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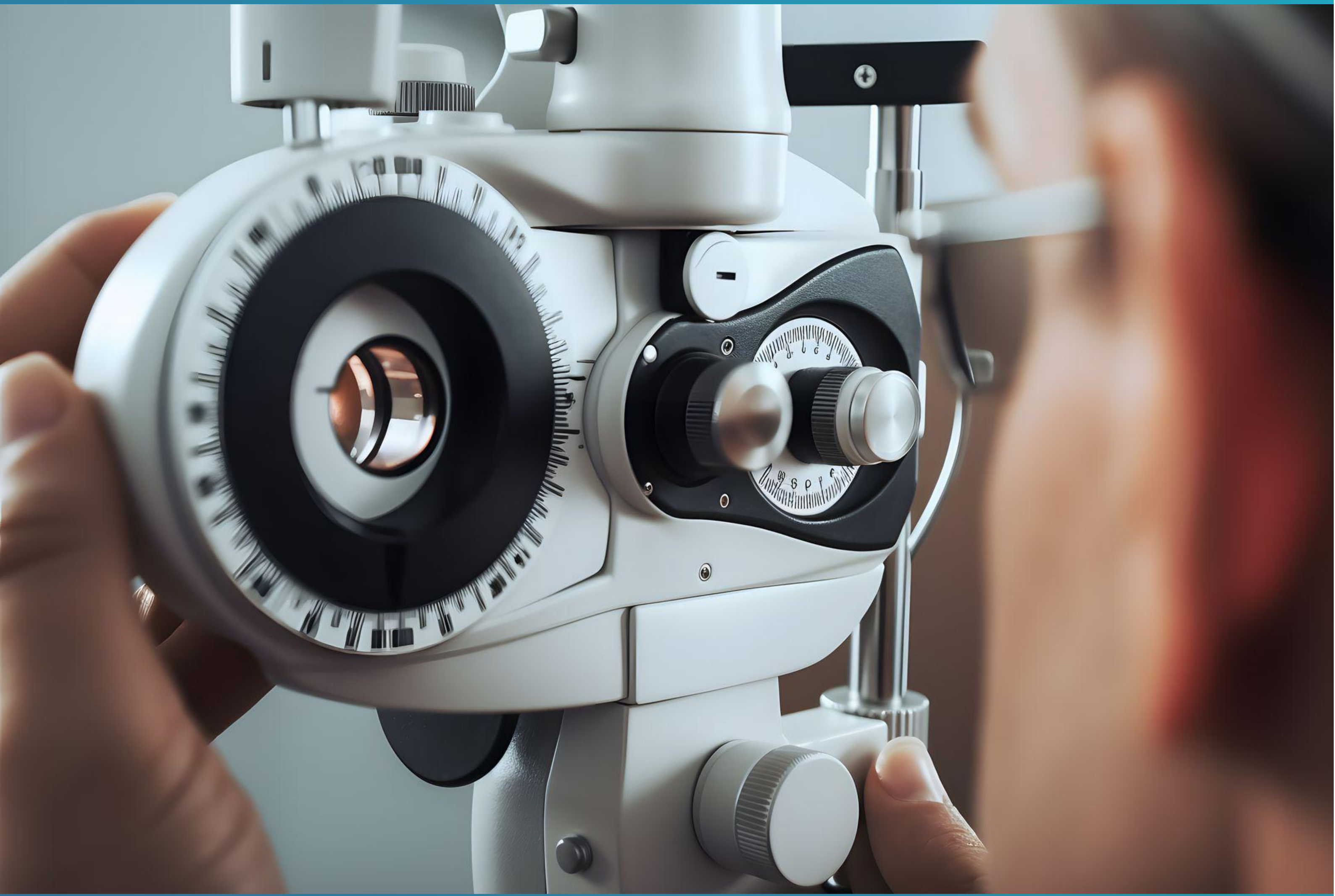

Population screening for diabetic retinopathy without mydriasis

A Scoping Review

Version 1.0

Mae'r ddogfen yma ar gael yn y Gymraeg/This document is available in Welsh

Details of Evidence Review Report

Title: Population screening for diabetic retinopathy without mydriasis: a scoping review

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Contents

1. Executive summary

Background:

Diabetic retinopathy is a common complication for people with diabetes. With increasing levels of diabetes in Wales, the prevalence of diabetic retinopathy and associated morbidity is also likely to increase over time, placing additional demands on hospital eye services. Diabetic Eye Screening Wales (DESW) aims to detect diabetic retinopathy before sight loss occurs, facilitating referral to hospital eye services for treatment to reduce the risk of sight loss. Currently, DESWs service consists of patients undergoing pharmacological pupil dilation then having retinal fundus images taken using specialist cameras, to ascertain if diabetic retinopathy is present, and its severity. Pharmacological pupil dilation enhances image clarity to support detection of diabetic retinopathy. However, it can cause temporary blurred vision, making driving inadvisable. This side effect may contribute to anxiety about the screening process and has been identified as a potential barrier to attendance (Strutton et al., 2016; NHS England, 2025b).

This scoping review was designed to inform the planned evaluation of Topcon NW500 non-mydriatic fundus cameras within the DESW programme. These cameras have been purchased by the service and make use of the retina's reflective properties to capture retinal fundus images without the need to dilate the pupils. The review aimed to assess whether non-mydriatic fundus imaging using the Topcon NW500 or comparable devices can provide sufficient image quality for diabetic retinopathy grading without pharmacological pupil dilation, and to identify groups which the literature suggests may be more likely to produce poor quality images, therefore potentially still requiring pupil dilation during screening. This is with a view to ensuring adequate evaluation of image quality is conducted in these groups when evaluating the non-mydriatic Topcon NW500 cameras for use in Wales.

Aims and method:

The review aimed to examine whether:

1) In people with diabetes undergoing retinal screening, can non-mydriatic retinal imaging using the Topcon NW500 or comparable devices produce sufficient image quality for diabetic retinopathy grading without the use of pharmacological pupil dilation?

2) What factors (e.g. age, ocular comorbidities, ethnicity, environments) are associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening?

Comprehensive searches of bibliographic databases and grey literature identified studies published since 2015. Identified studies were screened in duplicate against prespecified inclusion criteria, and the methodological quality of included studies was appraised with study design specific checklists.

Key findings:

- Fifteen studies met the inclusion criteria for the review; with eight addressing diagnostic accuracy and nine exploring factors associated with image quality.
- No studies have evaluated the Topcon NW500 specifically, and none were conducted in Wales or the UK, limiting the direct applicability of findings to the Welsh context.
- Across the evidence base, diagnostic accuracy of non-mydriatic 45° fundus cameras varied greatly. Only one study met the British Diabetic Association's recommended thresholds for both sensitivity (≥80%) and specificity (≥95%), though methodological concerns limit confidence in this result.
- Considerable heterogeneity in study aims and designs, camera models, imaging protocols, and reference standards limits comparability across studies and further restricts the generalisability of findings.
- Evidence on factors associated with ungradable images was limited. Older age was the most consistently associated factor, with two studies reporting significantly increased odds of ungradable images in older populations.
- Single-study findings also suggested associations with cataract, high spherical equivalent, reduced visual acuity, male sex, ethnic minorities (excluding white minorities), smoking, and high patient service throughput.
- Most included studies had notable quality concerns, including inconsistent reporting and unclear blinding. Additionally, many studies had different aims to this review, which impacted the relevance and completeness of reported outcomes.

Conclusion and recommendations:

Given the absence of evidence on the diagnostic accuracy of the Topcon NW500, a robust local evaluation of this particular camera is clearly justified. The diagnostic accuracy findings from comparable cameras also underlie this, as different cameras sensitivity and specificity varied greatly, limiting generalisability.

Although several characteristics were identified which were associated with increased rates of ungradable images, these were generally single-study associations, and therefore these findings should be cautiously applied to the context of diabetic retinopathy screening in Wales. Nevertheless, they could be a useful starting point for informing which variables to focus on in the upcoming Topcon NW500 evaluation in Wales. Collecting such characteristics, or utilising existing information if available to screening professionals from patient records, could be useful for ensuring groups are adequately sampled in the evaluation. This would help identify which groups of patients my benefit from a staged mydriasis approach in Wales, with the ultimate aim of improving service efficiency and patient convenience by identifying those that can avoid the need for pharmacological pupil dilation.

2. Background and purpose

Diabetic retinopathy

Diabetic retinopathy (DR) is a prevalent microvascular complication of diabetes (Shayam M, et al. 2025) and is one of the most common chronic retinal diseases worldwide. Given that its global prevalence is projected to rise (estimates of 130 million by 2030 and 160 million by 2045) (Teo Z, et al. 2021) and that it is already a major cause of blindness, particularly among working-age adults, it represents a substantial worldwide public health challenge.

In the Welsh context, in 2021/22 the number of adults (aged 17 years old or older) with diabetes was estimated to be 212,716 (Public Health Wales, 2023a). In 2022/23, diabetic retinopathy was detected in 14,424 (22.68%) of those screened, with 4.3% having sight threatening retinopathy/maculopathy (Public Health Wales, 2023b). By 2035/36, it is estimated that one in 11 adults (aged 17 years old or older) in Wales will have diabetes, equating to 260,000 people (an increase of 22%) and so this represents the potential for a significant increase in the prevalence of diabetic retinopathy, associated morbidity, and demands on screening and hospital eye services.

Diabetic Eye Screening Wales

Diabetic Eye Screening Wales (DESW) has been operational since 2003 (initially as the Diabetic Retinopathy Screening Service for Wales) with the aim of detecting diabetic retinopathy before sight loss occurs, thereby facilitating referral to hospital eye services for consideration of treatment to reduce this risk.

As part of its ongoing commitment to providing an excellent screening service to the population in Wales, DESW regularly reviews the processes it employs and equipment it uses. As part of this, DESW has recently invested in state-of-the-art Topcon's non-mydriatic retinal cameras (NW500). This type of camera (a non-mydriatic fundus camera) makes use of the retina’s reflective properties and as such is stated to be capable of capturing colour fundus images without the need to dilate the pupils. It can provide clinicians 50-degree imaging across the three traditional fixation positions (disc, centre, and macula).

Current mydriatic screening practice

In current diabetic retinopathy screening practice in Wales, pupil dilation and paralysis using Tropicamide 1% eye drops is routinely applied to all participants, unless contraindicated (e.g. due to allergy, eye injury, or infection). This approach is considered necessary to obtain images of sufficient clarity for grading. However, the use of eye drops may contribute to anxiety about the screening process and has been identified as a potential barrier to attendance (Strutton R, et al. 2016). Tropicamide 1% eye drops can have acute side effects including eye irritation and discomfort and result in blurred vision that may last for several hours. As such participants are advised they may not be able to drive or undertake skilled tasks for up to 4 hours or until vision clears following administration of eye drops. Less common adverse reactions can occur following Tropicamide 1% eye drop administration such as precipitating acute angle-closure glaucoma and complications due to systemic absorption.

However, there are differences across the UK nations in administration of tropicamide protocols. Scotland offer staged mydriasis using one-45-degree field non-mydriatic imaging and only administering tropicamide if this image is determined as inadequate by the screener. It is reported that 30% of those screened (ranging from 8.9% of those aged 35–44 to 62% of those aged 85 years and older) required tropicamide administration for pupil dilation in Scotland (Styles et al, 2020). Northern Ireland also offers a staged mydriasis approach for people aged under 50 years and only routinely offer tropicamide to those aged 50 years and over. Tropicamide protocols within Scotland and Northern Ireland are based on clinical experience and modifications to their operational delivery models such as the use of an automated grader within Scotland. Within Wales, the diabetic eye screening programme has followed the published guidance for the NHS diabetic eye screening (DES) programme (NHS England 2023). This aligns with the clinical guidance for the use of mydriatic drops for all population groups. As a staged mydriatic approach will be a modification to the established pathway in England and Wales, any change needs to be based on robust evidence of safety and effectiveness.

An evaluation of the Topcon NW500 cameras in Wales is currently planned to commence in October 2025. This scoping review aims to inform the design of that evaluation, by exploring the diagnostic accuracy of comparable non-mydriatic cameras, and by identifying groups which the literature suggests may be more likely to produce poor quality images, therefore potentially still requiring pupil dilation during screening. This is with a view to ensuring adequate evaluation of image quality is conducted in these groups when evaluating the non-mydriatic Topcon NW500 cameras for use in Wales.

3. Methods

The review aims to examine whether:

3) In people with diabetes undergoing retinal screening, can non-mydriatic retinal imaging using the Topcon NW500 or comparable devices provide sufficient image quality for diabetic retinopathy grading without the use of pharmacological pupil dilation?

4) What factors (e.g. age, ocular comorbidities, ethnicity, environments) are associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening?

3.1. Eligibility criteria

Studies were included where the population was people with type 1 or type 2 diabetes over the age of 12 years, and where diabetic retinopathy imaging was taken using a non-mydriatic camera, without pharmacological pupil dilation (mydriasis). Any study design was included, regardless of whether the study utilised a comparator group or not. Diagnostic accuracy outcomes were included to help answer question one, along with the rates of ungradable images, and factors identified that might affect the quality of images, to help answer question two. A more detailed inclusion/exclusion table can be found below (Table 1).

Table 1: Inclusion/exclusion criteria

	Patient population	Intervention	Comparator	Outcome	Study type
Include	Individuals with type 1 or type 2 diabetes aged ≥12 years.	Diabetic retinopathy imaging taken using a non-mydriatic camera, without mydriasis.* Diabetic retinopathy Imaging taken using staged mydriasis, with some non-mydriatic imaging.	Diabetic retinopathy imaging taken using a mydriatic or non-mydriatic camera, but using pharmacological pupil dilation (mydriasis). Images captures with antimuscarinic drugs e.g. tropicamide, phenylephrine, (cyclopentolate or atropine but these are not typically used in screening). No comparator/usual care.	Diagnostic accuracy outcomes from the Topcon NW500 and comparable other non-mydriatic retinal cameras.* Diabetic retinopathy grading outcomes of non-mydriatic imaging (such as % of gradable/ ungradable images). Factors that may affect the quality of images/the ability to grade images. E.g. participant factors and environmental factors.	Any quantitative primary study design including systematic reviews of relevant studies. Published including and after 2015. Published in English language.
Exclude	Non-diabetic participants; paediatric-only	Studies focusing on Maculopathy (if combined with		Prevalence outcomes.	Case reports.

	populations (<12 years). Anyone not identified as diabetic. Studies in participants with Gestational diabetes.	retinopathy, these could be included). Smartphone cameras. Artificial intelligence diagnostic/ grading systems. Cameras not comparable to the Topcon NW500*			Opinion pieces. Secondary literature (except for systematic reviews). Commentaries / Editorials. Conference abstracts. Protocols. Qualitative studies.

*Using cameras that met our criteria as 'comparable' (detailed in Appendix B).

3.2. Search methods

Comprehensive searches of five databases and four websites (detailed in Appendix A), including MEDLINE (via Ovid), EMBASE (via Ovid), CINHAL (via EBSCO) and Scopus were undertaken during July 2025. Search strings were constructed which utilised keywords and subject headings around the following concepts:

- Keywords and subject headings to cover the population e.g.: diabete*, "diabetic retinopathy"
- Keywords and subject headings to cover non-mydriatic imaging e.g.: non-mydria*, non-dilat*, undilated
- Keywords and subject headings to cover camera types e.g.: Topcon, Confocal, Canon, (digital or imag* or photo* or camera*) adj3 (retina* or fundus)

Draft search strings were peer reviewed by an information specialist, and updates were made to the final search string to reflect some of their feedback, and feedback received from the review stakeholders at Diabetic Eye Screening Wales. Searches were limited from 2015 to present, and English language only. The 2015 limit was chosen to reflect recent advances in camera imaging and screening technologies. The full final search strings are displayed in Appendix A.

3.3. Study record management

Results from each database/website search were exported into Rayyan (Ouzzani M, et al. 2016), where they were deduplicated ready for screening. Backup RIS files were obtained during each stage of the screening process.

