity to detect PDR, albeit above the 80% level set. Importantly, the sensitivity of

the ophthalmic grader pathway to detect high-risk PDR, with pre-retinal and/or vitreous haemorrhage, was higher (87%) when using ultra-wide field fundus images. It should be highlighted that the risk and consequences of a recurrence of PDR in eyes previously treated with PRP would not be expected to be as high and/or as severe, as if active disease were to occur in treatment naïve eyes. If a vitreous haemorrhage were to develop, patients would experience floaters and could be instructed to contact immediately ophthalmic clinics for timely evaluation. In most instances, the course of action would be observation until the haemorrhage clears, and then further PRP treatment, if required. With this in mind, the ophthalmic grader pathway for PDR would be considered adequate and justifiable, especially in areas, and at times, where high demand of services prevents people with severe eye diseases accessing timely care. Given that UWF images had higher sensitivity to detect high-risk PDR and were less costly than 7-field ETDRS, they may be preferred.

The specificity of the new pathway to detect DME (31%) and PDR (54-60%) was not high. The lower the specificity, the more "false positive" patients that have to be seen by the ophthalmologist. However even a poor specificity could provide useful savings in ophthalmologist time. It should be noted that, in EMERALD, images were evaluated without any information about patients (i.e. masked to any clinical data, including previous images). While this was a strength in scientific design, it is likely that if clinical information (e.g. location of previously identified new vessels) and previous images (e.g. SD-OCT scans of previously treated DME; images of new vessels following PRP treatment) were to be available, the sensitivity and specificity of the new pathway would have been higher. Indeed, if the new pathway is implemented in clinical practice, previous clinical information and images could be available to ophthalmic graders.

The new ophthalmic grader pathway, if implemented appropriately, would help health services to increase capacity, reduce waiting times for patients to be seen in clinics and,

subsequently, save sight. The pathway, for example, could be implemented as a "one-stop" clinic, with images and image review being done at the same session and ophthalmic graders providing the results to patients immediately. If ophthalmologists were to be running parallel clinics, they could provide advice to graders, if needed, in questionable cases, increasing the efficiency of the service and reducing the number of patients that would need to return for a further ophthalmologist assessment. If planned adequately, it may be even possible to do treatments to active patients requiring them on the same visit (e.g. once these clinics have been running for some time it would be possible to determine the average number of patients requiring input from the ophthalmologist as well as those requiring treatment, and plan accordingly). Patients with previously successfully treated and stable disease (DME, PDR, or both) could be pre-selected by ophthalmologists to go into the ophthalmic grader pathway. Based on EMERALD, patients could be moved to the grader's pathway as soon as further treatment for DME or PDR is not indicated. Alternatively, ophthalmologists may decide, for example, to refer to the grader's pathway patients with PDR with adequate laser PRP that have remained stable for a number of months already (e.g. 3-4 months); patients with DME that have received focal laser treatment and in whom DME has resolved; patients with DME that have received anti-VEGF therapy and who remained free of fluid for a certain period of time (e.g. 2-3 consecutive visits). Based on the focus group work conducted in EMERALD and in order to ensure acceptability by patients of the new pathway, it would be important that, from time to time, patients that remain inactive are seen still by ophthalmologists.

There is no clear view on what should be the minimal sensitivity and specificity acceptable for diagnostic or surveillance pathways. Figures of 80% for sensitivity and 95% for specificity have been quoted in many articles on screening for DR. These figures seem to have originated from a 1997 British Diabetic Association document, based on a consensus conference in 1995 (this document, however, is no longer accessible). Surveillance of

previously treated patients, in any case, is a rather different scenario and would pose different, known, risks, than DR screening, where people naïve to treatment are followed at less frequent intervals.

In the future, it may be possible to use automatic image analysis, including artificial intelligence (AI), to determine presence of active DME/PDR on fundus images and SD-OCT scans. Recent studies demonstrated excellent sensitivity and specificity of AI methods to determine presence of referable DR (defined as presence of moderate and higher stages of non-proliferative DR, PDR or DME) in fundus images when compared with evaluation by retinal specialists.[38,39] Indeed, an AI system (IDx-DR; IDx Technologies Inc, Coralville, IA, USA) has been developed and approved by the Food and Drug Administration (FDA) for the automated diagnosis of DR. However, studies on which this programme was developed included mostly treatment naïve patients and, thus, it remains to be elucidated if its diagnostic performance would be the same in the more complex group of previously treated patients who will have demonstrate alterations in retinal structure even when active disease is not present.

