Diabetic Retinopathy

Accuracy of Screening Methods for Diabetic Retinopathy: A Systematic Review

MONASH University

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Contributors and Acknowledgements

FUNDING AGENCIES

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Harold Mitchell Foundation

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CHIEF INVESTIGATORS

Professor Hugh Taylor

Professor Russell Gruen

PROJECT TEAM

Dr Peter Bragge (Project Manager; Author, Diabetic Retinopathy Report)

Ms Marisa Chau (Author, Diabetic Retinopathy Report)

Mr Jason Wasiak (Author, Trachoma Report)

Dr Alex Hewitt (Author, Trachoma Report)

Professor Andrew Forbes (Statistician)

Ms Anne Parkhill (Information Specialist)

Ms Ornella Clavisi (Database Development)

Ms Jenny Burchill (Administrative support)

Ms Judith Carrigan (Administrative support)

Ms Haifa Sekkouah (Designer)

COLLABORATING ORGANISATIONS

The University of Melbourne

Monash University

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Executive Summary

Rates of diabetes and Diabetic Retinopathy (DR) amongst Indigenous Australians are considerably higher than in mainstream Australia. Early DR detection facilitates sight-saving treatment. Therefore, efficient and effective strategies for screening for DR in remote Indigenous communities are integral to optimising management of this condition.

The aim of this systematic review was to examine the accuracy of screening methods for DR in all healthcare settings, and examine the relevance of this information to the Australian Indigenous context.

This report details all results of the systematic review, highlighting studies conducted in outreach settings. The report also contains a statistical analysis of the relevance of screening accuracy findings to the Australian Indigenous context. The key findings of the review are summarised below:

Eligible studies and study characteristics

- Sixty-two studies met inclusion criteria for the systematic review.
- Only nine of the sixty-two studies were conducted in outreach settings (findings from these studies are described separately, and highlighted in bold and italicised in tables)
- The most frequently investigated screening methods investigated were camera-based screening (n=33), a combination of camera and examination (n=15) and examination (n=11)
- The most frequent study locations were the UK (n=20) and the USA (n=17), with 1 – 3 studies conducted in all other countries represented. Just over half (n=34) were published between 2001 – 2009
- A total of 13 different classification systems were used in defining the levels of DR, with the majority using that of the ETDRS (n=16)
- Thirty-two studies (51.6%) did not explicitly define 'referrable DR' for the purpose of their study.
- Twenty-six studies reported DR prevalence in their study sample. The mean prevalence of DR (all levels) across these studies was 37.3% (range 9 - 83).

Screening methods

- The 62 included studies compared one (n=30), two (n=19) or three or more (n=13) screening interventions against a gold standard. A total of 122 screening interventions were investigated
- The most frequently studied screening methods in terms of instrument and mydriatic status were mydriatic fundoscopy (n=31), non-mydriatic digital camera (n=22), mydriatic digital camera (n=16) and mydriatic film camera (n=10)
- Of the 87 screening methods involving photography, 32 photographed one field, 8 photographed two fields, 14 photographed three fields and five each photographed five, seven and nine fields

- Reference standards used to evaluate screening accuracy were dilated examination by an eye specialist (n=39), seven-field mydriatic photography (n=16) and combination / multiple reference standards (n=7).

Results: Sensitivity and Specificity and Kappa

- Forty-three studies reported measures of sensitivity / specificity, generating 197 sensitivity / specificity measures
- Twenty studies measured Kappa, generating 103 Kappa measures
- Following re-classification of outcome categories from various classification systems using the International Clinical DR Severity Scale (see Methods), a total of 25 outcome categories for sensitivity / specificity and kappa measures were identified
- Only three outcome categories generated over 20 sensitivity / specificity / kappa measures: 'Any DR' (40 Sensitivity / Specificity measures), 'Moderate NPDR as a threshold' (29 Sensitivity / Specificity measures) and 'Agreement across a grading system' (44 Kappa measures). Mean kappa values were almost identical for mydriatic (0.65) and non-mydriatic (0.64) measures.

Results: Statistical analysis of the relevance of screening accuracy findings to the Australian Indigenous context

- Sensitivity to detect 'Any DR' was not influenced by variations in mydriatic status or imager qualifications, either in isolation or in combination
- Mydriatic status did not significantly influence sensitivity to detect 'Mod NPDR as a threshold'
- Variations in imager qualifications in isolation, and when combined with non-mydriatic methods, yielded significant differences in sensitivity to detect 'Mod NPDR as threshold'. However this was based on one comparison group with only two data points. Furthermore, the lower sensitivity values in these comparisons were in excess of the 60% threshold identified by Javitt (1990) to be cost-effective and because they were also relatively high (80.4, 77.9), this result may have limited clinical significance
- Use of mydriasis did not influence specificity to detect 'Any DR' but yielded significantly higher specificity values for 'Mod NPDR as threshold'
- Specialists yielded generally higher specificity values compared with non-specialists across both outcomes. This means the false positive rate amongst the non-specialist imagers was greater than for the specialists. Therefore, these differences would not be expected to result in adverse patient outcomes as the consequences of inappropriate referral to a specialist are less than those of missed cases of DR (as measured by sensitivity).
- In summary, this statistical analysis demonstrates that variations in two key characteristics of 'outreach' screening methods – mydriasis and imager qualifications – either have no significant impact on sensitivity and specificity to detect 'Any DR' or 'Moderate NPDR as threshold', or do not alter these measures of screening accuracy to a clinically significant degree. The screening combinations used in 'outreach' settings such as the Australian Indigenous setting are viable in terms of both screening accuracy and cost-effectiveness.

Results: Reliability

- Only 10 studies reported inter-rater reliability. Across all methods, inter-rater comparisons and outcomes, the mean kappa was 0.72 (range 0.34 – 1). Mean kappa values ranged from 0.60 (retinal specialist against grader; grader against grader) to 0.87 (retinal specialist against retinal specialist)

- Only seven studies reported intra-rater reliability. Across all methods, raters and outcomes, the mean kappa was 0.74 (range 0.43 – 0.97). For retinal specialists, the mean kappa across a grading system was 0.84

Results: Image quality, patient satisfaction, time, cost and other outcomes

- Thirty-three studies, representing a total of 53 methods, reported data on image quality. Mean ungradable image rates across studies for non-mydriatic cameras ranged from 8.1% - 16.6%; these were generally higher than comparable means for mydriatic cameras (range 5.0% - 13.6%)

- Ten studies reported the time taken to screen for DR. Screening times ranged from three minutes (direct fundoscopy, scanning laser) to 20 minutes (direct, indirect and slip lamp fundoscopy). Screening times for camera-based methods were 4 – 10 minutes

- Seven studies provided some costing data. Estimated total screening costs have been reported as follows:

-
    - Mobile retinal screening using mydriatic 3-field film photography £22.70 per screen: Harding (1995)

    - Mobile retinal screening van using fundoscopy examination plus mydriatic 1-field Polaroid photography: £12.50 per patient for photo (including capital replacement costs); £1095 per patient saved from visual loss. Operational costs £35 000 for 3500 patients screened: O'Hare (1996)

    - Approximately £12,000 (film alone) for screening the whole Exeter community (300 000) using mydriatic 1-field photography (35mm photo plus polaroid photo): Taylor (1999)

    - £7.50 per patient using mydriatic polaroid photography (number of fields not reported) plus fundoscopy (includes polaroid films, capital and maintenance costs, and salaries of primary screener): Pandit (2002)

- Patient satisfaction with screening methods was reported by five of the 62 included studies. Generally, patient satisfaction with digital cameras without pupil dilation was reported as high. Based upon the reported data, discomfort arising from flash does not appear to vary according to camera type; however clinical experience suggests that the lower flash intensity of digital cameras (10% of the intensity of Polaroid) minimises the effect on short-term loss of vision and pupil constriction and is much better accepted by patients.

Introduction

Project Overview

Overcoming Indigenous Disadvantage, or 'closing the gap' in health, education, housing and other key areas has been identified as a priority by the Australian Government, particularly in the last decade (Australian Government Productivity Commission 2009).

The Australian National Indigenous Eye Health Survey reveals substantial challenges in closing the gap in Indigenous Eye Health. Although vision loss is five times lower in Indigenous children than mainstream children, the rate of blindness in Indigenous adults is six times higher than in the mainstream (Taylor 2009).

Optimal prevention and treatment of Indigenous eye disease requires that practitioners and policy-makers have ready access to up-to-date research evidence. Therefore, systematic reviews in two priority topics in Indigenous Health were undertaken:

1. The effectiveness of various methods of screening for Diabetic Retinopathy
2. The effectiveness of oral Azithromycin in the management of Trachoma

The systematic review process involved:

1. Conducting a comprehensive search of literature addressing each question
2. Developing a taxonomy identifying key contextual features that may influence the application of this evidence to the Australian Indigenous setting
3. Building an evidence map that classified the retrieved studies according to key screening method and context characteristics identified in the taxonomy
4. Extracting, summarising and analysing the results of the identified studies
5. Describing the relevance of this information to Indigenous eye disease services and outlining the need for further research relevant to the priority questions.

This report contains the results of the systematic review on the effectiveness of various methods of screening for Diabetic Retinopathy.

Diabetic Retinopathy

Diabetic Retinopathy (DR) is a progressive eye disease that affects the retinal microvasculature, resulting in an abnormal change in vascular permeability and proliferation of new, but fragile, blood vessels. If left unmonitored, these pathologies can ultimately result in severe or permanent visual loss (CERA 2001; Mitchell 2008; Williams 2004). Duration of diabetes has been shown to be a significant and independent predictor of DR presence and severity (Lim 2008). The Wisconsin Epidemiology Study of DR (Klein 1984) reported a 25% prevalence of DR (any severity) in Type 1 diabetic patients 5 years after diagnosis of diabetes. This rose sharply to 60% at 10 years and 80% at 15 years. The prevalence of more severe Proliferative DR (PDR) was 0% at 3 years and 25% at 15 years. Similar trends have been observed in other DR prevalence studies (Kristinsson 1994).

The worldwide prevalence of diabetes in the year 2000 was estimated at 171 million (2.8% of the world's population) and is projected to escalate to 366 million (4.4%) in 2030, largely as a result of an increase in obesity prevalence and lack of physical exercise (Wild 2004). Studies from both Australia and other countries underline this forecast. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) surveyed 11, 247 Australians from 42 randomly selected regions and found a 7.4% prevalence of diabetes; one of the highest figures in the developed world (Dunstan 2002). This finding was mirrored by The Blue Mountains Eye Study (BMES), which reported a diabetes prevalence of 9.9%, of which 33.4% had diabetic retinopathy, in a survey of 3509 Australians (Cugati 2006). Diabetes prevalence has recently been reported at 4.3% for UK (Gonzalez 2009) and 5.5% for USA (CDC 2008). Diabetes prevalence is considerably higher in specific populations; the National Indigenous Eye Health survey found that the prevalence of diabetes in Indigenous Australians has increased markedly, from 0.03% in 1980 to 37.4%, and the rate of diabetic visual impairment was 13% (Taylor 2009); previous studies reported diabetes prevalence rates in this population ranging 11.6% to 20.7% (Daniel 2002; McDermott 2000). Therefore, DR, already the most common cause of blindness in adults aged 20 – 74 (Fong 2004), is one of the major medical challenges of the first half of this century.

DR is managed at two levels. First, the risk of developing DR is reduced by optimising diabetes management via strict control of glycaemic levels, blood pressure and serum lipid levels (CERA 2001; Klein 1988; Klein 2002; Matthews 2004; Mohamed 2007; Sinclair 2005). Second, once DR has developed, laser treatment is clinically effective in delaying the progression of DR and vision loss by sealing permeable blood vessels and destroying proliferative vessels (Hercules 1977). Numerous randomised controlled trials (RCTs), including two large, multicentre trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (EDTRS), have demonstrated that pan-retinal photocoagulation (PRP) results in a significant reduction in vision loss from PDR by at least 50%. Furthermore, focal or grid laser photocoagulation was found to reduce moderate visual loss from Clinically Significant Macular Oedema (CSME) also by at least 50%. In advanced cases of DR, vitrectomy is another recognised DR treatment according to the 2008 National Health and Medical Research Council (NHMRC) guidelines (Mitchell 2008).

As DR has few symptoms until the development of visual loss (Fong 2004), successful DR management is highly dependent on regular DR screening to detect pathology prior to the development of vision-threatening complications (Chabouis 2009). Recommended screening intervals vary between countries. Guidelines from the USA and Europe recommend annual screening (American Diabetes Association 2009; Royal College of Ophthalmologist 2005). Australian guidelines recommend 2-yearly DR screening intervals except for Aboriginal and Torres Strait Islander peoples for whom annual examination is recommended (Mitchell 2008; Mohamed 2007). The Australian NHMRC guidelines (Mitchell 2008) also stress the need for testing visual acuity in addition to screening for DR and referring a patient with abnormal results in either of these tests.

Some authors argue that screening intervals can be stretched to every 3 years, as the rate of progression in requiring laser treatment is very low (Younis 2003), and therefore this is a cost-effective strategy (Vijan 2000).

However, regardless of recommended screening intervals, DR screening rates are poor in both Australia and other countries. In a study of 3271 residents of Melbourne, Australia, The Melbourne Visual Impairment Project (MVIP) reported that 34.2% of participants with diabetes, and 25% of diabetics with diabetic retinopathy, had never seen an ophthalmologist (McCarty 1998). This parallels the findings of another Australian study, which reported that 36% of diabetic patients had never had an eye examination (McKay 2000). A US-based longitudinal analysis of Medicare claims data found that only 50 – 60% of diabetics had annual eye examinations in a 15-month period, well short of recommended screening rates (Lee 2003), while a Spanish study reported 37.2% of diabetics had never had a fundus examination (Soto-Pedre 2008). Importantly, Soto-Pedre (2008) also found that screening rates in the crucial first five years after diagnosis of diabetes were only 38.5%. Furthermore, patients in racial/ethnic minorities and others with limited ability to access care are even less likely to receive screening (Taylor 2007). Despite recommendations for annual eye screening of diabetics, only 20% of diabetic Indigenous people had an eye examination in the year preceding the National Indigenous Eye Health Survey (Taylor 2009).

In addition to identifying and addressing preventable vision loss from DR, increasing DR screening compliance has considerable cost-effectiveness benefits. Mathematical modelling has demonstrated that in Australia, increasing screening compliance from 30% to 80% would reduce screening costs from approximately $193 million to $178 million per year (NHMRC 1997). Therefore, increasing compliance with DR screening is a major priority in the management of this condition.

Dilated ophthalmological examination by a trained health professional (e.g. ophthalmologist) and seven-standard field 30° photography of the fundus with a trained photographer and reader are the two recognised DR screening techniques (Fong 2004; WHO 2006). However, the expected rise in the diabetic population (Wild 2004) is running counter to the slower growth in the specialist eye doctors required to perform these procedures (Porta 2008). These methods are also costly to both patients (Mash 2007; Porta 2008) and third-party funders (Porta 2008) and patients report discomfort and functional limitations arising from pharmacological mydriasis (Cavallerano 2005; Porta 2008). Furthermore, patients in remote areas have difficulty in accessing the specialist infrastructure and resources for these types of DR screening (Leese 1993; Taylor 1996). In order to sustainably increase DR screening rates, simpler, cheaper and more portable screening methods are therefore required.

This challenge, coupled with advances in imaging technology such as digital cameras, has stimulated the development of a range of DR screening techniques. These include non-mydriatic retinal cameras (Soto-Pedre 2008), variations in the number of imaging fields (Pugh 1993), use of non-specialist fundus photographers (Porta 2008) and non-eye specialists to perform retinal examination (Verma 2003), telemedicine approaches (Chabouis 2009; Taylor 2007) and outreach services that bring mobile screening to remote populations (Moss 1985).

The many possible combinations of these screening variables present a challenge to the establishment of optimum DR screening methods. Therefore, the aim of this review was to examine the effectiveness of various methods of DR screening, as compared to the two accepted reference standards outlined above. Specifically, we also sought to evaluate the influence of various screening variables such as use of mydriasis, type of screening instrument and training and qualifications of imager and interpreter on screening accuracy.

Search Description and Methodology

An Information Specialist (AP) in consultation with other review authors developed search strings for Diabetic Retinopathy screening. Search terms included both the databases' taxonomy terms and keywords for Diabetic Retinopathy, a range of screening terms specific to Diabetic Retinopathy (e.g. 'photography', 'screening', 'telemedicine') and generic terms designed to identify screening studies (e.g. 'sensitivity', 'predictive value', 'accuracy'). Six databases were searched; CINAHL (OVID; 1982 – present), the Cochrane Library (Wiley; all available years), Embase (OVID; 1980 – present), Indigenous Australia (Informit; all available years), Medline (OVID; 1950 – present) and RURAL (Informit; all available years). Search strategies were tailored to each database. An example of a search strategy is contained in Appendix 1. The electronic literature search was conducted in September 2008 and updated in June 2009. Reference lists of relevant clinical guidelines and literature reviews, either retrieved through electronic searching or known to review authors, were also searched to identify further relevant citations.

Study Selection

Two review authors independently screened citations and full text articles against the inclusion criteria outlined in Table 1:

Table 1: Inclusion / Exclusion criteria for review

Population	Patients with Diabetic Retinopathy (any form or severity) Patients at risk of Diabetic Retinopathy (i.e. with Diabetes) If mixed population, over 50% in above categories OR subgroup analysis of DR *Rationale:* DR is specific to diabetic populations therefore study samples for this review should be predominantly diabetic patients
Screening Method	Any screening method for DR, including mydriatic / non-mydriatic photography and examination, at all provider skill levels *Rationale:* The review was designed to examine the effectiveness of a broad range of DR screening tests and the influence of provider skill level on test effectiveness

Methods

Design	All primary studies in which the main focus of the study was to evaluate the effectiveness of a DR screening method were eligible for this review. The method(s) under investigation must have been compared to one of the following accepted reference standards for DR screening: 7 field mydriatic photography OR Dilated fundal examination by an ophthalmologist, retinal specialist or equivalent *Rationale:* The comparison of a screening method under investigation with an appropriate reference standard is consistent with accepted principles of screening studies (Greenhalgh 1997; Whiting 2003). The chosen reference standards are widely accepted in the field of ophthalmology (Fong 2004; Mitchell 2008).
Primary Outcomes	Sensitivity, Specificity, Kappa of the method(s) under investigation compared to the reference standard. *Rationale:* Sensitivity and Specificity are accepted measures of diagnostic test accuracy (Jones 2009). Sensitivity is of particular importance given that accurate identification of patients with this condition, for which there are known treatments that prevent permanent vision loss, is a paramount clinical consideration. Kappa statistics are particularly appropriate to categorical outcome data and inter-rater comparisons (Landis 1977), both of which are inherent in DR screening.
Secondary Outcomes	Statistical tests of inter and intra-rater agreement Image quality Patient satisfaction Time Cost *Rationale:* Information regarding effectiveness of DR screening techniques needs to be interpreted in the context of a range of effectiveness and reliability measures as well as consideration of clinical applicability and feasibility
Exclusions	Studies of automated analysis techniques and technologies: Rationale: Fully automated screening techniques are not currently standard practice and these emerging technologies were considered outside the scope of this review. Cost-Effectiveness Analyses: Rationale: These were not primary studies but mathematical models using data from primary studies. Such studies were identified but not further analysed for review purposes. Systematic Reviews: Rationale: Relevant systematic reviews were identified but are not primary studies. Non-English Studies: Rationale: Relevant non-English studies that may aid future reviews of the topic were identified, but not included in the review due to the time and other costs of translation.

Disagreements in study selection were resolved by either consensus between the screeners or, where topic-specific knowledge was required to adjudge inclusion, an experienced ophthalmologist (HT).

DATA EXTRACTION

A relational data extraction database was developed in Microsoft Access. Database items and classification categories were developed with ophthalmologist input (HT) and involved consideration of key contextual issues that may inform the transferability of research findings in this field, such as geographical setting, the skill level of the provider and the portability and simplicity of the screening technique. Data extraction was piloted using ten included studies and the resulting output tables used to further refine database items and protocols.

The following data, where reported, were extracted from relevant studies:

- *Study Characteristics:*
  - Country, region and setting of study (e.g. hospital, rooms, outreach)
  - Study design (classified based upon the revised Australian National Health and Medical Research Council Hierarchy of Evidence framework (Coleman 2008)
  - DR classification system used
  - Study definition of 'referrable' DR (i.e. for immediate referral to / management by an eye specialist)
  - Number of patients / eyes
  - Demographic characteristics (% male, age, type of diabetes mellitus (DM))
  - Details of diabetes across sample (years a diabetic, diabetic management as reflected by control of HbA1c, BP and lipids)
  - DR severity in sample (as reflected by outcomes of screening using the reference standard).

- *Screening Methods (for each method under investigation as well as the reference standard):*
  - Screening method (camera-based method - digital / polaroid / film, make and model, number and degree of fields taken, resolution / type of film; fundal examination method - details of fundoscopy equipment and technique)
  - Mydriasis (used / not used / used as required)
  - Location of screening (if camera, location of photo and interpretation)
  - Qualifications and training of personnel involved in screening (if camera, imager as well as interpreter of image).

- *Results:*
  - Sensitivity, Specificity, Kappa or other statistical measures of agreement (e.g. correlation) between method(s) under investigation and reference standard
  - Inter- and Intra-rater reliability measures (chance-corrected, for example Kappa, not raw percentage agreements)
  - Image quality, time, cost and patient satisfaction data.

Data extraction was shared between two reviewers experienced in use of Microsoft Access for this purpose (PB, MC). Data extraction protocols, for example outlining commonly used abbreviations, were developed and regularly updated. Approximately 10% of data were audited and appropriate corrections to data and data extraction protocols made.

For the primary outcomes of interest, (Sensitivity, Specificity, and Kappa) data were classified using Microsoft Excel by the Chief Investigator (PB) according to screening variables outlined in Table 2.

Table 2: Classification of Screening Variables

Screening Variable	Classification categories and definitions
Screening instrument	Digital camera Polaroid camera Film camera Examination Scanning Laser Ophthalmoscope
Number of photo fields	1 - 9
Mydriasis	Mydriatic Non-Mydriatic Mixed Mydriatic / Non-Mydriatic or Not Reported (NR)
Location of screening	Static (private rooms, hospital department) Outreach (the provision of portable infrastructure / personnel to enable a DR screening service to be given to a population)
Imager	Photographer / Technician (including grader) Photographer / Technician + (mix of photographer / technician and qualified healthcare professional) Nurse Optometrist GP Diabetologist Retinal Specialist Mixed (a mix of any of the above categories) Not Reported (NR) Not Applicable (NA) (exam)
Interpreter	Retinal Specialist Ophthalmologist Trainee Ophthalmologist Optometrist Optician Grader Grader + (mix of grader and qualified healthcare professional) Diabetologist / Endocrinologist GP Physician Assistant Mixed (a mix of any of the above categories) Not Reported (NR) Not Applicable (NA) (exam)

Due to variability in DR classification systems and protocols used across studies, a total of 59 different outcome categories were identified in studies measuring sensitivity and specificity. In order to facilitate meaningful analysis of these data, these categories were re-classified according to their equivalent level on the International Clinical Diabetic Retinopathy (ICDR) Disease Severity Scale (American Academy of Ophthalmology 2002).

This scale was designed to enable clinically important DR grades to be identified by less experienced screeners, therefore improving communication between the various health professions involved in DR screening (Mitchell 2008). It also specifies the equivalence of the most frequently used DR classification scale, the Early Treatment of Diabetic Retinopathy Severity Scale (ETDRS), to the ICDR, as shown in Table 3.

Further references (Aldington 1995; Gibbins 1998) were consulted to ascertain the equivalence of classification systems other than the ETDRS to the ICDR as required. Re-classifying outcome categories using the ICDR reduced the number of outcome categories from 59 to 25 (see results). The same method of re-classification was used for Kappa data.

Table 3: International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy	Derivation from ETDRS Levels	Risk Assessment	Management Options*
No apparent Retinopathy	No abnormalities	Levels 10: DR absent		Optimize medical therapy of glucose, blood pressure and lipids
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only	Level 20: Very mild NPDR		Optimize medical therapy of glucose, blood pressure and lipids
Moderate Non-proliferative Diabetic Retinopathy	More than just microaneurysms but less than Severe NPDR	Levels 35,43: moderate NPDR less than 4:2:1 Level 47: moderate NPDR less than 4:2:1	One year early PDR: 5.4 – 11.9% One year high risk PDR:1.2-3.6% One year early PDR 26.3% One year High Risk PDR: 8.1%	Refer to an ophthalmologist Optimize medical therapy of glucose, blood pressure and lipids Refer to an ophthalmologist Optimize medical therapy of glucose, blood pressure and lipids
Severe Non-Proliferative Diabetic Retinopathy	Any of the following: • Extensive (>20) intraretinal haemorrhages in each of 4 quadrants • Definite venous beading in 2+ quadrants • Prominent IRMA in 1+ quadrant • And no signs of proliferative retinopathy	53A-E: severe to very severe NPDR, 4:2:1 rule	One year risk for early PDR: 50.2% (severe NPDR) One year High Risk PDR: 14.6% (severe NPDR) – 45.0% (very severe NPDR)	Consider scatter (panretinal) laser treatment for patients with type 2 diabetes Optimize medical therapy of glucose, blood pressure and lipids
Proliferative Diabetic Retinopathy	One or more of the following: • Neovascularisation • Vitreous/preretinal haemorrhage	Levels 61, 65, 71,75, 81,85: PDR, high-risk PDR, very severe or advanced PDR		Strongly consider scatter (panretinal) laser treatment, without delay for patients with vitreous haemorrhage or neovascularisation within one disc diameter of the optic nerve head Optimize medical therapy of glucose, blood pressure and lipids

* These management options are provided as general practice patterns of care. Individualized treatment plans will vary, based on several clinical considerations and factors, based on the patient's circumstances, risk factors, systemic condition, etc. There are many modifiers or risk factors not included in this classification, but which are important in risk of disease progression and in managing individual patients. These factors should be taken into account by the clinician in decision-making, and in informing the patient and primary care physician/diabetologist.

Reproduced from http://www.icoph.org/pdf/Diabetic-Retinopathy-Detail.pdf, accessed 25 September 2009

Data Analysis

Information regarding study characteristics, screening methods and all results other than the primary outcomes (see below) was tabulated and narratively summarised, using basic summary statistics where appropriate.

Details of statistical analysis of the relevance of screening accuracy findings to the Australian Indigenous context are contained in the *'Statistical Analysis of the Relevance of Screening Accuracy Findings to the Australian Indigenous Context'* section.

Results

Search and Selection

Three-hundred and sixty three titles and abstracts were identified from electronic database and reference list searching. Of these, 188 full-text articles were evaluated against the inclusion criteria and 62 studies were eligible for this review. The most frequent reason for exclusion was lack of comparison of screening method(s) to an accepted reference standard (n=59). A detailed description of search and selection metrics is contained in Figure 1.

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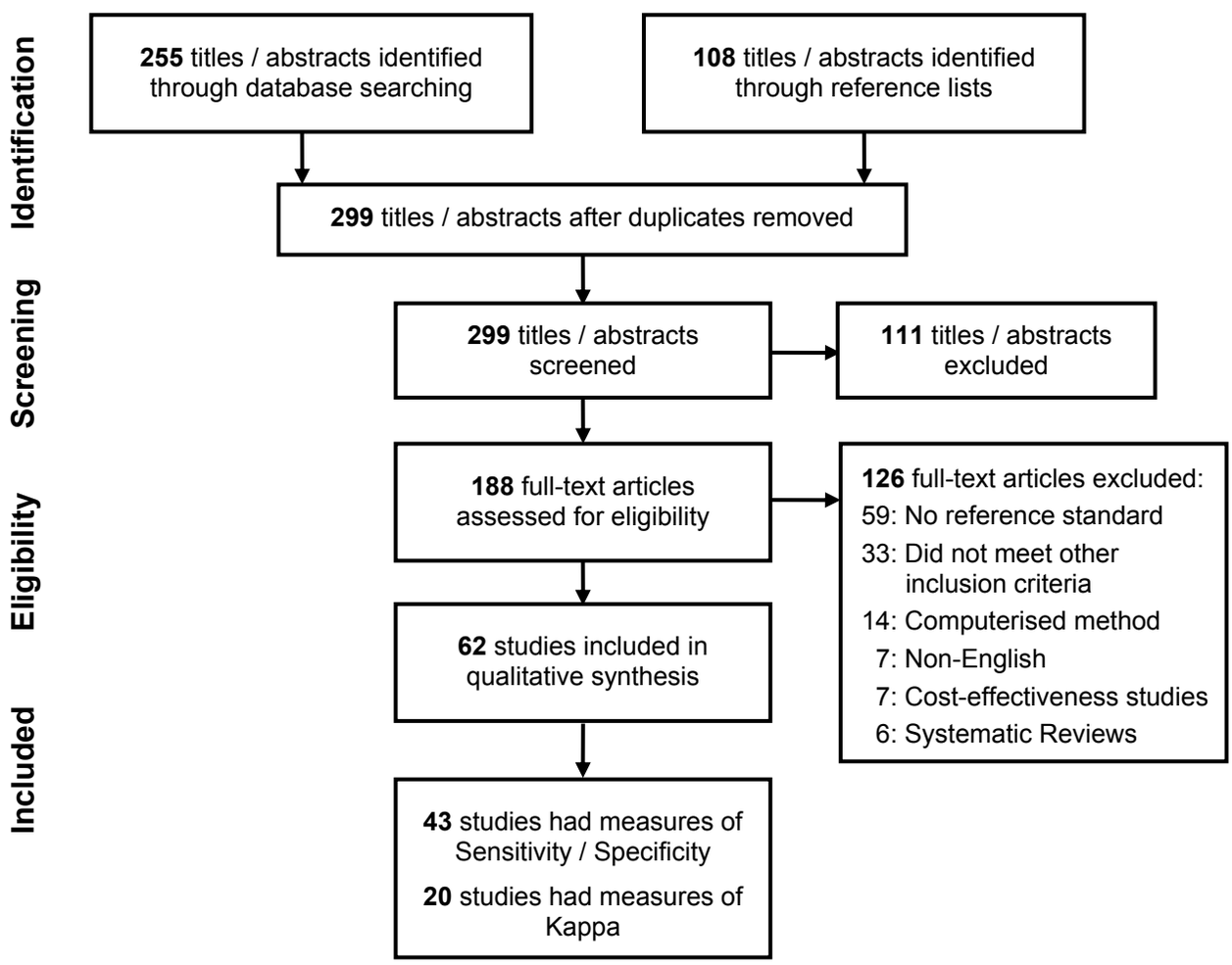

Figure 1: Study Search and Selection (based upon PRISMA Flow Diagram (Moher 2009))

Evidence Map of Screening Methods and Study Design

Table 4 categorises the eligible studies in terms of method under investigation, reference standard and study design.

Only nine of the 62 eligible studies involved outreach methods, i.e. the provision of portable infrastructure / personnel to enable a DR screening service to be provided to a population.

Over half of the included studies (n=33), including two outreach studies, investigated exclusively camera-based screening methods. Fifteen studies, including six in outreach settings, investigated a combination of camera and examination-based methods. Eleven studies investigated only examination-based methods. Two studies evaluated the effectiveness of the scanning laser ophthalmoscope and one study was based upon optician report, with no further details of screening method.

Reference standards used were predominantly examination (n=35). Sixteen studies used a camera-based method as a reference standard. One study used fluorescein angiography as a reference standard; the remaining ten studies used various combinations of these three methods.

The predominant study design was case series (n=56), with three case-control and one each of RCT, cohort and cross-sectional design.

Appendix 2 lists all included studies and identifies the primary outcomes (sensitivity / specificity, kappa) measured in each study.

A number of reviews and primary studies related to the topic but not meeting the inclusion criteria were also identified. These are summarised in Table 5 and all references listed in Appendix 3.

Results - Evidence Map

Table 4: Diabetic Retinopathy: Screening Interventions and Reference Standards by Study Design

Method Under investigation	Reference Standard	n	RCT	Cohort study	Case-control study	Cross-sectional study	Case series
Camera	Examination	15			1		14
Camera	Camera	8	1		1	1	5
Camera	Examination / Camera	6		1			5
Camera	Camera / Fluorescein Angiography	1					1
Camera	Fluorescein Angiography	1					1
Examination	Examination	8			1		7
Examination	Camera	2					2
Examination / Camera	Camera	5					5
Examination / Camera	Examination	3					3
Examination / Camera	Examination / Camera	1					1
Outreach - Examination / Camera	Examination	4					4
Outreach - Examination / Camera	Examination / Camera	2					2
Outreach - Camera	Examination	2					2
Outreach - Examination	Camera	1					1
Scanning Laser Ophthalmoscope (SLO)	Examination	2					2
Optician Report	Examination	1					1
TOTAL		**62**	**1**	**1**	**3**	**1**	**56**

Table 5: Diabetic Retinopathy: Reviews and other Primary Studies

Description of study	n
Systematic Reviews	6
Cost-Effectiveness Analyses	7
Studies investigating computerised evaluation screening methods	14
Studies relevant to outreach but not meeting review inclusion criteria	9
Non-English Studies	7
TOTAL	**43**

STUDY CHARACTERISTICS

Table 6a - Table 6c describe study setting, design, DR classification systems and referral thresholds used and demographic / diabetic characteristics of study samples.

Countries & Ethnicity

The majority of studies were conducted in the UK (20/62, 32.3%) and USA (17/62, 27.4%). Three studies were conducted in each of Australia, Canada, Germany and Spain (4.8%, total 19.0%); two each in Denmark, France and Japan (3.2%, total 9.5%); and one in Egypt, Hong Kong, India, Mexico, New Zealand, Taiwan, and The Netherlands (1.6%, total 11.3%).

Only five studies focused on specific racial populations. The patient population from these studies included Australian Aboriginal people (Diamond 1998), Cree (Maberley 2002), Indians (Mohan 1988), Oklahoma Indians (Lee 1993), Europeans (Mohan 1988) and Japanese-Americans (Kinyoun 1992).

Year of Publication

Of the 62 included studies, just over half (34) were published between 2001 and 2009, with the remainder (28) dating from 1982 to 2000.

Demographic Characteristics

Many studies did not report important information regarding demographics, referral thresholds and classification systems as indicated below.

The mean (range) of the following demographic characteristics were calculated as follows:

- sample size: 476.2 (range 11 - 4904) (reported by 56 studies)
- number of eyes: 453.21 (25 - 3356) (33)
- percentage male:55.8 (31 - 98.4) (37)
- age (years): 55.1 (35.3 - 69.6) (33)

- duration of diabetes(years): 11.3 (3.7 - 22) (26)
- percentage glycosylated haemoglobin in sample: 7.9 (7 - 9.8) (11)
- systolic / diastolic blood pressure (mmHg): 136.7 / 78.2 (121.7 - 151 / 70.1 - 85) (6)
- cholesterol level (mg/dl): 222.6 (1)

Most of the included studies (37 studies; 59.7% of eligible studies) did not report on the type of diabetes mellitus in their study samples. Of those that did report this information, study samples comprised mainly a combination of Type 1 and 2 diabetics (n=18, 29% of eligible studies). Five studies (8.1%) comprised only Type 2 diabetics; two studies (3.2%) included Type 2 diabetics and non-diabetics.

Classification System

A total of 13 different classification systems were used in defining the levels of DR, with the majority using that of the ETDRS (16 studies, 25.8% of eligible studies) and the modified version of AHC (8, 12.9%). Other classification systems used were:

- European Working Party (EWP) (3, 4.8%)
- EURODIAB (2, 3.2%)
- Field Guide Book (2, 3.2%)
- Airlie House Classification (AHC), ALFEDIAM (France), ICDR Severity Scale, modified version of the ETDRS, modified version of the Wisconsin Grading System, NHMRC Guideline, UK National Screening Program, and Wirral Diabetes Eye Study (one study each, 1.6%, total 12.7%).

Two studies used multiple classification systems, with one being both ETDRS and WCDRS, and the other being the modified version of the AHC and ETDRS. Of the remaining studies, one study was on photo quality and 20 studies (32.3%) did not report which classification system was used.

Referral Threshold Definitions

Thirty-two studies (51.6%) did not explicitly define ‘referrable DR’ for the purpose of their study. Of the 30 that did state a definition, 22 studies (35.5% of eligible articles) used ‘early’ referral thresholds (e.g. macular oedema, (Early Treatment Diabetic Retinopathy Study (ETDRS) level ≥ 35) whereas eight studies (12.9%) employed ‘late’ referral thresholds (e.g. ETDRS ≥ 53).

Prevalence of DR in study samples

Twenty-six studies reported DR prevalence in their study sample. The mean prevalence of DR (all levels) across these studies was 37.3% (range 9 - 83).

Outreach Studies

Five of the nine studies in outreach settings (highlighted in bold and italicised in Tables 6a – 6c) were conducted in the UK (Gloucestershire, Newcastle, Tayside, Liverpool, and one location not was reported) and one each in Canada (Ontario), USA (Wisconsin), Australia (Pilbara) and Japan (Fukushima). The studies were published between 1985 and 2003.

Demographic characteristics (mean, range, number of articles reporting) of outreach studies are summarised below:

- sample size: 925.8 (100 – 3611), reported by 9 studies
- number of eyes: 264 (200 – 328) (2)
- percentage male: 45.8 (31 – 67.5) (3)
- age (years): 51.4 (48.2 – 60.2) (5)
- duration of diabetes (years): 9 (7.5 – 10.5) (2)
- percentage glycosylated haemoglobin in sample: 8.1 (8 – 8.2) (2)
- systolic / diastolic blood pressure (mmHg): 134.5 / 77 (128 – 141 / 74 – 80) (2)
- cholesterol level (mg/dl): not reported by any outreach studies

Only one study (Shiba 2002) reported on the type of diabetes mellitus in their study sample; this study contained 93 Type 2 diabetics and 62 Type 1 diabetics.

