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Colour vision testing for diabetic retinopathy: a systematic review of diagnostic accuracy and economic evaluation

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Abstract

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Objective: To determine the diagnostic performance and cost-effectiveness of colour vision testing (CVT) to identify and monitor the progression of diabetic retinopathy (DR).

Data sources: Major electronic databases including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Database of Systematic Reviews were searched from inception to September 2008.

Review methods: A systematic review of the evidence was carried out according to standard methods. An online survey of National Screening Programme for Diabetic Retinopathy (NSPDR) clinical leads and programme managers assessed the diagnostic tools used routinely by local centres and their views on future research priorities. A decision tree and Markov model was developed to estimate the incremental costs and effects of adding CVT to the current NSPDR.

Results: In total, 25 studies on CVT met the inclusion criteria for the review, including 18 presenting 2×2 diagnostic accuracy data. The quality of studies and reporting was generally poor. Automated or computerised CVTs reported variable sensitivities (63–97%) and specificities (71–95%). One study reported good diagnostic accuracy estimates for computerised CVT plus retinal photography for detection of sight-threatening DR, but it included few cases of retinopathy in total. Results for pseudoisochromatic plates, anomaloscopes and colour arrangement tests were largely inadequate for DR screening, with Youden indices (sensitivity + specificity – 100%) close to zero. No studies were located that addressed patient preferences relating to CVT for DR. Retinal photography is universally employed as the primary method for retinal screening by centres responding to the online survey; none used CVT. The review of the economic evaluation literature found no previous studies describing the cost and effects of any type of CVT. Our economic evaluation suggested that adding CVT to the current national screening programme could be cost-effective if it adequately increases sensitivity and is relatively inexpensive. The deterministic base-case analysis indicated that the cost per quality-adjusted life-year gained may be £6364 and £12,432 for type 1 and type 2 diabetes respectively. However, probabilistic sensitivity analysis highlighted the substantial probability that CVT is not diagnostically accurate enough to be either an effective or a cost-effective addition to current screening methods. The results of the economic model should be treated with caution as the model is based on only one small study.

Conclusions: There is insufficient evidence to support the use of CVT alone, or in combination with retinal photography, as a method for screening for retinopathy in patients with diabetes. Better quality diagnostic accuracy studies directly comparing the incremental value of CVT in addition to retinal photography are needed before drawing conclusions on cost-effectiveness. The most frequently cited preference for future research was the use of optical coherence tomography for the detection of clinically significant macular oedema.

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Glossary and list of abbreviations

Glossary

Clinical terms

Deutanopia The colour receptors (cones) in the eyes of people with deutanopia are not sensitive to medium wavelengths (i.e. greens).

Diabetic retinopathy Damage to blood vessels in the retina, caused by diabetes.

Munsell colour system A colour space that defines colours based on three dimensions: hue, value (lightness) and chroma (colour purity or colourfulness).

Phakic eye An eye that still possesses its natural crystalline lens.

Protanopia The colour receptors (cones) in the eyes of people with protanopia are not sensitive to long wavelengths (i.e. reds).

Snellen Scale used to measure visual acuity. This has now been superseded by the development of the LogMAR scale.

Tritanopia Insensitivity to short wavelengths (i.e. blues).

Visual acuity The limit of spatial visual discrimination, commonly measured using letter or other geometric forms. Two of the scales used to measure visual acuity are the Snellen and LogMAR scales.

Diagnostic testing terms

Diagnostic case–control study Diagnostic accuracy study in which the test results of a series of patients with an established diagnosis are compared with those of a non-diseased control group.

Diagnostic cohort study Diagnostic accuracy study in which a group of individuals with a suspected disease undergo both the index test and the reference standard, and the results of the two tests are compared.

False-negative A test result which indicates that a person does not have a specific disease or condition when the person actually does have the disease or condition.

False-positive A test result which indicates that a person does have a specific disease or condition when the person actually does not have the disease or condition.

Likelihood ratio Describes how many times more likely a person with a disease is to receive a particular test result than a person without disease. A likelihood ratio of a positive test result is usually a number greater than 1; a likelihood ratio of a negative test result usually lies between 0 and 1.

Receiver operating characteristic A receiver operating characteristic curve represents the relationship between 'true-positive fraction' (sensitivity) and 'false-positive fraction' (1–specificity). It displays the trade-offs between sensitivity and specificity as a result of varying the cut-off value for positivity in case of a continuous test result.