The concept of what has been widely called ‘virtual clinics’ (evaluation of patients by looking at their images rather than through a face-to-face consultation in clinic) is not new. Published studies presented the experience of several groups using this form of evaluation for people with AMD[40] and other medical retinal diseases, including diabetic retinopathy,[41-44] and glaucoma.[45] These studies showed implementation of virtual clinics was feasible and reduced patient’s time in clinic, improving patient’s journey, and seemed to increase the efficiency of the service. Most studies, though, were based on the assessment of images by ophthalmologists, rather than allied non-medical staff, included newly referred patients, rather than previously treated ones, and had a selected population, rather than all-comers.

Very few studies evaluated the acceptability of virtual clinics to patients and health care professionals; these used questionnaires,[44,46] and had low ascertainment (46-61%).[44]

EMERALD findings may be of greatest relevance to countries with tax-funded health care systems, those having difficulties coping with health care demands, especially due to shortage of ophthalmologists, and in particular low and middle-income countries (LMIC) and rural and underserved populations, interested in identifying more efficient and less costly health care strategies. EMERALD could also serve as an example of using allied health care professionals to other areas of health care in ophthalmology and even outside this speciality.

Strengths of EMERALD include its multicentre nature, strong methodology, adequate power and recruitment and lack of patient selection, making results more generalisable and applicable to routine care. Caveats include the fact that images of the iris and anterior chamber angle were not obtained for the evaluation of people with PDR. Although it would be very rare that new vessels would develop in these structures in eyes previously treated with laser PRP with no concomitant active NVE or NVD, if present, they would be missed. Additionally, fluorescein angiography was not undertaken as part of the study to determine activity of PDR. It would be essential, if the new pathway is implemented, that recommendations from the focus group discussions were to be followed to ensure its acceptability to users.

Contributions

NL conceived the study, drafted this manuscript and revised it to its final format. NL, JAC, SA, HM, DMcA, TA, CB, VC, FG, PS, SS, DS, CS, AAB, and LP participated in the study design. JAC and NL determined the sample size for the study and JAC, WS and NL determined the statistical analysis plan. AW and JAC undertook the statistical analysis of the diagnostic accuracy data. NW and HM planned the health economic evaluation; NW, HM and MM undertook the health economic analysis. LP designed, planned and carried out the focus group discussions. CM, RR and AJ provided management coordination and data management to the study. NL, AS, CB, DS, FG, GM, HE, NA, SF, SS, SA, PHS, TA recruited and evaluated patients for the study. All authors evaluated and interpreted results, reviewed this manuscript, provided input to it and approved the final submitted version.

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Figure 1. EMERALD flow diagram

O-FTF = Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy; SD-OCT = spectral domain optical coherence tomography; DME = diabetic macular oedema; PDR = proliferative diabetic retinopathy.

Table 1. Demographic characteristics of EMERALD participants

	Patients with DME (N=317)	Eligible for DME in the new pathway (N=272)	Patients with PDR (N=287)	Eligible for PDR in the new pathway (N=281)	Total (N=397)
	n (%)	n (%)	n (%)	n (%)	n (%)
Sex					
Male	205 (65%)	175 (64%)	187 (65%)	185 (66%)	257 (65%)
Female	112 (35%)	97 (36%)	100 (35%)	96 (34%)	140 (35%)
Age					
18-59	135 (43%)	113 (42%)	151 (53%)	148 (53%)	188 (47%)
60 and over	182 (57%)	159 (58%)	136 (47%)	133 (47%)	209 (53%)
Ethnic Origin					
White	274 (86%)	240 (88%)	240 (84%)	234 (83%)	340 (86%)
Black	20 (6%)	17 (6%)	19 (7%)	19 (7%)	26 (7%)
Asian	16 (5%)	11 (4%)	20 (7%)	20 (7%)	22 (7%)
Middle Eastern	3 (1%)	1 (<1%)	5 (2%)	5 (2%)	5 (1%)
Other	4 (1%)	3 (1%)	3 (1%)	3 (1%)	4 (1%)

DME= Diabetic macular edema; PDR = proliferative diabetic retinopathy

Table 2. Diagnostic performance of the ophthalmic grader pathway for the diagnosis of diabetic macular edema.