Classification systems used in the outreach studies were specified by five of the nine studies. These were EWP (2), AHC (2) and ETDRS (1). Only four of the nine studies explicitly defined ‘referrable DR’. Two used ‘early’ referral thresholds (Macular Oedema) and two used ‘late’ referral thresholds (Severe NPDR, STDR).

Only two studies reported DR prevalence; Maberley (2002) reported a DR prevalence of 40% and Diamond (1998) 59.5%.

Table 6a: Study Characteristics: Studies with an 'Early' Diabetic Retinopathy Referral Threshold (n=22)

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Siu (1998)	Hong Kong (Causeway Bay)	Case series	Diabetic clinic	NR: Any DR	153	51	55.9 (23 -79)	NR	3.7 (0 - 21)	NR	No DR: 77.0% DR: 15.0%
Prasad (2001)#	UK	Case series	Diabetic clinic	Wirral Diabetes Eye Study: Bkgd DR + Maculo.	4904	52.8	< 16 yrs = 32 16-64 = 2268 > 64 = 2604	NR	NR	NR	NR
Hammond (1996)	UK (Cambridge-shire)	Case series	General practice	NR: ≥ moderate Bkgd DR	237 (474)	NR	NR	NR	NR	NR	Bkgd. DR: 26.0% Maculo.: 13.0%
Scanlon (2003a)	***UK (Gloucester -shire)***	***Case series***	***General practices***	***EWP: ≥ Maculopathy (3)***	***3611***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***
Murgatroy d (2004)	UK	Case series	Diabetes clinic	UK National Screening Program: Maculo., PDR or Pre-PDR	398 (794)	57	Median: 63	NR	9.3	NR	No DR: 61.3% Bkgd. DR: 12.7% Maculo.: 20.4% Pre-PDR/PDR: 4.7%
O'Hare (1996)	***UK***	***Case series***	***Primary care centre***	***NR: ≥ Maculopathy (2B)***	***1010***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***
Verma (2003)	India (New Delhi)	Case series	Ophthalmic clinic	NR: Maculo., Sev NPDR or PDR (STDR)	200 (400)	63	53.1 (20 - 81)	T1DM: 4% T2DM: 96%	10.9 (1.5mo-39)	NR	NR
Warburton (2004)	UK (Stockport)	Case series	NR (locally developed criteria)	NR: Maculopathy (STED)	3510	NR	NR	NR	NR	NR	Bkgd. DR: 16.2% Pre-PDR: 1.7% Maculo.: 3.3% PDR: 0.7% STED = 5.7%
Hulme (2002)	UK (St. Helens / Knowsley)	Case series	Diabetic screening program	NR: Maculopathy	439 (872)	NR	NR	NR	NR	NR	No DR: 556/872 Bkgd. DR: 258/872 Pre-PDR: 9/872 PDR: 11/872 Maculo.: 38/872
Phiri (2006)	Australia (East Melbourne)	Case series	Hospital outpatient clinic	Mod. Wisconsin Grading System: ≥ Mild NPDR (30)	196 (298)	Photos: 57 No photos: 54	Photos: 68.5 (10.1) No photos: 70.6 (9)	NR	Photos: 12.3 (7.7) No photos: 12.3 (7.2)	NR	No DR: 34.0% NPDR: 8.0% Mild/Sev. NPDR: 33.0% ME: 12.0% PDR: 0.7%

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Hansen (2004)	Denmark (Gentofte)	Case series	Diabetic clinic	ETDRS: ≥ Mild NPDR (35)	83 (165)	60	47 (11.2, 25 - 70)	T1DM: 73% T2DM: 27%	22 (11.8, 1 - 53)	NR	NR
Lin (2002)	USA Oakland)	Case series	Medical health centre	Mod. AHC & ETDRS: ≥ Mild NPDR (35)	197	58	NR	Mixed	NR	NR	NR
Boucher (2003)#	Canada (Montreal)	Case series	Hospital	ETDRS: ≥ Mild NPDR (35) WCDRS: ≥ Mild NPDR (2b)	98 (196)	47	59.9 (12.2, 26 - 92)	Mixed	NR	NR	Very mild/more sev. DR: 63.3% Mild/worse disease: 53.1% Sev. NPDR/PDR: 7.1%
Massin (2003)#	France (Paris)	Case series	Hospital-based DR unit	ETDRS: MoNPDR	74 (147)	62	52 (25 - 74)	T1DM: 11 T2DM: 63	8 (0 - 23)	NR	CSME: 12 eyes
Olson (2003)	UK	Case series	Diabetic clinic	ETDRS (Examination): MoNPDR	586	65	56.5 (15.9 - 85.4)	T1DM: 17.6% T2DM: 82.1% Secondary Diabetes: 0.3%	NR	NR	NR
Pugh (1993) #	USA (Texas)	Case series	Hospital outpatient clinic & Medical care centre	Mod. AHC: MoNPDR	352	76	NR	T1DM: 5 T2DM: 347	9.8	NR	NR
Molina Fernandez (2008)	Spain	Case series	Primary health centre	Mod. ETDRS: MoNPDR	NR (352)	NR	65.4 (9.9)	T2DM	NR	NR	Any DR: 28.7% Mild DR: 12.7% MoDR: 13.9% Sev. DR: 1.8% Very sev. DR: 0.3%
Cavalleran o (2005) #	USA (Boston)	Cohort (prospe-ctive)	Diabetes clinic	ETDRS: ≥ MoNPDR (43) JVN	52 (104)	56	47.7 (18 - 80)	T1DM: 19 T2DM: 33	11.5 (1.5 - 3.8)	**HbA1c:** 7.4	No DR: 63.4% Mild NPDR: 32.7% MoNPDR: 2.9% Ungradable: 1% ME: 1% CSME: 1%

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Massin (2005) #	France (Paris)	Case control	GP practice	ALFEDIAM: Moderate NPDR	882: Mtd A: 456 RS: 426	Mtd A: 62.6 RS: 62.1	Mtd A: 60.5 (12.8) RS: 60.8 (13.6)	Mixed	Mtd A: 6.4 (6.6) RS: 8.1 (8)	**HbA1c:** Mtd A: 7.6 (4.4) RS: 7.8 (1.8)	No DR: 89.6% DR: 10.4% Ungradable: 0%
Liesenfeld (2000)	Germany (Munich)	Case series	Hospital	Field Guide Book: MoNPDR	129	45	46.6 (17.5)	T1DM: 48% T2DM: 52%	9.9 (8.2)	**HbA1c:** 8.4 (1.9)	NR
Scanlon (2003b)	UK (Oxford / Norwich)	Case series	Diabetic clinic	EWP: ≥ Maculopathy (3) Mod. AHC: ≥ MoNPDR (43)	239	NR	NR	NR	NR	NR	NR
Friberg (2003)	USA	Case series	NR	NR: Clinically relevant macular exudation or PDR and wet macular degeneration	74	NR	NR	NR	NR	NR	*Previous PRP (eyes):* NVD + more PRP: 2 Stable post-PRP: 24 CSME: 2 *No previous PRP:* No DR: 12 Bkgd. DR: 18 Pre-PDR: 2 PDR: 4 CSME: 10

Key: # includes ungradable photos, Outreach studies in bold & italicised

Adv. DED: Advanced Diabetic Eye Disease
AHC: Airlie House Classification
Bkgd: Background
(s/d)BP: (systolic/diastolic) Blood Pressure
CSME: Clinically Significant ME
CWS: Cottonwool Spots
DM(T1/2): Diabetes Mellitus (Type 1/Type 2)
ETDRS: Early Treatment DR Study
EWP: European Working Party
Haem.: Haemorrhage
HbA1c: Glycosylated haemoglobin
GP: General Practitioner
HRC: High-risk characteristic
IOP: Intraocular pressure
JVN: Joslin Vision Network
MA: microaneurysm
Maculo.: Maculopathy
ME: Macular Oedema
Mtd: Method
NPDR: Non-PDR
NR: Not Reported
NVD: Neovascularisation of the disc
NVE: Neovascularisation elsewhere
mo: months
Mo: Moderate
PDR: Proliferative DR
Prev.: previous
PRP: Pan-Retinal Photocoagulation
Pts: patients
SD: Standard Deviation
Sev.: Severe
STDR: Sight-Threatening DR
STED: Sight-Threatening Eye Disease
VA: Visual Acuity
WCDRS: Welsh Community DR Study
yrs: years

Table 6b: Study Characteristics: Studies with a 'Late' Diabetic Retinopathy Referral Threshold (n=8)

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Bursell (2001)	USA (Boston)	Case series	Diabetic clinic	ETDRS: Sev. NPDR	54 (108)	57	48 (15.2, 20 - 75)	Mixed	17.7 (9.3,3-42)	NR	NR
Fransen (2002)	USA (Oklahoma)	Case series	Primary health centre	ETDRS: ≥ Sev. NPDR (53)	290	44.1	< 30 yrs = 2.1% 30-49 yrs = 25.9% > 49 yrs = 72.1%	NR	< 10 = 66.6% 10-19 = 29% > 19 = 3.1%	NR	DR & / or Maculo.: 19.3%
Pandit (2002)^	***UK (Newcastle)***	***Case series***	***Diabetic clinic***	***EWP: Sev. NPDR***	***609:*** ***HSP: 305*** ***DSP: 304***	***NR***	***58.8 (15.8)***	***NR***	***NR***	***HbA1c: 8.2 (1.6)*** ***sBP: 141 (23)*** ***dBP: 80 (12)***	***No STDR: 550 pts*** ***STDR: 56*** ***Poor Fundus view: 3*** ***Not screened: 0***
Bibby (1992)^	Scotland (Glasgow)	Case control	Hospital outpatient clinic (retrospective review)	NR: Pre-PDR	115	NR	NR	NR	NR	NR	NR
Taylor (1999)	UK (Exeter)	Case series	General practice	ETDRS: STDR	118	44	< 40 = 11 40 - 49 = 7 50 - 59 = 14 60 - 69 = 40 70 - 79 = 40 > 80 = 6	NR	0 - 5 = 26 6 - 10 = 42 11 - 20 = 30 > 20 = 2	NR	NR
Burns-Cox (1985)	UK (Bristol)	Case series	Ophthalmic hospital	NR: STDR	Study 1: 243	NR	NR	NR	NR	NR	NR

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Leese (2002)	***UK (Tayside)***	***Case series***	***Hospital***	***NR: STDR***	***408***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***
Baeza (2009)	Spain	Cross Section	Primary health centre	Field Guide Book: STDR	216 (432)	43.7	68.5 (10.5)	T1DM: 10% T2DM: 90%	12.8 (8.9)	**HbA1c:**7.97 (1.68) Prev. History of Hypertension: 75% Prev. History of hyperlipidaemia: 65%	No DR: 57% STDR: 14.3% MoDR: 26.9% MoDR, no ME: 4.4% Pre-PDR: 5.1% PDR: 4.7% Adv. DED: 0.9% ME: 5.8%

Key: ^ Includes poor fundus view, Outreach studies in bold & italicised

Adv. DED: Advanced Diabetic Eye Disease
AHC: Airlie House Classification
Bkgd: Background
(s/d)BP: (systolic/diastolic) Blood Pressure
CSME: Clinically Significant ME
CWS: Cottonwool Spots
DM(T1/2): Diabetes Mellitus (Type 1/Type 2)
ETDRS: Early Treatment DR Study
EWP: European Working Party
Haem.: Haemorrhage
HbA1c: Glycosylated haemoglobin
GP: General Practitioner
HRC: High-risk characteristic
IOP: Intraocular pressure
JVN: Joslin Vision Network
MA: microaneurysm
Maculo.: Maculopathy
ME: Macular Oedema
Mtd: Method
NPDR: Non-PDR
NR: Not Reported
NVD: Neovascularisation of the disc
NVE: Neovascularisation elsewhere
mo: months
Mo: Moderate
PDR: Proliferative DR
Prev.: previous
PRP: Pan-Retinal Photocoagulation
Pts: patients
SD: Standard Deviation
Sev.: Severe
STDR: Sight-Threatening DR
STED: Sight-Threatening Eye Disease
VA: Visual Acuity
WCDRS: Welsh Community DR Study
yrs: years

Table 6c: Study Characteristics: Studies with No Reported Diabetic Retinopathy Referral Threshold (n=32)

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Maberley (2002)	***Canada (Ontario)***	***Case series***	***Diabetic screening program (Cree patients)***	***AHC***	***100 (200)***	***31***	***54.6 (13.66, 24 - 82)***	***NR***	***NR***	***NR***	***No DR: 60.0% eyes MA only: 9.0% Mo/Sev. NPDR: 28.5% PDR: 2.5% CSME: 5.0%***
Herbert (2003)~	UK (Cambridge-shire)	Case series	Hospital	ETDRS	NR / 145 analysed	NR	NR	T1DM: 27% T2DM: 73%	NR	NR	DR: 26% eyes STDR: 3% eyes
Kinyoun (1992)	USA	Case series	Community Diabetes Study (Japanese-American patient)	ETDRS	393: T2DM: 124 C: 269	NR	T2DM: 62 (45- 74) C: NR	T2DM: 124 C: 269	T2DM: 6 (0 - 29) C: NR	NR	ME + ≥1 MA: 11 pts Haem. & MA<DR: 31 Haem. & MA>DR: 21
Kinyoun (1989)%	USA	Case series	NR	ETDRS	NR (3356)	NR	NR	NR	NR	NR	NR
Lopez-Bastida (2007)	Spain	Case series	Primary care centres	ETDRS	773 (1546)	48	Median: 50.8	T1DM: 30.5% T2DM: 69.5%	9.8	NR	No DR: 57.6% Bkgd. DR: 32.9% STDR: 9.6%
Mohan (1988)	UK (Ealing)	Case series	Diabetic clinic (Indian & European patients)	ETDRS	85 (170): Indian: 45 European: 40	Indian: 73 European: 58	Indian: 54.9 European: 62.1 (p < 0.01)	NR	Median: Indian: 8 European: 12	**BP:** Hypertension present (patients): Indian: 10 European: 12	Indian: No DR: 40 eyes DR: 41 Ungradable: 7 pts European: No DR: 31 eyes DR: 45 Ungradable: 3 pts
Moss (1985)	***USA (Wisconsin)***	***Case series***	***NR***	***ETDRS***	***1949***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Neubauer (2008a)	Germany (Erfurt / Munich)	RCT	Hospital outpatient clinic	ETDRS	64 (128)	62	60 (12)	T2DM: 86%	NR	**HbA1c:** 7.5 (1.4) **sBP**: 136.4 (17.6) **dBP**: 80.3 (8.9)	No / Mild DR (ETDRS ≤ 20): 20% Some degree of ME: 71% CSME: 41%
Rudnisky (2002)~	Canada	Case series	NR	ETDRS	120 (232)	60.6	Median: 60.2 (34 - 87)	T1DM: 16.5% T2DM: 83.5%	Median: 11.4 NR (1mo - 38)	NR	NR
Lawrence (2004)	USA (Minneapolis)	Case series	Diabetic clinic	ETDRS: Clinical examination: Retinopathy severity level 2-7 or hard exudates	254 (508): Mtd A: 151 Mtd B: 103	98.4: Mtd A: 98.7 Mtd B: 98.1	67.5: Mtd A: 67.9 Mtd B: 66.6	NR	12.4 (0 - 58): Mtd A: 11.2 (0 - 58) Mtd B: 14 (1 - 51)	**HbA1c:** 9.76 Mtd A: 9.6 Mtd B: 10	No DR: 37.4% DR question.: 5.7% MA: 11% Mild NPDR: 23.4% MoNPDR: 10.4% Mo.Sev.NPDR: 3.3% Sev. NPDR: 1.2% Mild PDR: 1% MoPDR: 1.8% PDR + HRC: 1% Ungradable: 3.7%
Ahmed (2006)	USA (Washington D. C.)	Case series	Health care centre	Mod. AHC	244 (482)	55	60 (11.3)	T1DM: 239 T2DM: 5	8.9 (6.4, 1mo - 24)	**HbA1c:** 7.5 (0.8)	No DR: 73% DR: 13% Not CSME: 10% CSME: 1.6% Ungradable: 21%
Gonzalez (1995)	Mexico (Mexico City)	Case series	NR	Mod. AHC	15 (30)	47	M: 59.6 (4.2), F: 55.1 (5.7)	T2DM	M: 18 (6.9) F: 16.6 (5.7)	**sBP:** M: 128.5 (31.4) F: 114.9 (15.7) **dBP:** M: 73.8 (13) F: 72.3 (7.1) **Cholesterol (mg/dl):** M: 201.1 (36.6) F: 244 (46.7)	NR
Harding (1995)	***UK (Liverpool)***	***Case series***	***Community health centres & hospital***	***Mod. AHC***	***326***	***NR***	***60.2***	***NR***	***NR***	***NR***	***NR***

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Kleinstein (1987)	USA	Case series	NR	Mod. AHC	14 (25)	50	NR (18 - 79)	NR	14.2 (3 - 23)	NR	No DR: 8 eyes Bkgd. DR: 6 Mo.Sev. NPDR: 7 Pre-PDR: 1 PDR no HRC: 1 ME: 1
Lee (1993)	USA (Oklahoma)	Case series	NR (Indian patients)	Mod. AHC	410 (795)	33	60.3 (8.4)	T2DM	17.3 (5.3)	NR	NR
Penman (1998)	Egypt (Cairo)	Case series	Population-based survey	Mod. AHC	456	35	53.7 (20 - 85)	NR	NR	**HbA1c:** 38% of sample ≥ 10%	No DR: 75% Non-STDR: 18% STDR: 1%
Peters (1993)~	USA	Case series	Diabetes program	Mod. AHC	522 (1044)	47	50.6	T1DM: 91 T2DM: 431	7	NR	NR
Kuo (2005)	Taiwan	Case series	Hospital	EURODIAB	100 (200)	61	59 (31 - 88)	NR	NR	NR	No DR: 49.0% Bkgd. DR: 24.5% Pre-PDR: 16.0% PDR or post-photocoag: 10.5% Ungradable: 0%
Moller (2002)	Denmark (Odense)	Case series	Ophthalmic hospital	EURODIAB	23 (44)	65	54.4 (25 -75)	T1DM: 13 T2DM: 10	NR (8 - 39)	NR	NR
Neubauer (2008b)	Germany (Munich)	Case series	Outpatient clinic	ICDR Severity Scale	51 (51)	NR	60 (12.1, 24 - 75)	NR	11 (10.1, 3 - 40)	**HbA1c:** 7.0 (1.3)	No DR: 18% Mild NPDR: 10% MoNPDR: 37% Sev. NPDR: 28% PDR: 8% No ME: 24% Mild ME: 22% MoME: 33% Sev. ME: 22% Not CSME: 39% CSME: 61%

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Schmid (2002)	Australia (Queensland)	Case series	University optometry clinic	NHMRC Guideline	10 patients & 12 retinal photographs	NR	NR (47 - 75)	NR	NR	NR	NR
Aiello (1998)	USA (Boston)	Case series	Diabetic clinic	NR	18: DM: 16 C: 2 (36)	67	NR (25 - 68)	NR	NR (8 - 48)	NR	NR
Diamond (1998)	***Australia (Pilbara)***	***Case series***	***Aboriginal communities***	***NR***	***164 (328)***	***39***	***48.2 (16 – 81)***	***NR***	***7.5 (1 – 35)***	***NR***	***DR & Maculo.: 26.8% pts, 22.6% eyes DR: 59.5% eyes***
Heaven (1992)	UK (Cosham)	Case series	Diabetic clinic	NR	100 (200)	NR	NR	NR	NR	NR	NR
Jones (1988)	UK	Case series	Diabetic clinic	NR	NR (127)	NR	NR	NR	NR	NR	No DR: 32 Bkgd. DR: 25 ME: 2 Pre-PDR: 5 PDR: 0
Lienert (1989)	New Zealand (Christchurch)	Case series	Diabetic clinic	NR	500 (1000)	52	52.6 (0 - 100)	Mixed	M: 10.6 (0-45) F: 11.6 (0-45)	**sBP:** M: 149, F: 153 **dBP:** M: 85, F: 85	No DR: 51.9% eyes Bkgd.DR & MA: 23.0% Bkgd. DR, MA & other lesions: 18.4% Pre-PDR: 3.6% PDR: 2.4% Adv. DR: 0.7% No maculo.: 92.9% Thr. maculo.: 5.6% Maculopathy: 1.4%
Nathan (1991)	USA (Boston)	Case series	Diabetic clinic	NR	67 (133)	NR	T1DM: 30.8 (10.7) T2DM: 58.2 (10.9)	T1DM: 38 T2DM: 29	T1DM: 16.7 (9.6) T2DM: 11.8 (6.6)	**BP:** Hypertension present: T1DM: 15.8% T2DM: 58.6%	No / insig. DR: 30% Min. NPDR: 31.3% Extensive NPDR / Pre-PDR/ME: 23.9% PDR: 14.9%
Reenders (1992)	The Netherlands (Hoogeveen)	Case series	General practices	NR	252	NR	NR	T2DM	NR	NR	DR: 9%

Citation	Country (Region)	Study Design	Setting	Classification System: Threshold (≥ level, if specified)	n (n eyes)	% Male	Age Mean (SD, Range)	Type of DM	Yrs diabetic Mean (SD, range)	HbA1c (%) BP (mmHg) Lipids (nmol/l) Mean (SD)	DR findings
Shiba (2002)	***Japan Gp 1: NR Gp 2: Fukushima***	***Case series***	***Gp 1: Outpatient clinic Gp 2: Summer camp***	***NR***	***Gp 1: 94 Gp 2: 61***	***Gp 1: 89 Gp 2: 46***	***Gp 1: 56 (8) Gp 2: 14.5 (3)***	***Gp 1: T1DM: 1, T2DM: 93 Gp 2: T1DM***	***Gp 1: 14 (11) Gp 2: 7 (4)***	***HbA1c: Gp 1: 8 (1), Gp 2: 7.9 (1.4) sBP: Gp 1: 128 (20), Gp 2: NR dBP: Gp 1: 74 (9) Gp 2: NR***	***Gp 1 (44 eyes): [Severity Scale (SD): 0=none, 1=very mild, 2=mild, 3=moderate] Collage / 3 x 3 form: 1.1 (1.1) / 1.0 (1.1)***
Sussman (1982)	USA	Case series	Hospital	NR	11 (438): DM: 10, C: 1	NR	NR	NR	NR	NR	PDR: 33.3% eyes
Williams (1986)	UK	Case series	Diabetic clinic	NR	62 (120)	NR	NR	NR	NR	NR	*DR detected:* Method A: 58.0% Method B: 58.0% RS: 60.0% *Maculo.:* Method B: 32 eyes
Shiba (1999)	Japan (Tokyo)	Case control	NR	NA - Photo quality study	38: DM: 16, C: 22	DM: 81 C: NR	DM: 54.8 (9.1, 34 - 68) C: NR (20 - 59)	T1DM: 1 T2DM: 15	10.6 (5.8, 2-22)	**HbA1c:** 7.8 (1.4) **sBP:** 142 (19) **dBP:** 80 (12)	NR

Key: ~ Patients were referred; % Patients already has either NPDR or early PDR<HRC +/- ME, Outreach studies in bold & italicised

Adv. DED: Advanced Diabetic Eye Disease
AHC: Airlie House Classification
Bkgd: Background
(s/d)BP: (systolic/diastolic) Blood Pressure
C: Control
CSME: Clinically Significant ME
CWS: Cottonwool Spots
DM(T1/2): Diabetes Mellitus (Type 1/Type 2)
ETDRS: Early Treatment DR Study
EWP: European Working Party
Haem.: Haemorrhage
HbA1c: Glycosylated haemoglobin
GP: General Practitioner
Gp: Group
HRC: High-risk characteristic
Insig.: Insignificant
IOP: Intraocular pressure
JVN: Joslin Vision Network
MA: microaneurysm
Maculo.: Maculopathy
ME: Macular Oedema
Mtd: Method
NA: Not applicable
NPDR: Non-PDR
NR: Not Reported
NVD: Neovascularisation of the disc
NVE: Neovascularisation elsewhere
mo: months
Mo: Moderate
PDR: Proliferative DR
Prev.: previous
PRP: Pan-Retinal Photocoagulation
Pts: patients
SD: Standard Deviation
Sev.: Severe
STDR: Sight-Threatening DR
STED: Sight-Threatening Eye Disease
Thr.: threshold
VA: Visual Acuity
WCDRS: Welsh Community DR Study
yrs: years

SCREENING METHODS

Table 7, 8, and Table 9a - c detail the screening methods used in eligible studies.

Screening Methods Investigated

A total of 122 screening methods were investigated in the 62 included studies. Thirty of the 62 studies investigated one screening method, 19 studies investigated two methods, and the remaining 13 investigated three or more screening methods.

Table 7 summarises all screening methods in terms of instrument and use of pharmacological mydriasis. The most frequent combinations of these two variables were mydriatic fundoscopy (n=31), non-mydriatic digital camera (n=22), and mydriatic digital camera (n=16).

Table 7: Screening Methods Investigated from Included Studies (n=122)

Instrument / Mydriasis	Digital Camera	Film Camera	Polaroid Camera	Fundoscopy	SLO	Camera (type unspecified)	Digital Camera and Fundoscopy	Polaroid Camera and Fundoscopy	Other	NR	Total
Mydriatic	16	10	3	31		1	1	4			**66**
Non-Mydriatic	22	7	8	2	2	2					**43**
Mixed Mydriatic / Non-Mydriatic	3										**3**
NR		4		2		1			1	2	**10**
Total	**41**	**21**	**11**	**35**	**2**	**4**	**1**	**4**	**1**	**2**	**122**

Key: SLO: Scanning Laser Ophthalmoscope

Outreach screening methods

The majority of screening methods (107) were conducted in static settings (e.g. hospital department, ophthalmological practice). Only 16 screening methods across nine studies involved outreach (i.e. the provision of portable infrastructure / personnel to enable a DR screening service to be given to a population). These outreach methods are summarised in terms of instrument and use of pharmacological mydriasis in Table 8.

Table 8: Screening Methods Investigated in Outreach Settings (n=16)

Instrument / Mydriasis	Digital Camera	Film Camera	Polaroid Camera	Fundoscopy Exam	Digital Camera with Fundoscopy	Polaroid Camera with Fundoscopy	Total
Mydriatic		1	2	3	1	3	**10**
Non-Mydriatic	2	1	2				**5**
Mixed Mydriatic / Non-Mydriatic	1						**1**
Total	**3**	**2**	**4**	**3**	**1**	**3**	**16**

Photo Fields

Of the 87 screening methods that involved photography, 32 photographed one-field, 8 photographed two-fields, 14 photographed three-fields (in three cases, these three fields were used to create six fields), and five each photographed five, seven and nine-fields. The number of photo fields was not reported for 18 screening methods.

Table 9a – 9c contain a detailed description of all screening methods outlining camera type, make / model, number and degree of fields taken, resolution / type of film, details of fundoscopy equipment and technique, use of mydriasis, location of screening and (if camera) interpretation of image, and qualifications and training of imager and interpreter.

Studies using camera-based reference standards (n=16) are listed in Table 9a; those with examination-based reference standards (n=39) in Table 9b and those using multiple reference standards (n=7) in Table 9c.

Table 9a: Screening Methods: Studies with a Camera (Digital, Polaroid or Film) as the Reference Standard (n=16)

Citation	Clinical Examination: Screening Method (n, n eyes) Instrument Mydriatic / Non-mydriatic Location Clinician	Camera: Screening Method (n, n eyes) Instrument; n fields; resolution Mydriatic / Non-mydriatic Location of Photo / Interpreter Photographer / Interpreter	
Baeza (2009)	***Reference standard*** (216, 432 eyes) Film: Topcon CRW6S; 7 x 30° Mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist	***Method under investigation A*** (216, 432 eyes) Film: Topcon CRW6S; 1 x 45° (macula) Non-mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist	***Method under investigation B*** (216, 432 eyes) Film: Topcon CRW6S; 2 x 45° (macula/disc) Non-mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist
Baeza (2009) cont...		***Method under investigation C*** (216, 432 eyes) Film: Topcon CRW6S; 3 x 45° (macula/disc/above macula) Non-mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist	***Method under investigation D*** (216, 432 eyes) Film: Topcon CRW6S; 1 x 45° (macula) Mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist
Baeza (2009) cont...		***Method under investigation E*** (216, 432 eyes) Film: Topcon CRW6S; 2 x 45° (macula/disc) Mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist	***Method under investigation F*** (216, 432 eyes) Film: Topcon CRW6S; 3 x 45° (macula/disc/above macula) Mydriatic Primary Care Centre / NR Primary Care Physician / Ophthalmologist
Bursell (2001)	***Reference standard*** (54, 108 eyes) Film: Zeiss FF4, 35mm Kodachrome 64 film; 7x30° Mydriatic Diabetes Centre / Reading Centre (onsite) NR	***Method under investigation A*** (54, 108 eyes) Digital: Topcon TRC NW5S; 3x45°; 640x480p Non-mydriatic Diabetes Centre / Reading Centre (onsite) NR / Two independent Graders (+ adjudicator)	
Fransen (2005)	***Reference standard*** (290) Film: Zeiss FF450, 35mm, stereoscopic; 7x30° Mydriatic Primary Care Clinic / Reading Centre (offsite) Certified Photographer / Non-Phys. trained graders x2 (indep.)	***Method under investigation A*** (290) Digital: Kodak DCS520, stereoscopic; 7x30°; 1152x1152p Mydriatic Primary Care Clinic / Reading Centre (offsite) Certified Photographer / Non-Phys. trained graders x2 (indep.)	
Gonzalez (1995)	***Reference standard*** (15, 30 eyes) Film: Topcon 50x, Ektachrome ASA 100; 7 std. field; stereo. Mydriatic NR / Fundus Photo Reading Centre (University) Ophthalmologist x 2 / Certified graders (Indep.)	***Method under investigation A*** (15, 30 eyes) Film: Topcon 50x, Ektachrome ASA 100; 7 std. field; stereo. Mydriatic NR / Retinal Specialist location Ophthalmologist x 2/ Retinal Specialist x 11	
Hansen (2004)	***Reference standard*** (83, 165 eyes) Film: Canon CF-60UVI, 35mm Ektachrome 64 film; 7 field Mydriatic Hospital Ophthalmological Department / same location Trained Photographer / NR	***Method under investigation A*** (83, 165 eyes) Digital: Topcon NW6S; 5x45°; 1450x1026p Non-mydriatic (Physiological dilation) Hospital Ophthalmological Department / same location Trained Photographer / NR	***Method under investigation B*** (83, 165 eyes) Digital: Topcon NW6S; 5x45°; 1450x1026p Mydriatic Hospital Ophthalmological Department / same location Trained Photographer / NR
Hansen (2004) cont...		***Method under investigation C*** (59) Digital: Topcon NW6S; 5x45° non-stereo.; 1450x1026p Non-mydriatic Optician shop / Hospital Ophthalmological Department Optician / NR	

Citation	**Clinical Examination:** **Screening Method (n, n eyes)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n, n eyes)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Kleinstein (1987)	***Reference standard*** (14, 25 eyes) Camera: stereoscopic; 7 field NR NR Photographer x 2 / Retinal Specialist	***Method under investigation A*** (14) Fund.: Direct + / or indirect Mydriatic NR Optometrist (university) x 11	***Method under investigation B*** (14) Fund.: Direct + / or indirect Mydriatic NR Optometrist (community) x 8
Lin (2002)	***Reference standard*** (197) Film: Zeiss FF4, Ektachrome film; 7x30° Mydriatic Medical Centre / Reading Centre (remote) Trained Photographers / Trained Grader	***Method under investigation A*** (197) Digital: Canon CR5 45NM; 1x45° (fovea / disk); 640x480p Non-mydriatic Medical Centre / Reading Centre (remote) Research Associate / Trained Grader	***Method under investigation B*** (197) Fund.: Indirect & Slit-lamp biomicroscopy (90D) Mydriatic Medical Centre Ophthalmologist x 9
Massin (2003)	***Reference standard*** (74 + 110 in second series) Film: Canon CF 60 UV, 35mm film; 7 field Mydriatic Hospital Diabetic Retinopathy Clinic / Reading Centre Certified Photographer / Retinal Specialist x 3 (indep.)	***Method under investigation A*** (74 + 110 in second series) Digital: Topcon TRC-NW6S; 5x45°; 800x600p Non-mydriatic Hospital Diabetic Retinopathy Clinic / Reading Centre Ophthalmologist, Nurse or Orthoptist / Retinal Sp. x 3 (indep.)	***Method under investigation B*** (74 + 110 in second series) Fund.: NR Mydriatic Hospital Diabetic Retinopathy Clinic Retinal Specialist
Moller (2002)	***Reference standard A***(19, 36 eyes) Film: Topcon FD31, Ektachrome 64 ASA film, & F. Angio.; 7x30° NR NR NR / Ophthalmologist x3 (Indep.; Consensus / Results of RS B)	***Reference Standard B*** (19, 36 eyes) F. Angio. NA NR NR / Investigators in plenum	***Method under investigation A*** (19, 36 eyes) Film: Canon CF60, Ektachrome 64 ASA film; 1x60° NR Hospital Clinic NR / Ophthalmologist x2 (Indep.; consensus)
Moss (1985)	***Reference standard (1949)*** ***Camera: 7 std. field*** ***Mydriatic*** ***Outreach (mobile van) / Reading Centre*** ***Ophth., Trained Opto., Tech/Trained Grader***	***Method under investigation A (1949)*** ***Fund.: Direct (& if required, indirect)*** ***Mydriatic*** ***Outreach (mobile van)*** ***Ophthalmologist, Trained Optometrist or Trained Technician***	
Nathan (1991)	***Reference standard*** (NR) Camera: Zeiss, stereoscopic; 7 field Mydriatic Non Study Office Setting / same location NR / Retinal Specialist x 2 (indep.; consensus)	***Method under investigation A*** (67) Fund.: Direct Non-mydriatic Hospital Diabetic Clinic Diabetologist x 2	***Method under investigation B*** (20) Fund.: Direct Non-mydriatic Hospital Diabetic Clinic Endocrinology Fellows
Nathan (1991) cont...		***Method under investigation C*** (28) Camera: Canon CR4, stereoscopic; 45° (macula / disk) Non-mydriatic Hospital Diabetic Clinic / NR NR / Diabetologist x 2 (indep.; consensus)	***Method under investigation D*** (67) Fund.: Indirect (if required, slit-lamp biomicroscopy) Mydriatic Non-Study Office Setting Ophthalmologist x 3
Neubauer (2008a)	***Reference standard*** (64, 128 eyes) Digital: FF450 plus; 7x30°; 5mp Mydriatic Hospital Outpatient Clinic / Reading Centre NR / Retinal Specialist	***Method under investigation A*** (64, 128 eyes) Digital: Visucam PRO NM; 7x30°; 5mp Mydriatic Hospital Outpatient Clinic / Reading Centre NR / Retinal Specialist	

Citation	**Clinical Examination:** **Screening Method (n, n eyes)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n, n eyes)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Phiri (2006)	***Reference standard*** (196, 392 eyes) Film: Topcon TRC 50X, 35mm Fuji 100 film, stereoscopic; 7x30° Mydriatic Hospital / NR NR / Retinal Specialist & Ophthalmologist	***Method under investigation A*** (196, 392 eyes) Digital: Canon CR6 45NM; 1x45°; 1600x1200p Non-mydriatic (Physiological dilation) Hospital / NR NR / Retinal Specialist & Trained Ophthalmologist	***Method under investigation B*** (196, 392 eyes) Polaroid: Canon CR5 45NM; 1x45° Non-mydriatic (Physiological dilation) Hospital / NR NR / Retinal Specialist & Trained Ophthalmologist
Pugh (1993)	***Reference standard*** (352) Camera: Zeiss, stereoscopic; 7x30° NR NR / Reading Centre Certified Retinal Photographer / NR	***Method under investigation A*** (352) Film: Canon CR3, Kodachrome 64 ASA film; 1x45° (disc / fovea) Non-mydriatic NR / Reading Centre Nurses or Physician assistant / Grader	***Method under investigation B*** (352) Film: Canon CR3, Kodachrome 64 ASA film; 3x45° Mydriatic NR / Reading Centre Nurses or Physician assistant / Grader
Pugh (1993) cont…		***Method under investigation C*** (348) Fund.: Direct & Indirect Mydriatic NR Ophthalmologist x 8 & Retinal Specialist x 2	***Method under investigation D*** (250) Fund.: Direct Mydriatic NR Physician assistant x 2
Pugh (1993) cont…		***Method under investigation E*** (352) Film: Canon CR3, Kodachrome 64 ASA film; 1x45° Non-mydriatic NR Nurses or Physician assistant / Self-trained Internists	***Method under investigation F*** (352) Film: Canon CR3, Kodachrome 64 ASA film; 3x45° Mydriatic NR Nurses or Physician assistant / Medical resident or Intern
Shiba (1999)	***Reference standard*** (22 control) Digital: Topcon TRC NW5S, stereoscopic; 9x45° Mydriatic NR Physician or Nurse or Tech/Ophthalmologist x2; Diabetologist	***Method under investigation A*** (22 control) Digital: Topcon TRC NW5S, stereoscopic; 9x45° Non-mydriatic NR Physician or Nurse or Tech/Ophthalmologist x2; Diabetologist	***Method under investigation B*** (16 diabetic) Digital: Topcon TRC NW5S, stereoscopic; 9x45° Non-mydriatic NR Physician or Nurse or Tech/Ophthalmologist x2; Diabetologist
Taylor (1999)	***Reference standard*** (118) Film: 35mm film, stereoscopic; 7x30° NR West of England Eye Unit / Reading Centre NR	***Method under investigation A*** (197) Digital: Topcon; 1x45° (disc/macula); 640x480p Mydriatic GP-based Retinal Screening Clinic / NR NR / NR	***Method under investigation B*** (534) Digital: Canon CR5 45NM; 1x45° (disc / macula); 768x576p Mydriatic GP-based Retinal Screening Clinic / NR NR / NR
Taylor (1999) cont...		***Method under investigation C*** (NR) Polaroid: Canon CR4 45NM; 1x45°; Polaroid 600 extreme gloss Mydriatic GP-based Retinal Screening Clinic / NR NR / Experienced Grader	***Method under investigation D*** (NR) Fund.: Direct Mydriatic GP-based Retinal Screening Clinic NR