3.4. Selection process

Each record at title and abstract were screened independently in duplicate using Rayyan (Ouzzani M, et al. 2016). Those included by both reviewers were moved over to full text screening. Conflicts between reviewers were resolved by discussion or in consultation with a third reviewer.

Initial screening included identifying studies utilising any non-mydriatic camera, but it was decided during title and abstract screening that the volume of relevant studies was becoming unmanageable, and it was questioned whether some of the camera types would truly be comparable to the Topcon NW500 that has been purchased for evaluation in Wales. With stakeholder support, the list of cameras for inclusion was refined (detailed in Appendix B) and the protocol amended to reflect this in readiness for full text screening.

Records included at title and abstract were rescreened at full text, independently in duplicate, and those meeting the newly refined inclusion criteria were included in the review. Disagreements in decisions were resolved via discussion or in consultation with a third reviewer.

At each stage of the searching and screening process study numbers were recorded (identified, included, excluded) in a PRISMA flow diagram (Page M, et al. 2021) shown in figure 1.

3.5. Critical appraisal

Critical appraisal of included studies was conducted using an appropriate Joanna Briggs Institute critical appraisal checklist corresponding to the publications study design. One reviewer appraised each study, and a subset of these were consistency checked by a second reviewer to identify any issues with interpretation. Where there were disagreements on quality, these were discussed and a consensus formed.

Summaries of study quality can be found in sections 4.2.2 and 4.3.2, for questions 1 and 2 respectively.

3.6. Data extraction

Data was extracted from each included study into MS Word data extraction tables. Extracted information included the study aim, design, country, dates/durations, setting, population inclusion criteria, number of participants studied, non-mydriatic camera model used, image capture conditions, who captured/graded images, comparators (if applicable), outcomes assessed, and relevant findings.

All data extraction was consistency checked by a second reviewer to ensure accuracy and completeness. Full data extraction tables for each study can be found in Appendix C.

3.7. Synthesis

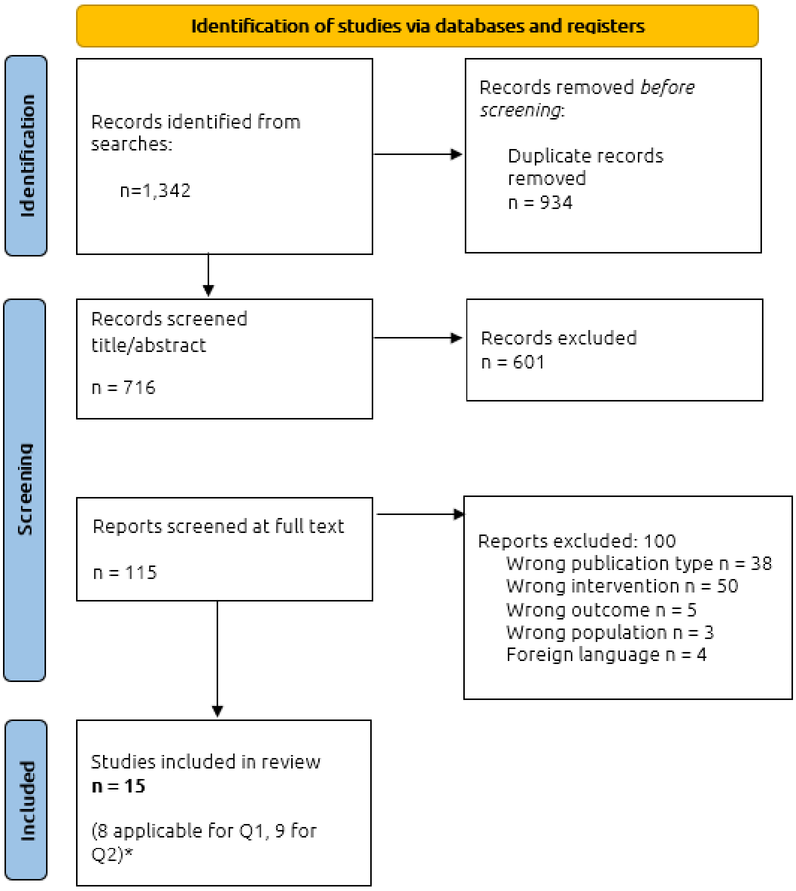
Relevant findings from studies have been summarised narratively and structured around the two review questions. Diagnostic accuracy findings have been reported where described for question one, including information on a cameras sensitivity and specificity for diagnosing diabetic retinopathy. Where analysis of image quality has been undertaken, this has been summarised for question two; including data on percentages of gradable vs ungradable images and any analysis into potential reasons affecting image quality. No meta-analysis has been undertaken as this is a scoping review designed to explore the available evidence base to help inform an evaluation, rather than provide evidence of effectiveness.

4. Results

4.1. Study Selection

Searches identified 716 studies (after deduplication) for title and abstract screening. Six-hundred and one of these were excluded at title/abstract screening, with 115 records progressing to full text screening. Of these, 100 were excluded, leaving 15 studies which met the inclusion criteria for this scoping review (Figure 1). Six of these provided information for question one only (Piyasena M, et al. 2018; Hu J, et al. 2019; Bastion M, et al. 2022; Memon M, et al. 2020; Fahadullah M, et al. 2019; Ryan M, et al. 2015), and seven for question two only (Banaee T, et al. 2017; Dow E, et al. 2023; O'Halloran R, et al. 2018; Porta M, et al. 2017; Rico-Sergado L, et al. 2016; Rosses A, et al. 2017; Szabo D, et al. 2015), with two studies providing information relevant to both questions (Toy B, et al. 2016; Lee J, et al. 2019). No studies were identified which looked specifically at the Topcon NW500; as purchased in Wales, with the studies that were identified examining non-mydriatic cameras on the UK National Screening Committee (UK NSC) approved camera list, as of August 2025 (NHS England, 2025), or comparable non-mydriatic 45° imaging models.

Figure 1: Flow of studies through the review



*Two studies were applicable to both questions

4.2 Question one: In people with diabetes undergoing retinal screening, can non-mydriatic retinal imaging using the Topcon NW500 or comparable devices provide sufficient image quality for diabetic retinopathy grading without the use of pharmacological pupil dilation?

4.2.1 Characteristics of included studies:

Eight studies met our reviews inclusion criteria, providing information relevant to our first question of interest:

1) In people with diabetes undergoing retinal screening, can non-mydriatic retinal imaging using the Topcon NW500 or comparable devices provide sufficient image quality for diabetic retinopathy grading without the use of pharmacological pupil dilation?

The included studies were published between 2015 and 2022. Two were systematic reviews which included a total of 26 (Piyasena M, et al. 2018) and 10 (Hu J, et al. 2019) studies, respectively. All studies included in the two reviews were published prior to 2015, however, we have included the reviews here for the sake of completeness, as it became apparent during the review process that many studies exploring the diagnostic accuracy of non-mydriatic 45° cameras specifically, were undertaken prior to 2015. There was a small amount of overlap in included studies between the two reviews (n = 4 studies). The other six studies comprised of five cross-sectional studies (Ryan M, et al. 2015; Fahadullah M, et al. 2019; Lee J, et al.2019; Memon M, et al. 2020; Bastion M, et al. 2022) and one longitudinal cohort study (Toy B, et al. 2016). All studies aimed to assess the diagnostic accuracy of a non-mydriatic camera.

The studies were undertaken across a range of countries; two from the USA (Lee J, et al. 2019; Toy B, et al. 2016), two from Pakistan (Fahadullah M, et al. 2019; Memon M, et al. 2020), and one each in India (Ryan M, et al. 2015), and Malaysia (Bastion M, et al. 2022). The two systematic reviews did not impose any country limits. The review by Piyasena M, et al. (2018) included 23 studies which they categorised as from 'high income' countries and three they categorised as from 'upper-middle income' countries. The review by Hu J, et al. (2019) did not include any information on the countries the included studies were conducted in.

The numbers of participants across the six included primary studies ranged from 83 to 6,911. For the reviews, sample sizes ranged from 51 to 1,549 in the Piyasena M, et al. (2018) review, and 55 to 352 in the Hu J, et al. (2019) review.

All six primary studies used non-mydriatic 45° fundus cameras, consistent with our inclusion criteria and comparable to the current model used in Wales. However, the specific camera models varied across studies. There was also variation in the number of images taken for each eye (1- field, 2- field etc.) and image capture conditions which was less frequently reported in studies. Camera models and image capture field information is displayed in table 2. For the two included systematic reviews, Hu J, et al. (2019) only assessed the diagnostic accuracy of 1-field non-mydriatic photography, whereas the inclusion criteria for the Piyasena M, et al. (2018) review was much broader, and the review included a range of studies examining 1-field, 2-field and greater than non-mydriatic and mydriatic cameras.

4.2.2 Quality of included studies

Both systematic reviews (Piyasena M, et al., 2018; Hu J, et al., 2019) clearly articulated their review questions, applied appropriate inclusion criteria, and based their implications for policy, practice, and future research in the findings presented. Each review employed rigorous data extraction methods, including the use of structured templates and independent, duplicate extraction with mechanisms for resolving discrepancies. The authors also demonstrated appropriate consideration of statistical analysis, ensuring that heterogeneity was assessed before combining study results. However, methodological limitations were evident. Neither review searched grey literature, which may have led to the omission of relevant unpublished studies. Additionally, Hu J, et al. (2019) did not report their search strategy, raising concerns about the transparency and reproducibility of their evidence identification process. Piyasena M, et al. (2018) did not assess the likelihood of publication bias, and when considered alongside the absence of grey literature searching, this introduces uncertainty around the effect of publication bias on overall findings.

For the six primary studies, the QUADAS-2 critical appraisal tool was used to assess the risk of bias (Whiting P, et al. 2011). All studies appropriately avoided a case control design and ensured that the index test was conducted prior to – and therefore without knowledge of – the reference standard results. Furthermore, all participants received the same reference standard, supporting consistency in outcome verification. Most studies also reported an appropriate interval between the index test and reference standard, typically conducted on the same day or within a short timeframe; however, one study (Toy B, et al. 2016) did not report the interval, introducing some uncertainty.

Despite these strengths, several limitations were identified. In terms of patient selection, some studies (Toy B, et al. 2016; Ryan M, et al. 2015) included referred patients or stratified participants based on diabetes duration, which may introduce selection bias. Applicability concerns were also noted regarding the reference standard: in some cases (Bastion M, et al. 2022; Lee J, et al. 2019), the reference standard was not a recognised gold standard but rather a component of routine screening practice, raising questions about its diagnostic accuracy. Additionally, while most studies reported that test interpreters were masked to the results of the other test, this was not clearly stated in several cases (Toy B, et al. 2016; Memon M, et al. 2020; Ryan M, et al. 2015), increasing the risk of observer bias.

The flow and timing domain was generally well addressed, with all patients receiving both tests; however, Toy B, et al. (2016) did not clearly report whether all participants were included in the final analysis. Overall, while the studies demonstrated methodological strengths, concerns in some studies exist regarding the use of suboptimal reference standards, unclear blinding procedures, and incomplete reporting in some domains, which may affect the internal validity and generalisability of the findings.

4.2.3 Findings

All the included studies reported the sensitivity and specificity of their non-mydriatic cameras of interest, with some also calculating the positive predictive value (PPV) and negative predictive value (NPV) (n = 4 studies), area under the receiver operating curve (n = 3 studies) and kappa statistics comparing the agreement between the index text and reference standard (n = 6 studies). The reference standards used varied across studies, although in all cases included pharmacological pupil dilation.

Table 2 below gives the diagnostic accuracy findings reported in each primary study, as well as the pooled findings from the meta-analyses conducted in the two included systematic reviews. The accepted standard for a screening test for sight-threatening diabetic retinopathy, set by the British Diabetic Association, is that the test should achieve a sensitivity (probability of getting a positive test result in subjects with diabetic retinopathy) of ≥ 80%, and a minimum specificity (proportion of participants without diabetic retinopathy that the test correctly identifies as not having it) of 95% (British Diabetic Association, 1997). We have highlighted which study findings exceed these thresholds in table 2.

Table 2: Included studies and diagnostic accuracy findings for question one

Study	Camera	Image type	Reference standard	Findings
Piyasena M, et al. (2018) Systematic Review	Multiple camera types	One field, two field and more than two field.	Early Treatment of Diabetic Retinopathy Study (ETDRS) Seven-field image interpretation (gold standard), mydriatic bio-microscopy/ ophthalmoscopy (clinical standard)	Pooled overall findings from meta-analysis (for non-mydriatic): • Sensitivity: 86% (95% CI: 85 to 87%; 18 studies)* • Specificity: 93% (95% CI: 92 to 93%; 16 studies) 1 field (non-mydriatic): • Sensitivity: 78% (95% CI: 76 to 80%; 8 studies) • Specificity: 91% (95% CI: 90 to 92%; 8 studies) 2 field (non-mydriatic): • Sensitivity: 91% (95% CI: 90 to 93%; 4 studies)* • Specificity: 94% (95% CI: 93 to 95%; 4 studies) More than 2 field (non-mydriatic): • Sensitivity: 88% (95% CI: 86 to 91%; 6 studies)* • Specificity: 94% (95% CI: 93 to 96%; 4 studies)
Hu J, et al. (2019) Systematic review	Non-mydriatic fundus camera (multiple types)	One field 45° images	7 field fundus photography, or slit-lamp microbioscopy	Pooled findings from meta-analysis: • Sensitivity: 68% (95% CI: 59 to 76%; 10 studies) • Specificity: 94% (95% CI: 89 to 97%; 10 studies) • PLR: 11.2 (95% CI: 6.1 to 20.8; 10 studies) • NLR: 0.34 (95% CI: 0.26 to 0.44; 10 studies) • Pooled DOR estimate (using random-effects model): 33 (95% CI: 17 to 65; 10 studies)

				• Summary AUC value 0.88 (95% CI: 0.85 to 0.90; 10 studies)
Bastion M, et al (2022) Cross-sectional study	Non-mydriatic fundus camera (Canon CR-2 Plus)	Two field 45° images	Dilated fundus examination	• Area under the receiver operating curve (AUROC): 0.7955 (95% CI: 0.73036 to 0.86055) • Sensitivity: 77.27% (95% CI: 65.3 to 86.7%) • Specificity: 81.82% (95% CI: 72.2 to 89.2%) • PPV: 76.1% (95% CI: 64.9 to 85.3%) • NVP 82.7% (95% CI: 72.8 to 89.7%) • Moderate to substantial agreement with DFE for DR assessment for specialists 1 and 2 respectively (k=0.59 and 0.64)
Toy B, et al. (2016) Cohort study	Non-mydriatic fundus camera (Nidek NM-1000)	45° 1-field fundus image centered on the macular.	Dilated fundus examination, including slit lamp biomicrospcopy and indirect ophthalmoscopy	Compared to the clinical International Clinical Diabetic Retinopathy (ICDR) grade: • Sensitivity: 91%* • Specificity: 97%* • PPV: 85% • NPV: 98% • Kappa: 0.86 Moderate Non-Proliferative Diabetic Retinopathy (NPDR) or worse disease: • Sensitivity: 93%* • Specificity: 75% • PPV: 42% • NPV: 98% • Kappa: 0.45 • AUROC: 0.97
Memon M, et al (2020) Cross-sectional study	Non-mydriatic camera (Canon CR-1)	Two 45° retinal images one center to macula and other center to optic disc	Fundus lens and slit lamp after pupil dilation	• Sensitivity 76% • Specificity 96.63%* • PPV 84.3% • NPV 90.7% • K=0.725
Fahadullah M, et al (2020)	Non-mydriatic camera (Canon CR-1)	Single 45° fundus image	90-D fundus lens and slit lamp, after pupil dilation	• Sensitivity: 72% • Specificity: 86.3% • PPV: 62% • NPV: 90% • K=0.551

Cross-sectional study				
Ryan M, et al. (2015) Cross-sectional study	Non-mydriatic camera (Nidek Model AFC-230)	Three 45° images	7-field fundus photography using the Zeiss FF450 Plus	Any diabetic retinopathy: • Sensitivity: 81% (95% CI: 75-86)* • Specificity: 94% (95% CI: 92-96) • K= 0.76 (95% CI: 0.71 to 0.82) Vision-threatening diabetic retinopathy: • Sensitivity: 54% (95% CI: 40-67) • Specificity: 99% (95% CI: 98-100)* • K= 0.64 (95% CI: 0.52 to 0.76)
Lee J, et al. (2019) Cross-sectional study	Non-mydriatic camera (Topcon TRC-NW8)	One, two and three-field 45° images	Mydriatic ophthalmoscopy	1-field: • Sensitivity: 87.88%* • Specificity: 75.86% • Under-reads: 26.26% • Over-reads: 15.38% • Proportion of agreement: 57.81% • Kappa statistic: 0.55 (P < 0.001) 2-field: • Sensitivity: 93.94%* • Specificity: 68.97% • Under-reads: 20.20% • Over-reads: 25.96% • Proportion of agreement: 57.81% • Kappa statistic: 0.52 (P < 0.001) 3-field: • Sensitivity: 100%* • Specificity: 79.31% • Under-reads: 5.05% • Over-reads: 23.08% • Proportion of agreement: 77.34% • Kappa statistic: 0.72 (P < 0.001)

*Mean sensitivity or specificity value ≥ British Diabetic Association (1997) criteria for DR screening methods (sensitivity: ≥ 80%, specificity: ≥ 95%).