	Test positive	Reference standard	Diagnostic parameter	n/N	Estimate (95% CI)
Main	Ophthalmic graders referral [a] for DME based on SD-OCT images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy with the addition of SD-OCT scans to assess active DME in either eye	Sensitivity (%)	142/147	97% (92–99%)
			Specificity (%)	35/113	31% (23–40%)
			Positive likelihood ratio	··	1·40 (1·23–1·59)
			Negative likelihood ratio	··	0·11 (0·04–0·27)
SENA 1	Ophthalmic graders identified active DME based on SD-OCT images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy with the addition of SD-OCT scans to assess active DME in either eye	Sensitivity (%)	139/146	95% (90–98%)
			Specificity (%)	43/113	38% (30–47%)
			Positive likelihood ratio	··	1·54 (1·32–1·78)
			Negative likelihood ratio	··	0·13 (0·06–0·27)
SENA 2	Ophthalmic graders referral for DME based on SD-OCT images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy with the addition of SD-OCT scans to assess active DME in either eye requiring treatment	Sensitivity (%)	81/85	95% (89–98%)
			Specificity (%)	36/175	21% (15–27%)
			Positive likelihood ratio	··	1·20 (1·10–1·31)
			Negative likelihood ratio	··	0·23 (0·08–0·62)
SENA 3	Ophthalmic graders identified central involving active DME based on SD-OCT images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy with the addition of SD-OCT scans to assess central involving active DME in either eye	Sensitivity (%)	121/129	94% (88–97%)
			Specificity (%)	72/128	56% (48–65%)
			Positive likelihood ratio	··	2·14 (1·75–2·62)
			Negative likelihood ratio	··	0·11 (0·06–0·22)
SENA 6	Ophthalmic graders referral for DME based on SD-OCT images in routine clinic	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy with the addition of SD-OCT scans to assess active DME in either eye in routine clinic	Sensitivity (%)	81/85	95% (89–98%)
			Specificity (%)	26/65	40% (29–52%)
			Positive likelihood ratio	··	1·59 (1·30–1·95)
			Negative likelihood ratio	··	0·12 (0·04–0·32)

Note: SENA = sensitivity analysis; SD-OCT = spectral domain optical coherence tomography; DME = Diabetic macular edema.

[a] grader referral for DME = “active” + “unsure” + “ungradable”

Table 3. Diagnostic performance of the ophthalmic grader pathway for the diagnosis of proliferative diabetic retinopathy