Key: Outreach studies in bold & italicised

F. Angio: Fluorescein Angiography *GP: General Practitioner* *mp: megapixels* *NR: Not Reported* *Opto: Optometrist* *std: standard* *Tech: Technician*
Fund.: Fundoscopy *indep: independent* *Non-Phys.: Non-Physician* *Ophth.: Ophthalmologist* *p: pixels* *stereo.: stereoscopic*

Table 9b: Screening Methods: Studies with Clinical Examination as the Reference Standard (n=39)

Citation	Clinical Examination: Screening Method (n) Instrument Mydriatic / Non-mydriatic Location Clinician	Camera: Screening Method (n) Instrument; n fields; resolution Mydriatic / Non-mydriatic Location of Photo / Interpreter Photographer / Interpreter	
Ahmed (2006)	***Reference standard*** (244) Fund.: Slit-lamp Mydriatic Secondary or specialist care Ophthalmologist (87%) & Optometrist (13%)	***Method under investigation A*** (244) Digital: Topcon TRC NW5S or TRC NW6S; 3x45° Non-mydriatic Primary Care Clinic / Reading Centre (Ophthalmology Clinic) Trained Technician / Retinal Specialist	
Bibby (1992)	***Reference standard*** (115) Fund.: Direct & Indirect Mydriatic NR Ophthalmologist	***Method under investigation A*** (49) Fund.: Direct NR NR Trained Non-Consultant Hospital Physicians	***Method under investigation B*** (66) NR NR NR Non-trained Junior Physicians
Burns-Cox (1985) - (Study 1 only)	***Reference standard - Study 1*** (158) Fund.: Direct & Indirect Mydriatic Hospital Ophthalmologist	***Method under investigation A*** (844 eyes) NR NR Mixed Ophthalmic Optician	
Diamond (1998)	***Reference standard (164)*** ***Fund.: Indirect (20D)*** ***Mydriatic*** ***Secondary or specialist care (Outreach)*** ***Ophthalmologist***	***Method under investigation A (164)*** ***Polaroid: Canon CR5 45NM*** ***Non-mydriatic*** ***Secondary or specialist care (Outreach) / NR*** ***Photographer / Ophthalmologist***	***Method under investigation B (68 re-examined)*** ***Polaroid: Canon CR5 45NM*** ***Mydriatic*** ***Secondary or specialist care (Outreach) / NR*** ***Photographer / Ophthalmologist***
Friberg (2003)	***Reference standard*** (NR) Fund.: Indirect (20D) & Slit-lamp biomicroscopy (78D) Mydriatic NR Retinal Specialist	***Method under investigation A*** (NR) SLO: Optos; 200° panoramic; 2000x2000p Non-mydriatic NR Photographer or Technician / Retinal Specialist	
Hammond (1996)	***Reference standard*** (237) Fund.: Direct, Slit-lamp bio. (78D), & if required, Indirect Mydriatic GP practice / Optician practice Ophthalmologist	***Method under investigation A*** (237) Fund.: Direct, Slit-lamp bio. (78D), & if required, Indirect Mydriatic GP practice / Optician practice Optician	
Harding (1995)	***Reference standard (326)*** ***Fund.: Slit-lamp (60 & 90D), stereoscopic*** ***NR*** ***NR*** ***Retinal Specialist***	***Method under investigation A (326)*** ***Film: Canon CR4 45NM, Kodachrome 64; non-stereo.; 3x45°*** ***Mydriatic*** ***Outreach (mobile unit) / NR*** ***Tech. / Ophthalmic Clinical Assistant (& arbitration as req.)***	***Method under investigation B (326)*** ***Fund.: Direct (Welch Allen 3.5V halogen)*** ***Mydriatic*** ***Hospital Clinic*** ***Ophthalmology Registrar***
Heaven (1992)	***Reference standard*** (100) Fund.: Indirect & Slit-lamp biomicroscopy Mydriatic NR Ophthalmologist	***Method under investigation A*** (100) Polaroid: Canon CR3 45NM; 45° Non-mydriatic Hospital Diabetic Clinic / Eye Department Nurse technician / Ophthalmic Registrar	

Citation	Clinical Examination: Screening Method (n) Instrument Mydriatic / Non-mydriatic Location Clinician	Camera: Screening Method (n) Instrument; n fields; resolution Mydriatic / Non-mydriatic Location of Photo / Interpreter Photographer / Interpreter	
Herbert (2003)	***Reference standard*** (145 + 18 re-examined at 3mo) Fund.: Slit-lamp NR Hospital Retinal Specialist	***Method under investigation A*** (145) Digital: TRC NW5S; 1x45°; JPEG Mydriasis as required Hospital / NR Nurse / Retinal Specialist (examined 18 at 3mo)	
Hulme (2002)	***Reference standard*** (439) Fund.: Slit-lamp (Volk) Mydriatic NR Ophthalmologist	***Method under investigation A*** (439) Fund.: Slit-lamp (Volk 78D) Mydriatic Optometrist Practice Optometrist (x13)	
Jones (1988)*	***Reference standard*** (127, 125 assessed) F. Angio.: Carl Zeiss, Ilford FP4 film, post. pole, 5 pt. survey NR Hospital / NR Medical Photographer / Ophthalmologist	***Method under investigation A*** (127, 105 assessed) Polaroid: Canon CR3 NM, Polaroid 779 Non-mydriatic Hospital / NR Medical Photographer x 6 / Ophthalmologist	***Method under investigation B*** (127, 124 assessed) Film: Canon CR3 NM, 35 mm Ektachrome 64 film Mydriatic Hospital / NR Medical Photographer / Ophthalmologist
Lee (1993)	***Reference standard*** (410: 795 eyes) Fund.: Indirect & Slit-lamp biomicroscopy (90D) Mydriatic NR Retinologist x 3	***Method under investigation A*** (410: 795 eyes) Film: Canon CR4 45NM; 1 x 45° Mydriatic NR / Reading Centre Trained Technicians x 3; Optometrist / Grader	
Lopez-Bastida (2007)	***Reference standard*** (773) Fund.: Indirect & Slit-lamp Mydriatic Primary care (community health centre) Retinal Specialist	***Method under investigation A*** (773) Digital: Topcon TRC NW6S; 2x45°& 2x30° Non-mydriatic Hospital / NR Retinal Specialist / NR	
Kinyoun (1989)	***Reference standard*** (3356 eyes + 1464 at 1yr f/up) Fund.: Direct, Indirect & Contact lens biomicroscopy NR NR Retinal Specialists (22 clinical centres)	***Method under investigation A*** (3356 eyes + 1464 at 1yr f/up) Camera: stereoscopic; colour; 1x30° centred on the macula NR NR / Reading Centre NR / Trained Graders	
Kinyoun (1992)	***Reference standard*** (393; 135 had 2 exams) Fund.: Direct & Indirect Mydriatic Hospital Inpatient Retinal Specialist	***Method under investigation A*** (124; 9 had 2 photos; 133 read) Film: Zeiss, Kodachrome film; 7 field NR NR ETDRS-certified Photographer / Retinal Specialist	***Method under investigation B*** (124; 9 had 2 photos, 59 read) Film: Zeiss, Kodachrome film; 7 field NR NR ETDRS-certified Photographer / Trained Photographic Grader
Kuo (2005)	***Reference standard*** (100) Fund.: Indirect & Slit-lamp biomicroscopy (78 or 90D) Mydriatic NR Ophthalmologist	***Method under investigation A*** (100) Digital: Canon CR6 4NM; 1x45° Non-mydriatic Hospital / NR Trained technician / Retinal Specialist	***Method under investigation B*** (100) Digital: Canon CR6 4NM; 1x45° Non-mydriatic Hospital / NR Trained Technician / Endocrinologist

Citation	**Clinical Examination:** **Screening Method (n)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Leese (2002)	***Reference standard (100 STED referrals)*** ***Fund.: Slit-lamp (if required, F. Angio.)*** ***NR*** ***Ophthalmology clinic*** ***Ophthalmologist (consultant or specialist registrar)***	***Method under investigation A (408)*** ***Polaroid*** ***Non-mydriatic*** ***Outreach (mobile van) / NR*** ***NR / Diabetologist x7 (4 consultant, 3 registrar)***	***Method under investigation B (408)*** ***Fund.: Direct*** ***Mydriatic*** ***Hospital*** ***Diabetologist x7 (4 consultant, 3 registrar)***
Lienert (1989)	***Reference standard*** (500: 985 eyes) Fund.: Direct (Welch-Allen, red-free light) Mydriatic Hospital Diabetic Clinic Ophthalmologist	***Method under investigation A*** (24) Fund.: Direct (Welch-Allen, red-free light) Mydriatic Hospital Diabetic Clinic GP (x2)	***Method under investigation B*** (233) Fund.: Direct (Welch-Allen, red-free light) Mydriatic Hospital Diabetic Clinic Junior Medical Staff (x25)
Lienert (1989) cont...		***Method under investigation C*** (239) Fund.: Direct (Welch-Allen, red-free light) Mydriatic Hospital Diabetic Clinic Diabetes Physicians (x3; DP1: 121 Pts, DP2: 48, DP3: 70)	
Liesenfeld (2000)	***Reference standard A*** (129) Fund.: Slit-lamp Mydriatic NR Ophthalmologist x 6	***Reference Standard B*** (129) Film: Topcon TRC 50X; Ektachrome 100; non-stereo.; 2x50° Mydriatic NR / NR Trained Med. or Non-Med. / Expert Grader	***Method under investigation A*** (129) Digital: Topcon TRC 50X, non-stereo; 2x50°; 768x576p Mydriatic NR / Reading Centre x5 & Ophthalmologist from RS (A) Trained Med, non-Med. / Diabet. x2, Ophth. x8, Retinal Grader
Maberley (2002)	***Reference standard (100)*** ***Fund.: Indirect, Slit-lamp bio. (78D) & Ant. Segment Slit-lamp*** ***Mydriatic*** ***NR*** ***Retinal Specialist***	***Method under investigation A (100)*** ***Digital: Topcon TRC NW5SF; 1x45°*** ***Mixed (i.e. dilation as required)*** ***Hospital (Outreach)/ University or Retinal Research Unit*** ***Photographer or Health Care Worker / Retinal Specialist***	
Massin (2005)	***Reference standard*** (426, 417 completed) Fund. Mydriatic NR Ophthalmologist	***Method under investigation A*** (456, 417 completed) Digital: Topcon TRC NW6S; 5x45°; 1490x960p Non-mydriatic Screening Centre / Hospital Ophthalmological Department Orthoptist / Ophthalmologist x 2	
Mohan (1988)	***Reference standard*** (85: 45 Indian, 40 European) Fund.: NR Mydriatic Hospital Diabetic Clinic Ophthalmologist	***Method under investigation A*** (85: 45 Indian, 40 European) Polaroid: Canon CR3 45NM; 1 field Non-mydriatic Hospital Diabetic Clinic / NR NR	

Citation	**Clinical Examination:** **Screening Method (n)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Molina Fernandez (2008)	***Reference standard*** (328 eyes) Fund.: Slit-lamp & Contact/Non-contact (VOLK/Ocular Mainster) NR NR / Hospital (via email) Ophthalmologist x2 (independently)	***Method under investigation A*** (99 eyes) Digital: Topcon TRC50 EX; 3 photos divided into 6 fields; JPEG Mydriatic Primary Care / Hospital (via email) GP / GP or Ophthalmologist	***Method under investigation B*** (112 eyes) Digital: Topcon NW100; 3 photos divided into 6 fields; JPEG Non-mydriatic Primary Care / Hospital (via email) GP / GP or Ophthalmologist
Molina Fernandez (2008) cont...		***Method under investigation C*** (135 eyes) Digital: Topcon NW100; 3 photos divided into 6 fields; JPEG Mixed (i.e. dilation if poor photo) NR / Hospital (via email) GP / GP or Ophthalmologist	
Murgatroyd (2004)	***Reference standard*** (398) Fund.: Slit-lamp Mydriatic NR Ophthalmologist	***Method under investigation A*** (398) Digital: Topcon NW6S; 1x45°; 1024x768p Non-mydriatic NR Photographer or Technician / Ophthalmologist & Diabetologist	***Method under investigation B*** (398) Digital: Topcon NW6S; 1x45°; 1024x768p Mydriatic NR Photographer or Technician / Ophthalmologist & Diabetologist
Murgatroyd (2004) cont...		***Method under investigation C*** (398) Digital: Topcon NW6S; 3x45°; 1024x768p Mydriatic NR Photographer or Technician / Ophthalmologist & Diabetologist	
Neubauer (2008b)	***Reference standard*** (51) Fund.: NR, stereoscopic & Slit-lamp biomicroscopy (78D) Mydriatic University Ophthalmology Department Clinic Experienced Retina Physician	***Method under investigation A*** (51) SLO: Optomap Panoramic 200; 200° Non-Mydriatic University Ophthalmology Department Clinic Experienced Tech or Study Author / Experienced Re S x 3	
Olson (2003)	***Reference standard*** (586) Fund.: Slit-lamp Mydriatic Secondary or specialist care Ophthalmologist	***Method under investigation A*** (485) Fund.: Slit-lamp Mydriatic Secondary or specialist care Optician or Optometrist	***Method under investigation B*** (586) Film: Topcon 50X, 35mm Kodachrome 64 film Mydriatic NR Photographer or Technician / Research Registrar
Olson (2003) cont...		***Method under investigation C*** (586) Digital: Topcon 50X; 2x50°; 1024x1024p Mydriatic NR Photographer or Technician / Research Registrar	***Method under investigation D*** (NR) Digital images stored on CDs NR NR NR
Pandit (2002)	***Reference standard (609)*** ***Fund.: Slit-lamp (90 & 60D), & if required, indirect (20D)*** ***Mydriatic*** ***NR*** ***Ophthalmologist***	***Method under investigation A (305)*** ***Polaroid: Canon CR6 45NM, & F: Direct (HSP)*** ***Mydriatic*** ***Specialist clinic / NR*** ***Diabet. x 25 (mixed levels) / Diabet. x 25 (mixed levels)***	***Method under investigation B (304)*** ***Polaroid: Canon CR6 45NM, & Fund.: Direct (DSP)*** ***Mydriatic*** ***Community (Outreach) / NR*** ***Trained Retinal Screeners x 3/Trained Retinal Screeners x 3***

Citation	**Clinical Examination:** **Screening Method (n)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Penman (1998)	***Reference standard*** (427) Fund.: Indirect & Slit-lamp biomicroscopy Mydriatic NR Trained Resident Ophthalmologist x 3	***Method under investigation A*** (417) Camera: non-stereo.; 1 x 45° Mydriatic NR / Reading Centre Trained Resident Ophthalmologist x 3 / Grader	
Peters (1993)	***Reference standard*** (522) Fund.: Direct, Indirect & Slit-lamp (90D Volk/corneal contact) Mydriatic NR Retinal Specialist x 2	***Method under investigation A*** (522) Polaroid: Canon CR4 45NM, Colour Film 779; 1 x 45° Non-mydriatic (Physiological dilation) NR Nurse-Clinicians / Diabetologist	
Prasad (2001)	***Reference standard*** (845) Fund.: Slit-lamp (90 & 60D), & if required, Indirect Mydriatic Ophthalmologist Practice Ophthalmologist	***Method under investigation A*** (4904) Fund.: Slit-lamp Mydriatic Optometrist Practice Trained Optometrist x 27	
Reenders (1992)	***Reference standard*** (252) Fund.: Direct (Heine) Mydriatic Hospital Ophthalmologist x2	***Method under investigation A*** (252) Fund.: Direct (Heine) Mydriatic NR GP x19	
Rudnisky (2002)	***Reference standard*** (104) Fund.: Contact lens bio. (Volk Centralis), Slit-lamp (Haag Streit) Mydriatic Retina Practice Retinal Specialist	***Method under investigation A*** (104) Digital: Zeiss FF450, stereoscopic; 1x30°; 3040x2008p Mydriatic Retina Practice Trained Ophthalmic Photographer / Retinal Specialist	
Scanlon (2003a)	***Reference standard (1549)*** ***Fund.: Direct & Slit-lamp biomicroscopy (78D)*** ***Mydriatic*** ***General Practice (Outreach)*** ***Ophthalmologist***	***Method under investigation A (3611)*** ***Digital: Topcon NRW5S; 1x45°; 1024x768p*** ***Non-mydriatic*** ***General Practice (Outreach) / NR*** ***Photographer or Technician / Ophthalmologist***	***Method under investigation B (3611)*** ***Digital: Topcon NRW5S; 2x45°; 1024x768p*** ***Mydriatic*** ***General Practice (Outreach) / Reading Centre*** ***Photographer or Technician / Ophthalmologist & NR***
Shiba (2002)	***Reference standard (NR)*** ***Fund.: NR*** ***Mydriatic*** ***NR*** ***Ophthalmologist***	***Method under investigation A (95 eyes, Study 1)*** ***Digital: Topcon, non-stereo.; 9x45°; 3x3 form/A4 collage*** ***Mydriatic*** ***Outpatient clinic*** ***NR / Ophth. (& Diabetic Specialist x2; image grading)***	***Method under investigation B (95 eyes, Study 1)*** ***Digital: Topcon, non-stereo.; 9x45°; 3x3 form/A4 collage*** ***Non-mydriatic*** ***Outpatient clinic*** ***NR / Ophth. (& Diabetic Specialist x2; image grading)***
Shiba (2002) cont...		***Method under investigation C (61, Study 2)*** ***Digital: Topcon, non-stereo.; 9x45°; 3x3 form on Monitor*** ***Non-mydriatic*** ***Summer camp (outreach) / Ophthalmologist (telemedicine)*** ***NR / Ophthalmologist x3***	***Method under investigation D (61 eyes, Study 2)*** ***Film: Topcon, non-stereo.; 1field (fundus); A6 colour film*** ***Non-Mydriatic*** ***Summer camp*** ***NR / NR***

Citation	**Clinical Examination:** **Screening Method (n)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
Siu (1998)	***Reference standard*** (150) Fund.: Indirect (20 & 78D) & Haag Streit slit-lamp Mydriatic NR Ophthalmologist	***Method under investigation A*** (153) Polaroid: Canon CR 45 UAF; 45° Non-mydriatic (Physiological dilation) Hospital Diabetes Centre / NR Nurse / Ophthalmologist	***Method under investigation B*** (153) Fund.: Direct Mydriatic Hospital Diabetes Centre Diabetes Centre Physician
Sussman (1982)	***Reference standard*** (Photo: 11, F. Angio.: 7) Photography & F. Angio.; 7 field stereoscopic Mydriatic NR NR / Retinal Specialist x3 (consensus / majority)	***Method under investigation A*** (11) Fund.: Direct Mydriatic NR Interns x10	***Method under investigation B*** (11) Fund.: Direct Mydriatic NR Senior Medical Resident x4
Sussman (1982) cont…		***Method under investigation C*** (11) Fund.: Direct Mydriatic NR Diabetologist x2	***Method under investigation D*** (11) Fund.: Indirect Mydriatic NR Ophthalmologist x4
Sussman (1982) cont…		***Method under investigation E*** (11) Fund.: Indirect Mydriatic NR Retinal Specialist x3	
Verma (2003)	***Reference standard*** (200) Fund.: Direct (Beta 200, Heine) Mydriatic Medical Ophthalmology Clinic Ophthalmologist	***Method under investigation A*** (200) Fund.: Direct (Beta 200, Heine) Mydriatic Medical Ophthalmology Clinic Trained GP	***Method under investigation B*** (200) Fund.: Direct (Beta 200, Heine) Mydriatic Medical Ophthalmology Clinic Trained Optometrist
Warburton (2004)	***Reference standard A*** (99 screen -ve) Fund.: Indirect Slit-lamp & Handheld Lens Mydriatic NR Ophthalmologist	***Reference standard B*** (93 / 140 screen +ve) NR NR NR Ophthalmologist	***Method under investigation A*** (3510: 99 screen +ve, +93 –ve) Fund.: Indirect, Slit-lamp & Hand-held (91%), Direct / NR (9%) Mydriatic unless contraindicated (criteria NR) Community Optometrist Optometrist
Williams (1986)	***Reference standard*** (62: 120 eyes) Fund.: Direct & Indirect Mydriatic NR Ophthalmologist	***Method under investigation A*** (62: 120 eyes) Fund.: NR Mydriatic General Diabetic or Diabetic Eye Clinic GP with interest in diabetes	***Method under investigation B*** (62: 120 eyes) Camera: Kowa/Canon CR3; Pol. /Kodachrome 200 film; 1 x45° Non-mydriatic General Diabetic or Diabetic Eye Clinic / NR NR / Ophthalmologist x 2

Key: Outreach studies in bold & italicised

Ant.: Anterior
bio.: biomicroscopy
D: dioptre
Diabet.: Diabetologist
DP: Diabetes Physician
DSP: District Screening Program
F. Angio.: Fluorescein Angiography
Fund.: Fundoscopy
F/up: follow-up
GP: General Practitioner
HSP: Hospital Screening Program
Indep.: Independent
Med.: Medical Personnel
mo: months
non-stereo.: non-stereoscopic
NR: Not Reported
p: pixels
Ophth: Ophthalmologist
Pt(s): patient(s)
Post.: posterior
Re S.: Retinal Specialist
SLO: Scanning Laser Ophthalmoscope
STED: Sight-threatening Eye Disease
Tech.: Technician
+ve: positive
-ve: negative
yr(s): year(s)

Table 9c: Screening Methods: Studies with Multiple Reference Standards (n=7)

Citation	Clinical Examination: Screening Method (n) Instrument Mydriatic / Non-mydriatic Location Clinician	Camera: Screening Method (n) Instrument; n fields; resolution Mydriatic / Non-mydriatic Location of Photo / Interpreter Photographer / Interpreter	
Aiello (1998)	***Reference standard A*** (18; 36 eyes) Fund.: Indirect & Slit-lamp biomicroscopy Mydriatic Diabetes Centre Clinical Practice Retinal specialist	***Reference Standard B*** (7) Digital: Topcon TRC 50X; 7x30° + / or results from RS (A) Mydriatic Diabetes Centre Clinical Practice/ NR NR	***Reference Standard C*** (16, + / - medical records) Film: Zeiss, 35mm film; 7x30°+ / or results from RS (A) Mydriatic Diabetes Centre Clinical Practice or medical records NR
Aiello (1998) cont...		***Method under investigation A*** (18; 36 eyes) Digital: JVN Topcon TRC NW55; 1x45° (disc / macula) Non-mydriatic Diabetes Centre Clinical Practice/ NR Photographer or Optometrist / Trained Graders	***Method under investigation B*** (18; 36 eyes) Film: JVN Topcon TRC NW55; 2x45° (superior / nasal to disk) Non-mydriatic Diabetes Centre Clinical Practice / NR Photographer or Optometrist / Trained Graders
Boucher (2003)	***Reference standard A***(98) Camera: stereoscopic; 7x30° Mydriatic Hospital Diabetic Clinic Photographer / Re S. & O. Res. (indep., RS adjudicated)	***Reference Standard B*** (98) Fund.: Slit-lamp Mydriatic Hospital Diabetic Clinic Retinal Specialist	***Method under investigation A*** (98) Digital: Topcon CRW6; 1x45°/60° (vert./horiz.); 1024x768p Non-mydriatic Hospital Diabetic Clinic NR / Retinal Specialist x 2 (indep., O. Res. adjudicated.)
Cavallerano (2005)	***Reference Standard A*** (52) Film: 35mm film, stereoscopic; 7 field Mydriatic Diabetes Centre / same location NR / Certified JVN Graders x 3 (masked)	***Reference Standard B*** (52) Fund. Mydriatic Diabetes Centre Retinal Specialist	***Method under investigation A*** (52) Digital: JVN digital video retinal system; 3 x 45° Non-mydriatic Diabetes Centre / same location Certified JVN imagers / Certified JVN Graders x 3 (masked)
Lawrence (2004)	***Reference standard A*** (254) Film: Topcon TRC 50VT; 7x30° NR Hospital / Reading Centre NR	***Method under investigation A*** (151) Digital: Topcon TRC NW5SF; 1x45°; 640x480p Non-mydriatic Hospital / Reading Centre Photographer or Technician / Ophthalmologist	***Method under investigation B*** (151) Digital: Topcon TRC NW5SF; 3x45°; 640x480p Mydriatic Hospital / Reading Centre Photographer or Technician / Ophthalmologist
Lawrence (2004) cont…	***Reference standard B*** (254) Fund.: Direct, Indirect & Slit-lamp biomicroscopy Mydriatic Hospital Ophthalmologist	***Method under investigation C*** (103) Digital: Topcon TRC NW6S; 1x45°; 800x600p Non-mydriatic Hospital / Reading Centre Photographer or Technician / Ophthalmologist	***Method under investigation D*** (103) Digital: Topcon TRC NW6S; 3x45°; 800x600p Mydriatic Hospital / Reading Centre Photographer or Technician / Ophthalmologist

Citation	**Clinical Examination:** **Screening Method (n)** **Instrument** **Mydriatic / Non-mydriatic** **Location** **Clinician**	**Camera:** **Screening Method (n)** **Instrument; n fields; resolution** **Mydriatic / Non-mydriatic** **Location of Photo / Interpreter** **Photographer / Interpreter**	
O'Hare (1996)	***Reference standard (NR)*** ***Fund.: NR + Polaroid: Canon CR4 45NM, 1 field (macula)*** ***Mydriatic*** ***Outreach (mobile van) / NR*** ***Ophthalmologist, Photographer / Ophthalmologist***	***Method under investigation A (517)*** ***Fund.: NR*** ***Mydriatic*** ***Outreach (mobile)*** ***GP***	***Method under investigation B (517)*** ***Fund.: NR + Polaroid: Canon CR4 45NM, 1 field (macula)*** ***Mydriatic*** ***Outreach (mobile van) / NR*** ***GP, Photographer / GP***
O'Hare (1996) cont…		***Method under investigation C (493)*** ***Fund.: NR*** ***Mydriatic*** ***Outreach (mobile)*** ***Optician***	***Method under investigation D (493)*** ***Fund.: NR + Polaroid: Canon CR4 45NM, 1 field (macula)*** ***Mydriatic*** ***Outreach (mobile van) / NR*** ***Optician, Photographer / Optician***
O'Hare (1996) cont…		***Method under investigation E (NR)*** ***Polaroid: Canon CR4 45NM; 1 field*** ***Mydriatic*** ***Outreach (mobile) / NR*** ***Photographer / Ophthalmological Specialist***	
Scanlon (2003b)	***Reference standard A*** (239) Film: Zeiss 7x30° (Oxford), Topcon 50X 7x35° (Norwich) Mydriatic Hospital DR Clinic or Diabetes Clinic / Grading Centre NR / NR	***Reference standard B*** (239) Fund.: Direct & Indirect (78D) Mydriatic Hospital DR Clinic or Diabetes Clinic Ophthalmologist	***Method under investigation A*** (239) Digital: Canon CR5 (Oxford), CR6 (Norwich); 2x45°; 768x568p Mydriatic Hospital DR Clinic or Diabetes Clinic / Reading Centre NR / Study Author
Schmid (2002)	***Reference standard A*** (10) Fund. Mydriatic NR Department of Optometry staff member (indep.)	***Method under investigation A*** (10) Fund.: Direct, Indirect or Fundus lens Mydriatic Secondary or specialist care Optometrist x 19	***Method under investigation B*** (12 slides) Film NR NR NR / Optometrist x 19
Schmid (2002) cont...	***Reference standard B*** (12 slides) Film NR NR NR / Department of Optometry staff member		

Key: Outreach studies in bold & italicised

D: dioptre
F. Angio.: Fluorescein Angiography
Fund.: Fundoscopy
GP: General Practitioner
horiz.: horizontal
Indep.: Independent
JVN: Joslin Vision Network
non-stereo.: non-stereoscopic
NR: Not Reported
O. Res: Ophthalmology Resident
p: pixels
RS: Reference standard
Re S: Retinal Specialist
vert.: vertical

Sensitivity and Specificity

Summary of Sensitivity / Specificity and Kappa outcome measures

Following re-classification of outcome categories using the ICDR (see Methods), a total of 25 outcome categories were identified, comprising a mix of 'stand-alone categories' and 'categories as thresholds' (i.e. where the outcome was defined as that category or worse on the ICDR scale).

Forty-three of the 62 studies measured Sensitivity / Specificity, generating a total of 197 Sensitivity / Specificity measures. Twenty studies measured Kappa, generating 103 Kappa measures.

Table 10 describes the frequency of these outcome measures by outcome category (in some cases, Specificity was not reported; counts are based upon sensitivity measures). Only three outcome categories generated over 20 measures; 'Any DR' (40 Sensitivity / Specificity measures), 'Agreement across a grading system' (44 Kappa measures) and 'Moderate NPDR as a threshold' (29 Sensitivity / Specificity measures).

Table 10: Summary of Sensitivity / Specificity and Kappa outcome measures

Outcome Measure	n (S_n / S_p) Mydriatic	n (S_n / S_p) Non-Mydriatic	n (S_n / S_p) Mixed / NR	n (S_n / S_p) TOTAL	n (Kappa) Mydriatic	n (Kappa) Non-Mydriatic	n (Kappa) Mixed / NR	n (Kappa) TOTAL	TOTAL
Any DR	23	12	5	**40**	6	6	4	**16**	67
ME	9	6	0	**15**	3	3	0	**6**	21
Extent of ME					1	3	0	**4**	4
≥ ME	1	1	0	**2**	0	1	0	**1**	15
CSME	4	4	1	**9**	1	1	1	**3**	12
Agreement across a Grading System	1	4	0	**5**	18	18	8	**44**	49
Mild NPDR	1	0	1	**2**					2
≥ Mild NPDR	1	1	0	**2**	1	1	0	**2**	4
Moderate NPDR	1	3	1	**5**	0	1	0	**1**	6
≥ Moderate NPDR	17	10	2	**29**	2	3	0	**5**	41
Severe NPDR	0	1	0	**1**	0	1	0	**1**	2
≥ Severe NPDR	6	3	0	**9**	1	1	0	**2**	11
Mild, Moderate & Severe NPDR	0	0	1	**1**					1
PDR	2	1	2	**5**	1	1	0	**2**	7
≥ PDR	4	3	0	**7**	0	1	0	**1**	8
Mild or Moderate NPDR & ME	12	0	0	**12**					12
≥ Moderate NPDR & / or ME or Ungradable	1	3	0	**4**					3
≥ Moderate NPDR or ME	13	4	0	**17**	7	3	0	**10**	27
Moderate NPDR or CSME					0	1	0	**1**	1
≥ Moderate NPDR & CSME					0	1	0	**1**	1
≥ Moderate NPDR or CSME	6	0	0	**6**					6
≥ Moderate NPDR & / or ≥ ME	13	0	0	**13**					1
≥ Severe NPDR or ME	9	2	0	**11**	2	1	0	**3**	14
≥ Severe NPDR & ME	1	0	0	**1**					1
PDR or CSME	0	1	0	**1**					1
TOTAL	**125**	**59**	**13**	**197**	**43**	**47**	**13**	**103**	**317**

Key:
CSME: Clinically Significant ME; ME: Macular Oedema; NPDR: non-proliferative DR; NR: Not Reported; PDR: proliferative DR; S_n: Sensitivity; S_p: Specificity

Sensitivity / Specificity for all outcome measures

Table 11a – 11v detail all Sensitivity and Specificity measures for all outcome categories. Figures generated from outreach methods are highlighted in bold and italicised in tables, and described separately in text. For each outcome, the screening methods are divided according to mydriatic status (mydriatic, non-mydriatic, mixed / not reported) and where appropriate, means for each category of mydriasis have been calculated.

Table 11a: Sensitivity and Specificity to detect ANY DR (n=40)

Mydriatic (n=23)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	99 (97 - 100)	86 (74 - 90)
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	85	81
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	66	86
Murgatroyd (2004)	Digital	3	Photo. / Tech.	Ophth.	NR	90 (86 - 93)	90 (88 - 93)
Olson (2003)	Digital	2	Photo. / Tech.	Trainee Ophth.	NR	83 (77 - 89)	79 (75 - 83)
Olson (2003)	Digital	1	Photo. / Tech.	Trainee Ophth.	NR	80 (74 - 86)	88 (84 - 91)
Murgatroyd (2004)	Digital	1	Photo. / Tech.	Ophth.	NR	86 (82 - 90)	91 (89 - 94)
Taylor (1999)	Digital	1	NR	NR	S	74 (68 - 80)	96 (94 - 98)
Baeza (2009)	Film	3	GP	Ophth.	S	85 (80 - 90)	94 (91 - 97)
Baeza (2009)	Film	2	GP	Ophth.	S	86 (81 - 91)	95 (92 - 98)
Olson (2003)	Film	2	Photo. / Tech.	Trainee Ophth.	NR	89 (84 - 94)	89 (86 - 92)
Olson (2003)	Film	1	Photo. / Tech.	Trainee Ophth.	NR	86 (80 - 92)	92 (88 - 94)
Baeza (2009)	Film	1	GP	Ophth.	S	77 (71 - 83)	98 (96 - 99)
Taylor (1999)	Polaroid	1	NR	Grader	S	72 (66 - 78)	88 (85 - 91)
Hulme (2002)	Exam	-	-	Opto.	S	72	77
Kleinstein (1987)	Exam	-	-	Opto.	NR	74 (67 - 81)	84 (73 - 96)
Olson (2003)	Exam	-	-	Optician / Opto.	S	75 (67 - 83)	82 (79 - 86)
Reenders (1992)	Exam	-	-	GP	NR	52	84
Siu (1998)	Exam	-	-	Diabet. / Endo.	S	41 (20 - 62)	93 (88 - 97)
Verma (2003)	Exam	-	-	GP	S	97.7	83.6
Verma (2003)	Exam	-	-	Opto.	S	86.5	88.1
Williams (1986)	Exam	-	-	GP	S	93	93
Taylor (1999)	Polaroid + Exam	1	NR	NR	S	92 (86 - 98)	89 (87 - 91)
				Mean (Range)		***S_n:*** 80.1 (41 - 99)	***S_p:*** 88.1 (77 - 98)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Results - Sensitivity and Specificity

Non-Mydriatic (n=12)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Lopez-Bastida (2007)	Digital	4	Re S	NR	S	92 (90 - 94)	96 (95 - 98)
Bursell (2001)	Digital	3	NR	Grader	S	94	76
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	66	66
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	76	45
Murgatroyd (2004)	Digital	1	Photo. / Tech.	Ophth.	NR	83 (78 - 88)	91 (88 - 94)
Baeza (2009)	Film	3	GP	Ophth.	S	79 (73 - 86)	96 (93 - 99)
Baeza (2009)	Film	2	GP	Ophth.	S	76 (70 - 83)	97 (94 - 95)
Baeza (2009)	Film	1	GP	Ophth.	S	68 (60 - 75)	98 (96 - 100)
Peters (1993)	Polaroid	1	Nurse	Diabet. / Endo.	NR	85	93
Siu (1998)	Polaroid	NR	Nurse	Ophth.	S	64 (43 - 85)	90 (84 - 96)
Friberg (2003)	SLO	NR	Photo. / Tech.	Re S	NR	94	83
Williams (1986)	Polaroid or Film	1	NR	Ophth.	S	96	98
				Mean (Range)		***S_n:*** 81.1 (64 - 96)	***S_p:*** 85.8 (45 - 98)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Mixed Mydriatic / Non-Mydriatic or Mydriasis Not Reported (n=5)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Molina Fernandez (2008)	Digital	3	GP	Ophth.	S	76.6 (64.3 - 85.9)	95.2 (90.7 - 97.9)
Molina Fernandez (2008)	Digital	3	GP	GP	S	78.4 (67.3 - 87.1)	78.6 (72.4 - 84)
Herbert (2003)	Digital	1	Nurse	Re S	S	38.2	95.5
Maberley (2002)	***Digital (85% patients were dilated)***	***1***	***Mixed***	***Re S***	***O***	***84.4***	***79.2***
Schmid (2002) ~	Exam + Slide (archive)	NR	NR	Opto.	S	94 (91.1 - 96.9)	93.6 (88.1 - 99.1)
				Mean (Range)		***S_n:*** 74.3 (38.2 - 94.0)	***S_p:*** 88.4 (78.6 - 95.5)

Key: ~ Dilation was not reported; GP: General Practitioner; NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto.: Optometrist; Re S: Retinal Specialist; S: Static

Sensitivity for mydriatic (mean 80.1, 23 measures) and non-mydriatic (81.1, n=12) methods were similar, with a slightly lower mean value for mixed / not reported (74.3, n=5). Specificity for mixed / not reported (88.4) and mydriatic (88.1) were similar, compared to non-mydriatic (85.8) which was instead lower.

One outreach study (Maberley 2002) measured sensitivity and specificity for 'Any DR'. This study of 100 patients used mixed mydriasis (85% of sample mydriatic) and a 1-field digital camera (mix of imagers, graded by a retinal specialist) and yielded a sensitivity of 84.4 (higher than all group means) and a specificity of 79.2 (lower than all group means).