Sensitivity:

Both systematic reviews and all six primary studies reported sensitivity outcomes. Neither of the overall pooled findings from the two systematic reviews exceeded a sensitivity of ≥ 80% (Piyasena M, et al. 2018; Hu J, et al. 2019). However, the review by Piyasena M, et al. (2018) conducted sub-analyses by image type, and found that the pooled findings from analyses of 2-field cameras and more than 2-field cameras alone did both exceed the ≥ 80% sensitivity value (2-field 91% [95% CI: 90 to 93%; four studies]; more than 2-field 88% [95% CI: 86 to 91%; six studies]).

For the included primary studies, sensitivity ranged from 72% to 100%, with three out of the six exceeding a sensitivity of ≥ 80% when testing non-mydriatic imaging. The three studies which exceeded this threshold all differed, with one testing the accuracy of 1-field imaging compared to a reference standard of dilated fundus examination, including slit lamp biomicrospcopy and indirect ophthalmoscopy (Toy B, et al. 2016). One testing 3-field imaging compared to a reference standard of 7-field fundus photography undertaken on a different camera type, (Ryan M, et al. 2015) and one which tested the diagnostic accuracy of both 1, 2 and 3-field imaging (Lee J, et al. 2019) compared to a reference standard of mydriatic ophthalmoscopy.

Specificity:

Both systematic reviews and all six primary studies reported specificity outcomes. Neither of the overall pooled or sub-analyses findings from the two systematic reviews exceeded a specificity of ≥ 95% (Piyasena M, et al. 2018; Hu J, et al. 2019). For the included primary studies, specificity ranged from 69% to 97%. Two out of six met or exceeded the ≥95% specificity value (Toy B, et al. 2016; Memon M, et al. 2020), with only one of these (Toy B, et al. 2016) also meeting the sensitivity value above. Additionally, the study by Ryan M, et al. (2015), did not meet or exceed the specificity value for detecting any diabetic retinopathy, but the authors did report a specificity of 99% (95% CI: 98 to 100%) for detecting vision-threatening diabetic retinopathy. The studies utilised different camera models and image types, and diagnostic accuracy was tested against differing reference standards.

Other outcomes:

The included studies looked at various other diagnostic accuracy outcomes alongside sensitivity and specificity.

One systematic review (Hu J, et al. 2019) calculated how much more likely a positive test result would be in subjects with diabetic retinopathy compared to those without diabetic retinopathy (pooled positive likelihood value) for those undergoing non-mydriatic 1-field camera imaging. The review found a positive likelihood ratio of 11.2 (95% CI: 6.1 to 20.8; 10 studies). The same review also calculated how much less likely a negative test result is to occur in patients with diabetic retinopathy compared to those without diabetic retinopathy (pooled negative likelihood value) for those undergoing non-mydriatic 1-field camera imaging. They found a negative likelihood ratio of 0.34 (95% CI: 0.26 to 0.44; 10 studies).

Four of the six primary studies (Toy B, et al. 2016; Memon M, et al. 2020; Fahadullah M, et al. 2019; Bastion M, et al. 2022) calculated the percentage of patients with positive test results from non-mydriatic camera imaging from the total number of subjects with diabetic retinopathy (positive predictive value), and the percentage of subjects with negative test results from non-mydriatic camera imaging from the total number of subjects without diabetic retinopathy (negative predictive value). Percentages ranged from 62% to 85% for positive predictive value, and 82.7% to 98% for negative predictive value.

Two out of six primary studies calculated area under the receiver operating curve (Bastion M, et al. 2022; Toy B, et al. 2016), which is a measure used to calculate how effective the test (in this case, the non-mydriatic camera imaging) is at differentiating between those with diabetic retinopathy and those without diabetic retinopathy. A perfect diagnostic test would have an area under the curve value of 1.0 whereas a poorly discriminating test would have an area of 0.5 or less (Simundic A. 2009). Bastion M, et al. (2022) calculated an area under the receiver operating curve of 0.7955 for non-mydriatic fundus photography (95% CI: 0.73036 to 0.86055) suggesting the non-mydriatic camera had a fairly good level of discrimination between those with and without diabetic retinopathy. Toy B, et al. 2016 calculated an area under the curve of 0.97 for the sensitivity of non-mydriatic photography to detect non-proliferative diabetic retinopathy or worse disease, suggesting the non-mydriatic camera had a very good ability to discriminate between those with and without diabetic retinopathy.

One systematic review also calculated the pooled area under the receiver operating curve from 10 studies (Hu J, et al. 2019), with a value of 0.88 (95% CI: 0.85 to 0.90) suggesting that 1-field non-mydriatic cameras have good ability to discriminate between those with and without diabetic retinopathy.

4.3 Question two: What factors are associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening?

4.3.1 Characteristics of included studies

Nine studies met our reviews inclusion criteria providing information relevant to answering our second question of interest:

- What factors (e.g. age, ocular comorbidities, ethnicity, environments) are associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening?

The included studies were published between 2015 and 2023. Three were undertaken in the USA (Dow E, et al. 2023; Lee J, et al. 2019; Toy B, et al. 2016), and one each in Australia (O'Halloran R, et al. 2018), Brazil (Rosses A, et al. 2017), Hungary (Szabó D, et al. 2015), Iran (Banaee T, et al. 2017), Italy (Porta M, et al. 2017) and Spain (Rico-Sergado L, et al. 2016).

A variety of study designs were utilised, including two before and after studies (Banaee T, et al. 2017; Rosses A, et al. 2017), two case series' (Porta M, et al. 2017; Szabó D, et al. 2015), two cross sectional studies (Dow E, et al. 2023; Lee J, et al. 2019), one retrospective comparative study (O'Halloran R, et al. 2018), one case-control study (Rico-Sergado L, et al. 2016), and one longitudinal cohort study (Toy B, et al. 2016).

The numbers of participants included in each study ranged from 128 to 22,466, although six out of the nine studies included less than 300 participants (Banaee T, et al. 2017; Lee J, et al. 2019; O'Halloran R, et al. 2018; Rico-Sergado L, et al. 2016; Rosses A, et al. 2017; Szabó D, et al. 2015).

All nine studies used non-mydriatic 45° fundus cameras, as per our inclusion criteria (making them comparable to the current model in Wales), however, the specific models used varied. There was also variation in the number of images taken for each eye (1-field, 2-field, 3-field) and image capture conditions, although information on this was frequently not reported. A summary of the differences in camera and image capture conditions can be found in Table 3.

Studies also differed in terms of who captured the images (e.g. a trained photographer, nurse, technician etc.) and who graded the images for diabetic retinopathy, along with how the images were graded. Seven used a version of the International Clinical Diabetic Retinopathy Disease Severity Scale to grade the severity of diabetic retinopathy from the images taken (Lee J, et al. 2019; Dow E, et al. 2023; O'Halloran R, et al. 2018; Porta M, et al. 2017; Rosses A, et al. 2017, Szabo D, et al. 2015; Toy B, et al. 2016), whereas two studies (Banaee T, et al. 2017; Rico-Sergado L, et al. 2016) reported how they graded images, but did not state if this was based on any international classification system.

Table 3: Camera and Image types used across studies:

Study:	Camera used*:	Image type*:	Image capture conditions*:	Images captured by*:	Images graded by*:	Comparator:
Banaee T, et al. (2017)	Canon CR2-45NM	Non-stereoscopic 45° fundus	Ordinary room lighting	Trained photographer	Independently by two retinal specialists	Mydriasis level (undilated/ partially dilated/ fully dilated)

Dow E, et al. (2023)	CenterVue DRS or TopCon NW400	Single-field fundus	Not reported	Trained medical assistants	Vitreoretinal specialists	None
Lee J, et al. (2019)	TopCon TRC-NW8	Three field 45° retinal images in each eye	Not reported	Trained technician	Optometrist	Dilated ophthalmologic exam
O'Halloran R, et al. (2018)	CentreVue DRS[+]	45° colour fundus	Not reported	Nurses and Aboriginal health workers (trained operators)	Retinal photograph grader (for 45° colour fundus images), Ophthalmologist for Optical Coherence Tomography (OCT) images	TopCon 3D OCT-1 Maestro[$]
Porta M, et al. (2017)	CenterVue SpA DRS	Two partially overlapping non-stereoscopic 45° digital colour images	Not reported	Licenced eye care professionals, fully trained to use camera	Ophthalmologists	None
Rico-Sergado L, et al. (2016)	TopCon TRC-NW 100	45° colour images of each eye	Not reported	Trained nurse	Retinal specialist	Gradable images from same camera
Rosses A, et al. (2017)	Canon CR-2	Two field images	Dark room	A family physician	Family physicians and Ophthalmologists	Mydriatic images (tropicamide eye drops) taken using same camera
Szabó D, et al. (2015)	TopCon TRC-NW200	Three 45° colour fundus per eye	Not reported	Trained non-eye care assistants	Two independent Ophthalmologists	Mydriatic images for a subset, with same camera
Toy B, et al. (2016)	Nidek NM=1000	Single 45° field-of-view fundus image	Not reported	Not reported	Ophthalmologist	Dilated fundus exam including slit lamp biomicroscopy and indirect ophthalmoscopy

*as described in included study publication
+Control conditions reported, as that was the group we were interested in for the purposes of this review.
$Intervention group in publication, but reported as comparator group for the purposes of our review

Seven of the nine studies included a control group or comparison condition, for at least a subset of the study participants (Banaee T, et al. 2017; O'Halloran R, et al. 2018; Lee J, et al. 2019; Rico-Sergado L, et al. 2016; Rosses A et al. 2017; Toy B, et al. 2015; Szabó D, et al. 2015). In five cases, the comparison was mydriatic images taken on the same participant, or dilated ophthalmologic exam (Banaee T, et al. 2017; Lee J, et al. 2019; Rosses A, et al. 2017; Szabó D, et al. 2015, Toy B, et al. 2016). In one study (Rico-Sergado L, et al. 2016), which primarily examined image quality, participants with ungradable images were age and sex matched with control participants who had gradable images, with all images being taken using non-mydriatic cameras. In another study (O'Halloran R, et al. 2018), the intervention group undertook non-mydriatic 45° colour fundus imaging and an OCT scan, with the control group just undergoing the non-mydriatic 45° colour fundus imaging. Therefore, in this case, the control group was the more comparable group for our review in terms of its similarity to Wales, and therefore the group in which we were interested. Two studies did not include a comparison group or condition (Dow E, et al. 2023; Porta M, et al. 2017).

In two studies, the stated aim of the research was specifically to do with image gradability or quality, and factors affecting this (Banaee T, et al. 2017; Rico-Sergado L, et al. 2016), whereas in seven the focus of the research was different, but image gradability was assessed as an outcome, or in a sub-analysis (Dow E, et al. 2023; Lee J, et al. 2019; O'Halloran R, et al. 2018; Porta M, et al. 2017; Rosses A, et al. 2017; Szabó D et al. 2015; Toy B, et al. 2016). Ten findings reported in seven studies contained limited or no supporting analysis and these have been outlined in section 4.3.3.

4.3.2 Quality of included studies

The review utilised a range of study designs, and therefore we appraised studies with a variety of Joanna Briggs Institute (JBI) critical appraisal checklists (Barker T, et al. 2024; Moola S, et al. 2020; Munn Z, et al. 2020; Whiting P, et al. 2011), to ensure the most appropriate quality considerations were explored for each study. Methodological concerns which may affect the validity and reliability of the findings were noted across all studies, although these were quite heterogeneous in nature.

Three studies used an experimental design (Baanae T, et al. 2017; O'Halloran R, et al. 2018; Rosses A, et al. 2017) and were appraised using the JBI quasi-experimental checklist (Barker T, et al. 2024). Although the studies methods were generally well reported, some concerns were noted regarding the analysis of results. In the study by O'Halloran R, et al. (2018), which aimed to compare the use of OCT combined with a fundus camera, to non-mydriatic fundus camera only in a diabetic retinopathy screening programme of Aboriginal Australians, the validity of the findings on patient factors associated with ungradable images is unclear as no analysis was reported to back up the results. Furthermore, the studies main finding may have been impacted by confounding, as the paper mentions that the OCT camera used by the intervention was new to the screening programme and staff unfamiliarity with it may have impacted the rates of ungradable images, potentially confounding the true result. Poor reporting of the findings was also observed in the study by Rosses et al. (2017), with 183 images out of the full sample used in the analysis of ungradable images, with no justification as to why this was. The study by Baanae T, et al (2017) concludes that non-mydriatic fundus photographs have a high rate of ungradable images in patients with dark irides. While the data clearly show a higher proportion of ungradable images in the non-mydriatic group compared to partially or fully dilated groups, this conclusion appears to rest on an unverified assumption. Specifically, the authors do not report the actual proportion of participants with dark irides, instead presuming that most patients in their Iranian cohort possess this trait. No subgroup analysis or stratification based on iris pigmentation was conducted. As such, the generalisability of the conclusion to patients with dark irides is questionable, and the validity of attributing the observed image quality differences specifically to iris pigmentation is limited without further supporting evidence. Baanae T et al. (2017) also failed to report whether any power calculation had been undertaken for its statistical analysis. The O'Halloran R, et al. (2018) study cautions that the small sample size will have limited the studies power, and that for some analyses it was insufficient.

Four studies were observational in nature and appraised using an appropriate study design checklist. One was a case control (Rico-Sergado L et al. 2016), one was a cross-sectional study (Dow E, et al. (2023) and two were case-series' (Porta M, et al. 2017; Szabó D, et al. 2015). Some concerns were noted across the studies. Some demographic differences between case and controls were noted in the study by Rico-Sergado L et al. (2016), along with a lack of consideration of potential confounders. Confounding variables were identified in the cross-sectional study by Dow E, et al. (2023), however, it was unclear whether any assessment was undertaken around these. There were also some concerns with some of the statistical analysis, with inconsistencies across the study around ethnicity data, and how this was grouped and used in some analyses. There were some concerns relating to the two case series studies (Porta M, et al. 2017; Szabó D, et al. 2015).The study by Porta et al. (2016) did not achieve complete inclusion of participants, failing to include 2,007 participants due to a lack of complete demographic data from a total population of 24,473. The Szabó D, et al. (2015) study also included a pilot comparative study on a subset of participants, however, the sample size for the subset was very small and the authors did not report whether any power calculation had been undertaken, reducing confidence in the reliability of the results.

It is also worth noting that the cross-sectional study by Dow E, et al. (2023) is published on medRxiv; a preprint server, and has therefore not been subject to peer review.