Reference standard Established test(s) against which the accuracy of a new test for detecting a particular condition can be evaluated.

Screening A health service in which members of a defined population, who do not necessarily perceive that they are at risk of a disease or its complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatment.

Sensitivity (true-positive rate) The proportion of individuals with the target condition in a population who are correctly identified by a diagnostic test.

continued

Specificity (true-negative rate) The proportion of individuals free of the target condition in a population who are correctly identified by a diagnostic test.

Test accuracy The proportion of test results that are correctly identified by the test.

Economic evaluation terms

Cost-effectiveness acceptability curve A way of illustrating cost-effectiveness results by plotting the probability that the intervention is cost-effective (*y*-axis) against the maximum that society is willing to pay for an improvement in health (*x*-axis).

Cost-effectiveness plane A way of illustrating cost-effectiveness results by plotting the mean incremental cost and effectiveness on a four-quadrant graph. Interventions that are more costly and more effective fall in the north-east quadrant.

Incremental cost-effectiveness ratio The difference in costs between one intervention and an alternative, divided by the difference in outcomes.

Quality-adjusted life-year A measure of benefit of health care combining the impact of both expected length of life and quality of life.

Whole time equivalent Equivalent to one individual working full time (about 40 hours per week).

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CSMO	clinically significant macular oedema
CVM	colour vision meter
CVT	colour vision testing
DM	diabetes mellitus
DR	diabetic retinopathy
D-15	Lanthony desaturated D-15 test
ETDRS	Early Treatment of Diabetic Retinopathy Study
FM-100	Farnsworth–Munsell 100 hue test
FN	false-negative
FP	false-positive
HbA1c	glycosylated haemoglobin
ICER	incremental cost-effectiveness ratio
LR+	positive likelihood ratio
LR–	negative likelihood ratio
NCT	Lanthony New Colour Test
NICE	National Institute for Health and Clinical Excellence
NSC	National Screening Committee
NSPDR	National Screening Programme for Diabetic Retinopathy
NPDR	non-proliferative diabetic retinopathy
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUADAS	*Qua*lity for Assessing *D*iagnostic *A*ccuracy *S*tudies
ROC	receiver operating characteristic
SGM	Sussex Gratings Machine
STDR	sight-threatening diabetic retinopathy
TCCT	tritan colour contrast threshold
TCT	tritan contrast threshold (test)
TN	true-negative
TP	true-positive
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), has been used only once, or is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Diabetic retinopathy (DR) is caused by pathological changes in the blood vessels of the retina, which can lead to blindness.

All patients with diabetes mellitus (DM) are at risk of DR, and generally risk increases with duration of diabetes. Despite advances in the management of DM, visual impairment due to DR remains a significant complication, in terms of both its consequences for the functioning and quality of life of individual patients and its wider socioeconomic impacts. DR remains the commonest cause of blindness in the working age population.

The early stages of retinopathy are usually asymptomatic with respect to the quality of vision experienced by the patient. However, the changes observed in the early stages have been shown to be predictive of progression to sight-threatening proliferative retinopathy and maculopathy. Therefore, early identification and monitoring of retinopathy is crucial for successful management, and regular screening examinations for sight-threatening retinopathy are an essential part of effective diabetes care.

The existing DR screening programme is based on retinal photography, the performance of which is known to be dependent upon the experience of the examiners and the techniques used. The introduction of additional screening tests might improve performance but has significant cost implications.

Colour vision testing (CVT) may potentially provide a cost-effective tool for diagnosing DR as part of a battery of tests carried out by the National Screening Programme for Diabetic Retinopathy (NSPDR).

Objectives

This project had three main objectives. These were:

1. To report the findings of a systematic review to determine (1) the diagnostic performance of CVT options to identify and/or monitor the progression of DR, and (2) the preferences of patients in relation to incorporating CVT in the retinopathy screening programme.
2. To report the findings of a survey of the clinical leads and programme managers of the NSPDR to determine what tests are currently used in the detection and management of DR, over and above the requirements of the programme, as well as their views on future research priorities.
3. To review previous economic studies of DR screening with CVT and develop a cost-effectiveness model to evaluate the potential efficiency of incorporating CVT into the current DR screening programme.