Table 11b: Sensitivity and Specificity to detect Macular Oedema (n=15)

Mydriatic (n=9)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	95 (90 - 97)	84 (74 - 90)
Fransen (2002)	Digital	7	Photo. / Tech.	Grader	S	87.8	93.8
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	73.3	96
Olson (2003)	Digital	2	Photo. / Tech.	Trainee Ophth.	NR	83 (61 - 95)	83 (80 - 86)
Rudnisky (2002)	Digital	1	Photo. / Tech.	Re S	S	82	90
Pugh (1993)	Film	3	Nurse	NR	NR	68	99
Olson (2003)	Film	2	Photo. / Tech.	Trainee Ophth.	NR	83 (61 - 95)	84 (81 - 87)
Olson (2003)	Exam	-	-	Optician / Opto.	S	46 (19 - 75)	92 (90 - 95)
Williams (1986)	Exam	-	-	GP	S	94	95
				Mean (Range)		***S_n:*** 79.1 (46 - 95)	***S_p:*** 90.8 (83 - 99)

Key: GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; Opto.: Optometrist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=6)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	73.3	90.7
Hansen (2004)	Digital	5	Opto.	NR	S	91.7	91.5
Bursell (2001)	Digital	3	NR	Grader	S	62	95
Cavallerano (2005)	Digital	3	Photo. / Tech.	Grader	S	100	97.1
Pugh (1993)	Film	1	Nurse	NR	NR	89	79
Williams (1986)	Polaroid or Film	1	NR	Ophth.	S	100	96
				Mean (Range)		***S_n:*** 86.0 (62 - 100)	***S_p:*** 91.6 (79 - 97.1)

Key: NR: Not Reported; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician

Mean sensitivity was higher for non-mydriatic (86.0, n=6) than mydriatic methods (79.1, n=9). Specificity values were similar (non-mydriatic mean 91.6, mydriatic mean 90.8).

No outreach studies measured this outcome.

Table 11c: Sensitivity and Specificity to detect ≥ Macular Oedema as a threshold (n=2)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Hammond (1996)	Exam	-	-	Optician	S	77	NR

Key: NR: Not Reported; S: Static

Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	77.0	93.0

Key: NR: Not Reported; S: Static

Table 11d: Sensitivity and Specificity to detect Clinically Significant Macular Oedema (CSME) (n=9)

Mydriatic (n=4)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	91 (79 - 97)	80 (69 - 88)
Rudnisky (2002)	Digital	1	Photo. / Tech.	Re S	S	90.6	92.4
Harding (1995)	***Film***	***3***	***Photo. / Tech.***	***Optician / Opto.***	***O***	***61 (44 - 78)***	***99 (98 - 100)***
Harding (1995)	Exam	-	-	Ophth.	S	64 (47 - 81)	NR
				Mean (Range)		***S_n:*** 76.7 (61 - 91)	***S_p:*** 90.5 (80 - 99)

Key: NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=4)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	27	98
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	93	89
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	93	72
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	89	83
				Mean (Range)		**S_n:** 75.5 (27 - 93)	**S_p:** 85.5 (72 - 98)

Key: NR: Not Reported; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician; '+': includes qualified healthcare professional

Mixed Mydriatic / Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Maberley (2002)	***Digital (85% patients were dilated)***	***1***	***Mixed***	***Re S***	***O***	***90.0***	***97.1***

Key: O: Outreach; Re S: Retinal Specialist

Mean values were similar for sensitivity (mydriatic 76.7, n=4; non-mydriatic 75.5, n=4). Specificity was higher for mydriatic methods (90.5 vs. 85.5).

Two outreach studies measured sensitivity and specificity for 'CSME'. Harding (1995) studied 326 patients using mydriatic 3-field film camera (photographer / technician imager, graded by optician / optometrist) yielding a sensitivity of 61.0 (higher than all group means) and a specificity of 99.0 (higher than all group means). Maberley (2002) studied 100 patients using mixed mydriasis (85% of sample mydriatic) and a 1- field digital camera (mix of imagers, graded by a retinal specialist) and yielded a sensitivity of 90.0 (higher than all group means) and a specificity of 97.1 (higher than all group means) for this outcome.

Table 11e: Sensitivity and Specificity for Agreement across a Grading System (n=5)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Prasad (2001)	Exam	-	-	Opto.	S	66.0 (65 - 67)	97.0 (97 - 98)

Key: Opto.: Optometrist; S: Static

Non-Mydriatic (n=4)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Cavallerano (2005)	Digital	3	Photo. / Tech.	Grader	S	100	98.1
Ahmed (2006)	Digital	3	Photo. / Tech.	Re S	S	98	86
Kuo (2005)	Digital	1	Photo. / Tech.	Re S	S	53.8	89
Kuo (2005)	Digital	1	Photo. / Tech.	Diabet. / Endo.	S	45	75.3
				Mean (Range)		***Sn:*** 74.2 (45 - 100)	***Sp:*** 87.1 (75.3 - 98.1)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Mean values for the 4 non-mydriatic methods were 74.2 for sensitivity and 87.1 for specificity. Only one mydriatic method measured this outcome, yielding a sensitivity of 66.0 and specificity of 97.0.

No outreach studies measured this outcome.

Table 11f: Sensitivity and Specificity to detect Mild NPDR (n=2)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Schmid (2002)	Exam	-	-	Opto.	S	94.7	NR

Key: Opto.: Optometrist; S: Static

Mydriasis Not Reported (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Schmid (2002)	Film	NR	NR	Opto.	NR	92.1	NR

Key: NR: Not Reported; Opto.: Optometrist

Table 11g: Sensitivity and Specificity to detect ≥ Mild NPDR as a threshold (n=2)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Boucher (2003)	Exam	-	-	Re S	S	80.2	96.6

Key: Re S: Retinal Specialist; S: Static

Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Boucher (2003)	Digital	2	NR	Re S	S	86.4	95.4

Key: NR: Not Reported; Re S: Retinal Specialist; S: Static

Table 11h: Sensitivity and Specificity to detect Moderate NPDR (n=5)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Hammond (1996)	Exam	-	-	Optician	S	92.0	NR

Key: S: Static

Non-Mydriatic (n=3)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Phiri (2006)	Digital	1	NR	Re S	S	86.2 (65.8 - 95.3)	71.2 (58.1 - 81.1)
Bursell (2001)	Digital	3	NR	Grader	S	86	76
Phiri (2006)	Polaroid	1	NR	Re S	S	84.1 (65.5 - 93.7)	71.2 (58.1 - 81.1)
				Mean (Range)		S_n: 85.4 (84.1 - 86.2)	S_p: 72.8 (71.2 - 76)

Key: NR: Not Reported; Re S: Retinal Specialist; S: Static

Mixed Mydriatic / Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Maberley (2002)	***Digital (85% patients were dilated)***	***1***	***Mixed***	***Re S***	***O***	***91.2***	***82.2***

Key: O: Outreach; Re S: Retinal Specialist

Mean values for the 3 non-mydriatic methods were 85.4 for sensitivity and 72.8 for specificity. Only one mydriatic method measured this outcome, yielding a sensitivity of 92.0 (specificity not reported).

One outreach study measured sensitivity and specificity for 'Moderate NPDR'. Maberley (2002) studied 100 patients using mixed mydriasis (85% of sample mydriatic) and a 1-field digital camera (mix of imagers, graded by a retinal specialist) and yielded a sensitivity of 91.2 (higher than all non-mydriatic values, lower than mydriatic value) and a specificity of 82.2 (highest value of all) for this outcome.

Table 11i: Sensitivity and Specificity to detect ≥ Moderate NPDR as a threshold (n=29)

Mydriatic (n= 17)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	99 (94 - 100)	92 (73 - 99)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	95.2	95.2
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	82.7	NR
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	90.3	NR
Taylor (1999)	Digital	1	NR	NR	S	85 (80 - 90)	98 (96 - 100)
Harding (1995)	***Film***	***3***	***Photo. / Tech.***	***Optician / Opto.***	***O***	***47 (21 - 93)***	***100***
Pugh (1993)	Film	3	Nurse	Grader	NR	81	96
Pugh (1993)	Film	3	Nurse	Trainee Ophth.	NR	64	90
Taylor (1999)	Polaroid	1	NR	Grader	S	90 (86 - 94)	97 (95 - 99)
Lawrence (2004)	Exam	-	-	Ophth.	S	84.6	NR
Lawrence (2004)	Exam	-	-	Ophth.	S	85.6	NR
Harding (1995)	Exam	-	-	Ophth.	S	40 (15 - 65)	99 (98 - 100)
Lin (2002)	Exam	-	-	Ophth.	S	34	100
Boucher (2003)	Exam	-	-	Re S	S	73.3	99
Pugh (1993)	Exam	-	-	Ophth. / Re S	NR	33	99
Pugh (1993)	Exam	-	-	Phys. Ass.	NR	14	99
Taylor (1999)	Polaroid + Exam	1	-	NR	S	95 (91 - 99)	97 (95 - 99)
				Mean (Range)		***S_n:*** 70.0 (14 - 99)	***S_p:*** 97.0 (90 - 100)

Key: NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; Phys. Ass.: Physician Assistant; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=10)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	96.8	85.7
Hansen (2004)	Digital	5	Opto.	NR	S	97.7	87.5
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	77.3	NR
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	78.2	NR
Lopez-Bastida (2007)	Digital	4	Re S	NR	S	100	100
Lin (2002)	Digital	1	Photo. / Tech.	Grader	S	78	86
Lin (2002)	Digital	1	Photo. / Tech.	Grader	S	100	71
Boucher (2003)	Digital	2	NR	Re S	S	94	94.1
Pugh (1993)	Film	1	Nurse	Grader	NR	61	85
Pugh (1993)	Film	1	Nurse	Trainee Ophth.	NR	54	87
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	94	100
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	94	100
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	94	100
				Mean (Range)		***S_n:*** 83.6 (54 - 100)	***S_p:*** 90.7 (85 - 100)

Key: NR: Not Reported; Ophth.: Ophthalmologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Mixed Mydriatic / Non-Mydriatic (n=2)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Molina Fernandez (2008)	Digital	3	GP	Ophth.	S	92.7 (79 - 98.1)	99.5 (96.6 - 100)
Molina Fernandez (2008)	Digital	3	GP	GP	S	95.2 (82.9 - 99.2)	81.5 (75.9 - 86.1)
				Mean (Range)		***S_n:*** 94.0 (92.7 - 95.2)	***S_p:*** 90.5 (81.5 - 99.5)

Key: ~ Dilation was not reported; GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; Opto.: Optometrist; Re S: Retinal Specialist

Mean sensitivity was highest for mixed (94.0, n=2), followed by non-mydriatic (83.6, n=10) and mydriatic (70.0, n=17). Conversely, mean specificity was highest for mydriatic methods (97.0) followed by mixed (90.5) and non-mydriatic methods (90.7).

One outreach study (Harding 1995) measured sensitivity and specificity for 'Moderate NPDR as a threshold'. This study screened 326 patients using mydriatic 3-field film photography (technician imager, graded by optician / optometrist) and yielded a sensitivity of 47.0 (well below group mean) and specificity of 100 (higher than group mean).

Table 11j: Sensitivity and Specificity to detect Severe NPDR (n=1)

Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	57.0	99.0

Key: NR: Not Reported; S: Static

Table 11k: Sensitivity and Specificity to detect ≥ Severe NPDR as threshold (n=9)

Mydriatic (n=6)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Fransen (2002)	Digital	7	Photo. / Tech.	Grader	S	92	90.2
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	100	NR
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	100	NR
Lawrence (2004)	Exam	-	-	Ophth.	S	100	NR
Lawrence (2004)	Exam	-	-	Ophth.	S	91.7	NR
Boucher (2003)	Exam	-	-	Re S	S	33.3	100
				Mean (Range)		***S_n:*** 86.2 (33.3 - 100)	***S_p:*** 95.1 (90.2 - 100)

Key: Ophth.: Ophthalmologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=3)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Boucher (2003)	Digital	2	NR	Re S	S	14.3	100
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	92.3	NR
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	92.3	NR
				Mean (Range)		***S_n:*** 66.3 (14.3 - 92.3)	***S_p:*** 100

Key: NR: Not Reported; Ophth.: Ophthalmologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Mean sensitivity was higher for mydriatic (86.2, n=6) than non-mydriatic methods (66.3, n=3) for 'Severe NPDR as a threshold'. Only one of the three non-mydriatic methods reported a specificity value (100), and only two mydriatic methods reported specificity (mean 95.1).

No outreach studies measured this outcome.

Table 11l: Sensitivity and Specificity to detect Mild, Moderate and Severe NPDR (n=1)

Mydriasis Not Reported (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Moller (2002)	Film	1	NR	Ophth.	S	88.9	NR

Key: NR: Not Reported; Ophth.: Ophthalmologist; S: Static

Table 11m: Sensitivity and Specificity to detect PDR (n=5)

Mydriatic (n=2)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Sussman (1982)	Exam	-	-	Diabet. / Endo.	NR	49	84
Sussman (1982)	Exam	-	-	Re S	NR	96	93
				Mean (Range)		***S_n:*** 72.5 (49 - 96)	***S_p:*** 88.5 (84 - 93)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; NR: Not Reported; Re S: Retinal Specialist

Non-mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	89.0	97.0

Key: NR: Not Reported; S: Static

Mixed Mydriatic / Non-Mydriatic or Mydriasis Not Reported (n=2)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Maberley (2002)	***Digital (85% patients were dilated)***	***1***	***Mixed***	***Re S***	***O***	***100***	***99.7***
Schmid (2002) ~	Film	NR	NR	Opto.	NR	89.5	NR

Key: ~ Dilation was not reported

Only two mydriatic methods reported sensitivity (mean 72.5) and specificity (88.5). One non-mydriatic method yielded a sensitivity of 89 and a specificity of 97. Two methods in the mixed / not reported category reported a mean sensitivity of 94.8 and there was one sensitivity value in this group (99.7)

One outreach study measured sensitivity and specificity for 'PDR'. Maberley (2002) studied 100 patients using mixed mydriasis (85% of sample mydriatic) and a 1-field digital camera (mix of imagers, graded by a retinal specialist) and yielded a sensitivity of 100 (highest value of all) and a specificity of 99.7 (highest value of all) for this outcome.

Table 11n: Sensitivity and Specificity to detect ≥ PDR as threshold (n=7)

Mydriatic (n=4)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	100	NR
Lawrence (2004)	Digital	3	Photo. / Tech.	Ophth.	S	100	NR
Lawrence (2004)	Exam	-	-	Ophth.	S	100	NR
Lawrence (2004)	Exam	-	-	Ophth.	S	100	NR
				Mean (Range)		***S_n:*** 100	***S_p:*** NR

Key: Ophth.: Ophthalmologist; Photo.: Photographer; S: Static; Tech.: Technician

Non-Mydriatic (n=3)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	100	86
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	100	NR
Lawrence (2004)	Digital	1	Photo. / Tech.	Ophth.	S	100	NR
				Mean (Range)		***S_n:*** 100	***S_p:*** 86.0

Key: Ophth.: Ophthalmologist; Photo.: Photographer; S: Static; Tech.: Technician

All sensitivity values across mydriatic (n=4) and non-mydriatic (n=3) methods were 100. Of all measures, only one non-mydriatic method yielded a specificity value (86).

No outreach studies measured this outcome.

Table 11o: Sensitivity and Specificity to detect Mild or Moderate NPDR AND Macular Oedema (n=12)

Mydriatic (n=12)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
O'Hare (1996)	*Polaroid*	*1*	*Photo. / Tech.*	*Ophth.*	*O*	*55*	*90*
O'Hare (1996)	*Polaroid*	*1*	*Photo. / Tech.*	*Ophth.*	*O*	*61*	*90*
O'Hare (1996)	*Polaroid*	*1*	*Photo. / Tech.*	*Ophth.*	*O*	*58*	*90*
O'Hare (1996)	*Exam*	*-*	*-*	*GP*	*O*	*22*	*94*
O'Hare (1996)	*Exam*	*-*	*-*	*Optician*	*O*	*43*	*94*
O'Hare (1996)	*Exam*	*-*	*-*	*Mixed*	*O*	*33*	*94*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*GP*	*O*	*37*	*92*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*Optician*	*O*	*55*	*94*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*Mixed*	*O*	*47*	*93*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*Mixed*	*O*	*60*	*91*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*Mixed*	*O*	*71*	*92*
O'Hare (1996)	*Polaroid + Exam*	*1*	*Photo. / Tech.*	*Mixed*	*O*	*66*	*91*
				Mean (Range)		S_n: 50.7 (22 - 71)	S_p: 92.1 (90 - 94)

Key: GP: General Practitioner; O: Outreach; Ophth.: Ophthalmologist; Photo.: Photographer; Tech.: Technician

All values in 'Mild or Moderate NPDR and Macular Oedema' were derived from one outreach study (O'Hare 1996). This study of 1010 patients investigated multiple screening methods comprising stand-alone imaging (Polaroid 1-field), stand-alone examination and a combination of the two with various grader combinations (GP, Optician, Ophthalmologist). The mean sensitivity for the 12 mydriatic methods investigated was 50.7 and the mean specificity 92.1.

Table 11p: Sensitivity and Specificity to detect ≥ Moderate NPDR AND / OR Macular Oedema OR Ungradable (n=4)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Massin (2003)	Exam	-	-	Re S	S	82 (76 - 88)	97 (93 - 100)

Key: Re S: Retinal Specialist; S: Static

Non-Mydriatic (n=3)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Massin (2003)	Digital	5	Mixed	Re S	S	92 (86 - 98)	88 (81 - 95)
Massin (2003)	Digital	5	Mixed	Re S	S	100	85 (77 - 93)
Massin (2003)	Digital	5	Mixed	Re S	S	92 (86 - 98)	87 (79 - 95)
				Mean (Range)		***S_n:*** 94.7 (92 - 100)	***S_p:*** 86.7 (85-88)

Key: Re S: Retinal Specialist; S: Static

Non-mydriatic methods yielded a higher mean sensitivity (94.7, n=3) than for non-mydriatic method (82.0, n=1) for 'Moderate NPDR and / or Macular Oedema or Ungradable as a threshold'. Specificity value was instead higher for mydriatic method (97.0) compared to non-mydriatic (86.7).

No outreach studies measured this outcome.

Table 11q: Sensitivity and Specificity to detect ≥ Moderate NPDR OR Macular Oedema as a threshold (n=17)

Mydriatic (n=13)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Scanlon (2003a)	***Digital***	***2***	***Photo. / Tech.***	***Ophth.***	***O***	***87.8 (83 - 92.6)***	***86.1 (84.2 - 87.8)***
Olson (2003)	Digital	2	Photo. / Tech.	Trainee Ophth.	NR	93 (82 - 98)	87 (84 - 90)
Olson (2003)	Digital	1	Photo. / Tech.	Trainee Ophth.	NR	93 (83 - 98)	87 (84 - 90)
Scanlon (2003b)	Digital	2	NR	NR	S	80.2 (75.2 - 85.2)	96.2 (93.2 - 99.2)
Scanlon (2003b)	Digital	2	NR	NR	S	82.8 (78 - 87.6)	92.9 (89.6 - 96.2)
Scanlon (2003b)	Film	7	NR	NR	S	96.4 (94 - 98.8)	82.9 (77.4 - 88.4)
Baeza (2009)	Film	3	GP	Ophth.	S	95 (89 - 100)	98 (96 - 99)
Olson (2003)	Film	2	Photo. / Tech.	Trainee Ophth.	NR	96 (87 - 100)	89 (86 - 81)
Baeza (2009)	Film	2	GP	Ophth.	S	95 (89 - 100)	98 (97 - 100)
Baeza (2009)	Film	1	GP	Ophth.	S	82 (72 - 92)	99 (97 - 100)
Olson (2003)	Film	1	Photo. / Tech.	Trainee Ophth.	NR	95 (85 - 99)	89 (86 - 92)
Scanlon (2003b)	Exam	-	-	Ophth.	S	87.4 (83.5 - 91.5)	94.9 (91.5 - 98.3)
Olson (2003)	Exam	-	-	Optician / Opto.	S	73 (52 - 88)	90 (87 - 93)
				Mean (Range)		***S_n:*** 89.0 (73.0 - 96.4)	***S_p:*** 91.5 (82.9 - 99)

Key: GP: General Practitioner; NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician

Non-Mydriatic (n=4)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Scanlon (2003a)	***Digital***	***1***	***Photo. / Tech.***	***Ophth.***	***O***	***86 (80.9 - 91.1)***	***76.7 (74.5 - 78.9)***
Baeza (2009)	Film	3	GP	Ophth.	S	82 (71 - 92)	99 (98 - 100)
Baeza (2009)	Film	2	GP	Ophth.	S	80 (69 - 91)	99 (98 - 100)
Baeza (2009)	Film	1	GP	Ophth.	S	67 (54 - 80)	99 (98 - 100)
				Mean (Range)		***S_n:*** 78.8 (67 - 82)	***S_p:*** 93.4 (76.7 - 99)

Key: GP: General Practitioner; O: Outreach; Ophth.: Ophthalmologist; Photo.: Photographer; S: Static; Tech.: Technician

The mean value for mydriatic methods (89.0, n=13) was greater than that for non-mydriatic methods (78.8, n=4). Specificity values were similar, with means of 91.5 and 93.4 for mydriatic and non-mydriatic methods respectively.

One outreach study measured sensitivity and specificity for 'Moderate NPDR or Macular Oedema as a threshold'. Scanlon (2003a) studied 3611 patients using a mydriatic 2-field digital camera (photographer / technician imager, graded by an ophthalmologist) and yielded a sensitivity of 87.8 (lower than group mean) and a specificity of 86.1 (lower than group mean) for this outcome.

Table 11r: Sensitivity and Specificity to detect ≥ Moderate NPDR OR CSME as a threshold (n=6)

Mydriatic (n=6)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Diabet. / Endo.	NR	92 (64 - 99)	95 (89 - 98)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Grader	NR	85 (55 - 98)	94 (88 - 98)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Ophth.	NR	85 (55 - 98)	91 (84 - 96)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Ophth.	NR	85 (55 - 98)	88 (80 - 94)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Ophth.	NR	77 (46 - 95)	73 (62 - 81)
Liesenfeld (2000)	Digital	2	Photo. / Tech.	Diabet. / Endo.	NR	70 (39 - 91)	88 (80 - 94)
				Mean (Range)		***S_n:*** 82.3 (70 - 92)	***S_p:*** 88.2 (73 - 95)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; NR: Not Reported; Ophth.: Ophthalmologist; Photo.: Photographer; Tech.: Technician

Six mydriatic methods yielded a mean sensitivity of 82.3 and specificity of 88.2 for this outcome.

No outreach studies measured this outcome.

Table 11s: Sensitivity and Specificity to detect ≥ Moderate NPDR AND / OR ≥ Macular Oedema as a threshold (n=13)

Mydriatic (n=13)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Prasad (2001)	Exam	-	-	Opto.	S	76.0 (70 - 81)	95.0 (95 - 96)
O'Hare (1996)	***Polaroid***	***1***	***Photo. / Tech.***	***Ophth.***	***O***	***68***	***97***
O'Hare (1996)	***Polaroid***	***1***	***Photo. / Tech.***	***Ophth.***	***O***	***75***	***99***
O'Hare (1996)	***Polaroid***	***1***	***Photo. / Tech.***	***Ophth.***	***O***	***71***	***99***
O'Hare (1996)	***Exam***	***-***	***-***	***GP***	***O***	***56***	***98***
O'Hare (1996)	***Exam***	***-***	***-***	***Optician***	***O***	***75***	***93***
O'Hare (1996)	***Exam***	***-***	***-***	***Mixed***	***O***	***65***	***96***
O'Hare (1996)	***Polaroid+ Exam***	***1***	***Photo. / Tech.***	***GP***	***O***	***60***	***98***
O'Hare (1996)	***Polaroid + Exam***	***1***	***Photo. / Tech.***	***Optician***	***O***	***88***	***99***
O'Hare (1996)	***Polaroid + Exam***	***1***	***Photo. / Tech.***	***Mixed***	***O***	***73***	***99***
O'Hare (1996)	***Polaroid + Exam***	***1***	***Photo. / Tech.***	***Mixed***	***O***	***80***	***98***
O'Hare (1996)	***Polaroid + Exam***	***1***	***Photo. / Tech.***	***Mixed***	***O***	***88***	***99***
O'Hare (1996)	***Polaroid + Exam***	***1***	***Photo. / Tech.***	***Mixed***	***O***	***84***	***99***
				Mean (Range)		***S_n:*** 73.8	***S_p:*** 97.6

Key: GP: General Practitioner; Ophth.: Ophthalmologist; Opto.: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician

Thirteen mydriatic methods yielded a sensitivity of 73.8 and a specificity of 97.6 for '≥ Moderate NPDR and / or ≥ Macular Oedema as a threshold'.

One outreach study (O'Hare 1996) generated a total of 12 of the 25 mydriatic outcome measures. This study of 1010 patients investigated multiple screening methods comprising stand-alone imaging (Polaroid 1 field), stand-alone examination and a combination of the two with various grader combinations (GP, Optician, Ophthalmologist). Sensitivity values ranged from 56.0 – 88.0 and specificity values ranged from 93.0 – 99.0.

Table 11t: Sensitivity and Specificity to detect ≥ Severe NPDR OR Macular Oedema as a threshold (n=11)

Mydriatic (n=9)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Fransen (2002)	Digital	7	Photo. / Tech.	Grader	S	98.2 (90.5 - 100)	89.7 (85.1 - 93.3)
Murgatroyd (2004)	Digital	3	Photo. / Tech.	Ophth.	NR	83 (78 - 88)	93 (91 - 96)
Murgatroyd (2004)	Digital	1	Photo. / Tech.	Ophth.	NR	81 (76 - 87)	92 (90 - 94)
Verma (2003)	Exam	-	-	GP	S	95.8	86.5
Verma (2003)	Exam	-	-	Opto.	S	77.1	89.4
Warburton (2004)	Exam	-	-	Opto.	S	75.8 (49.3 - 100)	99 (98.6 - 99.3)
Pandit (2002)	***Polaroid + Exam***	***NR***	***Photo. / Tech. +***	***Grader +***	***O + S***	***83.3***	***96.8***
Pandit (2002)	Polaroid + Exam	NR	Diabet.	Diabet. / Endo.	S	82.5	98
Pandit (2002)	***Polaroid + Exam***	***NR***	***Photo. / Tech.***	***Grader***	***O***	***85.7***	***95.7***
				Mean (Range)		S_n: 84.7 (75.8 - 98.2)	S_p: 93.4 (86.5 - 99)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; GP: General Practitioner; NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Non-Mydriatic (n=2)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Murgatroyd (2004)	Digital	1	Photo. / Tech.	Ophth.	NR	77 (71 - 84)	95 (93 - 97)
Peters (1993)	Polaroid	1	Nurse	Diabet. / Endo.	NR	74	NR
				Mean (Range)		S_n: 75.5 (74 - 77)	S_p: 95.0

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; NR: Not Reported; Ophth.: Ophthalmologist; Photo.: Photographer; Tech.: Technician

Mean sensitivity for mydriatic (84.7, n=9) was greater than for non-mydriatic (75.5, n=2). Specificity values were similar, with a mean of 93.4 for mydriatic methods and a single value of 95 from one non-mydriatic method.

One outreach study generated two sensitivity and specificity measures for 'Severe NPDR or Macular Oedema as a threshold'. Pandit (2002) studied 609 patients using a combination of Polaroid photography and examination with variations in imager and grader, yielding two sensitivity measures (83.3, 85.7, either side of group mean) and two specificity measures (96.8, 95.7, both above group mean) for this outcome.

Table 11u: Sensitivity and Specificity to detect ≥ Severe NPDR AND Macular Oedema as a threshold (n=1)

Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Hulme (2002)	Exam	-	-	Opto.	S	87.0	91.0

Key: Opto.: Optometrist; S: Static

Table 11v: Sensitivity and Specificity to detect PDR or CSME (n=1)

Mixed Mydriatic / Non-Mydriatic (n=1)

Citation	Screening Instrument	Photo Fields	Imager	Grader	Location	Sensitivity (95% CI)	Specificity (95% CI)
Maberley (2002)	***Digital (85% patients were dilated)***	***1***	***Mixed***	***Re S***	***O***	***93.3***	***96.8***

Key: O: Outreach; Re S: Retinal Specialist

One outreach study measured sensitivity and specificity for 'PDR or CSME'. Maberley (2002) studied 100 patients using mixed mydriasis (85% of sample mydriatic) and a 1-field digital camera (mix of imagers, graded by a retinal specialist) and yielded a sensitivity of 93.3 and a specificity of 96.8.

STATISTICAL ANALYSIS OF THE RELEVANCE OF SCREENING ACCURACY FINDINGS TO THE AUSTRALIAN INDIGENOUS CONTEXT

Introduction

DR screening in the Australian Indigenous setting presents two key challenges. First, Indigenous adults have much higher rates of blindness than the mainstream Australian community (Taylor 2009). Second, geographical isolation and economic disadvantage create barriers to accessing and affording health services to address the causes of blindness (CERA 2001), which include diabetic eye disease (CERA 2001; Taylor 2009).

These dual challenges have been met by using a DR screening approach that is portable and cost-efficient. A screening program developed specifically for the Kimberley region of Australia employed a camera operated by two minimally trained local Aboriginal health care workers and one Aboriginal nurse, with photos interpreted remotely by an ophthalmologist (Murray 2005); a program designed for rural Victoria involved non-mydriatic polaroid photography performed by a photographer, remotely graded by an ophthalmologist (Harper 1998).

This approach is reflected in studies in comparable settings outside of Australia. Leese (1992) used non-mydriatic polaroid photography housed in a mobile unit with imaging performed by a photographer to evaluate DR prevalence in Tayside, United Kingdom, which has a population of 390 000 spread over 3000 square miles; in another UK-based study, Taylor (1990) evaluated non-mydriatic photography (imager not reported) using a camera mounted in a transit ambulance.

All 62 studies eligible for this review were classified into two categories based upon the location of DR screening: 'Static' (screening methods based in private rooms, hospital department) and 'Outreach' (the provision of portable infrastructure / personnel to enable a DR screening service to be given to a population). The majority of Diabetic Retinopathy screening methods in 'outreach' category were consistent with those described above (which did not meet the criteria for inclusion in this review). Specifically, they involved use of a camera operated by a person without specialist medical or eye qualifications with variable use of mydriasis. Of the sixteen screening methods investigated in the nine outreach studies, nine were camera-based, three involved examination, and four involved a combination of camera and examination. For ten of the 13 methods involving a camera, information regarding the person taking the image was available. In seven cases this was a photographer, technician or health care worker (n=7); in three cases, a qualified health professional, optician or trained retinal screener were involved in taking the image. Ten involved use of pharmacological mydriasis, five were non-mydriatic and one a mix of mydriatic / non-mydriatic.

In summary, the predominant features of 'outreach' screening methods are:

1. Camera-based rather than direct examination
2. Camera operated by a photographer / technician or minimally trained health worker, rather than a qualified health professional
3. Remote interpretation of the image by an eye specialist
4. Non-mydriatic rather than use of pharmacological mydriasis.

No previous reviews have statistically explored the relative effectiveness of such 'outreach' screening methods, compared to other DR screening methods. Therefore, the aim of this statistical analysis was to explore the effect of variations in two key characteristics of 'outreach' screening methods – mydriasis and imager qualifications - on the accuracy of DR screening as measured by sensitivity and specificity.

Methods

Data source

Sensitivity / specificity outcomes for which there were more than 25 outcome measures were identified from previously extracted review data (see previous section). These were:

a. 'Any DR' (40 sensitivity and specificity measures from 20 studies)
b. 'Moderate Non-Proliferative Diabetic Retinopathy (NPDR) as Threshold' (i.e. Moderate NPDR or worse according to the International Clinical DR Disease Severity Scale) (29 sensitivity measures from 11 studies; 23 specificity measures from 10 studies)

These outcome categories encompass the identification of any DR disease and the referral threshold of the International Clinical DR Disease Severity Scale (American Academy of Ophthalmology 2002).

To examine the differential effect of 'outreach' screening combinations on sensitivity and specificity, all screening methods from all review papers reporting these two outcomes were classified into one of the following six categories:

1. **Non-Mydriatic Camera, Non-specialist imager (NMNS):** Non-Mydriatic Photography performed by a person with no specialist eye qualifications (nurse, photographer, technician)
2. **Mydriatic Camera, Non-specialist imager (MNS):** Mydriatic Photography performed by a person with no specialist eye qualifications (nurse, photographer, technician)
3. **Non-Mydriatic Camera, Specialist imager (NMS):** 'Non-Mydriatic Photography performed by a trained health professional (GP, diabetologist) or person with specialist eye qualifications (ophthalmologist, retinal specialist, optometrist)
4. **Mydriatic Camera, Specialist imager (MS):** Mydriatic Photography performed by a trained health professional (GP, diabetologist) or person with specialist eye qualifications (ophthalmologist, retinal specialist, optometrist)
5. **Mydriatic Examination (ME):** All examination methods (all were mydriatic)
6. **Other (O):** All other methods (e.g. imager not reported, combinations of exam and camera)

The focus of the statistical analysis was the effect of mydriasis and imager qualifications on screening accuracy.

Statistical methods

As both the methodology and the quality of the description of the statistical methods varied greatly across studies, the unit of analysis for each test investigated within each study was taken to be the number of patients rather than number of eyes. This produces conservative inferences, in that precision for each test within each study may be less than that existent in the actual study. The quoted sensitivities and specifities in each paper were then applied to the number of patients, producing a standard 2x2 table for each test within each paper. Where specificities of 100% were present, these were modified to enable inclusion by reducing the number of true negatives by one. This is similar to the common practice of adding 0.5 to zero cells in a 2x2 table, except here the value of 1 was used to enable software program compatibility.

The computation of 95% confidence intervals for presentation of individual test sensitivities and specificities in the forest plots used the Wilson score interval method. This produces asymmetric confidence intervals when proportions are close to zero or unity. These intervals were provided for presentation only – they were not used in the calculation of the overall pooled sensitivity and specificity.

To account for multiple tests being reported within each study and for heterogeneity of sensitivity and specificity across studies, a three-level random-intercepts logistic regression model using 20 numerical quadrature points was employed to produce summary estimates (procedure xtmelogit in Stata v10.1). This model assumes that conditional upon the random effects at study and test-wthin-study level, that the number of true positive (or negative) test assessments are independently binomially distributed. This model accommodates heterogeneity in the sensitivity/specificity (on the logit scale) between studies, and also between tests within the same study. It produces pooled (combined) odds ratios and confidence intervals on the logit scale and both the estimates and CI endpoints were back-transformed to the probability scale for presentation.

An inevitable limitation of the model structure above arises because the individual level data was not available. The model therefore assumes that each test within a study involves a different set of subjects. As such, the within-study comparisons of tests are conservative (ie produce larger SE's) because the within-test-within-individual correlation (assuming it is positive) is not taken into account in these analyses due to the data not being available.

Ideally, when assessing differences between subgroups of tests (e.g. mydriasis vs. no mydriasis), one would allow the between study heterogeneity to vary across the subgroups, and also for the between-test-within-study heterogeneity to vary across subgroups. However, the small number of studies and tests within studies precluded reliable estimation of these additional variance components, and hence all models assume that each subgroup has a common level of heterogeneity across studies and tests-within-studies.

Some convergence problems arose with fitting the three level random intercept models, particularly when the number of studies was very small. In these cases the test-within-study variance component was omitted, and modelling proceeded using the between-study variance component only. Omitting the test-within-study random effect involves an assumption of independence of observations within the same study, and that the true (logit of) sensitivity and specificity for a test differs from the true study value only because of a common systematic effect of the test across all studies, rather than there being an additional random element for this difference.

Additional models were fit for each of the subgroups separately. These produced estimates of sensitivity and specificity very close to those of the combined models. However the width of the confidence intervals did differ occasionally due to differing between-study and between-test-within-study heterogeneity across subgroups being present. As mentioned above, these sources of additional heterogeneity were not modelled in the combined analyses. However the combined analyses posses the distinct advantage of being able to directly assess differences in sensitivity/specificity across subgroups (e.g. Mydriasis vs. No Mydriasis). This is not able to be performed from the individual subgroup analyses due to the overlap in the source studies of the two subgroups producing correlated estimates, and for which the correlation is unknown.

Results

Influence of Mydriasis and Imager Qualifications on Sensitivity and Specificity to Detect 'ANY DR'

Table 12: Effect of Mydriatic Status and Imager Qualifications on Sensitivity and Specificity to Detect 'ANY DR'

Test (n tests, n studies)	Sensitivity (%)	Sensitivity 95% CI	Specificity (%)	Specificity 95% CI
OVERALL (40, 20)	82.4	76.0 - 88.7	88.2	84.7 - 91.6
Mydriatic Status				
Mydriasis (23, 12)	85.2	79.0 - 91.4	88.8	84.8 - 92.7
No Mydriasis (12, 9)	81.6	74.0 - 89.2	86.8	81.9 - 91.7
MX (5, 4)	74.8	55.7 - 93.8	88.5	80.5 - 96.6
P value Mydriasis vs. No Mydriasis	***p = 0.611***		***p = 0.795***	
Imager Qualification				
Specialist (7, 2)	86.2	71.2 - 99.9	96.0	93.5 - 98.5
Non-Specialist (13, 5)	83.1	74.4 - 91.9	87.3	83.5 - 91.1
Mydriatic Examination (8, 7)	73.0	61.1 - 84.9	83.8	79.2 - 88.4
Other (12, 9)	85.6	77.6 - 93.7	87.4	82.6 - 92.1
P value Specialist vs. Non-Specialist	***p = 0.753***		***p = 0.001***	
Odds Ratio (OR) for Specialist vs. Non-Specialist Imager among those with the same mydriatic status	***OR = 1.39, p = 0.616***		***OR = 4.08, p <0.001***	
OUTREACH				
NMNS (5, 4)	80.6	71.1 - 90.1	83.6	77.8 - 89.4
MNS (8, 3)	84.2	75.8 - 92.6	88.9	85.2 - 92.7
NMS (4, 2)	84.8	68.4 – 99.9	96.4	93.9 – 98.9
MS (3, 1)	90.1	78.5 - 1.00	94.8	90.6 - 99.0
ME (8, 7)	73.0	61.1 - 84.9	83.8	79.2 - 88.4
O (12, 9)	85.6	77.6 - 93.7	87.4	82.6 - 92.1
Odds Ratio (OR) for MS vs. MNS	***OR = 1.61, p = 0.535***		***OR=2.42, p = 0.94***	
Odds Ratio (OR) for NMS vs. NMNS	***OR = 1.31, p = 0.777***		***OR=5.65, p <0.001***	

Key: ME: Mydriatic Examination; MNS: Mydriatic Camera & Non-Specialist Imager; MS: Mydriatic Camera & Specialist Imager; NMNS: Non-mydriatic Camera & Non-Specialist Imager; NMS: Non-mydriatic Camera & Specialist Imager; MX: Mydriasis mixed or Not Reported

Note: Non-Specialist = Non-Specialist Imager (e.g. photographer, technician or nurse) using a camera-based method
Specialist = Specialist Imager (e.g. eye specialist, General Practitioner) using a camera-based method
O = Other, that is all other method (imager qualification or mydriatic status not reported, and a combination of camera & examination)

There was no significant difference in sensitivity or specificity to detect ‘Any DR’ between mydriatic and non-mydriatic methods.