Toy B, et al. (2016) and Lee J, et al. (2019) both assessed the diagnostic accuracy of non-mydriatic fundus cameras, but each had notable limitations. Toy B, et al. (2016) used a retrospective cohort design with a poorly described and likely non-representative sample, unclear selection criteria, and differing thresholds to grade diabetic retinopathy between the index and reference tests. Blinding procedures and grader details were not reported, and the selection of a subset of patients based on more severe disease status raises concerns about bias. In contrast, Lee J, et al. (2019) employed a cross-sectional comparative design and selected participants to ensure even distribution across diabetic retinopathy grades, which may not reflect real-world screening populations. Although both tests were assessed using standard classification criteria, the reference standard (ophthalmoscopy) used by Lee J, et al. (2019) was noted to have reduced sensitivity compared to the gold standard, and the interval between tests, potentially up to six months, could have affected diagnostic accuracy due to disease progression.

4.3.3 Findings

Percentage ungradable images:

Eight of the nine identified studies included information on the percentages of images taken without mydriasis that were classified as 'ungradable,' 'unreadable' or of insufficient quality to assess diabetic retinopathy status.

Six of these (Banaee T, et al. 2017; Dow E, et al. 2023; Lee J, et al. 2019; O'Halloran R, et al. 2018; Rosses A, et al. 2017; Szabó D, et al. 2015) calculated the percentage of ungradable images across all participants who had imaging taken without mydriasis (one [Banaee T, et al. 2017] gave two percentages as images were graded independently by two graders). **The median percentage across these six studies was 13.8% (Range 9.4% to 50.3%).**

Of the remaining three studies, one (Toy B, et al. 2016) only reported the percentage of ungradable images from a subset of the total study participants. They reported that 13% of images from a subset of 856 (12%) of the total patients were graded unreadable.

One further study was a case-control study (Rico-Sergado L, et al. 2016) which included 211 ungradable images as cases, matched with 211 gradable images as controls, but mentioned that 10.25% of the initial eyes reviewed to identify 'cases' were ungradable.

In the final study meeting our inclusion criteria (Porta M, et al. 2017), 3,447 out of 22,466 (15.34%) images were ungradable. However, some participants had imaging taken with mydriasis, and the analysis of ungradable images was not broken down to distinguish how many were from participants who had or hadn't received mydriatic drops.

Two of the nine studies (Banaee T, et al. 2017; Rosses A, et al. 2017) compared the percentage of ungradable images not using any mydriasis, to those taken in either fully or partially dilated eyes. One uncontrolled before and after study (Banaee T, et al. 2017) compared the quality of fundus photographs before and after instillation of one drop of tropicamide eye drops in participants with dark irides. **Ungradable images were significantly more common in the non-mydriatic state** (38.1% and 50.3% for graders 1 and 2) compared to partially dilated (4.6% and 11.5%) or fully dilated eyes (15.4% and 10.0%) ($P < 0.001$ for both graders). Another before and after study (Rosses A, et al. 2017) also comparing mydriatic and non-mydriatic images in the same participants found that **Mydriasis was associated with better image quality (ungradable images: non-mydriatic= 14.8%, mydriatic= 8.7%, P=0.008).**

One case series (Porta M, et al. 2017) analysed 22,466 participants, 39.1% of whom were assessed using mydriasis, found that **using mydriasis was less likely to result in the collection of low-quality images (OR 0.33, 95% CI: 0.30-0.36; P<0.001).**

Reasons for ungradable images:

Age:

Four studies (Dow E, et al. 2023; O'Halloran R, et al. 2018; Porta M, et al. 2017; Rosses A, et al. 2017) looked at the effect age may have on non-mydriatic image quality in diabetic retinopathy screening. Three of these found some sort of positive association between older age and poorer image quality.

One case series analyzing 3,477 ungradable images (Porta M, et al. 2017) found that overall, **higher age was significantly associated with low-quality images in those without mydriasis** (OR 1.58, 95% CI: 1.52 – 1.64). A significant increase in odds of obtaining an ungradable image was apparent in those aged 40 to 49 years (OR 3.16, 95% CI: 1.49 – 6.87), 50 to 59 (OR 4.01, 95% CI: 1.90 – 8.71), 60 to 69 (OR 6.35, 95% CI: 2.98 – 13.54), 70 to 79 (OR 11.58, 95% CI: 5.44 – 24.68) and ≥ 80 (OR 19.92, 95% CI: 9.22 – 43.02).

One cross-sectional study of 760 patients (Dow E, et al. 2023) **found that ungradable images (n=77) were significantly more likely to be obtained from older patients** (median age: 68.1 years for ungradable images, vs. 58.5 years for gradable images; p<0.0001).

One before and after study of 219 patients (Rosses A, et al. 2017), which analysed factors associated with image readability, found that **patients with unreadable images had a median age of 72.5 (± 9.8 years) whilst those with readable or questionable images had lower median ages (62.6 and 64.3 years, respectively),** however, it is unclear if this finding was statistically significant. This was across mydriatic and non-mydriatic conditions. The authors also undertook a stratified analysis by age, examining whether mydriasis was associated with improved image readability in those aged under 65 (89 patients) or 65 and over (94 patients). **A significant association between pharmacologic mydriasis and improved image readability was only found in the in 65 and over age group analysis** (p=0.008).

The final retrospective comparative study (O'Halloran R, et al. 2018) comparing images on a standard non-mydriatic camera (control camera) to images with a non-mydriatic camera and OCT scan (intervention camera) reported no significant association between photograph quality and age. No statistical analysis was reported in the paper, and it was unclear whether this statement related to the OCT camera, the control non-mydriatic camera, or both.

Eye/Visual characteristics:

Five of the included studies explored the effect of visual or eye characteristics on image quality or gradability for diabetic retinopathy screening (Lee J, et al. 2019; O'Halloran R, et al. 2018; Rico-

Sergardo L, et al. 2016; Szabo D, et al. 2015; Toy B, et al. 2016). However, not all these studies undertook a full analysis.

Rico-Sergado L, et al. (2016) conducted the most comprehensive analysis exploring visual or eye characteristics. This was a case control study evaluating the effect of decreased visual acuity on image quality obtained by non-mydriatic retinal photography in diabetic subjects The study explored the association between the frequency of ungradable scans, and several visual characteristics including corrected visual acuity, spherical equivalence, astigmatism, and cataract status, along with some clinical characteristics discussed in the clinical factors section of this review. The authors undertook a multivariable analysis and found that the following were **significantly associated with an increased likelihood of ungradable images**:

- **Corrected distance visual acuity worse than 20/40** (OR 5.23, 95% CI: 2.82 to 9.71; p<0.0001)
- **High Spherical Equivalent (refractive error worse than -6.0 D SE or +5.0 D SE)** (OR 13.21, 95% CI: 2.61 to 66.77; p=0.002)
- **Cataract grading of 2+ cataract, compared to those with no cataract** (OR 3.36; 95% CI: 1.42-7.95, P=0.006).

The authors found **no evidence of an association between high astigmatism and ungradable scans** in the multivariable analysis.

An analysis of 45 participants undertaken in the O'Halloran R, et al. (2018) study found a significant association between photograph quality and vision impairment (visual acuity <6/12). **They found that adequate fundus photographs were less common when vision impairment was present (51.1% vs 80.6%, OR: 0.25, 95% CI: 0.13 to 0.51, P<0.05)**. And that **those aged over 55 years were significantly more likely to be identified with vision impairment than those under age 55 (29% vs 13.9%, OR: 2.53, 95% CI: 1.26 to 5.08; P<0.05).** However, this was a quasi-experimental study comparing the effectiveness of OCT with a fundus camera to a non-mydriatic fundus camera alone, and it is unclear whether the vision impairment analysis above includes participants from the intervention group, control group or both. The authors do however report that there was no significant difference in visual impairment between the two groups (22.9% vs 19.0%, OR: 1.27, 95% CI: 0.63 to 2.54, P<0.05).

Lee J, et al. (2019) reported that ungradable photographs were mostly due to poor pupillary dilation or media opacity, however, no statistical analysis for this was reported in the paper.

Two of the studies (Szabo D, et al. 2015; Toy B, et al. 2016) reported rates of ungradable images, and described the visual characteristic reasons for these. Szabo D, et al (2015) reported that the percentage of ungradable photographs in the study due to cataract, small pupil size or vitreous opacity, was 10.1%. Toy B, et al. (2016) went slightly further and gave percentages for each reason. Where an identified cause for the unreadable non-mydriatic photo could be found, 53% were due to eyes having cataract, 18% due to refractive issues with the eye, 11% due to glaucoma 6% due to proliferative diabetic retinopathy and 6% due to retinopathy .

Gender:

Two studies explored whether gender might be associated with poor non-mydriatic image quality in diabetic retinopathy screening, the findings of which were mixed. One retrospective comparative study (O'Halloran R, et al. 2018) found no significant association between photograph quality and gender (statistics not reported). However, a case series analysing 3,447 ungradable images (Porta M, et al. 2017) found that **male sex was significantly associated with greater numbers of low quality images in patients without mydriasis** (OR 1.21, 95% CI: 1.10 to 1.34; p<0.001).

Ethnicity:

Only one cross-sectional study examined ethnicity and its potential association with ungradable non-mydriatic diabetic retinopathy imaging. Dow E, et al. (2023) found that **patients who self-reported as being in an ethnic minority group (excluding white minorities) were also more likely to have ungradable non-mydriatic images (white 5.5%, ethnic minorities (excluding white minorities)13.3%. Chi-squared 7.5107; p<0.006).** Additionally, they report that this trend could not be accounted for by differences in age as ethnic minority (excluding white minority) participants in the study were a decade younger than their white counterparts on average (76.9 years for white vs 66.1 years for ethnic minorities (excluding white minorities) participants; p<0.002).

Other clinical factors:

Three studies looked at various clinical factors and their association with image quality in diabetic retinopathy screening (Rico-Sergado L, et al. 2016; Rosses A, et al. 2017; Porta M, et al. 2017). However, the level of detail and analysis across these studies varied. Rosses A, et al. (2017) reported that factors such as diabetes duration, presence of hypertension and presence of nephropathy did not influence readability of fundus photographs, however they did include any statistical analysis.

A case series (Porta M, et al. 2017) evaluating the use of telemedicine retinal screening in Italy, and which examined factors associated with the collection of low quality photographs, found that **smoking was significantly associated with more low-quality images (OR 1.18, 95% CI: 1.04 to 1.35, P<0.012)**, but the **association between hypertension and low-quality images was not significant (OR 0.97, 95% CI: 0.84 to 1.12; p=0.671).**

The final study which was also a case series (Rico-Sergado L, et al. 2016), explored the association between the frequency of ungradable scans and a range of visual and clinical characteristics. The authors univariable analysis found **a statistically significant association between participants with moderate non-proliferative DR and ungradable scans**, with the odds of a scan being classified as ungradable in subjects with moderate non-proliferative diabetic retinopathy vs no diabetic retinopathy being 3.37 (95% CI: 1.47 to 7.70; p=0.004). However, no significant associations were found between participants with mild non-proliferative, severe non-proliferative, or proliferative diabetic retinopathy and ungradable images. Similarly, **no statistically significant associations were found between duration of diabetes and ungradable images** (10-19 years vs 0-9 years: p=0.773, 20 years or more vs 0-9 years: p=0.080).

Screening context & operational factors:

Two studies included information on screening context and operational factors and whether these may affect image quality when screening for diabetic retinopathy. The retrospective comparative study by O'Halloran R, et al. (2018), which aimed to evaluate the use of OCT with fundus photography compared to non-mydriatic photography only, and which took place in one urban clinic and one rural clinic, **found no significant association between photograph quality and screening site (statistics not reported)**.

However, one case series (Porta M, et al. 2017), which took place across 33 diabetic outpatient clinics in Italy found that **higher patient throughput at clinic was associated with a significant reduction in ungradable images in patients without mydriasis (OR 0.96, 95% CI: 0.94 to 0.97; p<0.001).**

5. Discussion

5.1. Summary of evidence

This scoping review includes a total of 15 studies, eight of which met the inclusion criteria for question one and nine for question two.

Overall, the findings from studies meeting our inclusion criteria for question one (n=8) suggest that the diagnostic accuracy of non-mydriatic 45° degree fundus cameras varies, with most studies (n=7) unable to achieve the British Diabetic Association threshold values for sensitivity and sensitivity. Differences in camera models, imaging protocols (e.g. number and type of images), and reference standards used across studies introduce substantial heterogeneity, limiting the ability to draw generalisable conclusions beyond individual study results. Notably, none of the studies evaluated the specific camera model of interest (Topcon NW500) that has been procured for use in Wales, further reducing the applicability of findings to current practice. Evidence is therefore lacking on the diagnostic accuracy of the Topcon NW500 when used without pharmacological pupil dilation, further justifying the need for a robust local evaluation.

The British Diabetic Associations guidance proposes that cameras in screening programs used for diabetic retinopathy detection should achieve sensitivity and specificity values of ≥80% and ≥95% respectively, combined with a technical failure rate of less than 5% (British Diabetic Association, 1997). Only one primary study included in our review (Toy B, et al. 2016) met this threshold for both sensitivity and specificity. This was a longitudinal cohort study aiming to compare non-mydriatic fundus photography screening for diabetic retinopathy with clinical dilated fundus examination in a safety-net setting in the USA. They tested the diagnostic accuracy of a Nidek NM-1000 camera, taking a single 45° field-of-view fundus image centered on the macular, and compared this with the clinical ICDR Disease Severity Scale grade from dilated fundus examination, in subset of 1,521 patients from 6,911 who participated in the cohort study overall.

Although the technical failure rate for this subset was not reported, so we cannot be sure whether it was less than 5%, the ungradable image rate reported in a different subset of patients from this study was reported to be 13%. The authors do however mention that in the subset of 1,521 patients, when unreadable photographs were included in the diagnostic accuracy analysis, sensitivity dropped to 93% and specificity dropped to 75%, taking it below the British diabetic association's recommendations. However, the reliability of these findings is limited by several sources of potential bias, including different diabetic retinopathy grading systems used between tests, unclear selection criteria, lack of blinding, and the use of a non-representative subset of patients with potentially more severe disease, which may have inflated diagnostic performance estimates.

The review by Hu J, et al. (2019) completed a subgroup analysis to calculate the sensitivity and specificity according to the reference standard used in their included studies. They found differences in the sensitivity and specificity of 1-field non-mydriatic fundus photography when compared to a reference standard of 7SF photography and slit-lamp biomicroscopy. This suggests the chosen reference standard may have an influence on the interpretation of the diagnostic accuracy of fundus photography images, and so **careful consideration should be given to the reference standard in any planned evaluation for the Topcon NW500 in Wales, to ensure the findings are clinically meaningful for the Welsh context.**

To further help inform the planned evaluation, this scoping review also attempted to identify factors associated with ungradable or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening. A limited number of studies (n=9) met the inclusion criteria for this question. These studies varied greatly in the level of detail and analysis, with 10 findings reported across seven studies providing no, or limited analysis to support their findings.

Factors identified across the included studies that showed a statistically significant association with poorer image quality or increased likelihood of ungradable images were:

- Older age (n = 2 studies): higher odds of ungradable images in non-mydriatic screening (significant ORs ranging from 3.16 [95% CI: 1.49 – 6.87] in ages 40–49 increasing every decade to 19.92 [95% CI: 9.22 – 43.02] in ages ≥80). One reported a higher median age in patients with ungradable images compared to those with gradable images (68.1 vs. 58.5 years; p<0.0001).

- High Spherical Equivalent (n = 1 study): OR 13.21, 95% CI: 2.61 to 66.77; p=0.002. Corrected distance visual acuity worse than 20/40 (n = 1 study): OR 5.23, 95% CI: 2.82 to 9.71; p<0.0001.
- Cataract (n = 1 study): OR 3.36; 95% CI: 1.42-7.95, P=0.006.
- Male sex (n = 1 study): OR 1.21, 95% CI: 1.10 to 1.34; p<0.001.
- Ethnic minorities (excluding white minorities) (n = 1 study): ungradable images: white 5.5%, ethnic minorities (excluding white minorities) 13.3%. Chi-squared 7.5107; p<0.006.
- Smoking (n = 1 study): OR 1.18, 95% CI: 1.04 to 1.35, p<0.012

Higher patient throughput at screening sites was associated a significant reduction in ungradable images in patients without mydriasis (OR 0.96, 95% CI: 0.94 to 0.97; p<0.001).