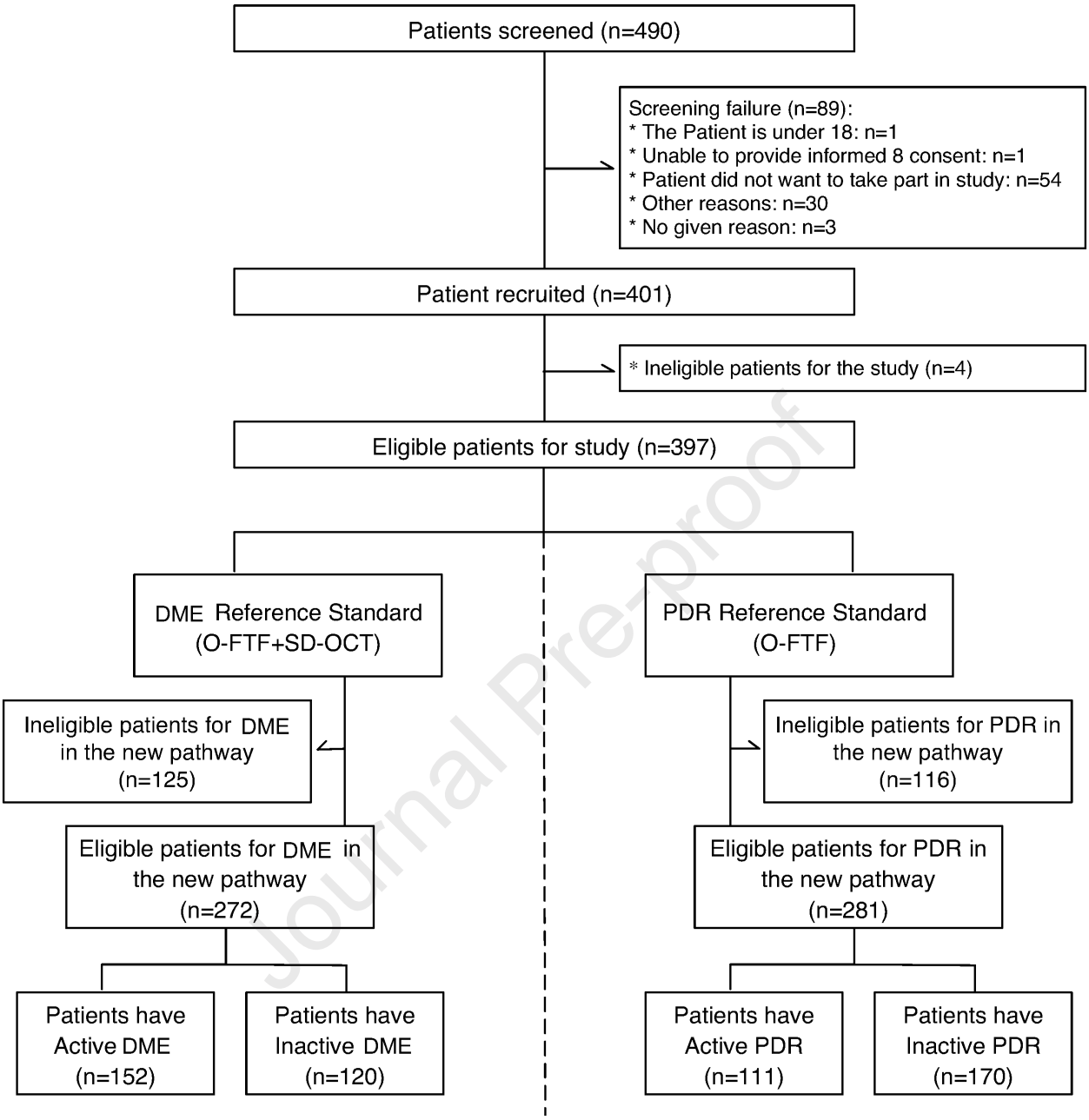
	Results	Reference standard	Diagnostic parameter	n/N	Estimate (95% CI)
Main	Ophthalmic graders referral [a] for PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	87/105	83% (75–89%)
			Specificity (%)	86/160	54% (46–61%)
			Positive likelihood ratio	··	1·79 (1·48–2·16)
			Negative likelihood ratio	··	0.32 (0·20–0·50)
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	87/102	85% (77–91%)
			Specificity (%)	77/160	48% (41–56%)
			Positive likelihood ratio	··	1·64 (1·39–1·95)
			Negative likelihood ratio	··	0·31 (0·19–0·50)
SENA1	Ophthalmic graders identified active PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	66/105	63% (53–71%)
			Specificity (%)	116/159	73% (66–79%)
			Positive likelihood ratio	··	2·32 (1·73–3·12)
			Negative likelihood ratio	··	0·51 (0·39–0·66)
	Ophthalmic graders identified active PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	70/99	71% (61–79%)
			Specificity (%)	110/158	70% (62–76%)
			Positive likelihood ratio	··	2·33 (1·78–3·04)
			Negative likelihood ratio	··	0·42 (0·30–0·58)
Additional 1	Ophthalmologist assessment identified active PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	74/103	72% (62–80%)
			Specificity (%)	137/159	86% (80–91%)
			Positive likelihood ratio	··	5·19 (3·46–7·80)
			Negative likelihood ratio	··	0·33 (0·24–0·45)
	Ophthalmologist assessment identified active PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye	Sensitivity (%)	65/98	66% (57–75%)
			Specificity (%)	134/154	87% (81–91%)
			Positive likelihood ratio	··	5·11 (3·31–7·87)
			Negative likelihood ratio	··	0·39 (0·29–0·51)
SENA2	Ophthalmic graders referral for PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye requiring treatment	Sensitivity (%)	77/90	86% (77–91%)
			Specificity (%)	91/175	52% (45–59%)
			Positive likelihood ratio	··	1.78 (1·49–2·13)
			Negative likelihood ratio	··	0.28 (0·16–0·47)
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in	Sensitivity (%)	74/84	88% (79–93%)
			Specificity (%)	82/178	46% (39–53%)
			Positive likelihood ratio	··	1·63 (1·40–1·91)
			Negative likelihood ratio	··	0·26 (0·14–0·47)