Methods

A systematic review of the diagnostic performance of CVT and patient preferences towards CVT was carried out. Both published and unpublished literature were identified from systematic searches of electronic sources including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database (from database inception to September 2008); hand searching; consultation with experts in the field; and the NSPDR.

Study selection, data extraction and quality assessment were undertaken by two reviewers independently. Studies were assessed for methodological quality using QUADAS (Quality for Assessing Diagnostic Accuracy Studies) and were combined in a structured narrative synthesis. Sensitivities and specificities were plotted in receiver operating characteristic space when appropriate.

A survey of NSPDR clinical leads and programme managers was carried out using an online survey that was emailed to 192 potential participants. The objective of the survey was to assess which

diagnostic tools are used routinely by the local centres over and above those specified by the NSPDR, as well as to assess the views of the clinical leads and programme managers on future research priorities.

We identified previous economic evaluations of CVT screening for DR by adapting the diagnostic accuracy search strategy by replacing diagnostic filter terms with economics filter terms. We expanded the electronic sources searched to include specialist economic evaluation databases.

Based on studies identified in the systematic review of diagnostic accuracy, we developed a decision tree and Markov model to estimate the incremental costs and effects of adding CVT to the current NSPDR using digital photography of the retina. Evidence on additional parameters, such as the incidence of DR in the screened population, costs of diagnosis and treatment, and the effectiveness of laser photocoagulation therapy, was collected through critical appraisal of the literature. We developed two models to evaluate cost per quality-adjusted life-year (QALY) in type 1 and type 2 diabetes.

Results

A total of 25 studies were located reporting on CVT, including 18 presenting 2×2 diagnostic accuracy data. The quality of studies and reporting was generally poor.

The automated or computerised CVTs reported variable sensitivities (63–97%) and specificities (71–95%). One study reported good diagnostic accuracy estimates for the combination of computerised CVT and retinal photography for detection of sight-threatening diabetic retinopathy, but this single study included very few cases of retinopathy in total. Results for the other types of CVT (pseudoisochromatic plates, anomaloscopes, and colour arrangement tests) were heterogeneous but largely inadequate for screening for DR; most performed little better than chance, having Youden indices (sensitivity + specificity – 100%) close to zero.

No studies were located that addressed patient preferences relating to colour vision screening for DR.

Retinal photography is universally employed as the primary method for retinal screening by centres responding to the survey of current practice; none used CVT. The most frequently cited preference for future research was the use of optical coherence tomography for the detection of clinically significant macular oedema.

Our search of the economic evaluation literature found no previous studies describing the cost and effects of any type of CVT.

As only one small study directly compared the diagnostic accuracy of CVT with that of retinal photography, the results of our economic model, based on that study, are imprecise. Furthermore, that study estimated a high sensitivity and specificity of CVT compared with the other 17 CVT studies in our review. Therefore, the results of our economic model should be treated cautiously until further evidence is available.

Our economic evaluation suggested that the addition of CVT to the current national screening programme could be cost-effective if it adequately increases sensitivity and is relatively inexpensive. The base-case analysis indicated that the cost per QALY gained is £6364 and £12,432 for type 1 and type 2 diabetes respectively. However, our probabilistic sensitivity analysis highlighted the substantial probability that CVT is not diagnostically accurate enough to be either an effective or a cost-effective addition to current screening methods. Better quality diagnostic accuracy studies directly comparing the incremental value of CVT in addition to retinal photography are needed before drawing conclusions on cost-effectiveness.

Discussion

Not all CVTs have been evaluated; those that have were generally not considered in the context of a retinal photography-based screening setting. There are insufficient data on any predictive/protective value of CVT. There is a lack of primary studies evaluating the efficiency of including CVT in DR screening.

Conclusions

Implications for service provision

- There is insufficient evidence to support the use of CVT alone, or in combination with retinal photography, as a method for screening for retinopathy in patients with diabetes. The

evidence that is available is limited in quantity and is of generally poor quality.
- Limited evidence on variations of the automated Sussex Gratings Machine, when combined with retinal photography, indicated some promise. However, this technology has not been independently evaluated and cost-effectiveness has not been proven. Probabilistic sensitivity analysis highlighted the substantial probability that CVT is not diagnostically accurate enough to be either an effective or cost-effective addition to current screening methods.