However, the above only shows where a significant association had been found. **Many of these characteristics were only explored in a small number of studies, and across studies that did explore them the findings were mixed**. Nevertheless, including a representative sample of people with the characteristics above could be useful for the subsequent planned evaluation of the Topcon NW500 camera in Wales, to help determine if any of these associations are also present in a Welsh population, and therefore help further inform whether the service should still offer mydriasis to any particular defined groups.

The most frequently explored characteristic across the studies included in our review was age. We found some evidence suggesting that non-mydriatic diabetic retinopathy imaging may be more likely to produce poor-quality or ungradable images in older age groups, and single-study evidence demonstrating an increase in odds of obtaining an ungradable image as age increased. This aligns with findings from earlier research that did not meet our inclusion criteria suggesting that age may be a relevant factor influencing image quality, despite potential improvements in non-mydriatic 45° fundus camera technology. For example, a 2005 study by Scanlon P, et al. investigated the impact of age, duration of diabetes, cataract presence, and pupil size on image quality in both non-mydriatic and mydriatic diabetic retinopathy screening. The study reported an ungradable image rate of 19.7% for non-mydriatic photography. When analysed by age group, image quality declined with increasing age: ungradable image rates were 11.0% for those aged 50–59, rising to 16.5% in 60–69 year olds, 26.2% in 70–79 year olds, 40.1% in 80–89 year olds, and 68.9% in those aged 90 and above.

One notable finding is that **very little of our identified studies explored whether there were associations between screening settings or operational factors/characteristics and the quality of non-mydriatic imaging for diabetic retinopathy screening**. Operational characteristics were also often poorly reported, for example, only two studies (Banaee T, et al. 2017; Rosses A, et al. 2017) mentioned any image capture conditions, such as whether images were taken in natural lighting or a dark room. Conditions of capture could potentially impact image quality, Banaee T et al. (2017) mentions that normal room lighting is not the optimal condition for non-mydriatic fundus photography, and that dark room conditions may maximise pupil size and improve image quality.

However, no studies were identified which tested this hypothesis in our population of interest. This is a potential gap in the evidence that could be explored with further research and evaluation.

When screening studies for inclusion in this review, we found research examining other types of non-mydriatic camera which didn't meet our inclusion criteria, as they were less comparable to those approved for use in Wales and the United Kingdom. Nevertheless, studies in other camera types, such as handheld non-mydriatic cameras, wide-field non-mydriatic cameras, or optical coherence tomography may have also explored reasons for ungradable images, and there is the potential that other groups may have been identified in these that would also be useful to incorporate into the evaluation in Wales. However, given our limited timescales and resource capacity, we took the decision to stick to camera types that are both approved for use in the UK, and most comparable to the type which has been purchased for use and evaluation in Wales, in order to try to make our findings as relevant as possible.

5.2. Strengths and limitations

This scoping review employed abbreviated systematic review methods to ensure reliability and relevance within the timeframes required for the project. Despite making every effort to capture all relevant publications and reduce the risk of bias in our review process, it is possible that additional eligible publications may have been missed.

The review synthesises evidence for two questions that were prioritised for their relevance to current decision-making needs. The focused scope and framing of questions further enhances the utility of the findings for informing the evaluation of the implementation of the Topcon NW500 non-mydriatic fundus cameras in diabetic retinopathy screening pathways across Wales.

We identified several limitations of the evidence base included in the review. Firstly, no studies using the Topcon NW500 were identified and non-mydriatic cameras and imaging methods (e.g., photographic fields, image location, capture setting) used in included studies varied greatly, impacting the comparability of findings across studies. Furthermore, no relevant studies from Wales were identified, limiting the comparability of findings to the Welsh context.

A key objective of the scoping review was to identify evidence assessing factors associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening. The evidence was limited, with only two studies primarily focused on investigating the impact of a specific factor (decreased visual acuity: n=1, and dark irides: n=1) on image quality (Banaee T, et al. 2017; Rico-Sergado L, et al. 2016). Additionally, across all studies that examined characteristics associated with ungradable images, there was substantial variation in study designs, aims, analytical approaches, and reporting, likely influencing the consistency and comparability of findings.

Across the evidence base, study quality was generally limited, with methodological weaknesses common among both primary studies and systematic reviews. While some studies demonstrated strengths in design and reporting, these were often undermined by issues such as poor transparency, unclear blinding procedures, and flawed sampling procedures. In many cases, the primary focus of the studies differed from that of this review, which often impacted the relevance and completeness of reported outcomes, resulting in several findings reported across multiple studies lacking sufficient analysis for proper interpretation. Overall, quality concerns across included studies introduces considerable uncertainty and limits the strength and generalisability of the evidence to current screening practice.

6. Conclusions

Overall, the included systematic reviews and primary studies that evaluated the diagnostic accuracy of 45° non-mydriatic fundus cameras rarely achieved the thresholds set by the British Diabetic Association, with only one study doing so, although considerable methodological concerns make the reliability of this finding uncertain. Evidence on factors significantly associated with ungradable images was limited, though older age was linked to poorer image quality across two studies, and single-study findings identified associations with eye factors such as cataract, high spherical equivalent and corrected distance visual acuity worse than 20/40, as well as smoking, male sex and high patient service throughput. Crucially, none of the included studies assessed the Topcon NW500 camera, which has been procured for use in Wales. Given likely differences in performance between camera models, caution is warranted when applying these findings to current practice, and a robust local evaluation of the Topcon NW500 is clearly justified.

7. Implications for practice, policy, and future research

This scoping review found considerable variation in diagnostic accuracy across studies, with sensitivity and specificity values ranging widely. It also identified some evidence of characteristics that are associated with an increase in ungradable images, with older age being the most frequently associated factor that increased the likelihood of an ungradable image being obtained. Single-study findings also identified associations with eye factors such as cataract, high spherical equivalent and corrected distance visual acuity worse than 20/40, as well as smoking, male sex and high patient service throughput. This evidence should be cautiously applied to the context of diabetic retinopathy screening in Wales but could be useful to inform variables studied in the upcoming evaluation of the Topcon NW500.

None of the included studies were conducted in Wales, and differences in population characteristics and screening pathways may affect the relevance of their findings. Furthermore, the Topcon NW500 was not evaluated in any of the included studies meaning that outcomes for this particular camera could differ significantly to those reported.

Future research and evaluation should aim to evaluate the diagnostic accuracy and clinical effectiveness of the Topcon NW500 specifically and identify factors that may contribute to capturing ungradable images in current non-mydriatic cameras used for diabetic retinopathy screening in Wales. The findings identified in this scoping review could be a useful starting point to inform which variables to focus on in the upcoming Topcon NW500 evaluation in Wales. Collecting the characteristics identified, or utilising existing information if available to screening professionals from patient records, could be useful for ensuring groups are adequately sampled in the evaluation. This would help identify which groups of patients may benefit from a staged mydriasis approach in Wales, with the ultimate aim of improving service efficiency and patient convenience by identifying those that can avoid the need for pharmacological pupil dilation.

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9. Additional information

9.1. Competing interests

The authors declare they have no competing interests

Appendix A: Search Strategy

Ovid MEDLINE(R) ALL <1946 to July 17, 2025>

1 diabet*.ti,ab. 867885
2 Diabetes Mellitus, Type 2/ or Diabetes Mellitus/ or Diabetes Mellitus, Type 1/ or Diabetes complications/ or Diabetic Retinopathy/ 451355
3 1 or 2 921117
4 (non-mydria* or "non mydria*" or non-dilat* or "non dilat*" or "without dilation" or "without pupil dilation" or undilated or "un-dilated" or "pupil status" or "dilation free" or mydria*).ti,ab. 5908
5 mydriatics/ or mydriasis/ 3868
6 4 or 5 8294
7 (Topcon or Confocal or Canon).ti,ab. 98742
8 ((digital or imag* or photo* or camera*) adj3 (retina* or fundus)).ti,ab. 34571
9 (digital adj3 (imag* or photo* or camera*)).ti,ab. 34464
10 7 or 8 or 9 164687
11 6 and 10 903
12 3 and 11 474
13 limit 12 to (english language and yr="2015 -Current") 255
14 (Non-mydriatic fundus camera screening with diagnosis by telemedicine for diabetic retinopathy patients with type 1 and type 2 diabetes: a hospital based cross-sectional study).m_titl. 1
15 Effect of visual impairment on teleretinal imaging for diabetic retinopathy screening.m_titl. 1
16 "The Scanning CONfoCal Ophthalmoscopy foR DIAbetic eye screening (CONCORDIA)".m_titl. 2
17 "Addressing technical failures in a diabetic retinopathy screening program".m_titl. 3
18 "Systematic review and meta-analysis of diagnostic accuracy of detection of any level of diabetic retinopathy using digital retinal imaging".m_titl. 2
19 "Imaging modalities employed in diabetic retinopathy screening: a review and meta-analysis".m_titl. 1
20 14 or 15 or 16 or 17 or 18 or 19 10
21 20 and 13 7

SCOPUS: 18/07/2025

(TITLE-ABS (diabet*)) AND ((TITLE-ABS ("non-mydria*" OR "non mydria*" OR "non-dilat*" OR "non dilat*" OR "without dilation" OR "without pupil dilation" OR "undilated" OR "un-dilated" OR "pupil status" OR "dilation free" OR "mydria*")) AND ((TITLE-ABS (topcon OR confocal OR canon)) OR (TITLE-ABS ((digital or imag* or photo* or camera*) W/3 (retina* or fundus))) OR (TITLE-ABS ((digital) W/3 (imag* or photo* or camera*)))))) AND PUBYEAR > 2014 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE , "English"))

= 286 RESULTS

CINAHL (Ebsco): 18/07/2025

((XB diabet*) OR ((MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2") OR (MH "Diabetes Mellitus") OR (MH "Diabetic Retinopathy"))) AND (((XB (non-mydria* OR "non mydria*" OR non-dilat* OR "non dilat*" OR "without dilation" OR "without pupil dilation" OR undilated OR "un-dilated" OR "pupil status" OR "dilation free" OR mydria*)) OR ((MH "Mydriatics+"))) AND ((XB (Topcon OR confocal OR canon)) OR (XB ((digital) N3 (imag* OR photo* OR camera*))) OR (XB ((digital OR imag* OR photo* OR camera*) N3 (retina* OR fundus)))))

Appendix B: Comparable camera devices inclusion/exclusion criteria (utilised from full text screening)

Include	Exclude
Any camera from the UK NSC approved cameras list here (as of July 2025): Diabetic eye screening: guidance on camera approval - GOV.UK, provided it is a non-mydriatic tabletop camera.	Standard 7-Field 30 degree Colour Fundus Photography
1-, 2-, and 3-fields, nonmydriatic (NM), 45 degree colour photography	Ultrawide Pseudocolour Retinal Photography
2-field 45 degree retinal photographs (1 macular-centered field and 1 disc-centered field)	Wide Field Fundus Fluorescein Angiograph
Non-mydriatic images captured at an angle of 45 degree and a flash setting of 100 watt second	Ultra-widefield fundus imaging (UWFI) capable of capturing 200degree images of the retina
	Optos wide-field imaging versus conventional camera imaging
	Non-mydriatic Volk Pictor Plus camera
	Ultra-widefield fundus photography (UWF-FP) and macular optical coherence tomography
	Stereoscopic Biomicroscopy
	Non-mydriatic ultrawide field scanning laser ophthalmoscopy
	Seven standard field ETDRS ultrawide field SLO imaging
	UWF imaging with fluorescein angiography / indocyanine green angiography / pseudo colour imaging / fundus autofluorescence
	Mobile based funduscope
	Direct or indirect ophthalmoscopy
	Ophthalmoscopy with slit lamp using volk fundus lens
	Topcon 3D optical coherence tomography
	Fundus images from 3 fields using a smartscope camera
	Handheld cameras
	Confocal scanning laser ophthalmoscopy

	Non-stereoscopic cameras
	Eidon white light 60 degree field scanning confocal ophthalmoscopes
	Montage widefield imaging with a system that combines confocal technology with white-light emitting diode (LED) illumination

Notes:

- Most of the above exclusions in the table are due to the cameras using a different image capture protocol, or a not comparable device/examination technique

Appendix 2: Data Extraction Table

2) What factors (e.g. age, ocular comorbidities, ethnicity, environments) are associated with unsuccessful or poor-quality non-mydriatic retinal images in those undergoing diabetic retinopathy screening?							
Reference:	Study detail:	Population:	Intervention:	Outcomes Assessed:	Diagnostic accuracy findings:	Ungradable image findings:	Comments:
Banaee T, et al. (2017). Utility of 1% tropicamide in improving the quality of images for tele-screening of diabetic retinopathy in patients with dark irides. *Ophthalmic Epidemiology*, 24(4), pp.217-221. DOI: 10.1080/09286586.2016.1274039 Country: Iran	Study Design: Uncontrolled before and after study Study Aim: To compare the quality of fundus photographs taken before and after instillation of one drop of tropicamide in a population of diabetic patients with dark irides. Study dates/duration: Data collected between Jan 2013 – March 2014. Setting: Hospital	**Population inclusion criteria:** Adult patients with a diagnosis of diabetes mellitus, referred for ophthalmic examination. **Number:** 149 (79 females, 70 males). Average age 43 (± 14 years). Overall, 13% of eyes (39 eyes) were pseudophakic, and 39% of	**Camera model:** Canon CR2-45NM. **Image type:** Non-stereoscopic, 45° fundus photographs. **Image capture conditions:** Ordinary room lighting. **Images captured by:** Trained photographer. **Images graded by:** Independently by two retinal specialists (graders 1 and 2).	Image quality (Good/ Poor/ Ungradable) across mydriatic status (Undilated/Partially dilated/ Fully dilated). Inter-rater agreement for image quality. The difference in image quality according to image position (macula- and disc-centered).	N/A	**Percentage ungradable images**: There were more ungradable images (38.1% and 50.3% for graders 1 and 2, respectively) in the undilated than partially- (4.6% and 11.5%) or fully dilated (15.4% and 10.0%) states of the pupil ($p < 0.001$ for both reviewers). The difference between fully- and partially dilated states with regard to the proportion of ungradable images was not statistically significant.	This study did not assess dark irides within its population, however it presumed that most participants had dark irides due to the composition of the patient population in Iran. The authors infer that the higher percentage of ungradable photos in the current study might be related to smaller pupil size and possibly less cooperation by patients relative to other studies, and images taken under

		patients (58 cases) had cataract (of any degree and any type). 1,768 photos from the 149 patients were graded.	**Comparison camera/method:** Image quality was compared between level of mydriasis (Undilated/Partially dilated/ Fully dilated).			Good quality images were also reported significantly more in the partially and fully dilated states of the pupil than in the undilated state by both reviewers. In the undilated state only 11.5% and 13.8% of photos were graded as good quality by the two graders, increasing to 37.8% and 43.8% in photos taken after instillation of only one drop of tropicamide. **Analysis of reasons for ungradable images:** N/A	normal room lighting. However there is no analysis undertaken to explore this.
Dow E, et al. (2023). Improved access to diabetic retinopathy screening through primary care-based teleophthalmology during the COVID-19 pandemic. *medRxiv*, pp.2023-05. DOI: 10.1101/2023.05.03.23289435	**Study Design:** Cross sectional study **Study Aim:** To measure if using a primary care-based teleophthalmology program improves access to eye examinations for	**Population inclusion criteria:** Patients 18 years or older with type 1 or type 2 diabetes mellitus without a prior DR diagnosis or	**Camera model:** CenterVue DRS fundus camera at one clinic site and TopCon NW400 fundus camera at four clinic sites. **Image type:** Single-field fundus	**Primary measures:** Proportion and number of annual eye exams of diabetic patients in primary care clinics that participated in the teleophthalmology program compared to		**Percentage ungradable images:** Images were of sufficient quality to assess DR status in 713 of 790 screens (90.3%). **Analysis of reasons for ungradable images:**	If medical assistants deemed the image quality to be poor, they repeated image acquisition and did so up to 4 times. Mentioned in the discussion without

Country: USA (San Francisco Bay Area)	diabetic patients as reflected in Healthcare Effectiveness Data and Information Set (HEDIS) measures. **Study dates/duration:** Sept 2019 – April 2021. **Setting:** Five academic affiliated primary care sites.	a DR exam in the past 12 months. **Number:** 760 unique patients (790 screens). Median age of participating patients was 60.0 years (range 25-99), and 45.3% were women. 32.0% White, 25.6% Asian, 8.6% Black, 2.3% Native American / Pacific Islander, and 31.5% Other / Unknown based on self-reported race. Additionally, the study population was 21.9% Hispanic, 69.2% Non-Hispanic, and 8.9% Other /	Photography **Image capture conditions:** Not reported. **Images captured by:** Trained medical assistants. **Images graded by:** Vitreoretinal specialists as Byers Eye Institute of Stanford (BEIS), using the international clinical diabetic retinopathy disease severity scale **Comparison camera/method:** N/A	clinics that did not participate. **Additional measures** included the number of patients with DR who were identified through the program, gradeability of fundus photographs, and characteristics of the study population.		The ungradable images (N=77) were significantly more likely to be obtained from older patients (68.1 years for ungradable vs. 58.5 years for gradable; p < 0.0001). Additionally, patients who self-reported as ethnically non-White were also more likely to have ungradable images (White 5.5%, Non-White 13.3%. Chi-squared 7.5107; p < 0.006) (Figure 2). This trend could not be accounted for by differences in age since non-White patients were, on average, a decade younger than White patients (76.9 years for White vs. 66.1 for non-White; p < 0.002).	any analysis: “Ungradable fundus images were almost always too dark, which could arise from poor alignment of the eye’s visual axis with the camera’s imaging axis, small pupil, cataract or other media opacity, or increased pigmentation of the fundus.”