Comparison of specialist and non-specialist imagers yielded no significant difference in sensitivity, but specialist imagers had significantly higher specificity values.

When combining the mydriatic and specialist variables, no significant differences in sensitivity to detect ‘Any DR’ were identified when comparing specialist with non-specialist imagers for either mydriatic or non-mydriatic methods. This non-significant finding held for specificity using mydriatic methods, although there was a trend towards higher values for specialist imagers. However, for non-mydriatic methods, specialist imagers yielded significantly higher specificity values compared to non-specialist imagers.

Figures 2a - 2j present sensitivity and specificity figures, confidence intervals and pooled values overall for ‘Any DR’, and for these combinations of screening variables.

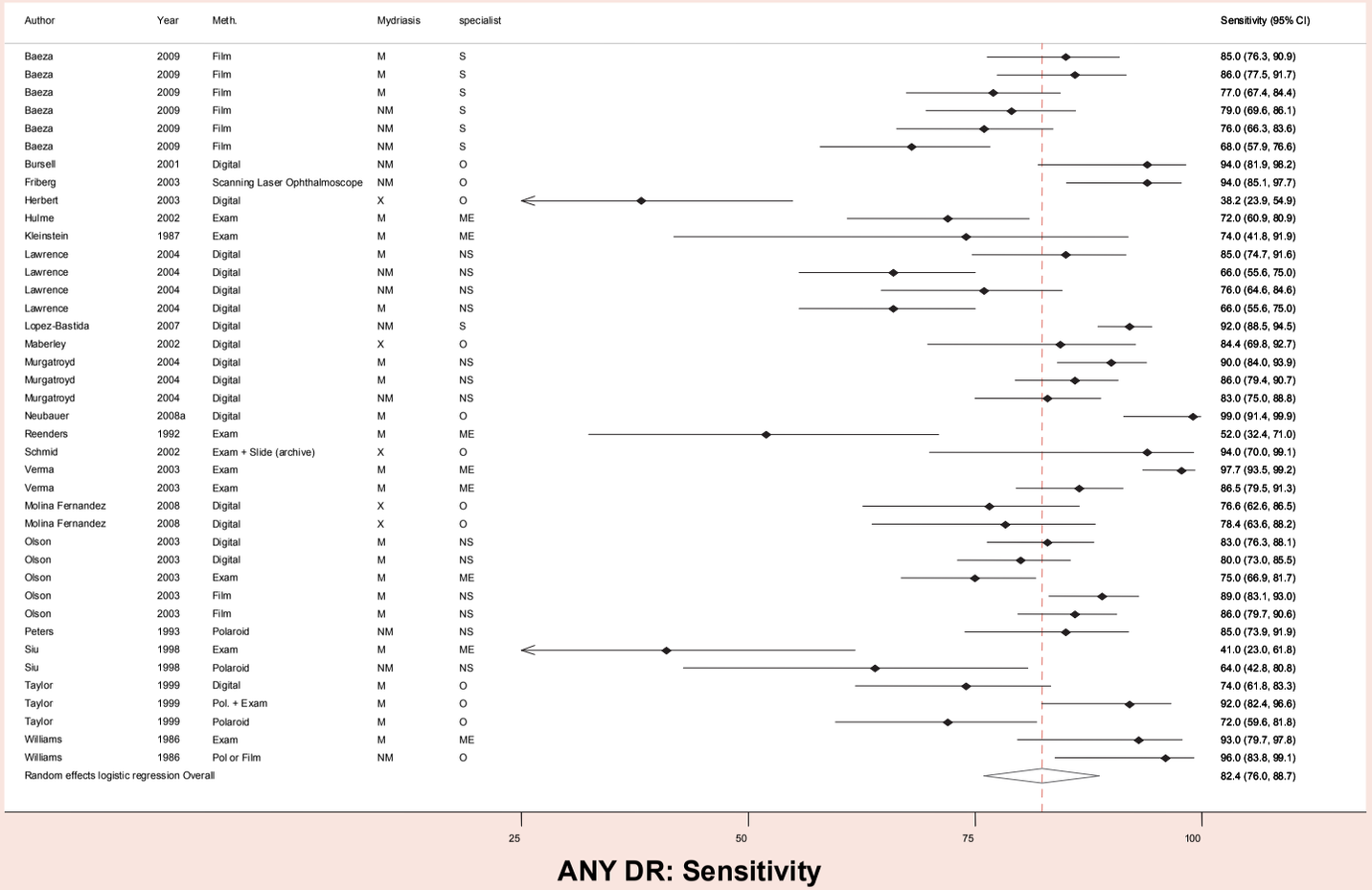

Figure 2a: Sensitivity to Detect 'ANY DR': All Studies

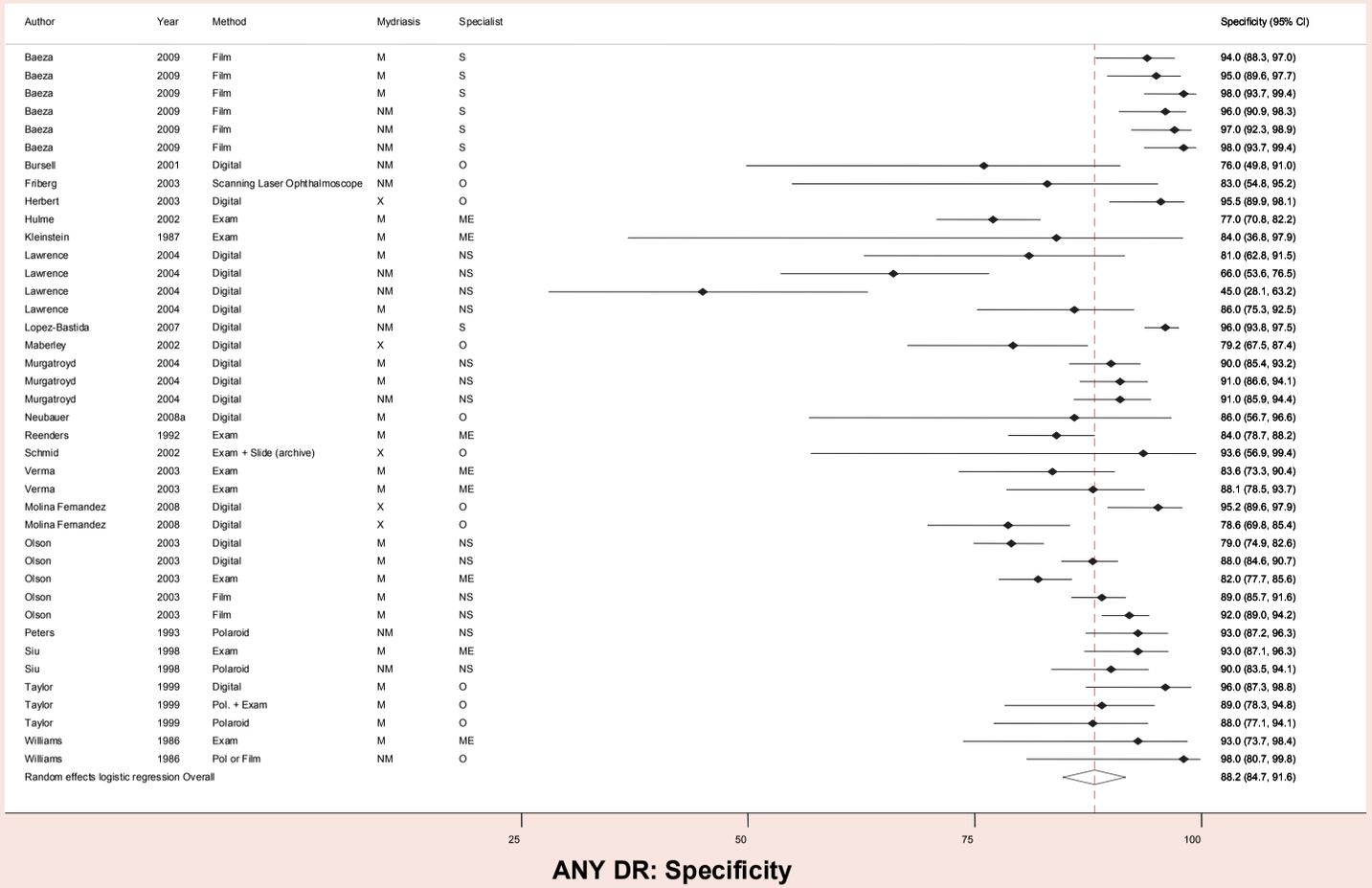

Figure 2b: Specificity to Detect 'ANY DR': All Studies

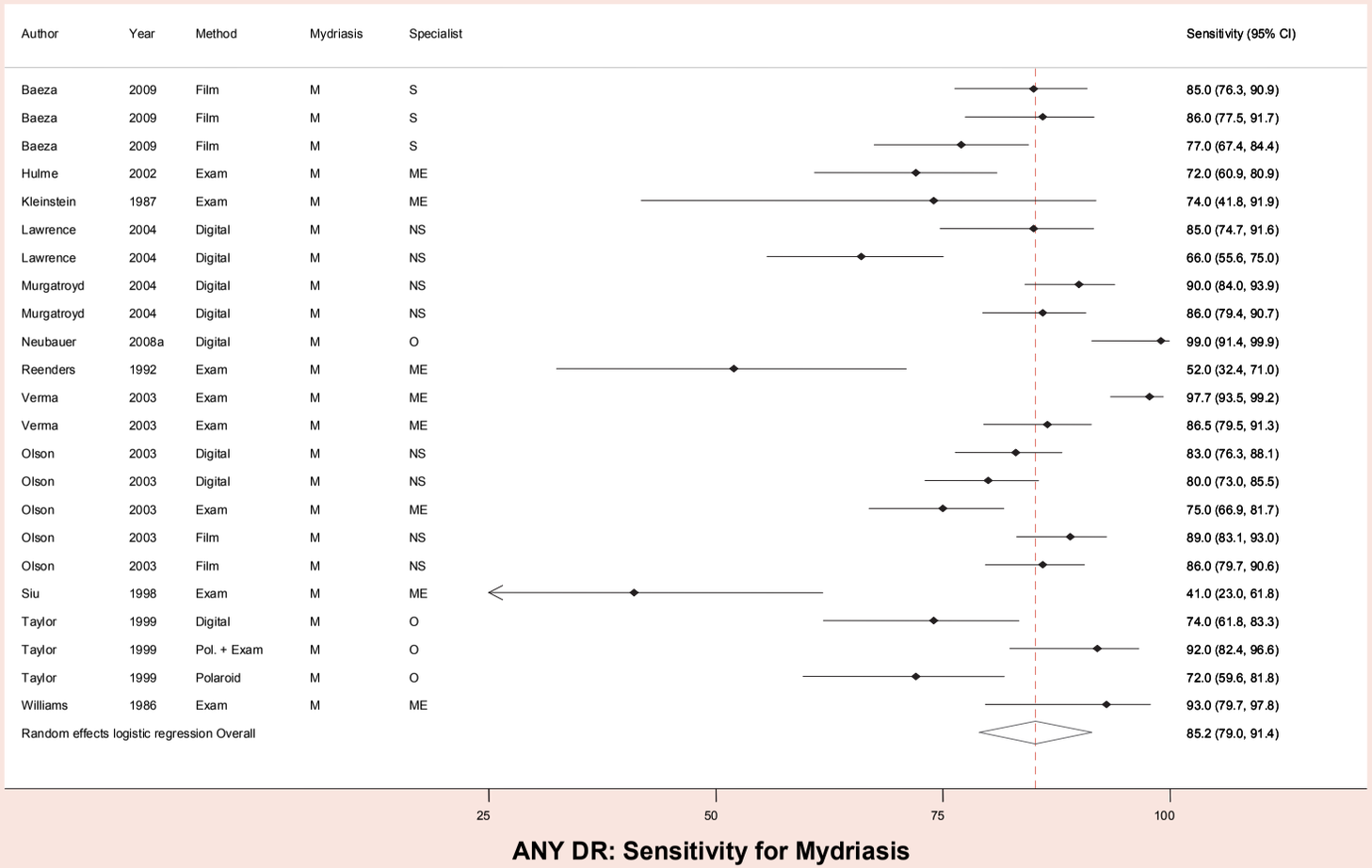

Figure 2c: Sensitivity to Detect 'ANY DR': Mydriasis

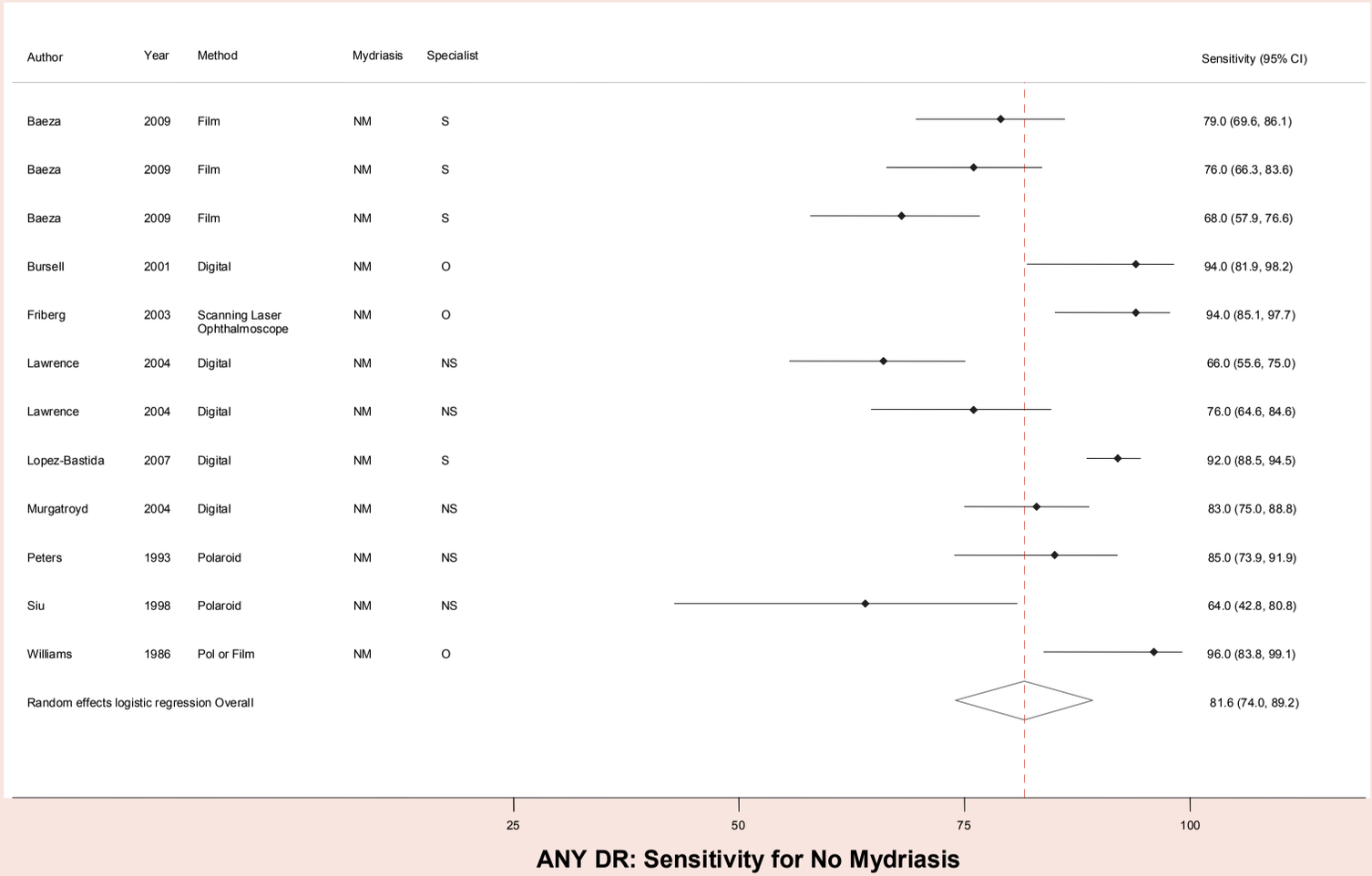

Figure 2d: Sensitivity to Detect 'ANY DR': No-Mydriasis

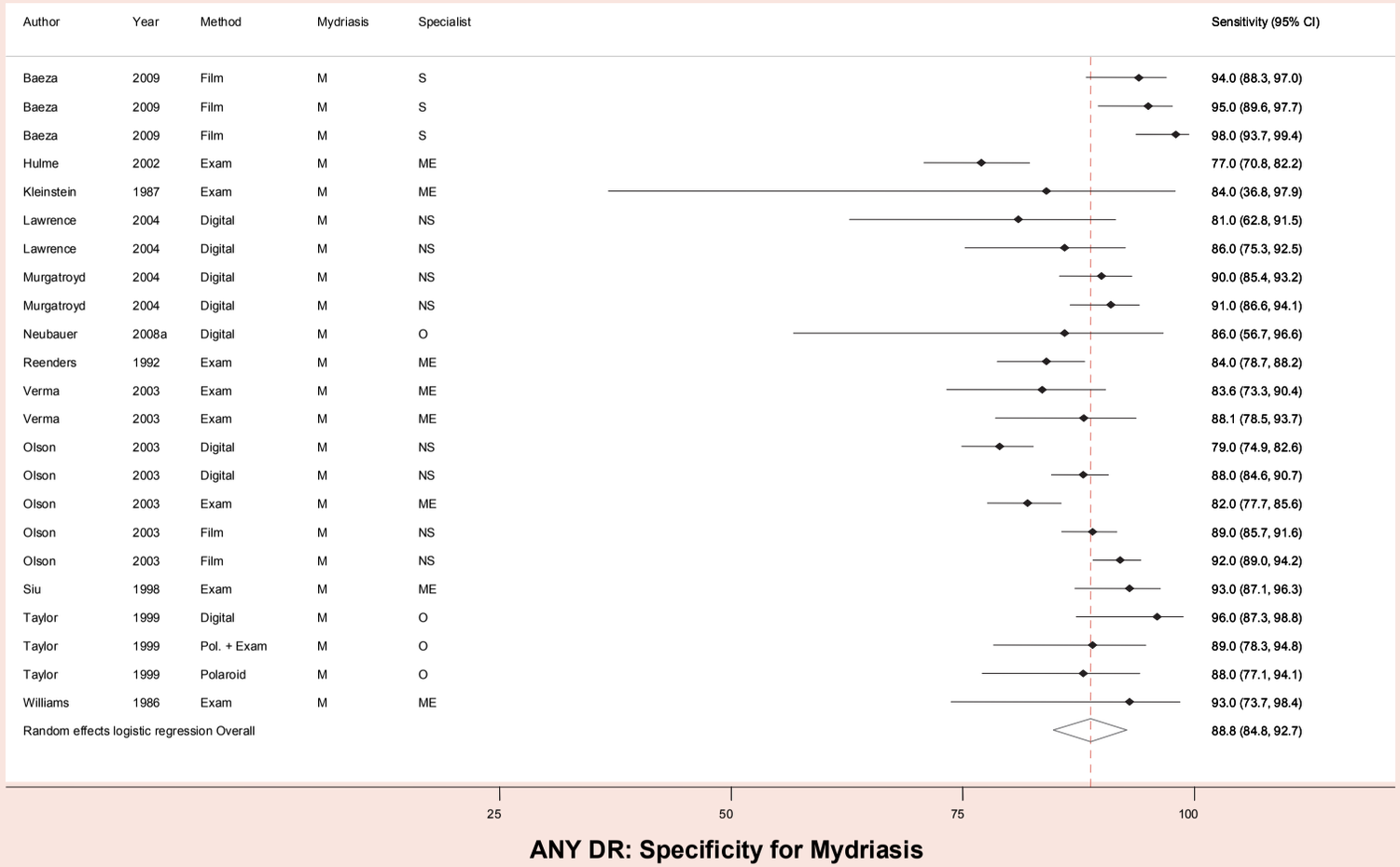

Figure 2e: Specificity to Detect 'ANY DR': Mydriasis

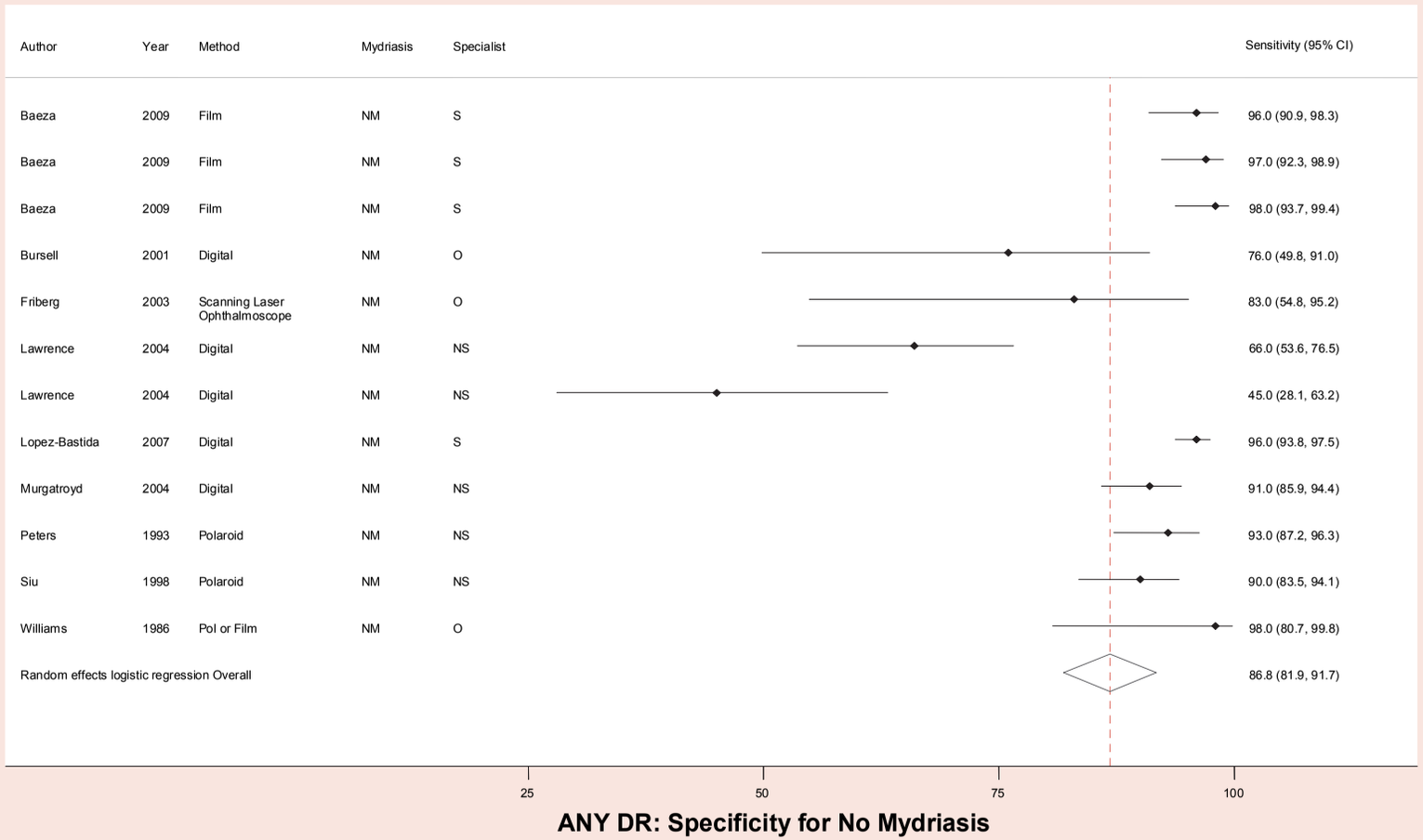

Figure 2f: Specificity to Detect 'ANY DR': No Mydriasis

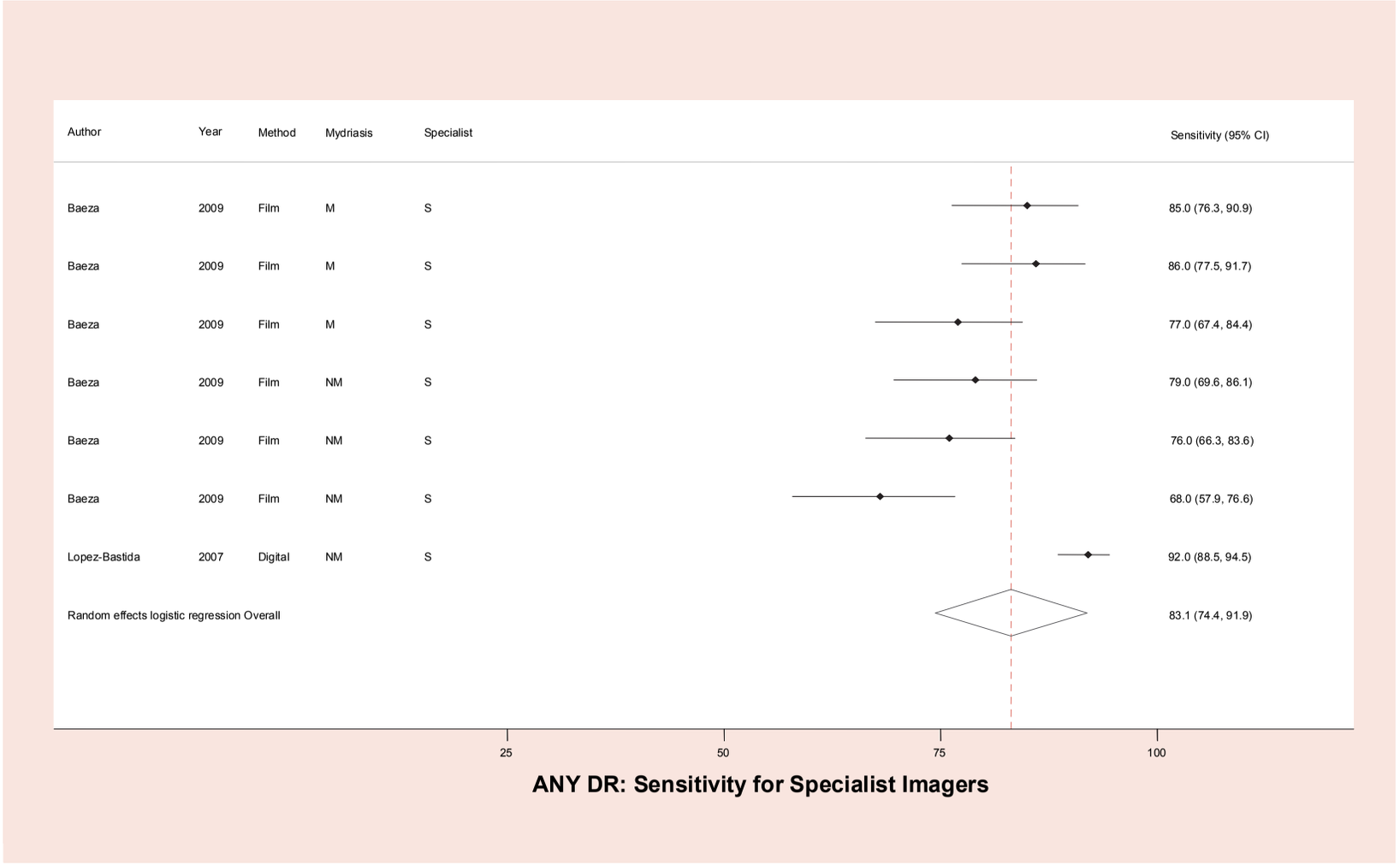

Figure 2g: Sensitivity to Detect 'ANY DR': Specialist Imager (Mydriatic & Non-Mydriatic Combined)

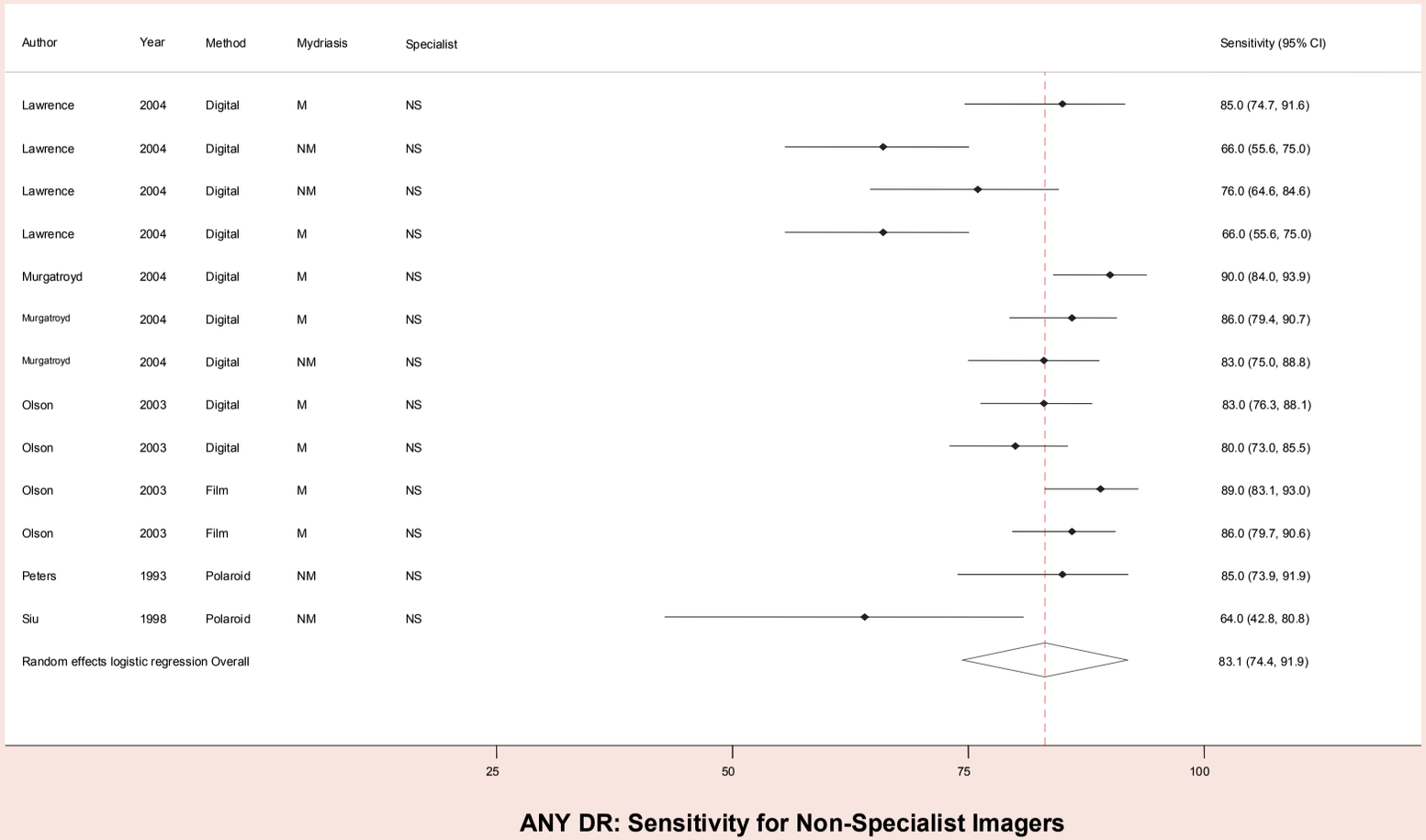

Figure 2h: Sensitivity to Detect 'ANY DR': Non-Specialist Imagers (Mydriatic & Non-Mydriatic Combined)

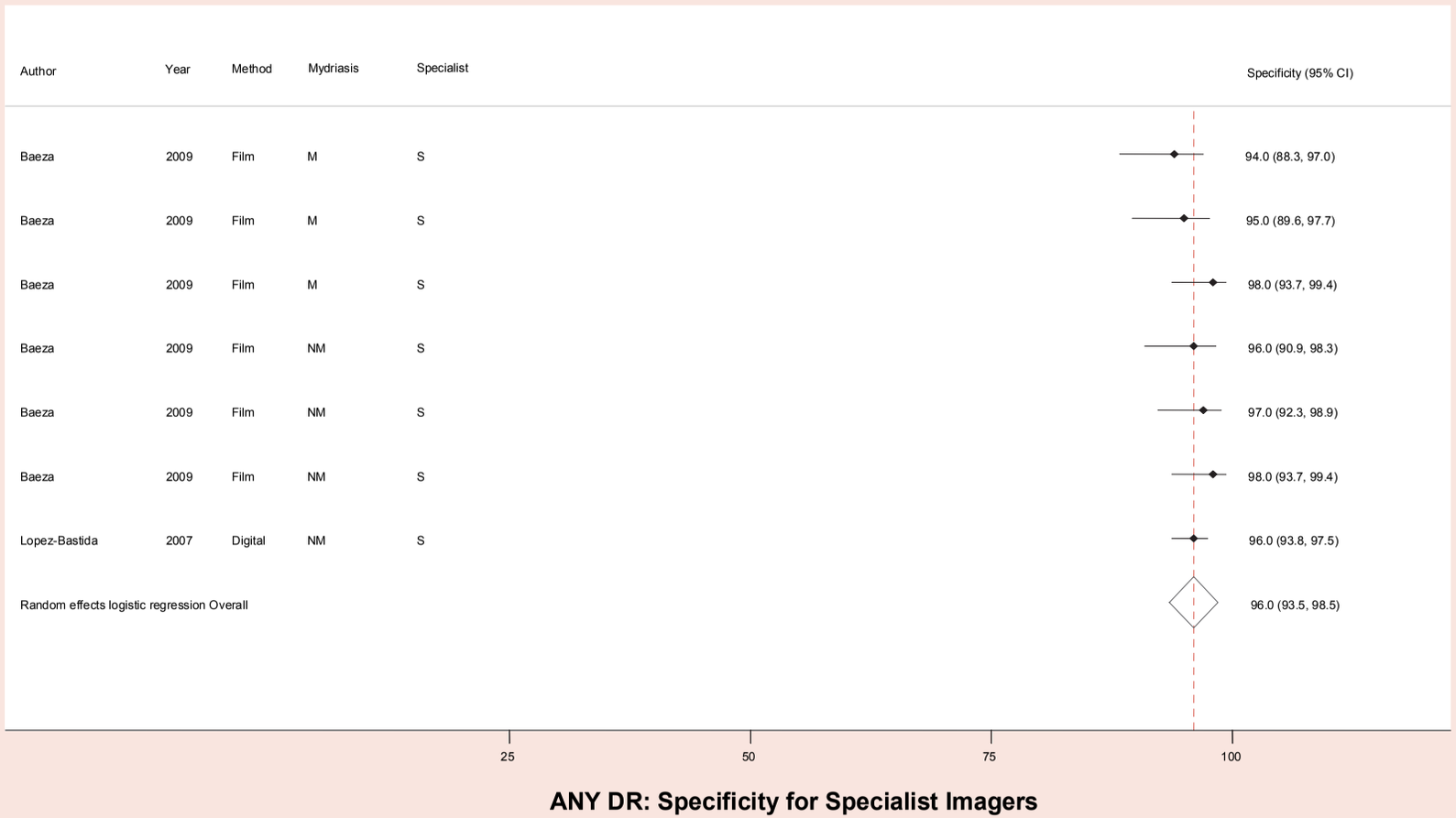

Figure 2i: Specificity to Detect 'ANY DR': Specialist Imagers (Mydriatic & Non-Mydriatic Combined)