Suggested research priorities

- CVT was not identified as a research priority by survey respondents; around one-third of respondents considered optical coherence tomography to be a research priority.
- Any study carried out to resolve outstanding uncertainties would have to evaluate the addition of CVT to retinal photography and be prospective; generalisable to a screening population; independent of test developers; designed to account for lens yellowing, iris colour, macular pigment density and other clinical factors; and compliant with STARD reporting guidelines.
- Any future studies should consider the consequences of positive and negative tests in terms of subsequent treatment/prevention options, costs and participant outcomes.
- Activity-based cost analyses detailing the resource use of the various manual and automated CVT strategies are also necessary. These studies should estimate the capital and labour costs of implementing CVT in typical primary care trust diabetic populations.

Chapter 1
Background

The aetiology, prevalence and diagnosis of diabetic retinopathy

Diabetic retinopathy (DR) is caused by pathological changes in the blood vessels of the retina, which can lead to blindness. The European Grading Protocol defines five levels of DR: (1) no evidence of retinopathy; (2) background retinopathy (development of microaneurysms, formation of hard exudates and/or mild retinal haemorrhage); (3) preproliferative retinopathy (multiple microvascular abnormalities, venous loops, cotton-wool spots, venous bleeding and severe retinal haemorrhage); (4) proliferative retinopathy (abnormal new vessel growth, preretinal or vitreous haemorrhage, preretinal fibrosis); and (5) maculopathy (retinal thickening and hard exudates near the centre of the macula).[1] The early stages of retinopathy are usually asymptomatic with respect to the quality of vision experienced by the patient. However, the changes observed in the early stages have been shown to be predictive of progression to sight-threatening proliferative retinopathy and maculopathy.[2] The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed the benefits of laser panretinal photocoagulation on long-term visual outcomes for patients with high-risk proliferative retinopathy (although photocoagulation was considered inappropriate, and potentially detrimental, in mild to moderate retinopathy).[3] Therefore, early identification and monitoring of retinopathy is crucial for successful management.

All patients with diabetes mellitus (DM) are at risk of DR and generally risk increases with duration of diabetes. Data collected during the 1970s indicated that the earliest stages of retinopathy may develop as early as during the first 5 years after onset of type 1 diabetes in young patients. However, eyesight-threatening proliferative retinopathy is unusual until at least 7 years approximately after onset of type 1 diabetes.[4] Type 2 diabetes is frequently diagnosed some years after its onset and as a result up to 39% of patients with type 2 diabetes have retinopathy at diagnosis and this is sight threatening in 4–8% of cases;[5,6] it is estimated that more than 60% of patients have DR 20 years after diagnosis of type 2 diabetes.[7]

Risk factors for the development and progression of DR include poor glycaemic control, hypertension, duration of diabetes, microalbuminuria and proteinuria, elevated tryglycerides and a low haematocrit level.[4,8–15]

Despite advances in the management of DM, visual impairment due to DR remains a significant complication, in terms of both its consequences for the functioning and quality of life of individual patients and its wider socioeconomic impacts. DR remains the commonest cause of blindness in the working age population.[16] The incidence of blindness in the European diabetes population is estimated at between 50 and 65 per 100,000 per year.[17–19] Regular screening examinations for sight-threatening retinopathy are an essential part of effective diabetes care. As new methods of screening are developed it is important that these be evaluated rigorously, applying the best available methodology.

A systematic review,[20] conducted for the National Institute of Clinical Excellence (NICE), reported limited evidence on the effectiveness of screening and monitoring tests for DR. No randomised controlled trials were identified, but analysis of the available diagnostic accuracy studies suggested that retinal photography through dilated pupils provides the most sensitive method of screening for sight-threatening retinopathy. The report further stated that sensitivities in excess of 80%, the acceptable threshold defined by Diabetes UK,[21] should be achievable in a screening programme. Longitudinal studies have shown a decrease in the annual incidence of blindness and partial sightedness arising from diabetes since the introduction of screening programmes.[22] Existing evidence therefore suggests that the recognition of early fundal changes in diabetes may provide opportunities for the delivery of effective interventions and an ultimate reduction in the negative impacts of diabetic eye disease. Current UK national guidance[7,23,24] recommends annual screening by trained individuals using retinal photography or slit-lamp biomicroscopy; screening

is recommended from diagnosis in type 2 diabetes and from age 12 years (or 3 years post diagnosis if onset is post puberty) in type 1 diabetes.