		Unknown ethnicity by self-report.					
Lee J, et al. (2019). Comparison of 1-field, 2-fields, and 3-fields fundus photography for detection and grading of diabetic retinopathy. *Journal of Diabetes and its Complications*, 33(12), epub.107441. DOI: 10.1016/j.diacomp.2019.107441 **Country:** USA	**Study Design:** Comparative cross-sectional study (diagnostic accuracy) **Study Aim:** To evaluate the sensitivity and specificity of 1-, 2-, and 3-fields, nonmydriatic (NM), 45° colour photography compared with mydriatic ophthalmoscopy for detection of diabetic retinopathy. **Study dates/duration:** July 2016 – Aug 2017 for NM teleretinal imaging, with subsequent dilated ophthalmologic exam within six months of NM image being taken. **Setting:** Primary care	**Population inclusion criteria:** Diabetic patients who underwent 3-fields NM teleretinal imaging to screen for DR , followed by a dilated ophthalmologic exam by an ophthalmologist within six months. Patients were excluded if they were <18 years old or had received surgery for diabetic retinopathy in either eye. **Number:** 128 Patients (256 eyes). All had type 2 diabetes	**Camera model:** Topcon TRC-NW8 nonmydriatic fundus camera. **Image type:** Three undilated 45° retinal photographs in each eye: one field is centred on the macula; another is centred on the optic disc; and the third is focused superior temporal to the macula. **Image capture conditions:** Not reported **Images captured by:** Trained technician. **Images graded by:** Optometrist (using the International	Sensitivity and specificity for each screening strategy. Proportions of agreement with the reference standard. Proportions of agreement and ungradable photographs by DR grades for each screening strategy. Inter- and intra-grader reliability between the fundus field readings.	1-field: Sensitivity: 87.88% Specificity: 75.86% Under-reads: 26.26% Over-reads: 15.38% Proportion of agreement: 57.81% Kappa statistic: 0.55 (P < 0.001) 2-field: Sensitivity: 93.94% Specificity: 68.97% Under-reads: 20.20% Over-reads: 25.96% Proportion of agreement: 57.81% Kappa statistic: 0.52 (P < 0.001) 3-field: Sensitivity: 100%	**Percentage ungradable images**: 9.4% of 1-field and 5.5% of 2-fields photographs were determined ungradable. Ungradable photographs did not vary significantly by DR severity. **Analysis of reasons for ungradable images:**	Discussion mentions that 'Ungradable photographs were mostly due to poor pupillary dilation or media opacity'. However no actual analysis/stats for this this reported.

		mellitus except for one subject. 29 patients did not have DR and 99 patients had DR (according to the reference standard). 75% of the subjects were Hispanic, 6.3% non-Hispanic white, 16.4% Black, 2.3% Asian. 50% were male, and the mean age of participants ranged from 50 – 55 depending on DR level).	Clinical Diabetic Retinopathy Disease Severity Scale). **Comparison camera/method:** The sensitivity and specificity of the 1-, 2-, and 3-fields, was compared to reference standard (dilated ophthalmologic exam by an ophthalmologist)		Specificity: 79.31% Under-reads: 5.05% Over-reads: 23.08% Proportion of agreement: 77.34% Kappa statistic: 0.72 (P < 0.001) In this study, 1-, 2- and 3- field strategies all exceed the threshold of 80% sensitivity, as defined by the British Diabetic Association for an acceptable screening programme.		
O'Halloran R, and Turner A. (2018). Evaluating the impact of optical coherence tomography in diabetic retinopathy screening for an Aboriginal population. *Clinical & experimental ophthalmology*, 46(2),	**Study Design:** Retrospective comparative study (unpaired non-randomised) **Study Aim:** To evaluate the use of optical coherence tomography combined (OCT) with a fundus	**Population inclusion criteria:** Patients with diabetes at two Aboriginal Health Services, not under review by other eye health	**Camera model:** Intervention group – Topcon 3D OCT-1 Maestro. **Image type:** 45° colour fundus photograph and an OCT scan (intervention	Rate of adequate fundus photographs.		**Percentage ungradable images:** There was a significantly higher rate of inadequate photographs in the OCT group compared with the DRS camera control group (31.0% and 13.8%,	Note: we are primarily interested in the control camera for the purposes of our review. Authors conclude that this study supports the continued use of

pp.116-121. DOI: 10.1111/ceo.13018 **Country:** Australia	camera, compared with a fundus camera only in a telehealth diabetic retinopathy screening programme for Aboriginal Australians. **Study dates/duration:** Intervention group studied prospectively during a 4-month period (May–August 2015). A control group was audited retrospectively during the same 4 months in 2014. **Setting:** Aboriginal Health Services (one urban and one remote).	professionals or in receipt of previous eye treatment. **Number:** 222 reports (OCT intervention group n= 142, DRS camera control group n= 80). Mean age 53.5 years (range 18 – 84 years). 52.7% of screening reports were for male participants and 47.3% for female participants.	camera). 45° colour fundus photograph (control camera). **Image capture conditions:** Not reported **Images captured by:** Nurses and Aboriginal health workers (trained operators). **Images graded by:** Control group fundus images were graded by a retinal photograph grader and Intervention group OCT grading was performed by one of two ophthalmologists (a consultant and fellow), masked to the retinal photograph report.			respectively) , shown with an odds ratio associating the intervention group with adequate photographs of 0.355 (95% CI 0.171–0.736, P < 0.05). **Analysis of reasons for ungradable images:** No significant association was shown between photograph quality and the screening site, age or gender. There was a significant association between inadequate photographs and vision impairment. **(no statistics or analysis reported for screening site, age or gender, and unclear if this is for the intervention OCT camera, the control DRS camera, or both).** For vision impairment (<6/12) in either eye (n=45), adequate	non-mydriatic retinal cameras for screening programmes.

			All photographs graded using international guidelines. **Comparison camera/method:** Control group - CentreVue DRS fundus camera.			fundus photographs were less common when vision impairment was present (51.1% vs 80.6%), with an OR of 0.25 (95% CI: 0.13 to 0.51, P<0.05). Patients 55 years and over were significantly more likely to be identified with vision impairment than those under age 55 (29% vs 13.9% OR: 2.53, 95% CI: 1.26-5.08, P<0.05). **Note: unsure if analysis on vision impairment included just participants from IG, CG, or both.** There was no significant difference in visual impairment between the IG and CG groups (22.9% vs 19.0%, OR 1.27, 95% CI: 0.63-2.54, P<0.05).	
Porta M, et al. (2017). Systematic screening of Retinopathy in Diabetes	**Study Design:** Case series	**Population inclusion criteria:**	**Camera model:** A fully automated nonmydriatic	Number of ungradable and		**Percentage ungradable images:**	8,755 (39.1%) patients were evaluated using

(REaD project): an Italian implementation campaign. *European Journal of Ophthalmology*, 27(2), pp.179-184. DOI: 10.5301/ejo.5000912 **Country:** Italy	**Study Aim:** To evaluate the use of telemedicine retinal screening in Italy and to identify potential elements of implementation of this system. **Study dates/duration:** Between mid-April 2013 and mid December 2015. **Setting:** 33 diabetic outpatient clinics in Italy.	Diabetic patients attending the clinics with either recent onset diabetes or who had no ophthalmologic visit over the previous two years. **Number:** 22,466 participants analysed. 57.6% male. 12.5% T1D 87.2% T2D 0.5% Other types of diabetes. Mean age: 60.8 (range 3-96). 8,755 (39.1%) of patients were assessed using mydriasis.	digital fundus camera (DRS; CenterVue SpA). **Image type:** Two partially overlapping non-stereoscopic 45° digital colour images. **Image capture conditions:** Not reported. **Images captured by:** Licensed eye care professionals, mainly nurses were trained to use a fully automated non-mydriatic fundus camera as part of the study. **Images graded by:** Ophthalmologists , according to a simplified version of the American Academy of Ophthalmology classification.	unobtainable images. Factors associated with collection of low-quality photographs.		3,447/22,466 images could not be graded. However it is unclear which of these images were with or without mydriasis. Of the 3,477 ungradable images, cited reasons were: low quality (n= 3,215), darkness (n=133), opacities (n=48), reflections (n=26), other (n=25). 132 images could not be obtained. However it is unclear which of these images were with or without mydriasis. Of the 132 , reasons included: severe cataract (n=80), glaucoma (n=19), previous surgery (n=13), keratoconus (n=16), traumatic injury (n=2), corneal transplant (n=3). **Analysis of reasons for ungradable images:** Mydriasis was less likely to result in collection of low-	mydriasis. Some of these results pool patients receiving mydriasis and no mydriasis. Imaging was performed by operators who received an initial training session and, consequently, a learning curve in photography practices was observed with progressive reduction in the number of low-quality images over time. This was particularly evident for screening in mydriasis.

			Comparison camera/method: N/A			quality images (OR 0.33 [95% CI: 0.30-0.36]; p<0.001). For non-mydriasis patients: - Higher patient throughput was associated with a significant reduction in ungradable images in patients without mydriasis (OR= 0.96 [95% CI: 0.94-0.97], p<0.001) - Higher age was significantly associated with low-quality images in those without mydriasis (OR= 1.58 [95% CI: 1.52-1.64]), this was apparent in patients 40 years and over - A significant increase in odds of obtaining an ungradable image was apparent in those	

						aged 40 to 49 years (OR 3.16, 95% CI: 1.49 – 6.87), 50 to 59 (OR 4.01, 95% CI: 1.90 – 8.71), 60 to 69 (OR 6.35, 95% CI: 2.98 – 13.54), 70 to 79 (OR 11.58, 95% CI: 5.44 – 24.68) and ≥ 80 (OR 19.92, 95% CI: 9.22 – 43.02) - Male sex was significantly associated more low-quality images in patients without mydriasis (OR= 1.21 [95% CI: 1.10-1.34], p<0.001) - Smoking was significantly associated with more low-quality images (OR= 1.18 [95% CI: 1.04-1.35), p<0.012) - A non-significant association between hypertension and low-quality	

						images (OR=0.97 [95% CI: 0.84 – 1.12], p=0.671).	
Rico-Sergado L, et al. (2016). Effect of visual impairment on teleretinal imaging for diabetic retinopathy screening. *Ophthalmic Surgery, Lasers and Imaging Retina*, 47(1), pp.42-48. DOI: 10.3928/23258160-20151214-06 **Country:** Spain	**Study Design:** Case-control study **Study Aim:** To evaluate the effect of decreased visual acuity on image quality obtained by non-mydriatic retinal photography in diabetic subjects. **Study dates/duration:** June 2013 and June 2015. **Setting:** Alicante University General Hospital.	**Population inclusion criteria:** Inclusion criteria for cases included eyes with un-gradable images from patients who had a diagnosis of type II diabetes mellitus and had attended the scheduled clinic visit. For each case, an age- (±3 years) and sex-matched control was randomly selected from the remaining type II diabetes patients who underwent digital photographic screening and	**Camera model:** Topcon TRC-NW 100. **Image type:** 45° colour images. Digital photographs were taken of each eye according to the EURODIAB protocol: one centred on the optic disk and one centred on the macula. **Image capture conditions:** Not reported **Images captured by:** A trained nurse at a primary care centre. **Images graded by:** A retinal specialist. image quality was	Association between Corrected distance visual acuity , spherical equivalence, astigmatism, cataract status, duration of diabetes, and diabetic retinopathy grade, and the frequency of ungradable scans.		**Percentage ungradable images**: 2,254 eyes from 1,130 patients were originally reviewed, with 231 eyes (10.25%) considered ungradable. 211 of these met the studies inclusion criteria and form the case group for this papers analysis. **Analysis of reasons for ungradable images:** Corrected distance visual acuity (CDVA) worse than 20/40 was significantly associated with an increased likelihood of the retinal image being classified as ungradable. OR 7.79 (95% CI: 4.19-14.50; *P* < .0001)	

		for whom retinal photo-graphs were considered gradable. Controls were only included if they had had a routine ophthalmic examination in the same outpatient clinic within 3 months of retinopathy screening. **Number:** 212 patients (422 eyes; 211 cases and 211 controls). 188 (55.66%) male Mean age of the sample was 70.30 years ± 8.25 years and 69.55 years ± 7.63 years (P = 0.337) in	judged on the macular view, and an eye was consid-ered ungradable when more than one-third of the picture was blurred or the large vessels of the temporal arcades were blurred, unless sight-threatening retinopathy was detected. **Comparison camera/method:** Gradable images from a matched control, same camera used.			Eyes with high spherical equivalent were also associated with an increased likelihood of ungradable images. The OR of a scan being considered ungradable in eyes with refractive error worse than −6.0 D SE or +5.0 D SE was 16.80 (95% CI: 2.14-131.88; P = 0.007). Of the 211 ungradable scans, 47 eyes (22.3%) had a diagnosis of advanced cataracts. Comparing both groups, a significant association between advanced cataracts and ungradable scans was observed. OR of a scan being classified as ungradable in subjects with 2+ cataract compared to no cataracts was 9.30 (95% CI: 3.88-22.29; P< 0.0001). Conversely, there was no relationship	

		the study and control groups, respectively.				between trace to 1+ cataract or pseudophakic and the likelihood of ungradable scans, with an OR of 1.48 (95% CI: 0.82-2.69; P = 0.197), and 1.39 (95% CI: 0.74-2.63; P = 0.306), respectively. Astigmatism: Worse than ±3.0 D vs. within ±3.0 D, OR= 1.21 (95% CI: 0.47-3.07), P=0.695 Corneal transparency: Corneal leucoma vs. transparent, OR= 3.03 (95% CI: 0.26-35.66), p=0.378 DR Grade: Mild non-proliferative vs. no DR: OR= 0.88 (95% CI: 0.38-2.00), p=0.756 Moderate non proliferative vs. no DR: OR= 3.37 (95% CI: 1.47-7.70), p=0.004 Severe non-proliferative vs. no DR: OR= 1.05 (95%	

						CI: 0.22-5.16), p= 0.950 Proliferative vs. no DR: OR= 1.40 (95% CI: 0.41-4.79) p= 0.588 Duration of Diabetes: 10-19 years vs. 0-9 years, OR= 0.85 (95% CI: 0.48-1.48), p= 0.773 20 years or more vs. 0-9 years OR=1.76 (95% CI: 0.93-3.32), p= 0.080 Multivariable Analysis: In the multivariable model, the correlation of visual acuity with ungradable scans remained significant. CDVA worse than 20/40 was significantly associated with an increased likelihood of ungradable images, with an OR of 5.23 (95% CI, 2.82-9.71; P < 0.0001). The association of high SE and ungradable	

						images also remained significant, with an OR of 13.21 (95% CI: 2.61-66.77; P = 0.002). On the contrary, there was no evidence of an association between high astigmatism and ungradable scans in either model. The effect of cataract grading remained significant in the multivariable model. Scans from subjects with 2+ cataract had an OR of 3.36 (95% CI: 1.42-7.95; P = 0.006) of being classified as ungradable compared to those with no cataracts.	
Rosses A, et al. (2017). Diagnostic performance of retinal digital photography for diabetic retinopathy screening in primary care. *Family Practice*, 34(5), pp.546-551. DOI: 10.1093/fampra/cmx020 **Country:**	**Study Design:** Before and after study **Study Aim:** To evaluate the diagnostic performance of retinal digital photography for diabetic retinopathy screening in primary care, accuracy	**Population inclusion criteria:** Adult patients with type 2 diabetes. Patients with a previous diagnosis of cataract were excluded.	**Camera model:** Canon CR-2 non-mydriatic retinal camera. **Image type:** Two fields **Image capture conditions:**	Factors associated with ungradable images (mydriatic vs non-mydriatic).		**Percentage ungradable images:** Non-mydriatic: n=27 (14.8%) Mydriatic: n=16 (8.7%). Mydriasis was associated with better image quality (P=0.008)	This study's primary aim was to assess the diagnostic accuracy of family physicians screening for diabetic retinopathy.