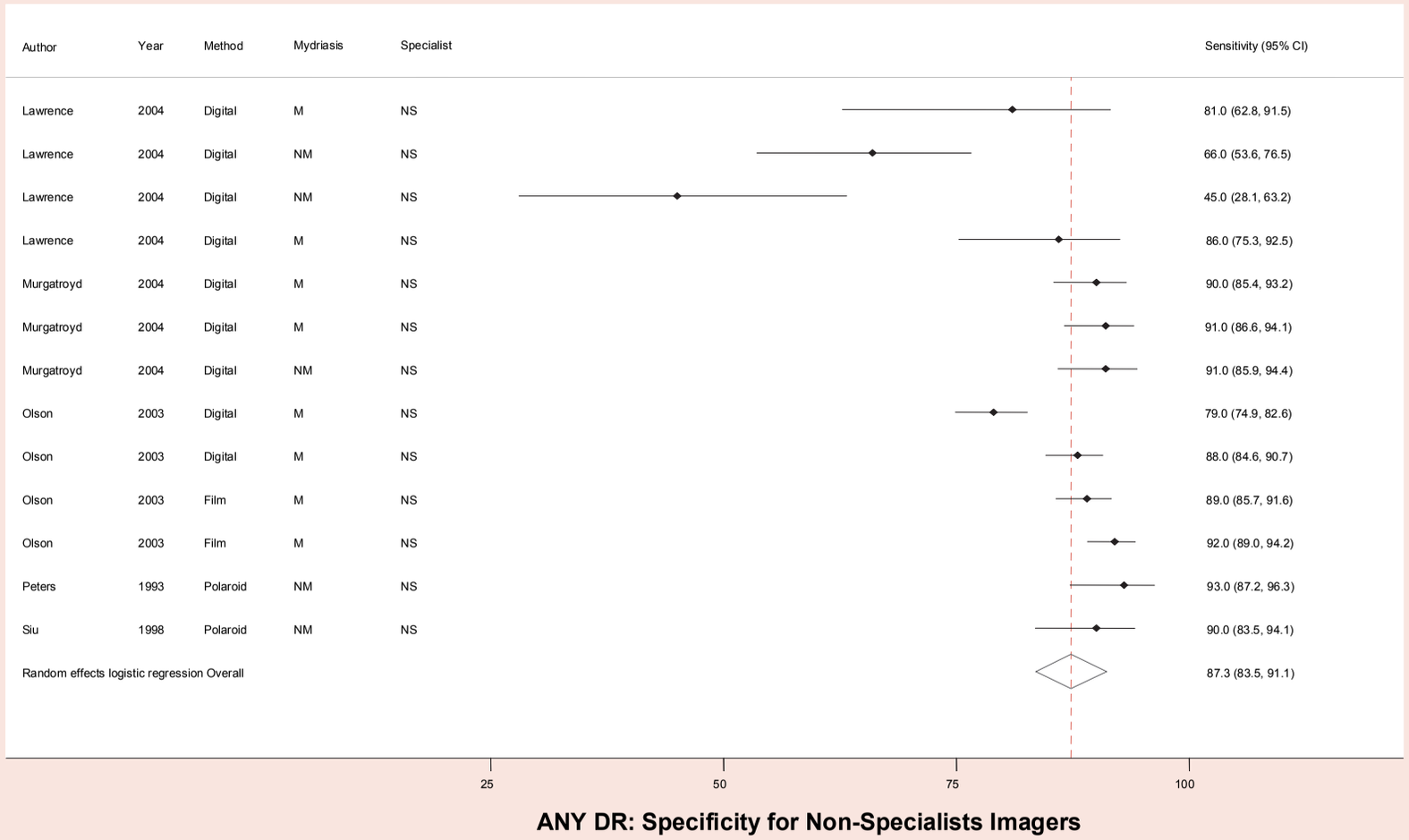

Figure 2j: Specificity to Detect 'ANY DR': Non-Specialist (Mydriatic & Non-Mydriatic Combined)

Influence of Mydriasis and Imager Qualifications on Sensitivity and Specificity to Detect 'Moderate NPDR as threshold'

Table 13: Effect of Mydriatic Status and Imager Qualification on Sensitivity and Specificity to Detect 'Moderate NPDR'

Test (n tests, n studies)	Sensitivity (%)	Sensitivity 95% CI	Specificity (%)	Specificity 95% CI
OVERALL (29, 11)	84.6	69.6 - 92.9	96.4	93.7 - 98.0
Mydriatic Status				
Mydriasis (17, 8)	81.7	64.1 - 91.7	98.1	95.4 - 99.2
No Mydriasis (10, 7)	89.4	76.4 - 95.7	93.1	84.2 - 97.1
MX (2, 1)	69.2	9.1 - 98.1	90.8	44.4 - 99.2
P value Mydriasis vs. No Mydriasis	***p = 0.097***		***p <0.001***	
Imager Qualification				
Specialist (2, 2)	97.4	83.2 - 99.7	99.0	93.0 - 99.9
Non-Specialist (12, 5)	80.4	65.5 - 90.8	93.9	86.7 - 97.3
Mydriatic Examination (7, 5)	58.4	38.4 - 75.9	99.1	97.7 - 99.7
Other (8, 5)	91.0	78.8 - 96.5	93.6	86.2 - 97.2
P value Specialist vs. Non-Specialist	***p = 0.040***		***p = 0.103***	
Odds Ratio (OR) for Specialist vs. Non-Specialist Imager among those without the same mydriatic status #	***OR = 7.25, p = 0.0.76***		***OR = 39.6, p <0.001***	
OUTREACH				
NMNS (6, 4)	77.9	60.2 - 89.1	83.4	75.5 - 89.1
MNS (6, 4)	83.0	67.3 - 92.1	95.3	92.1 - 97.2
NMS (2, 2)	97.4	83.0 - 99.6	99.3	97.7 - 99.8
MS (0, 0)	-	-	-	-
ME (7, 5)	58.5	38.6 - 75.9	99.3	98.5 - 99.6
O (8, 5)	91.0	78.8 - 96.5	94.1	90.4 - 96.4
Odds Ratio (OR) for MS vs. MNS #	-		-	
Odds Ratio (OR) for NMS vs. NMNS	***OR = 10.5 p = 0.031***		***OR = 29.4, p <0.001***	

Key: ME: Mydriatic Examination; MNS: Mydriatic Camera & Non-Specialist Imager; MS: Mydriatic Camera & Specialist Imager; NMNS: Non-mydriatic Camera & Non-Specialist Imager; NMS: Non-mydriatic Camera & Specialist Imager; MX: Mydriasis mixed or Not Reported

Note: #: No data for Specialist Imager with Mydriasis; Non-Specialist = Non-Specialist Imager (e.g. photographer, technician or nurse) using a camera-based method
Specialist = Specialist Imager (e.g. eye specialist, General Practitioner) using a camera-based method
O = Other, that is all other method (imager qualification or mydriatic status not reported, and a combination of camera & examination)

There was no significant difference in sensitivity to detect ‘Moderate NPDR as threshold’ between mydriatic and non-mydriatic methods, although a trend towards higher values for non-mydriatic methods was noted. Conversely, use of mydriasis resulted in significantly higher specificity values.

Use of specialist imagers yielded significantly higher sensitivity values but no significant difference in specificity, compared to non-specialist imagers. However, the specialist category in this analysis contained only two values.

When combining the mydriatic and specialist variables, for non-mydriatic methods, use of a specialist imager yielded significantly higher sensitivity and specificity to detect ‘Moderate NPDR as threshold’ (with only two values in the non-mydriatic specialist imager category). There were no data in which mydriasis was combined with a specialist imager; hence analysis of specialist versus non-specialist imager for mydriasis was not possible.

Figures 3a - 3j present sensitivity and specificity figures, confidence intervals and pooled values overall for ‘Mod NPDR as threshold’, and for the analysed combinations of screening variables.

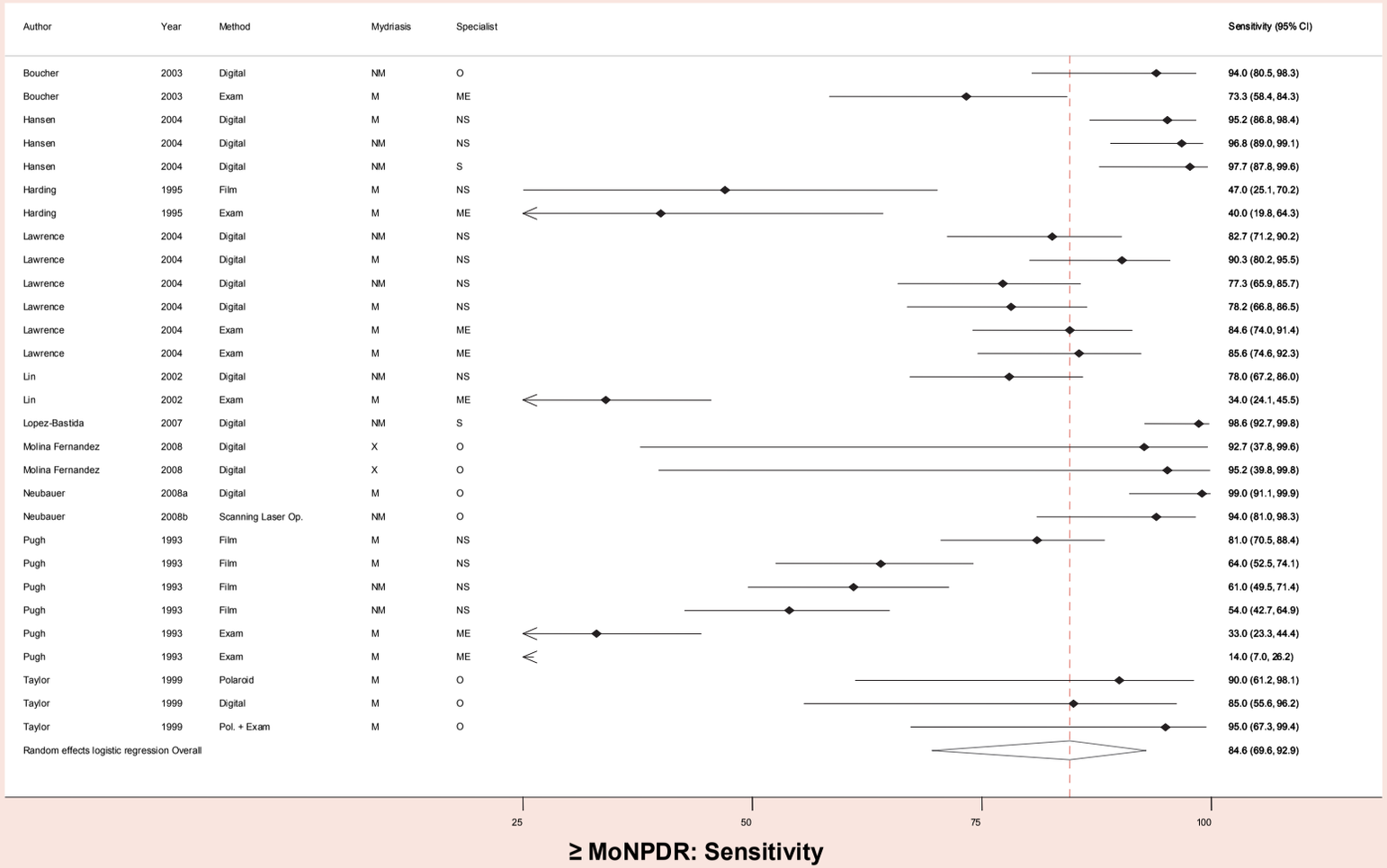

Figure 3a: Sensitivity to Detect '≥ MoNPDR': All Studies

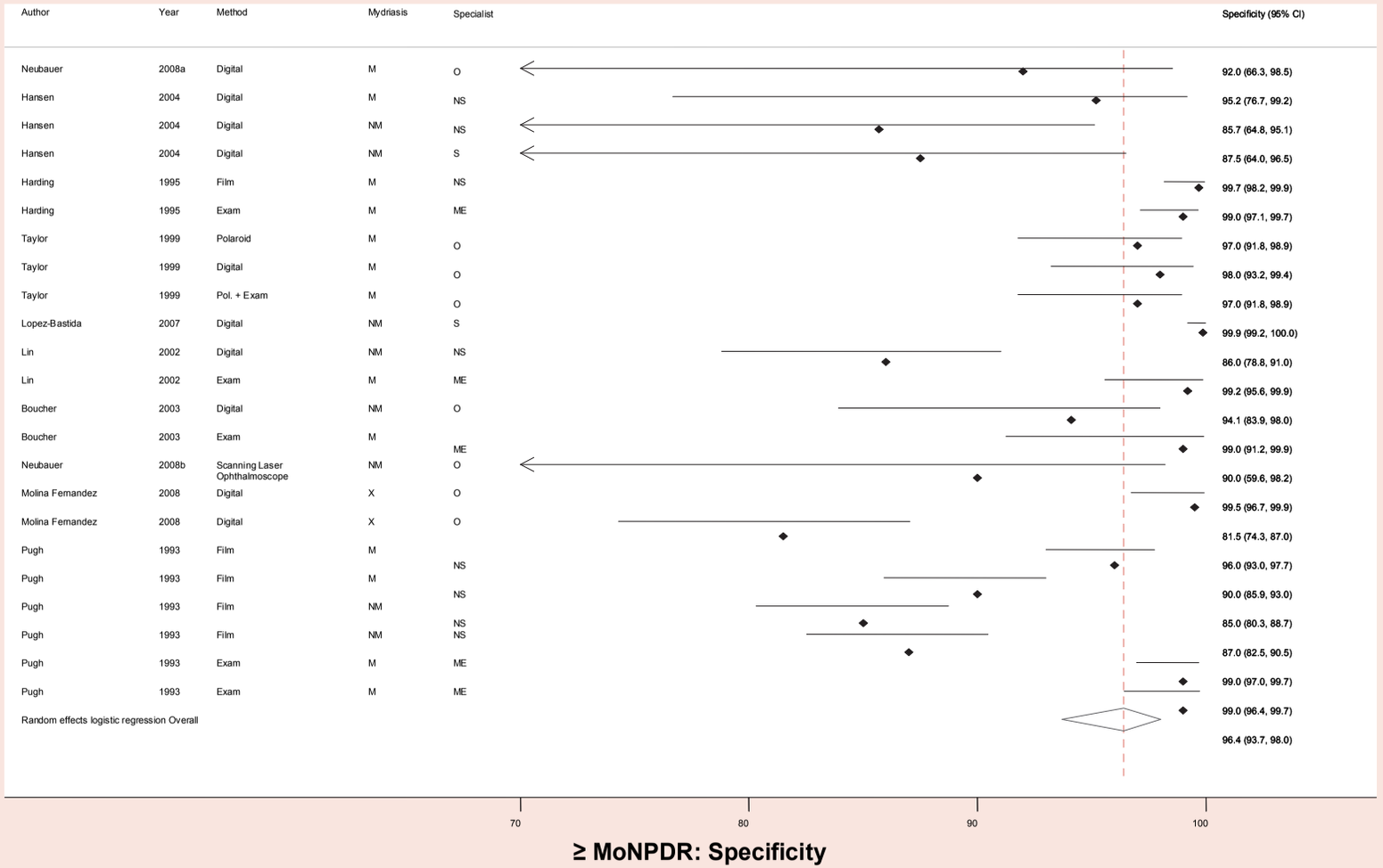

Figure 3b: Specificity to Detect '≥ MoNPDR': All Studies

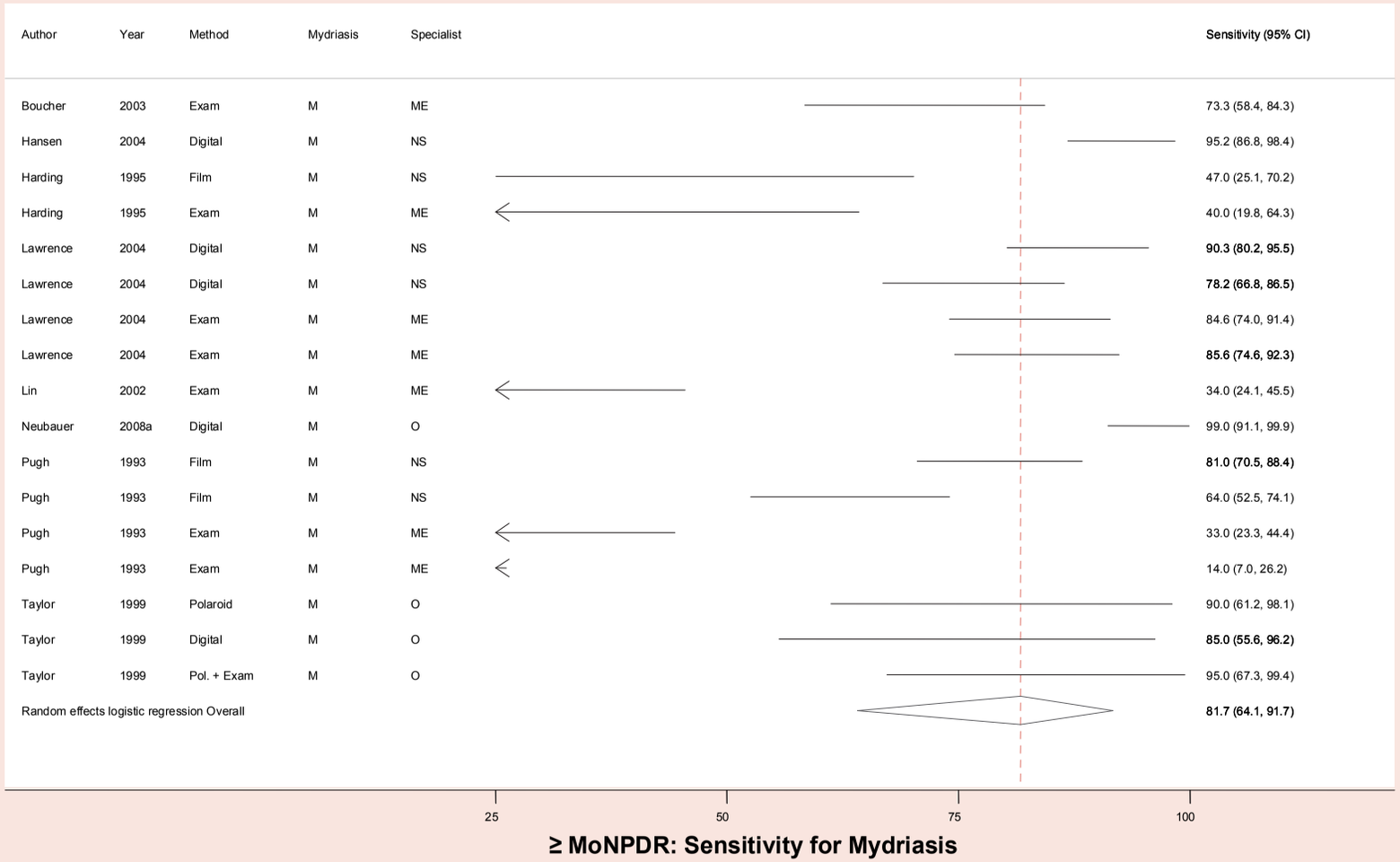

Figure 3c: Sensitivity to Detect '≥ MoNPDR': Mydriasis

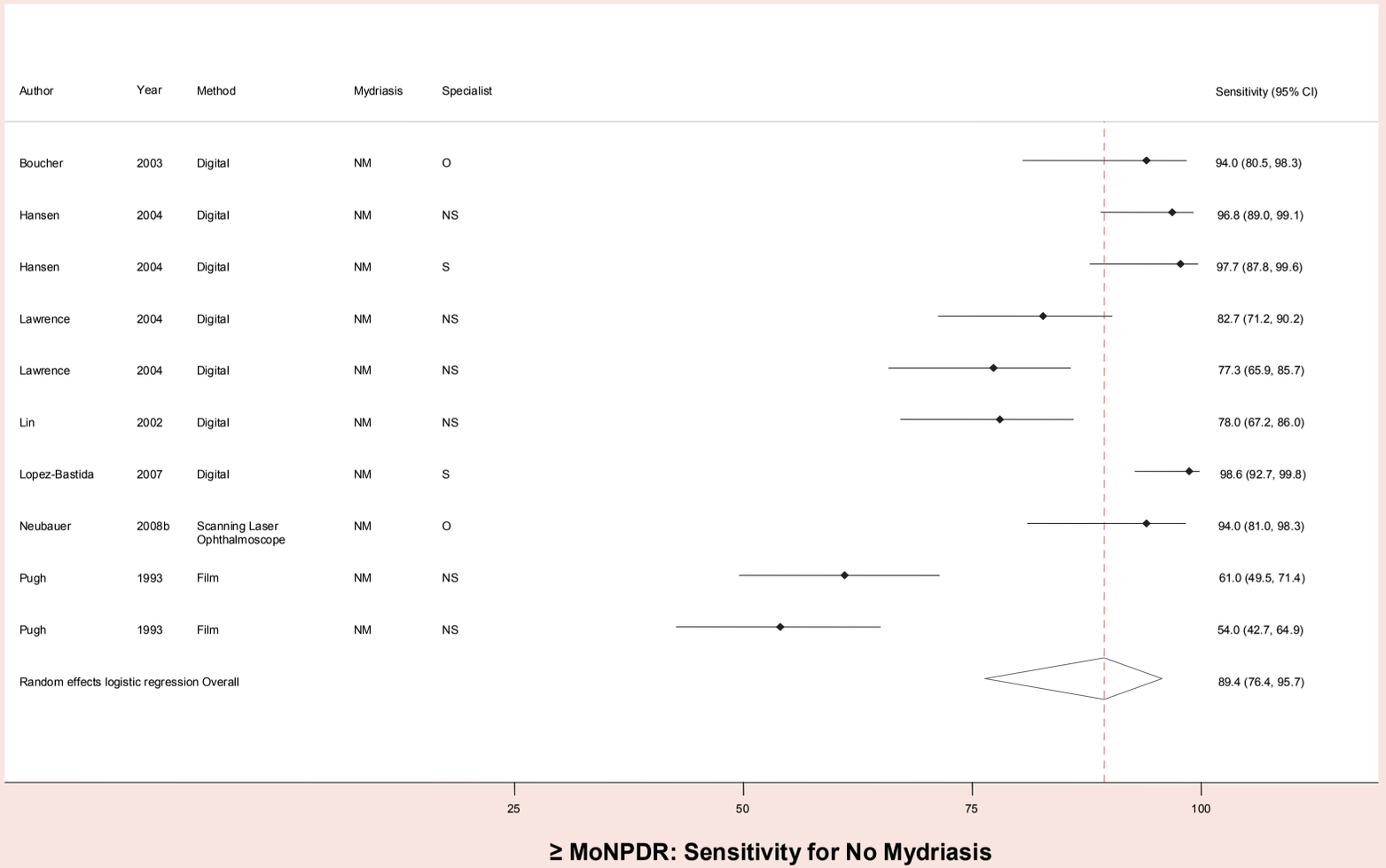

Figure 3d: Sensitivity to Detect '≥ MoNPDR': No Mydriasis

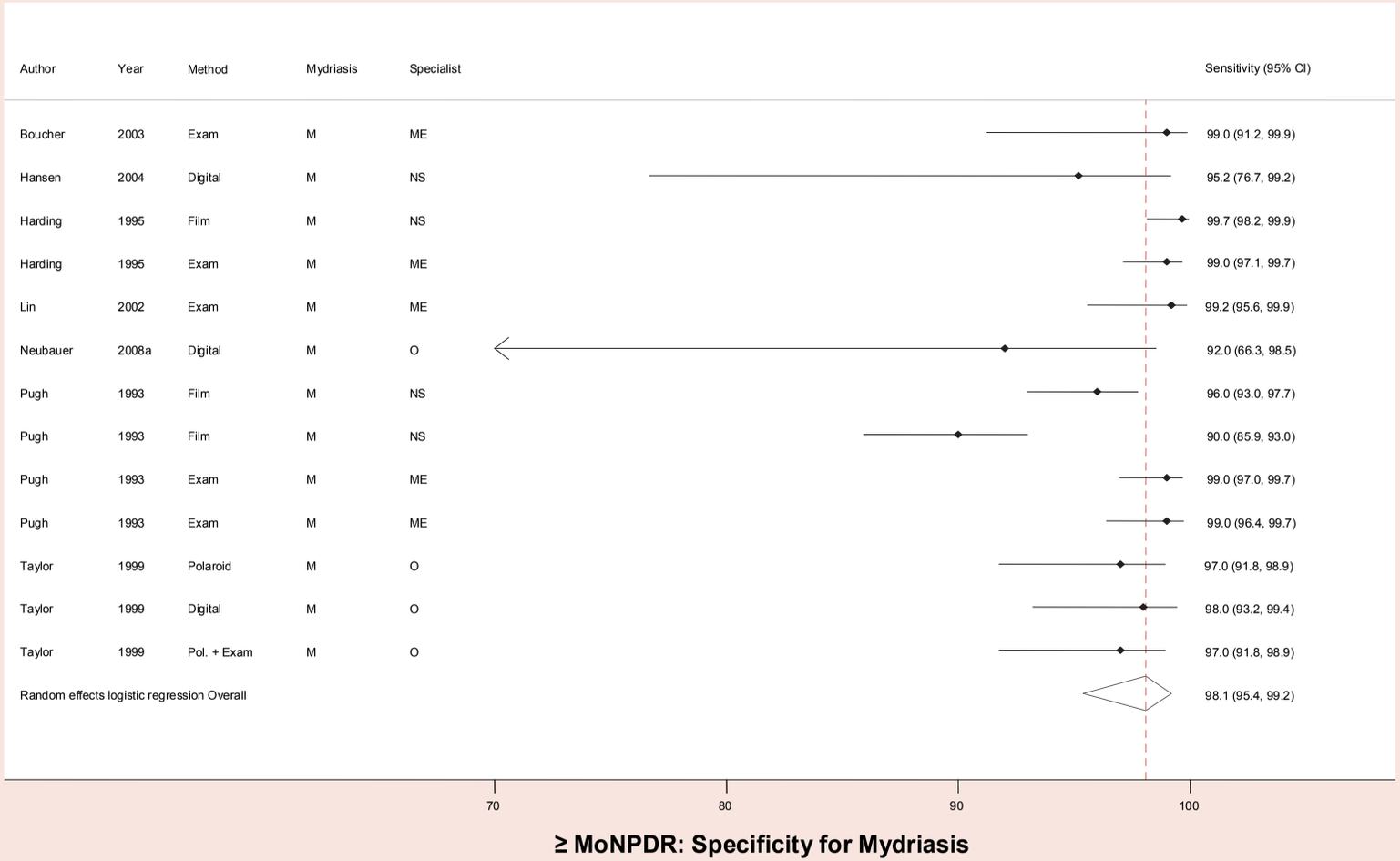

Figure 3e: Specificity to Detect '≥ MoNPDR': Mydriasis

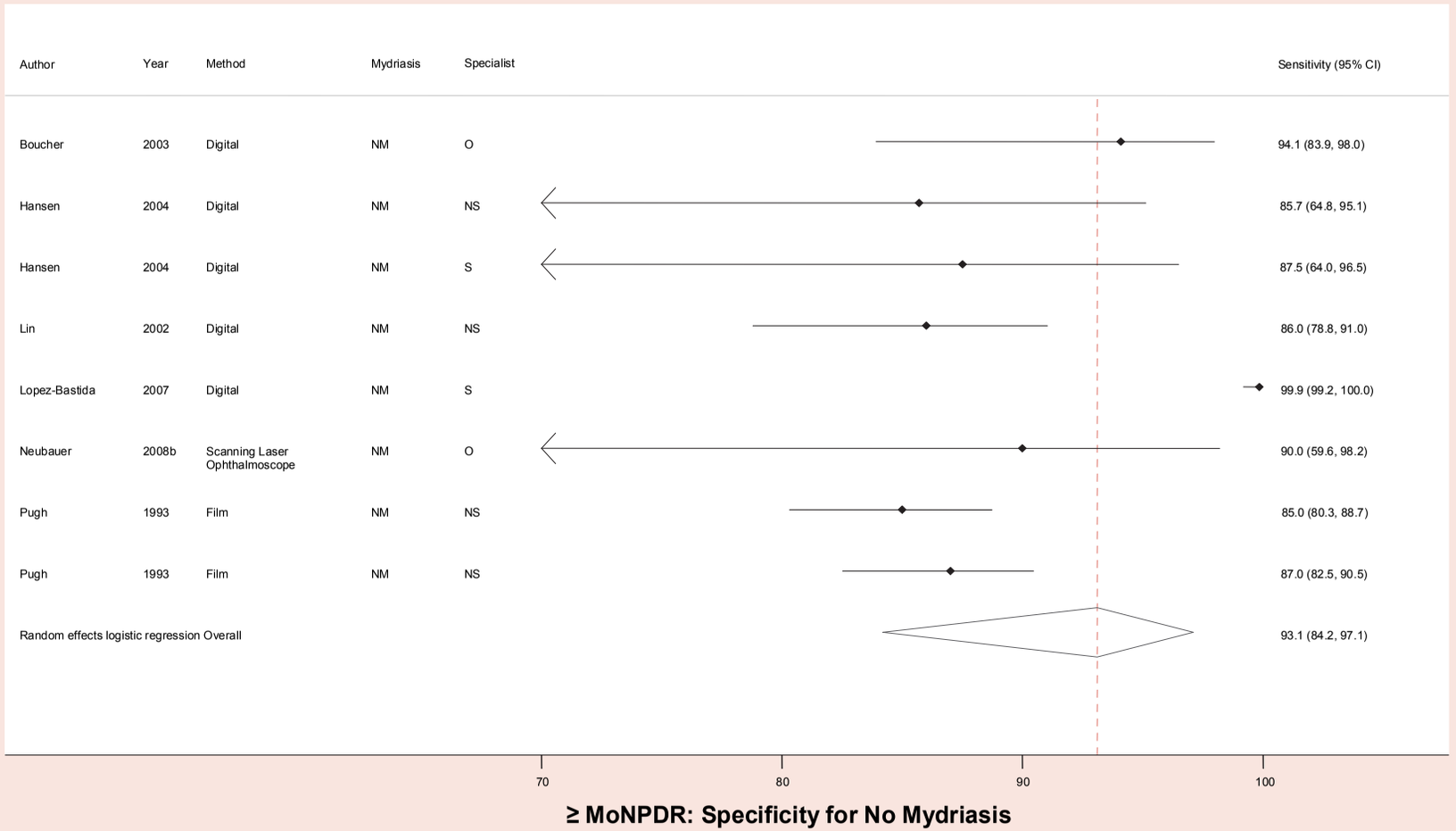

Figure 3f: Specificity to Detect '≥ MoNPDR': No Mydriasis

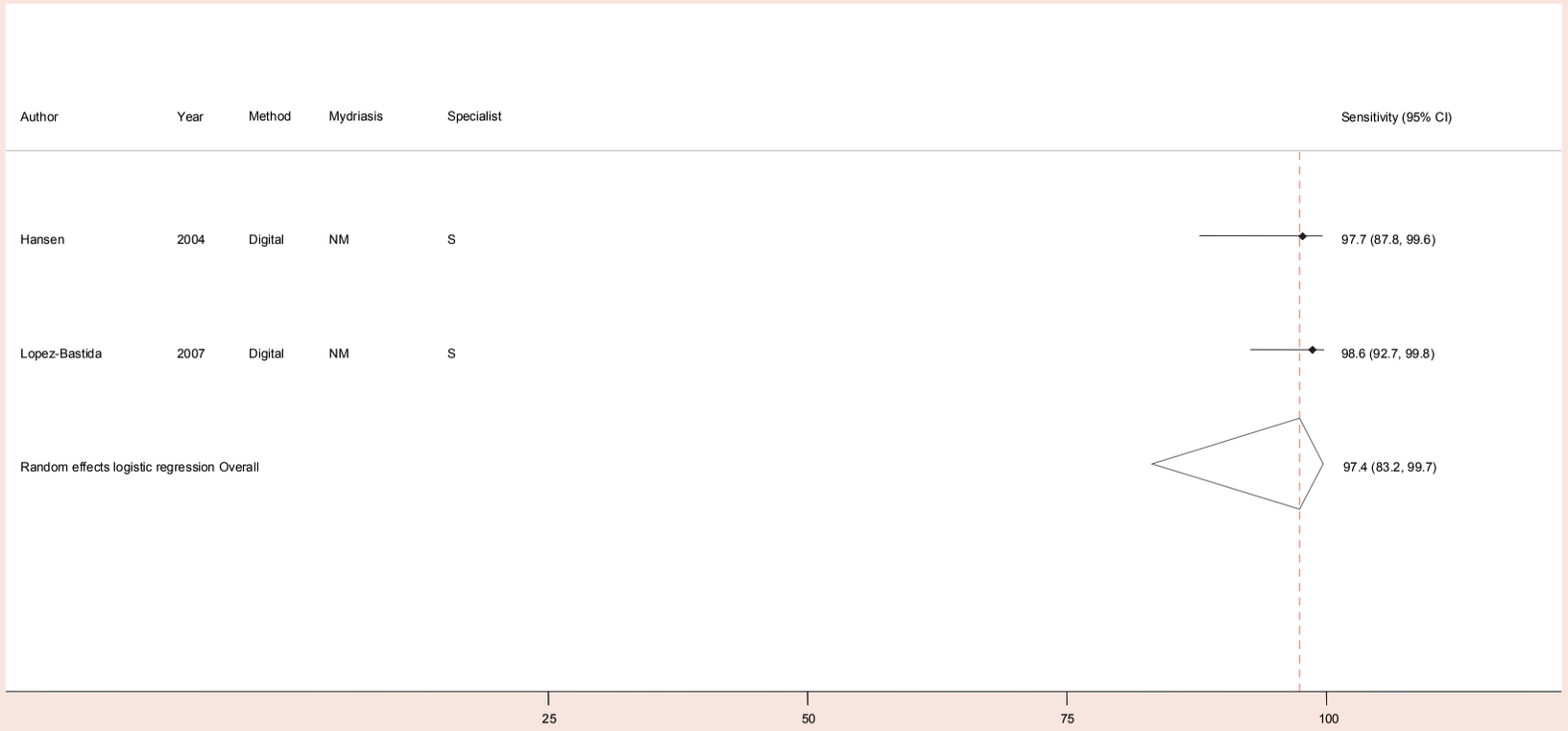

Figure 3g: Sensitivity to Detect '≥ MoNPDR': Specialist Imagers (Mydriatic & Non-Mydriatic Combined)

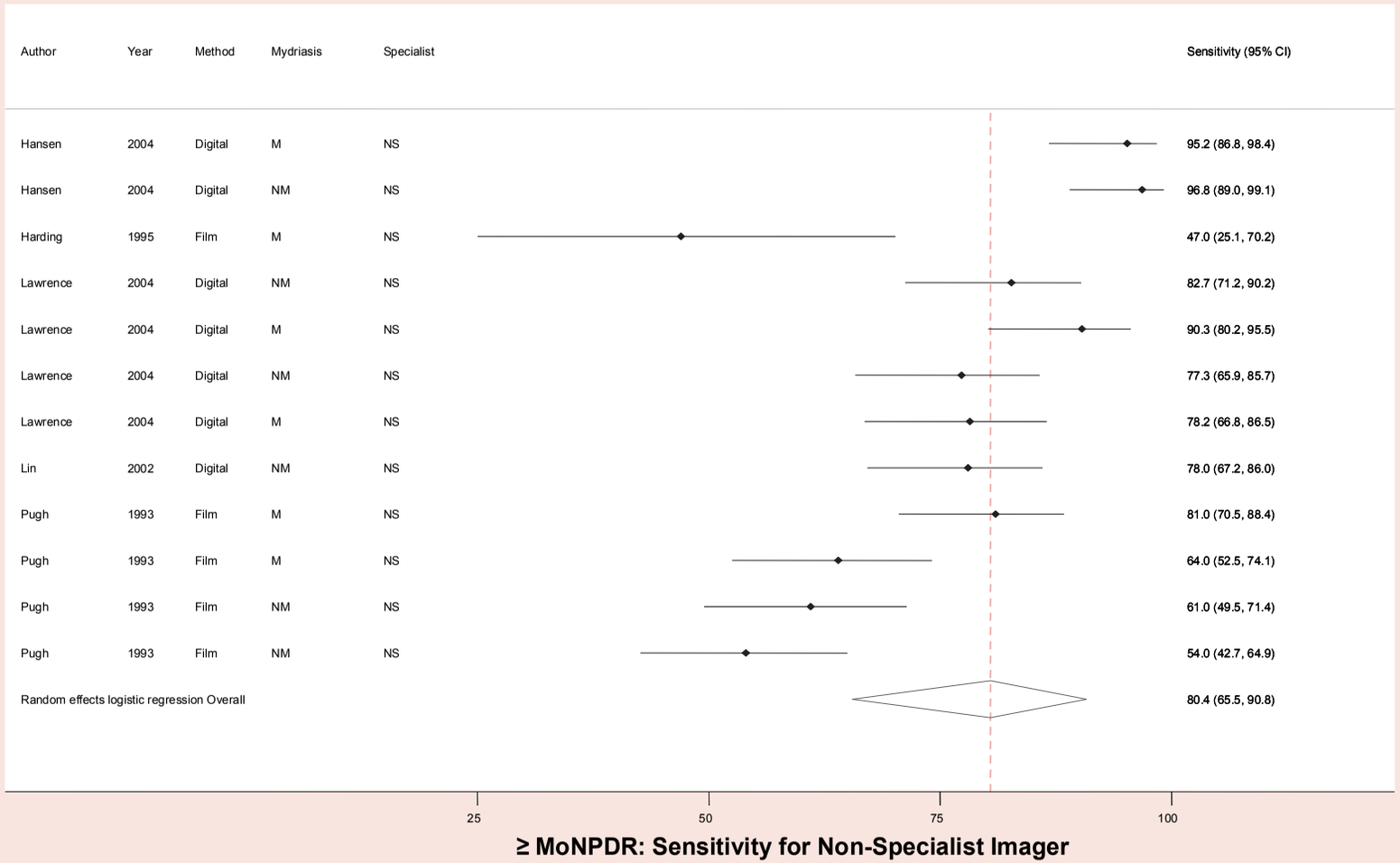

Figure 3h: Sensitivity to Detect '≥ MoNPDR': Non-Specialist Imager (Mydriatic & Non-Mydriatic Combined)