Current service provision

In 2001/2 the Diabetes National Service Framework[25] set a target of inviting 80% of people with diabetes in England to retinopathy screening by 2006, rising to 100% by the end of 2007. By December 2007, 85.7% of people diagnosed with diabetes were offered screening for DR.[26]

The Department of Health have prioritised quality and safety over chasing the 100% target and will continue to work with partners in Government, the NHS and the voluntary sector to improve the standard and quality of screening programmes across the country.[26] Colour vision testing (CVT) is not currently part of the national DR screening programme.

Description of technology under assessment

A group of tests have been assessed that all examine the colour vision of patients with diabetes as a means of differentiating between those people with and without retinopathy, and the different grades of the disease. For the purpose of this report we have grouped the tests into categories according to the different methods that they use. These groups are pseudoisochromatic plates, arrangement tests, automated/computerised hue discrimination tests and anomaloscopes.

Colour deficiencies can be congenital or acquired, and these two forms typically differ in several ways. Congenital colour deficiency is stable throughout life and affects both eyes equally, whereas acquired deficiency changes in severity over time, differs between eyes and is frequently more difficult to classify. Also, unlike congenital deficiency, acquired colour deficiency is often associated with reduced visual acuity and the occurrence of visual field defects.[27]

Acquired colour deficiency can be classified into three main types: acquired type 1 red–green defects, which resemble congenital protan deficiency and are associated with central retinal dystrophies; acquired type 2 red–green defects, which resemble congenital deutan deficiency and are associated with some lesions of the optic nerve; and acquired type 3 tritan (often referred to as 'blue-yellow') defects, which closely resemble congenital tritan defects.

The severity of colour deficiency has been seen to correspond with visual field loss and with the extent of macular involvement in diabetes patients with type 3 acquired defects. In proliferative retinopathy and maculopathy the patient is functionally tritanopic but all three colour mechanisms are affected and red–green errors as well as tritan errors are made on clinical tests.[27]

Pseudoisochromatic plates

The Ishihara pseudoisochromatic test has long been established as the most widely used test for screening for red–green colour vision deficiency. The test consists of a series of plates that require the participant to distinguish a coloured numeral from a coloured background. Depending upon the plate presented, the colour-deficient observer will either fail to distinguish the numeral or see a different numeral than would be seen by a normal trichromat. Other types of pseudoisochromatic plates that test for protan, deutan and tritan deficits, such as the Hardy, Rand and Rittler (HRR) plates, have also been developed.

Arrangement tests

Arrangement tests typically consist of a range of coloured caps that incrementally vary in hue. Test participants are required to place these caps in order of hue. Test scores are derived from the number and pattern of errors made in this procedure. These tests can generally be used to detect protan, deutan and tritan colour vision deficiencies.

Farnsworth–Munsell 100 hue test

The most comprehensive colour arrangement test, the Farnsworth–Munsell 100 hue test (FM-100), consists of four trays containing a total of 85 reference caps spanning the visible colour spectrum. The test is intended to evaluate hue discrimination ability (or colour vision aptitude). Hue discrimination ability is ascertained from the total error score, and the type of colour vision deficiency is established by interpreting a graphical illustration of the results.

Farnsworth D-15 and Lanthony desaturated D-15 tests

The Farnsworth D-15 test is an abridged version of the FM-100, consisting of 15 loose coloured caps and a single reference cap. Rather than measure overall hue discrimination ability, the original D-15 was developed to detect moderate and severe colour deficiencies and separate these from normal colour vision or more slight deficiencies. The Lanthony desaturated D-15 test is an arrangement test that is similar to the original D-15 but it has a Munsell value of 8 and chroma of 2 and should be presented under high levels of illumination (> 500 lux).[27]

Lanthony New Colour Test

The Lanthony New Colour Test (NCT) contains 70 Munsell samples – four series of 15 colours with Munsell value 6 and chroma of 2, 4, 6, and 8, and 10 grey caps representing a lightness scale. For each series participants must first separate the coloured caps from the grey caps before arranging the coloured caps in colour order and the grey caps in lightness scale. As with other arrangement tests the results are plotted graphically and an error score is calculated. The NCT is intended to distinguish between slight, moderate and severe colour deficiency.[27]

Mollon–Reffin Minimalist Test

Initially, participants must identify an orange 'demonstration' chip from among five grey chips of varying lightness. If successful, the participant must select a probe chip from the middle of a protan, deutan or tritan series. If successful, the participant is presented with a less saturated probe chip. If unsuccessful, a more saturated probe chip is presented. Participants are scored on the number of reliably identified coloured chips for each confusion line.