Brazil	of the family physician in diabetic retinopathy identification compared to the ophthalmologist, and the need for dilation. **Study dates/duration:** None reported **Setting:** A primary care centre (Basic Health Unit) in Southern Brazil.	**Number:** 219 patients. Mean age was 64.9±11.0 years. 131 were women (59.8%). The sample was predominantly white (89%) and hypertensive (90.4%); 20.5% of participants had nephropathy.	Participants were sent to a dark room and, after at least 3 minutes, two photos of each eye were taken, one centred at the macula and another at the optic disc. Participants then received mydriasis using tropicamide. **Images captured by:** A family physician. **Images graded by:** Family physicians and ophthalmologists. Diagnostic accuracy of family physicians was assessed using ophthalmologists as the gold standard. Diabetic retinopathy classified according to the International Clinical Classification			**Analysis of reasons for ungradable images:** Analysis of factors associated with readability identified that patients with unreadable images had a median age of 72.5 ± 9.8 years, while those with readable and questionable images were, on average, aged 62.6 ± 11.3 and 64.3 ± 9.8 years, respectively. When stratified by age, authors identified 89 patients (48.6%) under 65 years and 94 patients (51.4%) aged 65 or older. In the older group, pharmacologic mydriasis was associated with improved image readability (McNemar test, *P* = 0.008), but not among the younger group. (McNemar test, *P* = 0.579).	

			System for Diabetic Retinopathy and Diabetic Macular Edema. **Comparison camera/method:** Study compares non mydriatic vs mydriatic images, taken with same camera.			The other factors considered diabetes duration, presence of hypertension, presence of nephropathy did not influence readability of fundus photographs.	
Szabó D, et al. (2015). Telemedical diabetic retinopathy screening in Hungary: a pilot programme. *Journal of telemedicine and telecare*, 21(3), pp.167-173. DOI: 10.1177/1357633X15572712 **Country:** Hungary	**Study Design:** Case Series plus Uncontrolled before and after experimental design for the comparative subset **Study Aim:** To assess the efficacy of three-field non-mydriatic digital photos as a telemedical screening tool for diabetic retinopathy for the first time in Hungary, and compare it with three-field photos made in mydriasis, and with mydriatic slit lamp examination. **Study dates/duration:** Not reported.	**Population inclusion criteria:** Adult patients (18+) presenting at the tertiary diabetes centre with type 1 or type 2 diabetes. **Number:** 251 patients (images from 502 eyes). 108 male, 143 female. 59 patients with type 1 diabetes and	**Camera model:** Topcon TRC-NW200 . **Image type:** Three 45° colour fundus photographs (central, nasal, superotemporal) per eye. **Image capture conditions:** Not reported. **Images captured by:** Trained non-eye-care assistants. **Images graded by:**	Rate of non-gradable photographs. Comparative subset: Intermethod and intergrader agreements		**Percentage ungradable images**: Rate of non-gradable photographs (cataract, small pupil size, vitreous opacity) was 10.1% (51 eyes) overall; 5.9% (7 eyes) for type 1 diabetes and 11.4% (44 eyes) for type 2 diabetes. **Analysis of reasons for ungradable images:** As noted above (no further breakdown).	

	Setting: Tertiary diabetes centre.	192 with type 2 diabetes. Mean age 57.1 (±14.9 years). A comparative subset of 28 randomly selected patients was also undertaken (12 males, 16 females, with a mean age of 51.6 ± 13.7 years).	Two independent ophthalmologists graded using the Proposed International Diabetic Retinopathy and Macular Edema Severity Scales. **Comparison camera/method:** A subset of 28 randomly selected patients were also examined in mydriasis (dilated by tropicamide and phenylephrine) by an ophthalmologist (O method) and were also photographed in mydriasis (M method) with non-mydriatic camera.				
Toy B, et al. (2016). Non-mydriatic fundus camera screening for referral-warranted diabetic retinopathy in a northern California safety-net	**Study Design:** Retrospective longitudinal cohort study. **Study Aim:**	**Population inclusion criteria:** Adult patients who underwent non	**Camera model:** Nidek NM-1000. **Image type:** Single 45° field-of-view fundus	Comparisons of clinic and non-mydriatic fundus photography grades.	Subset of 1,521 patients who had non-mydriatic photographs taken were also evaluated in clinic	**Percentage ungradable images**: 1,187 (13%) of non-mydriatic images were graded unreadable, from 856	

setting. *Ophthalmic Surgery, Lasers and Imaging Retina*, 47(7), pp.636-642. DOI: 10.3928/23258160-20160707-05 **Country:** USA (California)	To compare non-mydriatic fundus photography screening for DR with clinical dilated fundus examination (DFE) in a safety net setting. **Study dates/duration:** April 2008 – September 2012. **Setting:** Santa Clara Valley Medical Center (a primary care based, safety-net hospital, serving predominantly uninsured or underinsured patients) diabetes clinic.	mydriatic DR screening. **Number:** 6,911 patients with a total of 9,125 pairs of non-mydriatic fundus images graded. 47% male. Mean age 55.4 years (±12.2) 46% Latino, 24% Asian/Pacific Islander, 17% White.	image centered on the macular. **Image capture conditions:** Not reported **Images captured by:** Not reported **Images graded by:** Single board certified ophthalmologist. **Comparison camera/method:** Patients with referral-warranted retinopathy or unreadable photos referred for ophthalmic evaluation and underwent DFE, including slit lamp biomicrospcopy and indirect ophthalmoscopy, graded using the ICDR disease severity scale.	Percentages of no, minimal & referral-warranted retinopathy and unreadable images.	with dilated fundus examination. Compared to the clinical ICDR grade from DFE, non-mydriatic photography was noted to have the following characteristics: Sensitivity: 91% Specificity: 97% PPV: 85% NPV: 98% Kappa: 0.86. Including unreadable photos, sensitivity of non-mydriatic photography to detect non proliferative DR or worse disease: Sensitivity: 93% Specificity: 75% PPV: 42% NPV: 98% Kappa: 0.45 AOC: 0.97	(12%) of the total patients. **Analysis of reasons for ungradable images:** Aetiology of 1,187 unreadable photos, from 305 patients who presented to eye clinic and had an identified cause for the unreadable non-mydriatic photo: Cataract: n=162 (53%) Refractive: n=54 (18%) Proliferative DR: n=19 (6%) Retinopathy: n=18 (6%) Glaucoma: n=35 (11%) Other n=17 (6%).	

Systematic Reviews Q1) Can non-mydriatic retinal imaging with the Topcon NW500 (or similar devices) provide sufficient image quality for diabetic retinopathy grading without pharmacological dilation in people with diabetes?			
Piyasena M, et al. (2018). Systematic review and meta-analysis of diagnostic accuracy of detection of any level of diabetic retinopathy using digital retinal imaging. *Systematic Reviews.* 7, 182. DOI: 10.1186/s-13643-018-0846-y	Review aim: The review aims to evaluate how different characteristics of the diabetic retinopathy screening test impact on diagnostic test accuracy, and its relevance to a low-income setting. Inclusion criteria: - Cross sectional study designs aiming to evaluate the accuracy of diabetic retinopathy screening using digital imaging as the index test. - Populations of people with diabetes, assessed at permanent healthcare facilities. - Early treatment diabetic retinopathy study (ETDRS) seven-field image interpretation as the gold standard, and mydriatic bio-microscopy/ophthalmoscopy by an ophthalmologist/retinologist as the clinical reference standard where the gold standard was not performed. - Outcome of any level of diabetic retinopathy Search dates: Databases searched from date of inception to September 2016. Quality assessment:	Description of included studies: 26 studies included in the review/meta-analysis. Mean sample size of studies was 316 participants (SE±72.3, 95% CI: 166 to 467, range 51-1549). Mean age of participants 57.4 years (SE±.0.52, 95% CI: 54.3 to 60.7, range 16-89 years). Mean age in non-mydriatic strategies only was 58.9 years. 50.5% male participants (SE±2.7, 95% CI: 44.8 to 56.3) 23 studies conducted in high income countries, with the remaining three conducted in upper middle-income countries (one in Thailand, one in China and one in Taiwan). 18 studies used non-mydriatic imaging strategies. Six studies reported diagnostic test accuracy in which the same participant underwent imaging before and after pupil dilation.	Author's conclusions: Diagnostic test accuracy for the detection of any level of DR showed that DRS using two fields delivered at non-primary care settings is a feasible approach. Dilatation of the pupils did not improve the detection of any level of DR for those with gradable images, but such a wide range of ungradable were presented in these studies that this aspect must be taken into account when setting up DRSP. Limitations: - Most studies included only gradable images, and studies differ in their approach to dealing with ungradable images (excluding from analysis vs grading as positive etc). - Definition of ungradable images also not uniform across studies. - The studies which used non mydriatic imaging techniques were more recent, being conducted after rapid advancements in technology for such imaging technology leading to better quality images using non-mydriatic systems without pupil dilatation as well and a major confounder in the meta-analysis Comments:

	QUADAS-2 **Synthesis:** Meta-analysis	Camera brands not reported, however of the 21 studies included in the meta-analysis, 18 used the following non-mydriatic imaging strategies: - 1 field (8 studies, 44.4%) - 2 field (4 studies, 22.2%) - Greater than two field (6 studies, 22.2%) Reference standard: To be included in the systematic review, studies must have used seven-field image interpretation as the gold standard or mydriatic bio-microscopy/ophthalmoscopy by an ophthalmologist/retinologist as the clinical reference standard where the gold standard was not performed. **Quality of included studies**: The methodological quality and applicability assessment of the included studies were according to the QUADAS-version 2 guidelines. In the assessment of bias, it was minimal (15.38% high risk) in conducting the index tests and reference tests. Nineteen percent of the studies showed high risk of bias in selection and 30.7% in participant flow and timing. In the assessment of applicability, risk was minimal in reference standard (3.8%) and 34% of the studies showed high risk in applicability with regard to patient selection and 50% in index test **Findings:** The pooled sensitivity of detection of any level of diabetic retinopathy using non-	

		mydriatic digital imaging was 86% (95% CI: 85 to 87%; 18 studies). The pooled specificity of detection of any level of diabetic retinopathy using non-mydriatic digital imaging was 93% (95% CI: 92 to 93%; 18 studies) Two field strategy only (4 studies): Sensitivity: 91% (95% CI: 90 to 93%) Specificity: 94% (95% CI: 93 to 95%) One field strategy only (8 studies): Sensitivity: 78% (95% CI: 76 to 80%) Specificity: 91% (95% CI: 90 to 92%) Greater than two field only (6 studies): Sensitivity: 88% (95% CI: 86 to 91%) Specificity: 95% (95% CI: 93 to 96%) Mean proportion of ungradable images in non-mydriatic methods was 18.4% (SE± 2.2, 95% CI: 13.6 to 23.3%). Non-mydriatic strategies showed very high discriminative power in ruling out the presence or absence of any level of DR, with a diagnostic odds ratio (DOR) OF 68.03 (95% CI: 35.5 to 130.0) and a positive likelihood ratio of 11.79 (SE 3.04, 95% CI: 7.1 to 19.5). After adjusting for ungradable images, the authors observed that the pooled sensitivity of detection of any level of DR was the same for non-mydriatic and mydriatic strategies: 86% (95% CI: 85 to 87%) for both	

		Sub analysis of studies which captured images on the same participant before and after pupil dilation (6 studies): - mydriasis (one field, two fields, three fields and five field: six studies, ten estimates) showed a high level of sensitivity: mydriatic 88% (95% CI 86–89) and non-mydriatic 82% (95% CI 80–84%). However, a higher level of specificity was shown in non-mydriatic methods in detecting any level of DR: non-mydriatic 92% (95% CI 91–93%) and mydriatic 89% (95% CI 88–90%).	
Hu J, et al. (2019). Single-Field Non-Mydriatic Fundus Photography for Diabetic Retinopathy Screening: A Systematic Review and Meta-Analysis. *Ophthalmic Research*, 62, pp. 61-67. DOI: 10.1159/000499106.	Review aim: To perform a meta-analysis to evaluate the diagnostic performance of the single field non-mydriatic fundus photography in detecting diabetic retinopathy. Additionally, to compare its efficacy in detecting diabetic retinopathy as compared with different reference standards (7SF and slit-lamp biomicroscopy). Inclusion criteria: - Prospective studies - Conducted in patients with known or suspected diabetic retinopathy - Using a 45° non-mydriatic camera, with focus on only one centre - Using 7SF or slit-lamp biomicroscopy as the reference standard - Using an ophthalmologist to grade images	Description of included studies: 10 studies included in the review/meta-analysis (published between 1993 and 2011). Numbers of participants ranged from 55 to 352 Age of participants ranged from 21 to 80+ (one study not recorded) % male participants ranged from 44% to 98.1% (one study not recorded) Included studies countries/settings not reported. Camera brands: - Topcon TRC-NW6S: n = 2 studies - Topcon TRC-NW5S: n = 2 studies	Author's conclusions: The results of the meta-analysis showed that 45-degree, single-field NMFP has a pooled sensitivity and specificity of 68 and 94%, respectively. Sensitivity values of 80% and specificity values of 95%, combined with a technical failure rate of less than 5%, are considered the standard values in retinopathy detection, as proposed by the British Diabetic Association. In this regard, single-field NMFP does not meet the technical requirements in DR screening and is thus not an ideal clinical practice. The subgroup analysis demonstrated the sensitivity and specificity of single-field NMFP were 0.73 and 0.91 when compared with 7SF photography, and they were 0.54 and 0.98 when compared

	Search dates: Studies up to May 19, 2018 **Quality assessment:** QUADAS-2 **Synthesis:** Narrative and meta-analysis.	- Topcon CRW6: n = 1 study - Topcon 45NM: n = 1 study - Canon CR5-45NM: n = 1 study - Canon CR6-45NM: n = 1 study - Canon CR3-45NM: n = 1 study - Nidek NM retinography device, 45°: n = 1 study Reference standard: - 7SF: n=7 studies - Slit-lamp biomicroscopy: n=3 studies **Quality of included studies**: Risk of bias assessed using QUADAS-2. Most domains rated as low risk of bias, across studies. Some 'unclear risk of bias' as follows: - Patient selection: n = 4 studies Most domains rated as low for applicability concerns, with some 'unclear' as follows: - Patient selection: n = 3 studies **Findings:** Overall findings (n=10 studies): - Pooled sensitivity: 0.68 (95% CI: 0.59 to 0.76; I^2 = 87%) - Pooled specificity: 0.94% (95% CI: 0.89 to 0.97. I^2 = 95%) - Pooled PLR: 11.2 (95% CI: 6.1 to 20.8) - Pooled NLR: 0.34 (95% CI: 0.26 to 0.44) - Pooled DOR estimate (using random-effects model): 33 (95% CI: 17 to 65) - Summary AUC value 0.88 (95% CI: 0.85 to 0.90)	with slit-lamp biomicroscopy, suggesting that the chosen reference standard may have an effect on the interpretation of the fundus photography images. In conclusion, the systematic review and meta-analysis suggested that single-field retinal imaging is insufficient to detect any DR. Additionally, different reference standards used in the diagnosis process could affect the final diagnostic results. **Limitations:** - The results of the meta-analysis suggested significant heterogeneity among the included studies - Only 10 studies included with relatively low numbers of participants - The meta-analysis included both RCTs and observational studies **Comments**: Key details on included studies not reported such as country/study designs.