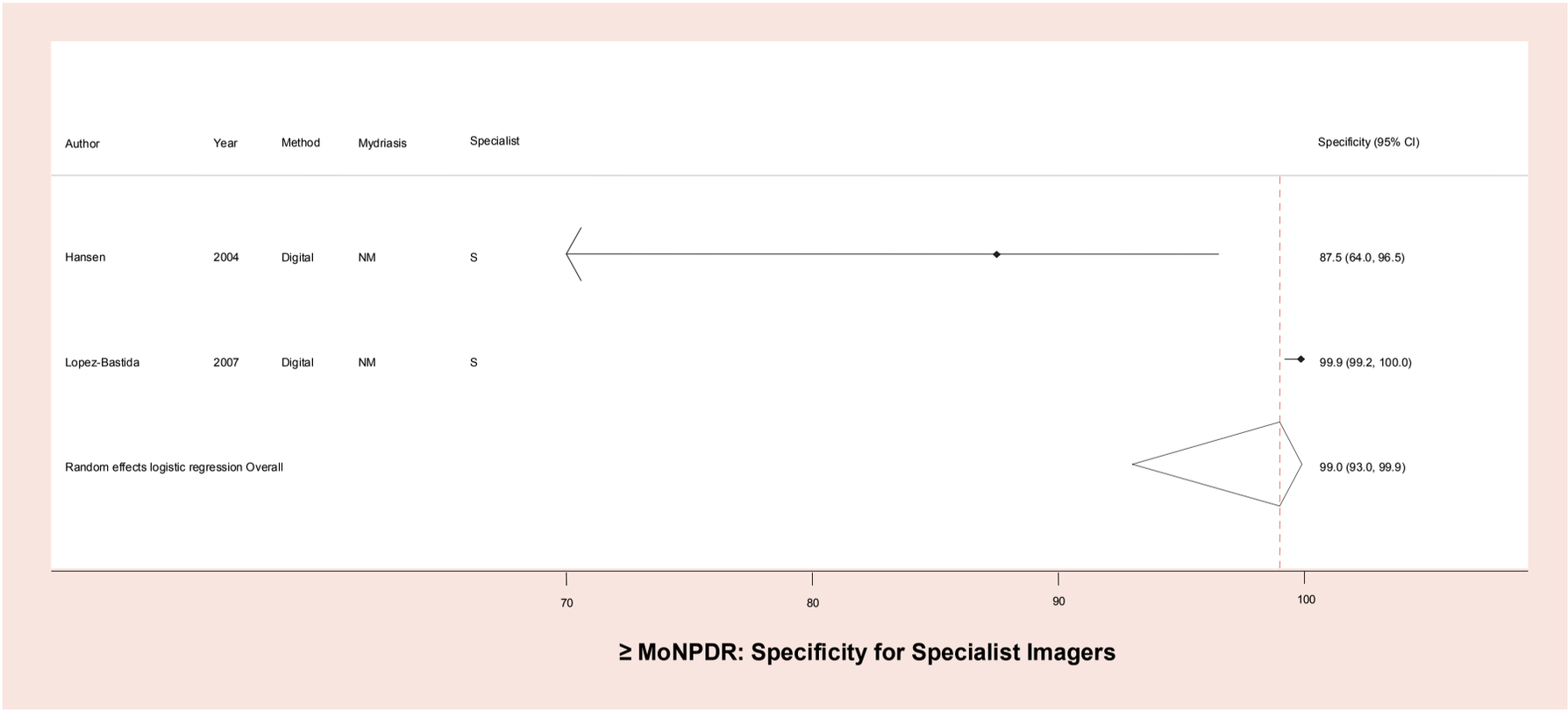

Figure 3i: Specificity to Detect '≥ MoNPDR': Specialist Imagers (Mydriatic & Non-Mydriatic Combined)

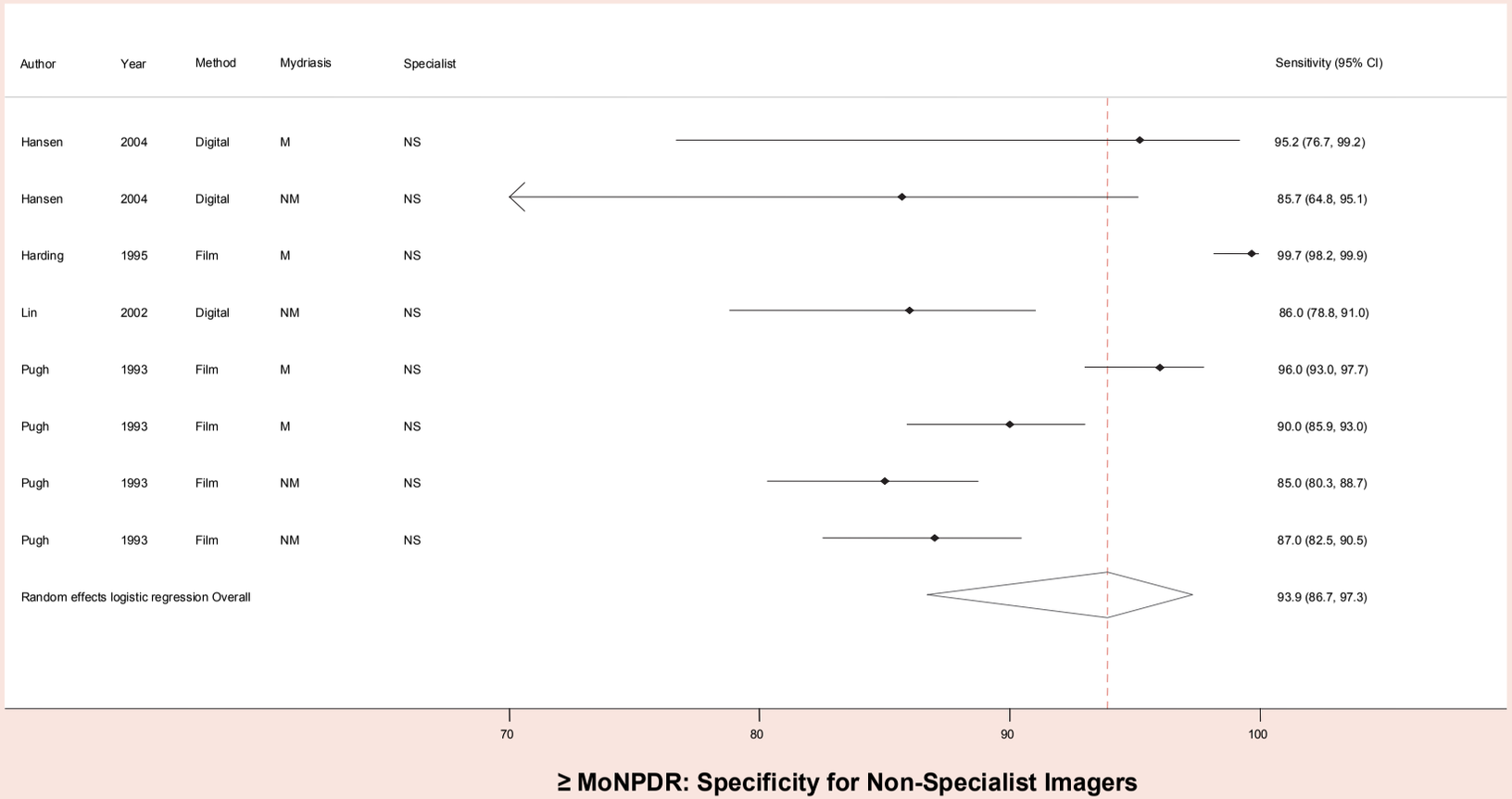

Figure 3j: Specificity to Detect '≥ MoNPDR': Non-Specialist (Mydriatic & Non-Mydriatic Combined)

Summary

Sensitivity

Sensitivity to detect 'Any DR' values was not significantly influenced by any variations in mydriasis or specialist qualifications, either in isolation or in combination.

Sensitivity to detect 'Mod NPDR as threshold' was not significantly influenced by mydriasis in isolation, with a trend to higher values with no mydriasis. However, use of a specialist imager resulted in significantly higher sensitivity values compared to a non-specialist, and the same finding was made when specialist and non-specialist imagers were compared for non-mydriatic screening methods. As noted above, both of these significant findings were based upon one of the comparison groups having only two sensitivity values.

All of the sensitivity values in these statistical comparisons were above 75%. Mathematical modelling conducted by Javitt (1990) demonstrated that sensitivity values above 60% for DR screening do not substantially add to person years of sight saved or reduce screening costs, based upon a strategy of screening patients every six months. According to Javitt (1990), the diminishing additional benefit of sensitivity values above 60% was due to the frequency of screening and the likelihood that DR cases missed on one visit will be detected on the next.

In the context of Javitt (1990), the results of the present analysis in this report indicate that all of the screening method categories analysed would optimise person years of sight saved and cost-effectiveness. Even for the two statistically significant findings for 'Mod NPDR as threshold', the lower sensitivity values (80.4, 77.9) still exceed the 60% threshold identified by Javitt (1990). This indicates that these statistically significant findings may not have serious clinical implications.

The effect of annual rather than six-monthly DR screening examinations is not possible to estimate without similarly detailed modelling to that performed by Javitt (1990). However, the effect of annual versus six-monthly screening could be partially offset by the fact that all sensitivity values are well above Javitt's 60% threshold.

Specificity

Specificity values were equivalent between mydriatic and non-mydriatic methods to detect 'Any DR'. However, use of mydriasis resulted in significantly higher specificity values for detection of 'Moderate NPDR or worse', although the absolute difference in values (98.1 vs. 93.1) was relatively small and may therefore have limited clinical implications.

Use of a specialist imager resulted in significantly higher specificity values for detection of 'Any DR' compared to a non-specialist imager. Although a similar trend was identified for 'Moderate NPDR or worse' this did not reach statistical significance.

When mydriatic status was held constant, specialist imagers yielded significantly higher specificity values in two out of three comparisons possible for 'Any DR' and 'Moderate NPDR as threshold', with a similar non-significant trend noted in the other comparison.

Conclusion

These results indicate that sensitivity to detect 'Any DR' was not influenced by variations in mydriatic status or imager qualifications, either in isolation or in combination. Mydriatic status did not significantly influence sensitivity to detect 'Mod NPDR as threshold'. Variations in imager qualifications in isolation, and when combined with non-mydriatic methods, yielded significant differences in sensitivity to detect 'Mod NPDR as threshold'. However this was based on one comparison group with only two data points. Furthermore, the lower sensitivity values in these comparisons were in excess of the 60% threshold

identified by Javitt (1990) to be cost-effective and because they were also relatively high (80.4, 77.9), this result may have limited clinical significance.

Use of mydriasis did not influence specificity to detect 'Any DR' but yielded significantly higher specificity values for 'Mod NPDR as threshold'. However this finding may also have limited clinical significance as the absolute difference is relatively small (98.1 vs. 93.1). All of the remaining three significant differences in specificity across the two outcomes indicate that specialists yielded higher specificity values compared with non-specialists and the non-significant results showed a similar trend. This means the false positive rate amongst the non-specialist imagers was greater than for the specialists. Therefore, these differences would not be expected to result in adverse patient outcomes as the consequences of inappropriate referral to a specialist are less than those of missed cases of DR (as measured by sensitivity).

In summary, this statistical analysis demonstrates that variations in two key characteristics of 'outreach' screening methods – mydriasis and imager qualifications – either have no significant impact on sensitivity and specificity to detect 'Any DR' or 'Moderate NPDR as threshold', or do not alter these measures of screening accuracy to a clinically significant degree. The screening combinations used in 'outreach' settings such as the Australian Indigenous setting are viable in terms of both screening accuracy and cost-effectiveness.

KAPPA

Table 14a - 14q detail Kappa measures for all outcome categories. Outreach methods are highlighted by use of bold and italicised text (as weighted Kappa statistics are in bold text). Where appropriate, means for each category of mydriatic status have been calculated.

Table 14a: Kappa to detect ANY DR (n=16)

Mydriatic (n=6)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Baeza (2009)	Film	3	GP	Ophth.	S	0.81
Baeza (2009)	Film	2	GP	Ophth.	S	0.82
Baeza (2009)	Film	1	GP	Ophth.	S	0.77
Lee (1993)	Film	1	Photo. / Tech. +	Grader	NR	0.74 (0.69 - 0.79)
Verma (2003)	Exam	-	-	GP	S	0.84
Verma (2003)	Exam	-	-	Opto.	S	0.72
				Mean (Range)		**κ** = 0.78 (0.72 - 0.84)

Key: GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Non-Mydriatic (n=6)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Lopez-Bastida (2007)	Digital	4	Re S	NR	S	**0.89**
Bursell (2001)	Digital	3	NR	Grader	S	0.71
Baeza (2009)	Film	3	GP	Ophth.	S	0.77
Baeza (2009)	Film	2	GP	Ophth.	S	0.77
Baeza (2009)	Film	1	GP	Ophth.	S	0.68
Diamond (1998)	***Polaroid***	***NR***	***Photo. / Tech.***	***Ophth.***	***O***	***0.41***
				Mean (Range)		**κ** = 0.71 (0.41 - 0.89)

Key: Weighted Kappa in Bold; GP: General Practitioner; NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Mydriasis Not Reported (n=4)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	0.68
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	0.58
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	0.49
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	0.79
				Mean (Range)		**κ** = 0.64 (0.49 - 0.79)

Key: NR: Not Reported; Photo.: Photographer; Re S: Retinal Specialist; Tech.: Technician

Kappa for mydriatic methods (mean 0.78, 6 measures) was higher for detection of 'Any DR' compared to non-mydriatic (0.71, n=6) and mydriasis not reported (0.64, n=4).

One outreach study (Diamond 1998) measured kappa. This study of 164 patients used non-mydriatic Polaroid camera (photographer / technician imager, graded by an ophthalmologist) and yielded a kappa of 0.41 (lowest of group means).

Table 14b: Kappa to detect Macular Oedema (n=6)

Mydriatic (n=3)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.65
Rudnisky (2002)	Digital	1	Photo. / Tech.	Re S	S	0.72 (0.63 - 0.82)
Lee (1993)	Film	1	Photo. / Tech. +	Grader	NR	0.44 (0.32 - 0.56)
				Mean (Range)		**κ** = 0.60 (0.44 - 0.72)

Key: NR: Not Reported; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Non-Mydriatic (n=3)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.37
Hansen (2004)	Digital	5	Opto.	NR	S	0.49
Bursell (2001)	Digital	3	NR	Grader	S	0.48
				Mean (Range)		**κ** = 0.45 (0.37 - 0.49)

Key: NR: Not Reported; Opto: Optometrist; Photo.: Photographer; S: Static; Tech.: Technician

Mean kappa was higher for mydriatic (0.60, n=3) than non-mydriatic methods (0.45, n=3) for 'Macular Oedema'.

No outreach studies measured this outcome.

Table 14c: Kappa to detect Extent of Macular Oedema (n=4)

Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	0.80 (0.81 - 0.92)

Key: NR: Not Reported; Re S: Retinal Specialist; S: Static

Non-Mydriatic (n=3)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Neubauer (2008b)	SLO	-	Photo. / Tech. +	Re S	S	0.20
Neubauer (2008b)	SLO	-	Photo. / Tech. +	Re S	S	0.27
Neubauer (2008b)	SLO	-	Photo. / Tech. +	Re S	S	0.25
				Mean (Range)		**κ** = 0.24 (0.20 - 0.27)

Key: Photo.: Photographer; Re S: Retinal Specialist; S: Static; SLO: Scanning Laser Ophthalmoscope; Tech.: Technician; '+': includes qualified healthcare professionals

A kappa mean value for the three non-mydriatic methods was 0.24 to detect 'Extent of Macular Oedema'. Only one mydriatic method measured this outcome, yielding a kappa of 0.80.

No outreach studies measured this outcome.

Table 14d: Kappa to detect ≥ Macular Oedema as a threshold (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.70

Key: NR: Not Reported; S: Static

Table 14e: Kappa to detect CSME (n=3)

Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Rudnisky (2002)	Digital	1	Photo. / Tech.	Re S	S	0.81 (0.73 - 0.89)

Key: Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.33

Key: NR: Not Reported; S: Static

Mydriasis Not Reported (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Kinyoun (1989)	Camera	1	NR	Grader	NR	0.61

Key: NR: Not Reported

Table 14f: Kappa for Agreement across a Grading System (n=44)

Mydriatic (n=18)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Neubauer (2008a)	Digital	7	NR	Re S	S	0.87 (0.81 - 0.92)
Fransen (2002)	Digital	7	Photo. / Tech.	Grader	S	**0.76**
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.76
Pugh (1993)	Film	3	Nurse	Grader	NR	0.74 (0.66 - 0.82)
Lee (1993)	Film	1	Photo. / Tech. +	Grader	NR	0.74 (0.7 - 0.79)
Pugh (1993)	Exam	-	-	Ophth. / Re S	NR	0.38 (0.32 - 0.45)
Pugh (1993)	Exam	-	-	Phys. Ass.	NR	0.25 (0.16 - 0.33)
Boucher (2003)	Exam	-	-	Re S	S	0.58
Lin (2002)	Exam	-	-	Ophth.	S	0.40
Moss (1985)	***Exam***	***-***	***-***	***Mixed***	***O***	***0.75***
Moss (1985)	***Exam***	***-***	***-***	***Mixed***	***O***	***0.72***
Moss (1985)	***Exam***	***-***	***-***	***Mixed***	***O***	***0.75***
Moss (1985)	***Exam***	***-***	***-***	***Mixed***	***O***	***0.76***
Verma (2003)	Exam	-	-	GP	S	0.80

Results - Kappa

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Verma (2003)	Exam	-	-	GP	S	0.79
Verma (2003)	Exam	-	-	Opto.	S	0.63
Verma (2003)	Exam	-	-	Opto.	S	0.63
Penman (1998)	Camera	1	Ophth.	Grader	NR	0.33 (0.27 - 0.39)
				Mean (Range)		**κ** = 0.65 (0.25 - 0.87)

Key: Weighted Kappa in Bold; GP: General Practitioner; NR: Not Reported; O: Outreach; Ophth.: Ophthalmologist; Opto: Optometrist; Photo.: Photographer; Phys. Ass.: Physician Assistant; Re S: Retinal Specialist; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Non-Mydriatic (n=18)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.66
Hansen (2004)	Digital	5	Opto.	NR	S	0.60
Massin (2003)	Digital	5	Mixed	Re S	S	0.6 (0.48 - 0.72)
Massin (2003)	Digital	5	Mixed	Re S	S	0.58 (0.45 - 0.70)
Massin (2003)	Digital	5	Mixed	Re S	S	0.43 (0.3 - 0.56)
Massin (2003)	Digital	5	`Mixed	Re S	S	0.80 (0.65 - 0.94)
Massin (2003)	Digital	5	Mixed	Re S	S	0.76 (0.61 - 0.90)
Massin (2003)	Digital	5	Mixed	Re S	S	0.60 (0.43 - 0.76)
Massin (2003)	Digital	5	Mixed	Re S	S	0.90 (0.81 - 0.98)
Bursell (2001)	Digital	3	NR	Grader	S	0.65
Boucher (2003)	Digital	2	NR	Re S	S	0.63
Lin (2002)	Digital	1	Photo. / Tech.	Grader	S	0.97
Lin (2002)	Digital	1	Photo. / Tech.	Grader	S	0.38
Pugh (1993)	Film	1	Nurse	Grader	NR	0.62 (0.54 - 0.70)
Leese (2002)	***Polaroid***	***NR***	***NR***	***Diabet. / Endo.***	***O***	***0.47***
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	0.68
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	0.68
Neubauer (2008b)	SLO	NR	Photo. / Tech. +	Re S	S	0.51
				Mean (Range)		**κ** = 0.64 (0.37 - 0.97)

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; NR: Not Reported; O: Outreach; Opto: Optometrist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Mydriasis Not Reported (n=8)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	**0.73**
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	**0.80**
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	**0.79**
Kinyoun (1992)	Film	7	Photo. / Tech.	Re S	NR	**0.69**
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	**0.56**
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	**0.62**
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	**0.69**
Kinyoun (1992)	Film	7	Photo. / Tech.	Grader	NR	**0.84**
				Mean (Range)		**κ** = 0.72 (0.56 - 0.84)

Key: Weighted Kappa in Bold; NR: Not Reported; Photo.: Photographer; Re S: Retinal Specialist; Tech.: Technician

Mean kappa for agreement across a grading system were similar for mydriatic (0.65, n=18) and non-mydriatic (0.64, n=18) methods, with a higher mean value for methods in which mydriasis was not reported (0.72, n=8).

Two outreach studies measured kappa for 'Agreement across a Grading System'. Moss (1985) generated four of the 18 mydriatic outcome measures. This study of 1949 patients investigated mydriatic examination (mixed graders) and kappa values ranged from 0.72 - 0.76. Leese (2002) studied 408 patients using non-mydriatic Polaroid camera (graded by diabetologist / endocrinologist) yielding a kappa 0.47, which is lower than the group mean.

Table 14g: Kappa to detect ≥ Mild NPDR as a threshold (n=2)

Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Boucher (2003)	Exam	-	-	Re S	S	0.76

Key: Re S: Retinal Specialist; S: Static

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Boucher (2003)	Digital	2	NR	Re S	S	0.82

Key: NR: Not Reported; Re S: Retinal Specialist; S: Static

Table 14h: Kappa to detect Moderate NPDR (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.60

Key: NR: Not Reported; S: Static

Table 14i: Kappa to detect ≥ Moderate NPDR as a threshold (n=5)

Mydriatic (n=2)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.88
Boucher (2003)	Exam	-	-	Re S	S	0.74
				Mean (Range)		**κ** = 0.81 (0.74 - 0.88)

Key: NR: Not Reported; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Non-Mydriatic (n=3)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Hansen (2004)	Digital	5	Photo. / Tech.	NR	S	0.84
Hansen (2004)	Digital	5	Opto.	NR	S	0.87
Boucher (2003)	Digital	2	NR	Re S	S	0.88
				Mean (Range)		**κ** = 0.86 (0.84 - 0.88)

Key: NR: Not Reported; Opto.: Optometrist; Photo.: Photographer; Re S: Retinal Specialist; S: Static; Tech.: Technician

Mean kappa for 'Moderate NPDR as a threshold' was 0.81 (n=2) for mydriatic methods, slightly lower than for non-mydriatic (0.86, n=3) methods.

No outreach studies measured this outcome.

Table 14j: Kappa to detect Severe NPDR (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.64

Key: NR: Not Reported; S: Static

Table 14k: Kappa to detect ≥ Severe NPDR as a threshold (n=2)

Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Boucher (2003)	Exam	-	-	Re S	S	0.50

Key: Re S: Retinal Specialist; S: Static

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Boucher (2003)	Digital	2	NR	Re S	S	0.24

Key: NR: Not Reported; Re S: Retinal Specialist; S: Static

Table 14l: Kappa to detect PDR (n=2)

Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Lee (1993)	Film	1	Photo. / Tech. +	Grader	NR	0.84 (0.76 - 0.92)

Key: NR: Not Reported; Photo.: Photographer; S: Static; Tech.: Technician; '+': includes qualified healthcare professionals

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.78

Key: NR: Not Reported; S: Static

Table 14m: Kappa to detect ≥ PDR as a threshold (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Bursell (2001)	Digital	3	NR	Grader	S	0.88

Key: NR: Not Reported; S: Static

Table 14n: Kappa to detect ≥ Moderate NPDR OR Macular Oedema as a threshold (n=10)

Mydriatic (n=7)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Scanlon (2003b)	Digital	2	NR	NR	S	0.73
Scanlon (2003b)	Digital	2	NR	NR	S	0.76
Scanlon (2003b)	Film	7	NR	NR	S	0.80
Baeza (2009)	Film	3	GP	Ophth.	S	0.89
Baeza (2009)	Film	2	GP	Ophth.	S	0.91
Baeza (2009)	Film	1	GP	Ophth.	S	0.84
Scanlon (2003b)	Exam	-	-	Ophth.	S	0.80
				Mean (Range)		**κ** = 0.82 (0.73 - 0.91)

Key: GP: General Practitioner; NR: Not Reported; Ophth.: Ophthalmologist; S: Static

Non-Mydriatic (n=3)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Baeza (2009)	Film	3	GP	Ophth.	S	0.86
Baeza (2009)	Film	2	GP	Ophth.	S	0.85
Baeza (2009)	Film	1	GP	Ophth.	S	0.75
				Mean (Range)		**κ** = 0.82 (0.75 - 0.86)

Key: GP: General Practitioner; Ophth.: Ophthalmologist; S: Static

Mean kappa values for 'Moderate NPDR or Macular Oedema as a threshold' were the same for mydriatic (0.82, n=7) and non-mydriatic (0.82, n=3) methods.

No outreach studies measured this outcome.

Table 14o: Kappa to detect ≥ Moderate NPDR OR CSME (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Leese (2002)	***Polaroid***	***NR***	***NR***	***Diabet. / Endo.***	***O***	***0.62***

Key: Diabet.: Diabetologist; Endo.: Endocrinologist; NR: Not Reported; O: Outreach

One outreach study measured kappa for 'Moderate NPDR or CSME'. Leese (2002) studied 408 patients using non-mydriatic Polaroid camera (graded by diabetologist / endocrinologist) and yielded a kappa of 0.62.

Table 14p: Kappa to detect ≥ Moderate NPDR AND CSME as a threshold (n=1)

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Lopez-Bastida (2007)	Digital	4	Re S	NR	S	**1.00**

Key: Weighted Kappa in Bold; NR: Not Reported; Re S: Retinal Specialist; S: Static

Table 14q: Kappa to detect ≥ Severe NPDR OR Macular Oedema as a threshold (n=3)

Mydriatic (n=2)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Verma (2003)	Exam	-	-	GP	S	0.82
Verma (2003)	Exam	-	-	Opto.	S	0.67
				Mean (Range)		**κ** = 0.74 (0.67 - 0.82)

Key: GP: General Practitioner; Opto.: Optometrist; S: Static

Non-Mydriatic (n=1)

Citation	Method of Investigation	Photo Field	Imager	Grader	Location	Kappa (95% CI)
Diamond (1998)	***Polaroid***	***NR***	***Photo. / Tech.***	***Ophth.***	***O***	***0.53***

Key: Photo.: Photographer; O: Outreach; Ophth.: Ophthalmologist; Tech.: Technician

Mean kappa for the two mydriatic methods was 0.74 to detect 'Severe NPDR or Macular Oedema as a threshold'.

One outreach study measured kappa for this outcome. Diamond (1998) studied 164 patients using non-mydriatic Polaroid camera (photographer / technician imager, graded by an ophthalmologist) and produced a kappa of 0.53, which is lowest value of all for this outcome.

RELIABILITY

Inter-rater reliability

Only 10 studies reported inter-rater reliability, across a range of methods and outcomes. Mean kappa values varied according to inter-rater comparison, ranging from 0.60 (retinal specialist against grader; grader against grader – 'moderate agreement') to 0.87 (retinal specialist against retinal specialist – 'almost perfect agreement') as summarised in Table 15.

Table 15: Summary of kappa statistics (mean, range) by inter-rater comparison

	Retinal Specialist	Ophthalmologist	Diabetologist	Grader
Retinal Specialist	0.87 (0.71 – 1) (3 studies / 9 measures)			
Ophthalmologist	0.64 (1 / 1)	0.75 (0.69 – 0.80) (2 / 3)		
Diabetologist		0.91 (0.86 – 1) (1 / 3)		
Grader	0.60 (0.34 – 0.90) (1 / 22)	0.67		0.60 (0.55 – 0.73) (2 / 5)

Across all methods, inter-rater comparisons and outcomes, the mean kappa was 0.72 (range 0.34 – 1), which equates to 'substantial agreement' according to Landis (1977).

Two outreach studies measured inter-rater reliability. Maberley (2002) consisted of 100 patients, and compared between two different retinal specialists using 1-field Digital camera (85% of patients were dilated). Inter-rater kappa values ranged from 0.80 - 0.91, where detecting 'PDR' produced the highest reliability, compared to 'Across a Grading System', which produced the lowest. Scanlon (2003a) studied 3611 patients using mydriatic Polaroid (2-field) camera, and compared the between two different ophthalmologists. For 'Severe NPDR as a threshold', inter-rater kappa were 0.69 and 0.75 for the two of the interpreters when compared to the reference standard. In addition, ophthalmologist was also compared to grader for 'Severe NPDR or Macular Oedema as threshold' and produced a kappa of 0.67.

A detailed summary of the inter-rater reliability for different raters compared for all measured outcomes is shown in Table 16.

Table 16: Inter-rater Reliability (Kappa, 95% CI unless stated)

Citation	Raters Compared	Method	Any DR	Across grading system	Mod NPDR (ICDR)	≥ Sev NPDR (ICDR)	PDR	ME	CSME	PDR or CSME	≥ Sev NPDR (ICDR) OR ME	Grading of image quality
Massin (2003)	Re S / Re S	Digital (5f) NM		0.90 (0.81 - 0.98) (ETDRS)								
Maberley (2002)	Re S / Re S	Exam M		1 (AHC)								
Maberley (2002)	***Re S / Re S***	***Digital (1f) MX (85% dilated)***	***0.85 (0.78 - 0.92)***	***0.80 (0.72 - 0.87) (AHC)***	***0.82 (0.73 - 0.90)***		***0.91 (0.73 - 1.00)***		***0.89 (0.76 - 1.00)***	***0.89 (0.78 - 0.99)***		***0.705 (SE 0.079) (p<0.01)***
Boucher (2003)	Re S / Re S	Digital (2f) NM		0.896 (SD 0.058) (EDTRS)								
Phiri (2006)	Re S / Ophth.	Digital (1f) NM		0.64 (Wisconsin)								
Gonzalez (1995)	Re S (x11) / Grader	Film (7f) M		Av: **0.57** Re S 1: **0.41** Re S 2: **0.80** Re S 3: **0.83** Re S 4: **0.41** Re S 5: **0.62** Re S 6: **0.34** Re S 7: **0.37** Re S 8: **0.49** Re S 9: **0.47** Re S 10: **0.66** Re S 11: **0.90** (AHC)				Av: **0.63** Re S 1: **0.58** Re S 2: **0.72** Re S 3: **0.74** Re S 4: **0.58** Re S 5: **0.68** Re S 6: **0.52** Re S 7: **0.48** Re S 8: **0.57** Re S 9: **0.61** Re S 10: **0.62** Re S 11: **0.80**				
Molina Fernandez (2008)	Ophth. / Ophth.	Exam		**0.80 (0.73 - 0.88)** (ETDRS)								
Scanlon (2003a)	***Ophth. / Ophth. (RS)***	***Digital (2f) M***				***Ophth. 1: 0.69*** ***Ophth. 2: 0.75***						
Murgatroyd (2004)	Ophth. / Diabet.	Digital (3f) M									0.88	

Citation	Raters Compared	Method	Any DR	Across grading system	Mod NPDR (ICDR)	≥ Sev NPDR (ICDR)	PDR	ME	CSME	PDR or CSME	≥ Sev NPDR (ICDR) OR ME	Grading of image quality
Murgatroyd (2004)	Ophth. / Diabet.	Digital (1f) M									0.86	
Murgatroyd (2004)	Ophth. / Diabet.	Digital (1f) NM									1	
Scanlon (2003a)	***Ophth. / Grader***	***Digital (2f) M***									***0.67***	
Bursell (2001)	Grader / Grader	Film (7f) M							0.60 (SEM 0.06) 0.55 (SEM 0.07) (extent of)			
Bursell (2001)	Grader / Grader	Digital (3f) NM							0.57 (SEM 0.07) 0.57 (SEM 0.07) (extent of)			
Kinyoun (1989)	Grader / Grader	Camera							0.73			

Key: Weighted kappa in bold; Outreach studies in bold & italicised

AHC: Airlie House Classification
Av: Average
CSME: Clinically Significant ME
Diabet.: Diabetologist
DR: Diabetic Retinopathy
ETDRS: Early Treatment DR Study
f: field
ICDR: International Clinical DR Severity Scale
ME: Macular Oedema
M: Mydriatic
MX: Mixed Mydriatic / Non-Mydriatic
NM: Non-Mydriatic
NPDR: Non-Proliferative DR
Ophth.: Ophthalmologist
PDR: Proliferative DR
RS: Reference Standard
Re S: Retinal Specialist
SE: Standard Error
SD: Standard Deviation
SEM: Standard error of the mean
Sev: Severe

Intra-rater reliability

Only seven studies reported intra-rater reliability (Table 17). Across all methods, raters and outcomes, the mean kappa was 0.74 (range 0.43 – 0.97), representing 'substantial agreement' (Landis 1977). For retinal specialists, the mean kappa across a grading system (3 studies, 5 measures) was 0.84 (range 0.76-0.97) ('almost perfect agreement'). All other intra-rater reliability measures were single values.

One outreach study measured intra-rater reliability for 'Severe NPDR or Macular Oedema as a threshold'. Scanlon (2003a) studied 3611 patients using mydriatic 2-field Digital camera, which produced a kappa of 0.78 for ophthalmologist.

Table 17: Intra-rater Reliability (Kappa, 95% CI unless stated)

Citation	Rater	Method	Across grading system	ME (extent of)	CSME	≥ Sev NPDR (ICDR) OR ME
Boucher (2003)	Re S	Camera 7f M	0.761 (SD 0.087) (ETDRS)			
Neubauer (2008a)	Re S	Digital 7f M	0.77 (0.64 - 0.89) (EDTRS)	0.60 (0.42 - 0.79)		
Massin (2003)	Re S	Digital 5f NM	Re S 1: 0.83 (0.74 - 0.93) Re S 2: 0.86 (0.77 - 0.94) (ETDRS)			
Boucher (2003)	Re S	Digital 2f NM	0.965 (SD 0.043) (EDTRS)			
Scanlon (2003a)	***Ophth.***	***Digital 2f M***				***0.78***
Phiri (2006)	Ophth.	Digital 1 f NM	0.65 (Wisconsin)			
Pugh (1993)	Internist	Film	**0.79 (0.64 - 0.93)** (AHC)			
Bursell (2001)	Grader	Film 7f M			Grader 1: 0.43 Grader 2: 0.65	

Key: Weighted kappa in bold; Outreach studies in bold & italicised

AHC: Airlie House Classification
CSME: Clinically Significant ME
DR: Diabetic Retinopathy
ETDRS: Early Treatment DR Study
f: field
ICDR: International Clinical DR Severity Scale
ME: Macular Oedema
M: Mydriatic
NM: Non-mydriatic
NPDR: Non-Proliferative DR
Ophth.: Ophthalmologist
Re S: Retinal Specialist
SD: Standard Deviation
Sev: Severe

Image Quality, Time, Cost, Patient Satisfaction and Other Results

The data presented in this section was extracted only from studies eligible for this review, which were selected with the primary aim of examining screening accuracy. Therefore, a range of studies reporting data on image quality, time, cost, patient satisfaction and other outcomes that not meet inclusion criteria for this review have not been included. The results below should be interpreted in this context.

Image Quality

Ungradable Images

Thirty-three studies, representing a total of 53 methods, reported data on photo quality (Table 18). For five methods, mydriasis use was either mixed or not reported. Three methods on the other hand, did not specify the type of camera used for screening patients.

Table 18: Percentage (Range, n = screening methods) of Ungradable Images by Screening Instrument and Mydriatic Status

Instrument / Mydriasis?	Digital Camera	Film Camera	Polaroid Camera	SLO	Camera (unspecified)
Mydriatic	5.0% (0 - 17.2%, 9)	7.0% (0 - 31.6%, 10)	6.4% (1)		13.6% (5.1 - 22.0%, 2)
Non-Mydriatic	13.6% (1.9 - 38.4%, 15)	16.6% (14 - 18.3%, 4)	11.6% (0 - 32.0%, 5)	8.1% (6.4 - 9.8%, 2)	
Mixed Mydriatic / Non-Mydriatic	15.7% (4.0 - 27.4%, 2)				
Not Reported		10.6% (3.7 - 17.4%, 2)			0.28% (1)

Key: SLO: Scanning Laser Ophthalmoscope

Pupil Size

Of the included studies that have investigated relationships between mydriasis / pupil size and photo quality / gradability:

- Murgatroyd (2004) found a significantly higher proportion of gradable photos using a mydriatic versus a non-mydriatic method
- Molina-Fernandez (2008) found no significant difference between mydriatic, non-mydriatic and mydriatic-as-required methods in terms of gradability
- Baeza (2009) found a significant relationship between photo quality and pupil size, with poor photo quality if pupil size is under 4 mm
- Lawrence (2004) found that pupil size was significantly different in gradable (mean 4.14 mm) vs. ungradable (mean 3.28 mm) images for two non-mydriatic methods, but not significantly different for two mydriatic methods (7.31 and 6.92 mm)

Use of Mydriasis as a result of poor photo quality

In five studies (covering six screening methods), screening protocols involved the use of mydriasis only in cases where the initial non-mydriatic photo was of insufficient quality for diagnostic analysis. In three studies (four screening methods), the mean proportion of subjects requiring mydriasis owing to poor non-mydriatic photo quality was 15.5% (range 7.2 - 27.4%) (Lopez-Bastida 2007; Molina Fernandez 2008; Pugh 1993). In the other two studies (Diamond 1998; Maberley 2002), initial poor quality non-mydriatic photos (Maberley 2002 reported a poor photo quality rate of 83%) led to an alteration in the screening protocol such that mydriasis was used for all subsequent patients (41.5% of the study sample for Diamond 1998; 85% of the study sample for Maberley 2002).

Time taken to screen and interpret

Ten studies reported the time taken to screen for DR (Baeza 2009; Friberg 2003; Massin 2005; Nathan 1991; Neubauer 2008b; Peters 1993; Shiba 1999; Shiba 2002; Siu 1998; Taylor 1999), with one study (Pugh 1993) also reported time taken to interpret screening images. Reported durations by method were:

- Direct fundoscopy: range 3-6.5min (data from two screening methods)
- Direct, indirect and slit-lamp fundoscopy: 15-20min (data from one method)
- Polaroid or film camera: range 5-10min (data from four methods)
- Digital camera: mean 4min 14s (data from six methods)
- SLO: range 3-5min (data from two methods)
- Interpretation of screening image: 2 – 3mins (data from one method).