Automated/computerised tests

More recently, technological advances have permitted the development of computerised CVTs, which in some cases dispense with the need for an operator to be present at the time of testing, as required with traditional arrangement tests. These automated systems may be based on colour contrast sensitivity or on variations of the principles used in colour arrangement tests. For example, the Sussex Gratings Machine (SGM) and its variants produce equiluminant, sinusoidal, chromatic gratings on a colour cathode ray tube monitor. The chromaticity of these gratings can be systematically altered along a red–green or tritan confusion axis until the value at which a participant can just perceive coloured stripes is established. Another automated system, the ChromaTest, uses a similar colour contrast sensitivity test procedure but with alphabetical letters being presented on an equiluminant background.

Anomaloscopes

The spectral anomaloscope is typically used to distinguish between normal vision and red–green deficits and to diagnose the type of colour deficiency, although newer instruments provide a colour match for classifying tritan defects.[27] In the traditional Nagel anomaloscope, two halves of a 3-degree circular bipartite field are respectively illuminated by monochromatic yellow and a mixture of red and green wavelengths. The testing procedure requires the participant first to make colour matches by adjusting both the red–green ratio and the luminance of the yellow field. The participant is then required to determine whether adjustments in the luminance of the yellow field can or cannot produce exact matches to red–green ratios set by the examiner. Normal trichromats make a precise colour match within a narrow range of red–green ratios. Participants with colour deficiencies show distinctively different colour-matching distributions.

Chapter 2
Research questions

Relevance of colour vision testing for diabetic retinopathy in the NHS

The existing screening programme for DR is based on retinal photography, the performance of which is known to be dependent upon the experience of the examiners and techniques used; Sharp *et al*. reported sensitivities of 83–85% and specificities of 71–83%.[28] The introduction of a combination of screening tests, used in parallel or sequentially, might improve performance but has significant cost implications.[29,30] The reference standard examination of fluorescein angiography is invasive and does not form part of the initial testing used in screening programmes. Consequently, there remains a potential role for a screening test that is inexpensive and simple to conduct, whilst giving reliably good diagnostic performance across different examiners. As uptake of retinopathy screening remains a challenge, non-invasive tests that could be performed with minimal discomfort and inconvenience to patients are particularly desirable. Recent studies[31,32] have proposed that CVT could be used for the detection of sight-threatening retinopathy. A thorough evaluation of the diagnostic performance of CVT in the context of DR screening, particularly in relation to its ability to detect the earlier stages of retinopathy and to predict progression, is therefore the goal of the current project.

Overall aims and objectives of assessment

This project has been divided into three elements that have the combined aim of assessing the usefulness of CVT as a diagnostic tool to be used by the National Screening Programme for Diabetic Retinopathy (NSPDR):

1. a systematic literature review of all studies reporting results on the diagnostic accuracy of CVT for DR
2. a survey sent to the clinical leads and programme managers of the NSPDR, which aimed to determine the current use of CVT and other screening modalities in the NSPDR and the future research priorities in this field
3. a systematic review to identify previous economic evaluations of CVT in screening for DR and development of an independent decision-analytic model of potential cost-effectiveness.

Methods for reviewing diagnostic accuracy

The systematic review was undertaken in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[33] and published guidelines on the meta-analysis of diagnostic tests.[34]

Search strategy

Studies were identified by searching the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Pascal, Science Citation Index, BIOSIS, Latin American and Caribbean Health Sciences (LILACS), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. In addition, information on studies in progress, unpublished research or research reported in the grey literature were identified by searching Inside Conferences, Dissertation Abstracts, NTIS, ClinicalTrials.gov, ReFeR, ClinicalStudyResults.org and Clinical Trial Results. All resources were searched from their inception to October 2007, with update searches conducted on the 17 September 2008. There was no restriction of study by country of origin, language or publication date.

Internet searches were carried out using the specialist search gateways intute (www.intute.ac.uk) and MedlinePlus (www.nlm.nih.gov/medlineplus/) to identify relevant resources. Potentially relevant websites identified during the initial internet gateway searches were then searched and browsed.