		either eye requiring treatment			
SENA4	Ophthalmic graders referral for PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with pre-retinal or vitreous haemorrhage in either eye	Sensitivity (%)	62/71	87% (78–93%)
			Specificity (%)	95/193	49% (42–56%)
			Positive likelihood ratio	··	1·71 (1·45–2·02)
			Negative likelihood ratio	··	0·26 (0·14–0·48)
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with pre-retinal or vitreous haemorrhage in either eye	Sensitivity (%)	53/66	80% (69–88%)
			Specificity (%)	79/196	40% (34–47%)
			Positive likelihood ratio	··	1·35 (1·14–1·59)
			Negative likelihood ratio	··	0·49 (0·29–0·82)
Additional 2	Ophthalmologist assessment identified active PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with pre-retinal or vitreous haemorrhage in either eye	Sensitivity (%)	57/70	81% (71–89%)
			Specificity (%)	153/192	80% (73–85%)
			Positive likelihood ratio	··	4·01 (2·96–5·42)
			Negative likelihood ratio	··	0·23 (0·14–0·38)
	Ophthalmologist assessment identified active PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with pre-retinal or vitreous haemorrhage in either eye	Sensitivity (%)	42/64	66% (53–76%)
			Specificity (%)	145/188	77% (71–83%)
			Positive likelihood ratio	··	2·87 (2·09–3·94)
			Negative likelihood ratio	··	0·45 (0·31–0·63)
SENA5	Ophthalmic graders referral for PDR based on ultra-wide field fundus images	Enhanced Reference Standard	Sensitivity (%)	110/138	80% (72–86%)
			Specificity (%)	76/127	60% (51–68%)
			Positive likelihood ratio	··	1·98 (1·58–2·49)
			Negative likelihood ratio	··	0·34 (0·24–0·49)
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images	Enhanced Reference Standard	Sensitivity (%)	111/135	82% (75–88%)
			Specificity (%)	68/127	54% (45–62%)
			Positive likelihood ratio	··	1·77 (1·45–2·17)
			Negative likelihood ratio	··	0·33 (0·22–0·49)
Additional 3	Ophthalmic graders referral for PDR based on ultra-wide field fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye plus Ophthalmologist	Sensitivity (%)	101/125	81% (73–87%)
			Specificity (%)	80/140	57% (49–65%)
			Positive likelihood ratio	··	1·89 (1·53–2·32)
			Negative likelihood ratio	··	0·34 (0·23–0·49)

		assessment identified active PDR in either eye based on ultra-wide field fundus images			
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye plus Ophthalmologist assessment identified active PDR in either eye based on 7-field ETDRS fundus images	Sensitivity (%)	103/122	84% (77–90%)
			Specificity (%)	73/140	52% (44–60%)
			Positive likelihood ratio	··	1·76 (1·46–2·13)
			Negative likelihood ratio	··	0·30 (0·19–0·46)
SENA6	Ophthalmic graders referral for PDR based on ultra-wide field fundus images in routine clinic	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye in routine clinic	Sensitivity (%)	63/77	82% (72–89%)
			Specificity (%)	47/92	51% (41–61%)
			Positive likelihood ratio	··	1·67 (1·32–2·11)
			Negative likelihood ratio	··	0·36 (0·21–0·60)
	Ophthalmic graders referral for PDR based on 7-field ETDRS fundus images in routine clinic	Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye in routine clinic	Sensitivity (%)	60/74	81% (71–88%)
			Specificity (%)	41/91	45% (35–55%)
			Positive likelihood ratio	··	1·48 (1·19–1·83)
			Negative likelihood ratio	··	0·42 (0·25–0·71)

Note: SENA = sensitivity analysis; PDR = proliferative diabetic retinopathy; ETDRS = Early treatment diabetic retinopathy study.

[a] grader referral for PDR = “active” + “unsure” + “ungradable”



Precis

Multimodal retinal imaging assessed by trained non-medical staff had acceptable sensitivity for the detection of recurrent diabetic macular edema and proliferative diabetic retinopathy in previously treated and stable patients and saved resources.