Cost in Screening for DR

Seven studies provided some costing data in regards to materials utilised, hiring of healthcare professionals, or other estimated DR screening costs.

Estimated costs of personnel were as follows:

- Trained registrar with a trained nurse: £2.90 per patient (Bibby 1992)
- Community-based opticians: £12.40 per patient (Bibby 1992)
- Ophthalmic opticians: £8.60 per eye examination (Burns-Cox 1985 [Study 1]))

In terms of materials, it has been reported by Taylor (1999) and Siu (1998) that polaroid photos cost approximately £1 and HKD$14 each, respectively. Taylor (1999) also reported the cost of a 35mm film photo to be approximately £0.30.

Estimated total screening costs have been reported as follows:

- Mobile retinal screening using mydriatic 3-field film photography £22.70 per screen (assuming 6000 screens per year, inclusive of staff, consumables and vehicle costs): Harding (1995)
- Mobile retinal screening van using fundoscopy examination plus mydriatic 1-field polaroid photography: £12.50 per patient for photo (including capital replacement costs). Assuming 80% of sight-threatened patients have their vision saved by treatment, £1095 per patient saved from visual loss. Operational costs of this screening service £35 000 for 3500 patients screened: O'Hare (1996)

- Approximately £12,000 (film alone) for screening the whole Exeter community (300 000) using mydriatic 1-field photography (35mm photo plus polaroid photo): Taylor (1999)
- Basic cost for screening £7.50 per patient using mydriatic Polaroid photography (number of fields not reported) plus fundoscopy (includes polaroid films, capital and maintenance costs, and salaries of primary screener): Pandit (2002)

Furthermore, a study in Ontario, Canada (Maberley 2003) (not from our included articles) that primarily investigated the cost-effectiveness in screening for DR, using digital retinal photography compared to travelling retinal specialists. Results showed that digital photography was far more cost effective, with $15 000 per quality-adjusted life year (QALY), compared to travelling retinal specialists, with $37 000 per QALY.

Further studies focusing solely on cost-effectiveness that were identified but not included in the review are referenced in Appendix 3.

Patient Satisfaction

Patient satisfaction with screening methods was reported by five of the 62 included studies.

A study by Massin (2005) evaluated the use of digital camera without mydriasis on patient satisfaction and reported that:

- 99% of patients found the delay from inclusion in the study to screening visit (mean delay 29.6 ± 43 days) acceptable
- 96% of the digital camera group (5-field) found the screening time (< 15min) acceptable, compared to 82% receiving the reference standard, dilated fundoscopy (χ^2 test, $p < 0.0001$)
- Impairment of vision via the digital camera's flash was absent / mild in 86% of cases, compared to 66% for the reference standard, dilated fundoscopy (χ^2 test, $p < 0.001$)
- Accessibility to the screening location was not difficult / slightly difficult in 82% of cases in the digital camera group versus 93% in the dilated fundoscopy group (χ^2 test, $p < 0.001$)
- 99.1% of the patients in the digital camera group would use the same screening method at their next screening exam

Generally, patient satisfaction with digital cameras without pupil dilation was reported as high; Cavallerano (2005) reported 100% satisfaction with this method and digital camera flash was reported to be comfortable in 81-90% of patients (Cavallerano 2005; Massin 2003). Moreover, 92% of the patients would opt to replace pupil dilation and clinical examination with digital cameras without pupil dilation (Cavallerano 2005).

Based upon the reported data, discomfort arising from flash does not appear to vary according to camera type. Digital camera flash discomfort was reported by 0 – 19% of patients across three studies (Cavallerano 2005; Massin 2003; Taylor 1999). Similar discomfort levels for polaroid camera's flash were reported in studies by Mohan (1988; 17.6%) and Taylor (1999; 16.5%). However, clinical experience shows that the use of 10% of light in the digital camera's flash intensity has a less of an effect on short-term loss of vision and pupil constriction.

Table 19 describes in detail all image quality, patient satisfaction, time, cost and other relevant findings (for example, pupil size, and data transfer times) from the 49 studies that reported this information.

Table 19: Image Quality, Patient Satisfaction, Time, Cost and Other Outcomes

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Ahmed (2006)	Ungradable for Digital (NM, 3f): 35%	**Screen Time** Fundoscopy (Slit-lamp, M): 15-20min
Aiello (1998)	Ungradable for JVN (NM): 2 patients	
Baeza (2009)	*Ungradable for Any DR, STDR* Film (NM, 1f): 15.3%, 16.0% Film (NM, 2f): 17.1%, 17.8% Film (NM, 3f): 17.6%, 18.3% Film (M, 1f): 1.4%, 1.4% Film (M, 2f): 1.6%, 1.6% Film (M, 3f): 2.1%, 2.1% Due to ungradable images, the percentage of referred patients increased from 1.4% (with mydriasis) to almost 19% (p<0.001)	**Screen Time** 5min per 6 photos (3 fields in each eye) taken Total Time per patient was 10min (with or without mydriasis) **Mean Pupil Size (95% CI)** Excellent: 4.88mm (4.70-5.07) Good: 4.42mm (4.29-4.55) Fairly Good: 4.00mm (3.86-4.151) Poor: 3.68 (3.46-3.89)
Bibby (1992)		**Cost** Screened by trained registrar with attendant nurse: £2.90 per patient Screened by community-based Optician: £12.40 per patient
Boucher (2003)	*Sufficient for Grading, Ungradable:* Camera (type unspecified, M, 7f): 96.4%, 5.1% Digital (NM, 1f): 87.8%, 17.4%	
Burns-Cox (1985) - (Study 1 only)		**Cost** Ophthalmic opticians were paid £8.60 per eye examination
Bursell (2001)	Ungradable for Digital (NM, 3f): 11.1%	
Cavallerano (2005)	*Ungradable for Level of DR, Degree of Macular Oedema:* Film (M, 7f): 1% (due to missing photographic fields), NR Digital (NM, 3f): 1.9%, 2.9%	**Patient Satisfaction** Satisfied or Very Satisfied for Digital (NM, 3f): 100% Digital (NM, 3f) more comfortable than Film (M, 7f): 90.4% Digital (NM, 3f) less comfortable than Film (M, 7f): 0% Would take opportunity to replace pupil dilation and retinal examination with Digital (NM, 3f): 92.3%
Diamond (1998)	*Polaroid (NM), Polaroid (M):* Excellent (p=0.00005): 54.2%, 75% Adequate (p=0.000001): 32.8%, 10% Inadequate (p=0.76): 13%, 15% Ungradable: 13% images, NR Second set of photos were retaken through dilated pupils in the last 68 patients	

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Fransen (2002)	Ungradable for Digital (M, 7f): 6.6% Proportion of ungradable image Digital (M, 7f) sets increased with ETDRS level (X^2 test, p=0.008)	
Friberg (2003)	*SLO (NM):* Ungradable: 6.4% Physician 1: 52% were Good or Better Physician 2:62% were Average	**Screen Time** <5min per patient
Hansen (2004)	*Digital (NM (physiological dilation), 5f), Digital (M, 5f), Digital (NM, 5f):* Excellent: 41%, 92%, 34% Good: 31%, 8%, 26% Acceptable: 10%, 0%, 21% Poor: 11%, 0%, 9% Ungradable: 7%, 0%, 10%	
Harding (1995)	*Ungradable:* Film (M, 3f): 46 patients Fundoscopy (Direct, M): 7 patients	**Cost** £22.70 per screen event, assuming a service related activity level of 6000 screens events per year
Herbert (2003)	Ungradable for Digital (dilation as required, 1f): 4% of eyes	
Jones (1988)	*Polaroid (NM), Film (M):* Excellent Clarity: 47.2%, 91.3% Definition of Most Retina: 35.4%, 6.3% Limited Definition: 14.2%, 1.6% Gross Detail Only Visible: 3.1%, 0.8% No Detail Visible: 0%, 0%	
Kuo (2005)	*Digital (NM, 1f):* Good: 47% Fair: 36% Poor: 17% Ungradable (Retinal Specialist): 8% Ungradable (Endocrinologist): 23.5%	
Lawrence (2004)	Ungradable for Film (7f): 3.7% Mean pupil size for Digital (NM, 1f) gradable images was 4.14mm, compared to 3.28mm for ungradable images (p<0.0001) Mean pupil size for dilated Digital (M, 3f) gradable images was 7.31mm, compared to 6.92mm for ungradable images (p=0.2329)	
Lee (1993)	*Ungradable:* Fundoscopy (Indirect & Slit-lamp, M): 1.1% Camera (type unspecified, M, 1f): 7.7%	

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Liesenfeld (2000)	*Ungradable:* Film (M, 2f): 11% Digital (M, 2f): Mean 5%	
Lin (2002)	Ungradable for Digital (NM, 1f): 8.1% patients	
Lopez-Bastida (2007)	Digital (NM, 2f): 7.2% of images were of poor quality, thus dilation was required	
Maberley (2002)	*Ungradable for Digital (dilation as required, 1f) - (Examiner 1, Examiner 2):* High: 87.5%, 92.5% Intermediate: 11%, 7.5% Low: 1.5%, 0.5% Subsequent 85 patients were photographed in the dilated state, following poor photo quality in the first 15 patients (Photo Quality - Good: 7%, Intermediate: 10%, Poor: 83%)	
Massin (2003)	**First Evaluation** *Digital (NM, 5f)*: *Right Eye: Posterior Pole field, Peripheral Retina field / Left Eye: Posterior Pole field, Peripheral Retina field* Excellent, Good Retinal Definition, & Easily Assessable: 66%, 54% / 69%, 47% Definition limited, Difficultly Assessable: 18%, 20% /15%, 27.5% Only Gross Detail Visible: 7%, 17% / 7%, 15% Ungradable: 9%, 9% / 10%, 10% **Second Evaluation** *Digital (NM, 5f)* *Right Eye: Posterior Pole, Peripheral Retina / Left Eye: Posterior Pole, Peripheral Retina* Excellent, Good Retinal Definition, & Easily Assessable: 81%, 70% / 76%, 62% Definition limited, Difficultly Assessable: 14%, 21.5% / 12%, 22% Only Gross Detail Visible: 3%, 6.5% / 9%, 10% Ungradable: 2%, 2% / 3%, 6%	**Patient Satisfaction** **First Evaluation:** Sixty patients found the camera flash comfortable and 14 patients found it uncomfortable
Massin (2005)	Ungradable for Digital (NM, 5f): 5%	**Screen Time** Digital (NM, 5f): <15min **Patient Satisfaction** 99% of patients considered mean delay of 29.6 ± 43 days (i.e. from inclusion to screening visit) acceptable 96% patients from Digital (NM, 5f) found the duration of testing acceptable, compared to 82% in Fundoscopy (M) (χ^2 test, $p<0.001$) 82% patients from Digital (NM, 5f) considered accessibility to screening location not or slightly difficult, compared to 93% from Fundoscopy (M) (X^2 test, $p<0.001$)

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Mohan (1988)	Ungradable for Polaroid (NM, 1f): 6% photos	**Patient Satisfaction** 15 patients (13 Indians, 2 Europeans) experienced some discomfort during the photographs
Molina Fernandez (2008)	*Ungradable:* Digital (M): 17.2% Digital (NM): 38.4% Digital (dilation as required): 27.4% Ophthalmologist: 28% (p=0.0027) GP: 13.6% Other ungradable eyes included a further 6 eyes which were lost, 4 due to storage errors, and 2 due to duplication on the same eye Dilation was required if the GP consider the photo of poor quality	
Moller (2002)	Ungradable for Film (1f): 4 patients	
Murgatroyd (2004)	Digital (NM, 1f) vs. Digital (M, 1f) in proportion of gradable photos: X^2 test, p<0.001 Digital (NM, 1f) vs. Digital (M, 3f) in proportion of gradable photos: X^2 test, p<0.001 *Ungradable Right, Left, & Either Eye:* Digital (NM, 1f): 25%, 27%, 36% Digital (M, 1f): 4%, 6%, 7% Digital (M, 3f): 4%, 5.5%, 6.5% Digital (NM, 1f) (Right vs. Left eyes) in proportion of ungradable photos: X^2 test, p=0.614	
Nathan (1991)		**Screen Time** ~3min (includes visual acuity testing)
Neubauer (2008a)	Digital (M, 7f, Visucam) (scored 2.2/5) vs. Digital (M, 7f, FF450) (scored 2.41/5): p<0.001 ETDRS level did not influence image quality Small pupil diameter (6-7mm) degraded image quality (p=0.003) in Digital (M, 7f, FF450) compared with Digital (M, 7f, Visucam) No significant difference between Digital (M, 7f, FF450) & Digital (M, 7f, Visucam) for pupil diameters >7mm	
Neubauer (2008b)	Ungradable for SLO (NM): 9.8%	**Screen Time** 3-5min (includes patient positioning)
O'Hare (1996)		**Cost** £1095 (including capital replacement cost) + £12.50 per patient screened with photographs (if 80% of sight-threatened patients are saved by treatment)

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Olson (2003)	*Ungradable:* Film (M): 11.9% Digital (M, 2f): 4.4% ***Repeated Images (due to poor quality in nasal area)*** *Ungradable:* Film (M): 8.1% Digital (M, 2f): 3.5%	
Pandit (2002)	Ungradable for Polaroid & Fundoscopy (Direct, M): 6.4%	**Basic Cost** £7.50 per patient
Penman (1998)	**Ungradable:** Fundoscopy (Indirect & Slit-lamp, M): 23 eyes Camera (M, 1f): 22% photos	
Peters (1993)	Ungradable for Polaroid (NM, 1f): 32%	
Phiri (2006)	Ungradable (screening instrument unspecified): 14% photos	**Other Results** No significant difference between Digital (NM, 1f) vs. Polaroid (NM, 1f) in detecting referrable DR (Odds Ratio 1.06 (95% CI, 0.80-1.40), p= 0.68) This study encountered nine cases of failed pupil dilation.
Prasad (2001)	Ungradable for Fundoscopy (Slit-lamp, M) due to technical failure: 0.2%	
Pugh (1993)	*Ungradable:* Camera (type unspecified, 7f): 1 patient Film (NM, 1f): 14% Film (M, 3f): 3.7% Fundoscopy (Direct & Indirect, M): 4 patients Fundoscopy (Direct, M): 102 patients 12% of total study population were dilated due to ungradable photos	**Screening + Interpretation Times** Fundoscopy: 6.5min screen Film Camera: 7min screen + 2-3min interpret
Rudnisky (2002)	*Ungradable for Digital (M, 1f):* Poor: 35 images Good: 134 images Excellent: 39 images Fifty-nine eyes had mildly under-exposed digital photographs (Digital (M, 1f)) were adjusted to optimal exposure using the Kodak DCS Twain software	

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Scanlon (2003a)	Digital (NM, 1f), Digital (M, 2f): Fully Assessable both eyes: 48%, 80.1% Fully & Partially: 13%, 8.5% Partially Assessable both eyes: 18.2%, 7% Fully & Not Assessable: 2.4%, 1.5% Partially & Not Assessable: 7.3%, 1.2% Not Assessable both eyes: 10%, 1% Not assessable & Referrable DR: 1%, 0.7% Ungradable: 19.7% (95% CI, 18.4-21), 3.7% (95% CI, 3.1-4.3)	
Scanlon (2003b)	*Ungradable:* Film (M, 7f): 151 eyes Fundoscopy (Direct & Indirect, M): 0 eyes Digital (M, 2f): 6 eyes	
Schmid (2002)		**Other Results** Correct classifications were significantly decreased in the mild DR group that had previous laser treatment (Pearson X^2 test, p=0.005) and increased referral rate (p=0.0005)
Shiba (1999)	**Mean (SD) Grades 1-5 (Best)** Digital (M, 9f): 4.8 (0.3) Digital (NM, 9f, control): 4.3 (0.6) Digital (NM, 9f, diabetic): 4.7 (0.4) Quality scores significantly correlated with pupil size (p < 0.0001)	**Screen Time Mean (SD)** Digital (M, 9f): 3min 26s (1min 17s) Digital (NM, 9f): 4min 36s (2min 5s)
Shiba (2002)	**Mean (SD) Grades 1-5 (Best)** *Study 1 - Adult Study* 3x3 Images (p<0.0001) Digital (M, 9f): 4.4 (0.4) Digital (NM, 9f): 3.8 (0.6) Collage Images (p<0.0001) Digital (M, 9f): 4.2 (0.6) Digital (NM, 9f): 4.0 (0.7) *Study 2 - Adolescent Study* Film (NM, 1f): 4.2 (0.6) 3x3 Images on Monitor - Digital (NM, 9f): First Eye: 4.4 (0.5), Second Eye: 4.2 (0.5)	**Screen Time Mean (SD)** *Study 1 - Adult Study* Digital (M, 9f): 5min 7s (2min 12s) Digital (NM, 9f): 3min 6s (57s) *Study 2 - Adolescent Study* Digital (NM, 9f): First Eye: 2min 53s (1min 11s), Second Eye: 2min 50s (1min 30s) **Data Transmission Duration Mean (SD)** 1min 19s (9s) per 3x3 image over a standard phone line **Data File Size Mean (SD)** 259 KB (30 KB) per file

Citation	Image Quality	Patient Satisfaction / Time / Cost / Other Results
Siu (1998)	*Ungradable:* Fundoscopy (Indirect, M): 4 patients Polaroid (NM): 10 (7%) patients Fundoscopy (Direct, M): 2 patients	**Screen Time** ~10min by nurse **Costs** Two Polaroid films: HKD$14
Sussman (1982)		**Other Results** Significant differences were observed on physician type in the mean error rates for overall errors and for serious errors ($p<0.001$) Further analyses were performed and reported significant differences when Fundoscopy (Direct, M, Interns or Senior Medical Resident or Diabetologist) were compared to Fundoscopy (Indirect, M, Ophthalmologist or Retinal Specialist) for both all errors and serious errors ($p<0.001$)
Taylor (1999)		**Screen Time** Digital (M, 1f) was on average 2min faster than Film (7f) **Costs** 35mm film: ~ £0.30 each Polaroids: ~ £1 each Photographing everyone in Exeter in single field: ~£12,000 for film alone **Patient Satisfaction** 29 of the 176 patients experienced discomfort with Polaroid (M, 1f) system flash levels 2 of the those 29 described their discomfort level as 'a lot' 4 of the 154 describe 'some' discomfort from the Digital (M, 1f) ($p<0.001$)
Williams (1986)	Camera (type unspecified) & Polaroid (NM): Excellent: 47% (56 eyes) Definition of Most Retina: 23% (27 eyes) Definition Limited: 7% (8 eyes) No Detail Visible: 6% (7 eyes)	

Key: Citations of outreach studies highlighted in bold & italicised

DR: Diabetic Retinopathy
ETDRS: Early Treatment Diabetic Retinopathy Study
f: field
GP: General Practitioner
M: Mydriatic
NM: Non-mydriatic
SLO: Scanning Laser Ophthalmoscope
STDR: Sight-threatening Retinopathy

Appendices

Appendix 1: Example of Search strategy: Medline database

1. Diabetic Retinopathy/

2. (diabet* adj2 retin*).mp.

3. or/1-2

4. retinal photography.mp.

5. exp Photography/ or (photo* or camera* or screen* or telemed*).mp.

6. or/4-5

7. ((non adj2 mydriatic*) or undilate*).mp.

8. and/3,6-7

9. (sensitiv: or predictive value:).mp. or accurac:.tw.

10. exp Eye/ or eye*.tw.

11. and/7,9-10

12. or/8,11

Appendix 2: Complete list of eligible studies indicating primary outcomes measures

Method under investigation = Camera
Reference Standard = Examination (15)

Reference	S_n/S_p data	Kappa data
Case-control study (1)		
Massin P, Erginay A, Ben Mehidi A, Vicaut E, Quentel G, Victor Z, et al. Evaluation of a new non-mydriatic digital camera for detection of diabetic retinopathy. Diabetic Medicine 2003;20(8):635-41.	✓	✓
Case series (14)		
Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA. The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. Diabetes Care 2006;29(10):2205-9.	✓	
Heaven CJ, Cansfield J, Shaw KM. A screening programme for diabetic retinopathy. Practical Diabetes 1992;9(2):43-45.		
Herbert HM, Jordan K, Flanagan DW. Is screening with digital imaging using one retinal view adequate? Eye 2003;17(4):497-500.	✓	
Kinyoun JL, Martin DC, Fujimoto WY, Leonetti DL. Ophthalmoscopy versus fundus photographs for detecting and grading diabetic retinopathy. Investigative Ophthalmology & Visual Science 1992;33(6):1888-93.		✓
Kinyoun J, Barton F, Fisher M, Hubbard L, Aiello L, Ferris F, 3rd. Detection of diabetic macular edema. Ophthalmoscopy versus photography--Early Treatment Diabetic Retinopathy Study Report Number 5. The ETDRS Research Group. Ophthalmology 1989;96(6):746-50; discussion 750-1.		
Kuo HK, Hsieh HH, Liu RT. Screening for diabetic retinopathy by one-field, non-mydriatic, 45 degrees digital photography is inadequate. Ophthalmologica 2005;219(5):292-296.	✓	
Lee VS, Kingsley RM, Lee ET, Lu M, Russell D, Asal NR, et al. The diagnosis of diabetic retinopathy. Ophthalmoscopy versus fundus photography. Ophthalmology 1993;100(10):1504-12.		✓
Lopez-Bastida J, Cabrera-Lopez F, Serrano-Aguilar P. Sensitivity and specificity of digital retinal imaging for screening diabetic retinopathy. Diabetic Medicine 2007;24(4):403-7.	✓	✓
Mohan R, Kohner EM, Aldington SJ, Nijhar I, Mohan V, Mather HM. Evaluation of a non-mydriatic camera in Indian and European diabetic patients. British Journal of Ophthalmology 1988;72(11):841-5.		
Molina Fernandez E, Valero Moll MS, Pedregal Gonzalez M, Calvo Lozano J, Sanchez Ramos JL, Diaz Rodriguez E, et al. Validation of the electronic mailing of retinographs of diabetic patients in order to detect retinopathy in primary care. Aten Primaria 2008;40(3):119-23.	✓	
Murgatroyd H, Ellingford A, Cox A, Binnie M, Ellis JD, MacEwen CJ, et al. Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. British Journal of Ophthalmology 2004;88(7):920-4.	✓	

Penman AD, Saaddine JB, Hegazy M, Sous ES, Ali MA, Brechner RJ, et al. Screening for diabetic retinopathy: the utility of nonmydriatic retinal photography in Egyptian adults. Diabetic Medicine 1998;15(9):783-7.		✓
Peters AL, Davidson MB, Ziel FH. Cost-effective screening for diabetic retinopathy using a nonmydriatic retinal camera in a prepaid health-care setting. Diabetes Care 1993;16(8):1193-5.	✓	
Rudnisky CJ, Hinz BJ, Tennant MT, de Leon AR, Greve MD. High-resolution stereoscopic digital fundus photography versus contact lens biomicroscopy for the detection of clinically significant macular edema. Ophthalmology 2002;109(2):267-74.	✓	✓

Method under investigation = Camera
Reference Standard = Camera (8)

Reference	S_n/S_p data	Kappa data
RCT (1)		
Neubauer AS, Rothschuh A, Ulbig MW, Blum M. Digital fundus image grading with the non-mydriatic Visucam(PRO NM) versus the FF450(plus) camera in diabetic retinopathy. Acta Opthalmologica 2008a;86(2):177-82.	✓	✓
Cross-sectional study (1)		
Baeza M, Orozco-Beltran D, Gil-Guillen VF, Pedrera V, Ribera MC, Pertusa S, Merino J. Screening for sight threatening diabetic retinopathy using non-mydriatic retinal camera in a primary care setting: to dilate or not to dilate? International Journal of Clinical Practice 2009;63(3): 433-8.	✓	✓
Case-control study (1)		
Shiba T, Maruo K, Akahoshi T. Development of a multi-field fundus photographing system using a non-mydriatic camera for diabetic retinopathy. Diabetes Research & Clinical Practice 1999;45(1):1-8.		
Case series (5)		
Bursell SE, Cavallerano JD, Cavallerano AA, Clermont AC, Birkmire-Peters D, Aiello LP, et al. Stereo nonmydriatic digital-video color retinal imaging compared with Early Treatment Diabetic Retinopathy Study seven standard field 35-mm stereo color photos for determining level of diabetic retinopathy. Ophthalmology 2001;108(3):572-85.	✓	✓
Fransen SR, Leonard-Martin TC, Feuer WJ, Hildebrand PL. Clinical evaluation of patients with diabetic retinopathy: accuracy of the Inoveon diabetic retinopathy-3DT system. Ophthalmology 2002;109(3):595-601.	✓	✓
Gonzalez ME, Gonzalez C, Stern MP, Arredondo B, Martinez S. Concordance in diagnosis of diabetic retinopathy by fundus photography between retina specialists and a standardized reading center. Mexico City Diabetes Study Retinopathy Group. Archives of Medical Research 1995;26(2):127-31.		
Hansen AB, Sander B, Larsen M, Kleener J, Borch-Johnsen K, Klein R, et al. Screening for diabetic retinopathy using a digital non-mydriatic camera compared with standard 35-mm stereo colour transparencies. Acta Ophthalmologica Scandinavica 2004;82(6):656-65.	✓	✓

Phiri R, Keeffe JE, Harper CA, Taylor HR. Comparative study of the polaroid and digital non-mydriatic cameras in the detection of referrable diabetic retinopathy in Australia. Diabetic Medicine 2006;23(8):867-72.	✓	

Method under investigation = Camera

Reference Standard = Examination / Camera (6)

Reference	S_n/S_p data	Kappa data
Cohort study (pros.) (1)		
Cavallerano JD, Aiello LP, Cavallerano AA, Katalinic P, Hock K, Kirby R, et al. Nonmydriatic digital imaging alternative for annual retinal examination in persons with previously documented no or mild diabetic retinopathy. American Journal of Ophthalmology 2005;140(4):667-73.	✓	
Case series (5)		
Aiello LM, Bursell SE, Cavallerano J, Gardner WK, Strong J. Joslin Vision Network Validation Study: pilot image stabilization phase. Journal of the American Optometric Association 1998;69(11):699-710.		
Boucher MC, Gresset JA, Angioi K, Olivier S. Effectiveness and safety of screening for diabetic retinopathy with two nonmydriatic digital images compared with the seven standard stereoscopic photographic fields. Canadian Journal of Ophthalmology 2003;38(7):557-68.	✓	✓
Lawrence MG. The accuracy of digital-video retinal imaging to screen for diabetic retinopathy: an analysis of two digital-video retinal imaging systems using standard stereoscopic seven-field photography and dilated clinical examination as reference standards. Transactions of the American Ophthalmological Society 2004;102:321-40.	✓	
Liesenfeld B, Kohner E, Piehlmeier W, Kluthe S, Aldington S, Porta M, et al. A telemedical approach to the screening of diabetic retinopathy: digital fundus photography. Diabetes Care 2000;23(3):345-8.	✓	
Scanlon PH, Malhotra R, Greenwood RH, Aldington SJ, Foy C, Flatman M, et al. Comparison of two reference standards in validating two field mydriatic digital photography as a method of screening for diabetic retinopathy. British Journal of Ophthalmology 2003b;87(10):1258-63.	✓	✓

Method under investigation = Camera

Reference Standard = Camera / Fluorescein Angiography (1)

Reference	S_n/S_p data	Kappa data
Case series (1)		
Moller F, Hansen M, Sjolie AK. Is one 60 degrees fundus photograph sufficient for screening of proliferative diabetic retinopathy? Diabetes Care 2002;24(12):2083-5.	✓	

Method under investigation = Camera
Reference Standard = Fluorescein Angiography (1)

Reference	S_n/S_p data	Kappa data
Case series (1)		
Jones D, Dolben J, Owens DR, Vora JP, Young S, Creagh FM. Non-mydriatic Polaroid photography in screening for diabetic retinopathy: evaluation in a clinical setting. British Medical Journal (Clin. Res. Ed.)1988;296(6628):1029-30.		

Method under investigation = Examination
Reference Standard = Examination (8)

Reference	S_n/S_p data	Kappa data
Case-control study (1)		
Bibby K, Barrie T, Patterson KR, MacCuish AC. Benefits of training junior physicians to detect diabetic retinopathy--the Glasgow experience. Journal of the Royal Society of Medicine 1992;85(6):326-8.		
Case series (7)		
Hammond CJ, Shackleton J, Flanagan DW, Herrtage J, Wade J. Comparison between an ophthalmic optician and an ophthalmologist in screening for diabetic retinopathy. Eye 1996;10 (Pt 1):107-12.	✓	
Hulme SA, Tin UA, Hardy KJ, Joyce PW. Evaluation of a district-wide screening programme for diabetic retinopathy utilizing trained optometrists using slit-lamp and Volk lenses. Diabetic Medicine 2002;19(9):741-5.	✓	
Lienert RT. Inter-observer comparisons of ophthalmoscopic assessment of diabetic retinopathy. Australian & New Zealand Journal of Ophthalmology 1989;17(4):363-8.		
Prasad S, Kamath GG, Jones K, Clearkin LG, Phillips RP. Effectiveness of optometrist screening for diabetic retinopathy using slit-lamp biomicroscopy. Eye 2001;15(Pt 5):595-601.	✓	
Reenders K, de Nobel E, van den Hoogen H, van Weel C. Screening for diabetic retinopathy by general practitioners. Scandinavian Journal of Primary Health Care 1992;10(4):306-9.	✓	
Verma L, Prakash G, Tewari HK, Gupta SK, Murthy GV, Sharma N. Screening for diabetic retinopathy by non-ophthalmologists: an effective public health tool. Acta Ophthalmologica Scandinavica 2003;81(4):373-7.	✓	✓
Warburton TJ, Hale PJ, Dewhurst JA. Evaluation of a local optometric diabetic retinopathy screening service. Diabetic Medicine 2004;21(6):632-5.	✓	

Method under investigation = Examination
Reference Standard = Camera (2)

Reference	S_n/S_p data	Kappa data
Case series (2)		
Kleinstein RN, Roseman JM, Herman WH, Holcombe J, Louv WC. Detection of diabetic retinopathy by optometrists. Journal of the American Optometric Association 1987;58(11):879-82.	✓	
Sussman EJ, Tsiaras WG, Soper KA. Diagnosis of diabetic eye disease. JAMA 1982;247(23):3231-4.	✓	

Method under investigation = Examination / Camera
Reference Standard = Camera (5)

Reference	S_n/S_p data	Kappa data
Case series (5)		
Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. American Journal of Ophthalmology 2002;134(2):204-13.	✓	✓
Massin P, Aubert JP, Eschwege E, Erginay A, Bourovitch JC, BenMehidi A, et al. Evaluation of a screening program for diabetic retinopathy in a primary care setting Dodia (Depistage ophtalmologique du diabete) study. Diabetes & Metabolism 2005;31(2):153-62.		
Nathan DM, Fogel HA, Godine JE, Lou PL, D'Amico DJ, Regan CDJ, et al. Role of diabetologist in evaluating diabetic retinopathy. Diabetes Care 1991;14(1):26-33.		
Pugh JA, Jacobson JM, Van Heuven WA, Watters JA, Tuley MR, Lairson DR, et al. Screening for diabetic retinopathy. The wide-angle retinal camera. Diabetes Care 1993;16(6):889-95.	✓	✓
Taylor DJ, Fisher J, Jacob J, Tooke JE. The use of digital cameras in a mobile retinal screening environment. Diabetic Medicine 1999;16(8):680-6.	✓	

Method under investigation = Examination / Camera
Reference Standard = Examination (3)

Reference	S_n/S_p data	Kappa data
Case series (3)		
Olson JA, Strachan FM, Hipwell JH, Goatman KA, McHardy KC, Forrester JV, et al. A comparative evaluation of digital imaging, retinal photography and optometrist examination in screening for diabetic retinopathy. Diabetic Medicine 2003;20(7):528-34.	✓	
Siu SC, Ko TC, Wong KW, Chan WN. Effectiveness of non-mydriatic retinal photography and direct ophthalmoscopy in detecting diabetic retinopathy. Hong Kong Medical Journal 1998;4(4):367-370.	✓	
Williams R, Nussey S, Humphry R, Thompson G. Assessment of non-mydriatic fundus photography in detection of diabetic retinopathy. British Medical Journal (Clin. Res. Ed.) 1986;293(6555):1140-2.	✓	

Method under investigation = Examination / Camera
Reference Standard = Exam / Camera (1)

Reference	S_n/S_p data	Kappa data
Case series (1)		
Schmid KL, Swann PG, Pedersen C, Schmid LM. The detection of diabetic retinopathy by Australian optometrists. Clinical & Experimental Optometry 2002;85(4):221-8.	✓	

Method under investigation = Outreach - Examination / Camera
Reference Standard = Examination (4)

Reference	S_n/S_p data	Kappa data
Case series (4)		
Harding SP, Broadbent DM, Neoh C, White MC, Vora J. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool Diabetic Eye Study. British Medical Journal 1995;311(7013):1131-5.	✓	
Leese GP, Ellis JD, Morris AD, Ellingford A. Does direct ophthalmoscopy improve retinal screening for diabetic eye disease by retinal photography? Diabetic Medicine 2002;19(10):867-9.		✓
Pandit RJ, Taylor R. Quality assurance in screening for sight-threatening diabetic retinopathy. Diabetic Medicine 2002;19(4):285-91.	✓	

Scanlon PH, Malhotra R, Thomas G, Foy C, Kirkpatrick JN, Lewis-Barned N, et al. The effectiveness of screening for diabetic retinopathy by digital imaging photography and technician ophthalmoscopy. Diabetic Medicine 2003a;20(6):467-74.	✓	

Method under investigation = Outreach - Examination / Camera
Reference Standard = Examination / Camera (2)

Reference	S_n/S_p data	Kappa data
Case series (2)		
O'Hare JP, Hopper A, Madhaven C, Charny M, Purewell TS, Harney B, et al. Adding retinal photography to screening for diabetic retinopathy: a prospective study in primary care. British Medical Journal 1996;312(7032):679-82.	✓	
Shiba T, Yamamoto T, Seki U, Utsugi N, Fujita K, Sato Y, et al. Screening and follow-up of diabetic retinopathy using a new mosaic 9-field fundus photography system. Diabetes Research & Clinical Practice 2002;55(1):49-59.		

Method under investigation = Outreach - Camera
Reference Standard = Examination (2)

Reference	S_n/S_p data	Kappa data
Case series (2)		
Diamond JP, McKinnon M, Barry C, Geary D, McAllister IL, House P, et al. Non-mydriatic fundus photography: A viable alternative to fundoscopy for identification of diabetic retinopathy in an Aboriginal population in rural Western Australia? Australian & New Zealand Journal of Ophthalmology 1998;26(2):109-115.		✓
Maberley D, Cruess AF, Barile G, Slakter J. Digital photographic screening for diabetic retinopathy in the James Bay Cree. Ophthalmic Epidemiology 2002;9(3):169-78.	✓	

Method under investigation = Outreach - Examination
Reference Standard = Camera (1)

Reference	S_n/S_p data	Kappa data
Case series (1)		
Moss SE, Klein R, Kessler SD, Richie KA. Comparison between ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy. Ophthalmology 1985;92(1):62-7.		✓

Method under investigation = Scanning Laser
Reference Standard = Examination (2)

Reference	S_n/S_p data	Kappa data
Case series (2)		
Friberg TR, Pandya A, Eller AW. Non-mydriatic panoramic fundus imaging using a non-contact scanning laser-based system. Ophthalmic Surgery, Lasers & Imaging 2003;34(6):488-97.	✓	
Neubauer AS, Kernt M, Haritoglou C, Priglinger SG, Kampik A, Ulbig MW. Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap). Graefes Archive for Clinical & Experimental Ophthalmology 2008b;246(2):229-35.	✓	✓

Method under investigation = Optician Report
Reference Standard = Examination (1)

Reference	S_n/S_p data	Kappa data
Case series (1)		
Burns-Cox CJ, Hart JC. Screening of diabetics for retinopathy by ophthalmic opticians. British Medical Journal (Clin. Res. Ed.) 1985;290(6474):1052-4.		

APPENDIX 3: REVIEWS AND RELATED PRIMARY STUDIES

Systematic Reviews (6)

Bachmann MO, Nelson SJ. Impact of diabetic retinopathy screening on a British district population: case detection and blindness prevention in an evidence-based model. Journal of Epidemiology & Community Health 1998;52(1):45-52.

Gutierrez A, Asua J. Analysis of the cost-effectiveness of the non-mydriatic retinal camera for diabetic retinopathy - primary research (Structured abstract). International Society of Technology Assessment in Health Care 1996.

Hutchinson A, McIntosh A, Peters J, O'Keeffe C, Khunti K, Baker R, et al. Effectiveness of screening and monitoring tests for diabetic retinopathy--a systematic review. Diabetic Medicine 2000;17(7):495-506.

Mason J, Drummond M, Woodward G. Optometrist screening for diabetic retinopathy: evidence and environment. Ophthalmic & Physiological Optics 1996;16(4):274-85.

Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, et al. The value of digital imaging in diabetic retinopathy. Health Technology Assessment 2003;7(30):1-119.

Swanson M. Retinopathy screening in individuals with type 2 diabetes: who, how, how often, and at what cost--an epidemiologic review. Optometry 2005;76(11):636-46.

Cost-Effectiveness Analysis (7)

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Contact

Professor Hugh R. Taylor AC,
Indigenous Eye Health Unit,
Melbourne School of Population Health,
The University of Melbourne,
Level 5, 207 Bouverie St,
Carlton, Victoria 3053
Australia
Website: www.iehu.unimelb.edu.au

Professor Russell Gruen MBBS PhD FRACS,
National Trauma Research Institute
Level 4, 89 Commercial Rd
Melbourne Victoria 3004
Australia
Website: www.ntri.com.au

Authorised by the Harold Mitchell Chair of Indigenous Eye Health, Melbourne School of Population Health.

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