		Subgroup analysis according to reference standard of 7SF (n=7 studies): - Pooled sensitivity: 0.73 (95% CI: 0.66 to 0.81) - Pooled specificity: 0.91 (95% CI: 0.85 to 0.97) Subgroup analysis according to reference standard of slit-lamp biomicroscopy (n=3 studies): - Pooled sensitivity: 0.54 (95% CI: 0.39 to 0.70) - Pooled specificity: 0.98 (95% CI: 0.95 to 1.00) No evidence of publication bias among included studies with a p value of 0.39 using Deeks' test.	

Primary Studies Q1) Can non-mydriatic retinal imaging with the Topcon NW500 (or similar devices) provide sufficient image quality for diabetic retinopathy grading without pharmacological dilation in people with diabetes?						
Reference:	Study detail:	Population:	Intervention:	Outcomes Assessed:	Diagnostic accuracy findings:	Comments:
Bastion M, et al. (2022). Comparison of Non-mydriatic Fundus Photography and Optical Coherence Tomography with dilated fundus examination for detecting diabetic retinopathy including diabetic macular edema. *Medicine and Health*; 17(1), pp. 88-104. DOI: 10.17576/MH.2022.1701.07 **Country:** Malaysia	**Study design:** Comparative cross-sectional study (diagnostic accuracy). **Study Aim:** To compare the reliability in terms of sensitivity, specificity and predictive values between OCT and non-mydriatic fundus photography as a screening tool for detecting diabetic retinopathy or diabetic macular edema, among patients with known diabetes mellitus undergoing screening for DR. **Study dates/duration:** Six week study period commencing 1st April 2024	**Population inclusion criteria:** Convenience sample of patients with diabetes (type 1 or 2) attending a medical centre eye clinic. **Number:** 83 patients (154 eyes – in 12 patients, only one eye was able to meet the set criteria). Mean age 62.9 ± 10.3 years (range 32-88years). 42.2% women (n=35) Ethnicity: 47.0% Malay (n=39) 35.0% Chinese (n=29) 18.0% Indian (n=15)	**Camera model:** Two assessed: Non-mydriatic fundus camera (Canon CR-2 Plus) OCT scanner (Specialist SD-OCT scanner) **Image type:** Non-mydriatic fundus camera: two field 45° degree images **Image capture conditions:** Dim room **Images captured by:** Technicians with minimum of 2 years' experience. **Images graded by:** Independently by two ophthalmologists of	Sensitivity, specificity and predictive values of non-mydriatic fundus photography and OCT, compared to diabetic fundus examination results (reference standard).	For non-mydriatic fundus photography: - Using DFE as standard, sensitivity of NMFP was 77.27% (95% CI: 65.3 to 86.7%) - Specificity 81.82% (95% CI: 72.2 to 89.2%) - Area under the receiver operating curve 0.7955 (95% CI: 0.73036 to 0.86055) - PPV 76.1% (95% CI: 64.9 to 85.3%) - NVP 82.7% (95% CI: 72.8 to 89.7%) - Moderate to substantial agreement with DFE for DR assessment for specialists 1 and	Screening using the Spectralis SD-OCT scanner was also performed and compared to the reference standard (see results).

	Setting: Medical centre eye clinic at tertiary referral centre In Kuala Lumpur	Mean duration of diabetes 13.8 ± 8.3 years (range 1-36 years).	at least 5 years' experience. International clinical DR severity scale used for grading, however DR not staged in this study, only presence or absence of DR recorded. **Reference standard:** Dilated fundus examination by an ophthalmologist.		2 respectively (k=0.59 and 0.64)	
Toy B, et al. (2016). Non-mydriatic fundus camera screening for referral-warranted diabetic retinopathy in a northern California safety-net setting. *Ophthalmic Surgery, Lasers and Imaging Retina*, 47(7), pp. 636-642. DOI: 10.3928/23258160-20160707-05 **Country:** USA (California)	**Study Design:** Retrospective longitudinal cohort study. **Study Aim:** To compare non-mydriatic fundus photography screening for DR with clinical dilated fundus examination (DFE) in a safety net setting. **Study dates/duration:** April 2008 – September 2012. **Setting:**	**Population inclusion criteria:** Adult patients who underwent non mydriatic DR screening. **Number:** 6,911 patients with a total of 9,125 pairs of non-mydriatic fundus images graded. 47% male. Mean age 55.4 years (±12.2)	**Camera model:** Nidek NM-1000. **Image type:** Single 45° field-of-view fundus image centered on the macular. **Image capture conditions:** Not reported **Images captured by:** Not reported **Images graded by:** Single board certified ophthalmologist.	Comparisons of clinic and non-mydriatic fundus photography grades. Percentages of no, minimal & referral-warranted retinopathy and unreadable images.	Subset of 1,521 patients who had non-mydriatic photographs taken were also evaluated in clinic with dilated fundus examination. Compared to the clinical ICDR grade from DFE, non-mydriatic photography was noted to have the following characteristics: Sensitivity: 91% Specificity: 97% PPV: 85% NPV: 98%	

	Santa Clara Valley Medical Center (a primary care based, safety-net hospital, serving predominantly uninsured or underinsured patients) diabetes clinic.	46% Latino, 24% Asian/Pacific Islander, 17% White.	**Reference standard:** Patients with referral-warranted retinopathy or unreadable photos referred for ophthalmic evaluation and underwent dilated fundus examination, including slit lamp biomicrospcopy and indirect ophthalmoscopy, graded using the ICDR disease severity scale.		Kappa: 0.86. Including unreadable photos, sensitivity of non-mydriatic photography to detect non proliferative DR or worse disease: Sensitivity: 93% Specificity: 75% PPV: 42% NPV: 98% Kappa: 0.45 AOC: 0.97	
Memon M, et al. (2020). Diagnostic accuracy of direct ophthalmoscopy and non-mydriatic retinal photography for screening of diabetic retinopathy. *Pakistan Journal of Opthalmology*, 36(2), pp. 120-124. DOI: 10.36351/pjo.v36i2.1015 **Country:** Pakistan	**Study Design:** Comparative cross sectional study (diagnostic accuracy) **Study Aim:** To validate the findings of an earlier study using non-mydriatic fundus cameras by optometrist. And to find out the diagnostic accuracy of direct ophthalmoscopy in the hands of optometrist.	**Population inclusion criteria:** Purposive sample. All newly registered type 2 diabetes patients age 40+, who were willing to have an eye exam with a dilated pupil were inducted. Those with type 1 diabetes, gestational diabetes or another eye disease were excluded. **Number:**	**Camera model:** Non-mydriatic camera (Canon CR-1) **Image type:** Two 45° retinal images (one centre to macular and one centre to optic disc) **Image capture conditions:** Not reported **Images captured by:** Optometrist A **Images graded by:**	Sensitivity Specificity PPV NPV Likelihood ratio Kappa statistics for inter-observer agreement.	Kappa statistic in terms of DR detection my NMFC as compared to reference standard was 0.725, indicating a good agreement between the observers of NMFC with standard. NMFC in the hands of an optometrist: - Sensitivity 76% - Specificity 96.63% - PPV 84.3% - NPV 90.7%	

	Study dates/duration: Oct-Dec 2018 **Setting:** Eye clinic of Al Ibrahim eye hospital	349 individuals with type 2 diabetes (698 eyes).	Unclear who graded images, but classified using Early treatment diabetic retinopathy study (ETDRS)– the modified Airlie House classification. **Reference standard:** Retinal examination by retina-trained ophthalmologist using fundus lens and slit lamp (reference standard). Results were also compared with direct ophthalmoscopy after pupil dilation (Tropicamide 0.1%), by Optometrist B		Non-Readable fundi with bio microscopy were 44 (6.3%), with NMFC were 142 (20.3%)	
Fahadullah M, et al. (2019) Diagnostic accuracy of non-mydriatic fundus camera for screening of diabetic retinopathy: A hospital based observational study in Pakistan. *Innovation*; 69(3), pp. 378-382 **Country:** Pakistan	**Study Design:** Cross sectional study (diagnostic accuracy) **Study Aim:** To determine the diagnostic accuracy of non-mydriatic fundus camera for the detection of diabetic retinopathy	**Population inclusion criteria:** Purposive sample of all diabetic patients visiting study facility during study period. Patients with a history of eye surgery, laser treatment or use of any ophthalmic drug	**Camera model:** Canon CR-1 **Image type:** Single 45° fundus image obtained in an un-dilated pupil **Image capture conditions:** Not reported	Sensitivity, specificity, PPV and NPV of NMFC vs reference standard.	Sensitivity of NMFC: 72% Specificity of NMFC: 86.3% PPV of NMFC: 62% NPV of NMFC: 90% Level of agreement for optometrist using NMFC compared to ophthalmologist (reference standard)	

	Study dates/duration: January – May 2015 **Setting:** Al Ibrahim Eye Hospital.	for glaucoma excluded. **Number:** 1485 (2970 eyes). Mean age 53.5±10.4years (range 20-95 years). 52.8% male (n=687) 47.2% female (n=706)	**Images captured by:** Trained optometrist **Images graded by:** Unclear, but DR classification using the International clinical disease severity scale. **Comparison camera/method:** Opthalmologist examination using 90-D fundus lens and slit lamp, after pupil dilation (using Mydriacyl 1% two drops) – reference standard in study.		was moderate (K=0.551).	
Ryan M, et al. (2015). Comparison among methods of retinopathy assessment (CAMERA) study: smartphone, nonmydriatic and mydriatic photography. *Opthalmology*. 122(10), pp. 2038-43. DOI: 10.1016/j.ophtha.2015.06.011 **Country:** India	**Study Design:** Comparative cross-sectional study (diagnostic accuracy) **Study Aim:** To compare smartphone fundus photography, nonmydriatic fundus photography and 7-field mydriatic fundus photography for their abilities to detect and	**Population inclusion criteria:** Adults aged 16 to 65 years, with a diagnosis of type 2 diabetes and a willingness to undergo photography with all three cameras. Excluded if they had a medical condition that was a contraindication to dilation, an overt	**Camera model:** Nidek Model AFC-230 **Image type:** Three 45° images taken of each eye. **Image capture conditions:** Darkened room **Images captured by:** photographer **Images graded by:**	Sensitivity and specificity of different methods (nonmydriatic & smartphone) for diagnosing DR (7-field fundus photography diagnosis as gold standard). Kappa statistic for agreement between gold	Any diabetic retinopathy: • Sensitivity: 81% (95% CI: 75-86) • Specificity: 94% (95% CI: 92-96) • K= 0.76 (95% CI: 0.71 to 0.82) Vision-threatening diabetic retinopathy:	

	grade diabetic retinopathy (DR) **Study dates/duration:** Patients recruited over a period of 5 months **Setting:** Eye department at Specialist diabetes centre in Chennai, India.	media opacity, or gestational diabetes. **Number:** 300 participants (600 eyes). Mean age 48 (±11 years) 67% Male (n=201) Minimum disease duration 0.1 years. Maximum 37.2 years.	Unclear who graded images, presence or absence of DR recorded. If DR present, severity scored using early treatment diabetic retinopathy study (ETDRS) criteria. Image quality graded on a 1-5 scale (excellent, good, satisfactory, poor, unreadable) **Reference standard:** Standard 7-field fundus photography performed by a trained optometrist. The performance of smartphone fundus photography (with mydriasis) was also assessed as part of the study.	standard and smartphone and nonmydriatic methods. Photographic quality	• Sensitivity: 54% (95% CI: 40-67) • Specificity: 99% (95% CI: 98-100) • K= 0.64 (95% CI: 0.52 to 0.76) Not gradable: 9 (1.5%) Satisfactory quality: 534 (89%)	
Lee J, et al. (2019). Comparison of 1-field, 2-fields, and 3-fields fundus photography for detection and grading of diabetic retinopathy. *Journal of Diabetes and its Complications*, 33(12), epub.107441. DOI: 10.1016/j.diacomp.2019.107441	**Study Design:** Comparative cross sectional study (diagnostic accuracy) **Study Aim:** To evaluate the sensitivity and	**Population inclusion criteria:** Diabetic patients who underwent 3-fields NM teleretinal imaging to screen for DR , followed by a dilated	**Camera model:** Topcon TRC-NW8 nonmydriatic fundus camera. **Image type:** Three undilated 45° retinal photographs	Sensitivity and specificity for each screening strategy. Proportions of agreement with the reference standard.	1-field: Sensitivity: 87.88% Specificity: 75.86% Under-reads: 26.26% Over-reads: 15.38% Proportion of agreement: 57.81%	

Country: USA	specificity of 1-, 2-, and 3-fields, nonmydriatic (NM), 45° colour photography compared with mydriatic ophthalmoscopy for detection of diabetic retinopathy. **Study dates/duration:** July 2016 – Aug 2017 for NM teleretinal imaging, with subsequent dilated ophthalmologic exam within six months of NM image being taken. **Setting:** Primary care	ophthalmologic exam by an ophthalmologist within six months. Patients were excluded if they were <18 years old or had received surgery for diabetic retinopathy in either eye. **Number:** 128 Patients (256 eyes). All had type 2 diabetes mellitus except for one subject. 29 patients did not have DR and 99 patients had DR (according to the reference standard). 75% of the subjects were Hispanic, 6.3% non-Hispanic white, 16.4% Black, 2.3% Asian. 50% were male, and the mean age of participants ranged from 50 – 55 depending on DR level).	in each eye: one field is centred on the macula; another is centred on the optic disc; and the third is focused superior temporal to the macula. **Image capture conditions:** Not reported **Images captured by:** Trained technician. **Images graded by:** Optometrist (using the International Clinical Diabetic Retinopathy Disease Severity Scale). **Comparison camera/method:** The sensitivity and specificity of the 1-, 2-, and 3-fields, was compared to reference standard (dilated ophthalmologic exam by an ophthalmologist)	Proportions of agreement and ungradable photographs by DR grades for each screening strategy. Inter- and intra-grader reliability between the fundus field readings.	Kappa statistic: 0.55 ($P < 0.001$) 2-field: Sensitivity: 93.94% Specificity: 68.97% Under-reads: 20.20% Over-reads: 25.96% Proportion of agreement: 57.81% Kappa statistic: 0.52 ($P < 0.001$) 3-field: Sensitivity: 100% Specificity: 79.31% Under-reads: 5.05% Over-reads: 23.08% Proportion of agreement: 77.34% Kappa statistic: 0.72 ($P < 0.001$) In this study, 1-, 2- and 3- field strategies all exceed the threshold of 80% sensitivity, as defined by the British Diabetic Association for an acceptable screening programme.	

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