The organisation websites searched were Diabetes UK, American Diabetes Association, Royal College of Ophthalmologists, College of Optometrists, American Academy of Ophthalmology, Association of Optometrists and the US National Eye Institute. In addition, the following websites were searched: NSPDR, British Association for Retinal Screeners, National Library for Health (NLH) Diabetes Specialist Library and the NLH Screening Specialist Library.

The following conference proceedings were searched: American Academy of Ophthalmology annual meeting (1999–2006), American Diabetic Association annual scientific sessions (2003–7), European Association for the Study of Diabetes annual meeting (2001–7) and Royal College of Ophthalmologists annual congress (2004–7).

Search alerts (details of newly published articles retrieved using a saved search sent by email) were set up in a number of journals: *American Journal of Ophthalmology*, *British Journal of Ophthalmology*, *Clinical and Experimental Ophthalmology*, *Diabetes*, *Diabetes Care*, *Diabetic Medicine*, *Investigative Ophthalmology and Visual Science*, and *Ophthalmology*. Search alerts were also set up to run weekly in MEDLINE and EMBASE.

Full details of the search strategies are given in Appendix 1.

Inclusion and exclusion criteria

Two reviewers independently screened titles and abstracts for relevance; disagreements were resolved by consensus. Full papers of potentially relevant studies were obtained and assessed for inclusion by one reviewer and checked by a second. Articles were selected according to the following criteria:

- *Population* Patients of any age with type 1 or type 2 DM with or without existing DR.
- *Index test* Any test of colour vision.
- *Reference standard* Fundus examination by fluorescein angiography, digital retinal photography, biomicroscopy or ophthalmoscopy (either at the time of colour vision screening for diagnostic detection studies or at follow-up for predictive studies).
- *Target condition* DR or grading of retinopathy status. Previous research[20] suggests that grading method is poorly reported in diagnostic accuracy studies of retinopathy screening. Grading method was therefore not used to exclude studies.
- *Outcomes* Sufficient data to construct 2×2 tables of test performance [numbers of true-positives (TPs), false-negatives (FPs), false-positives (FPs) and true-negatives (TNs); or sufficient data to allow their calculation]. In addition, 'phase I' studies comparing the range of test results in patients with and without retinopathy, or across stages of retinopathy, were included. Studies not reporting these outcomes were identified but not incorporated into the analyses.
- *Study designs* Diagnostic cohort studies or diagnostic case–control studies with a minimum of 20 participants, at least five of whom had evidence of retinopathy (any stage), or phase I diagnostic studies with a minimum of 20 participants with diabetes.
- *Preference studies* Any studies of attitudes or preferences of patients with diabetes in relation to CVT were included.

Data extraction strategy

Data extraction was performed by one reviewer and checked by a second using EPPI-Reviewer. Data extraction forms were piloted on a small selection of studies. Foreign language papers were extracted by one reviewer, accompanied by a speaker of that language, and the data were entered directly into the EPPI-Reviewer database. Data extraction of non-English language studies was not checked by a second reviewer.

The following information was extracted for all studies when reported: study details (identifier, aim, study design, location), participant details (age, sex, comorbidities, red–green colour vision status, treatment status, inclusion criteria), test details, reference standard details, 2×2 or correlation data on test performance, test result ranges (phase I studies only).

Quality assessment strategy

Diagnostic accuracy studies were assessed by one reviewer and checked by another for methodological quality using the 14-item QUADAS (Quality for Assessing Diagnostic Accuracy Studies) tool.[35] Detailed guidance specific to the review was produced on how to score QUADAS (Appendix 2).

Data analysis

Results were analysed by type of CVT. Within these groups tests were examined according to the specific CVTs or test combinations reported in the literature. For each test the range in sensitivity, specificity and likelihood ratios (of both positive and negative tests results) with 95% confidence intervals (CIs) were calculated and discussed.

Insufficient data were reported in the studies to allow for the statistical pooling of diagnostic data. Therefore results were presented in a narrative synthesis with sensitivity and specificity estimates plotted in receiver operating characteristic (ROC) space for illustration.

Chapter 3

Results of review of diagnostic accuracy

Studies included in the review

The literature searches identified 1243 references. These were screened for relevance and 316 were ordered for further evaluation. *Figure 1* shows the flow of studies through the review process and the numbers of studies excluded at each stage. A total of 25 studies evaluating the relationship between colour vision and retinopathy status in patients with diabetes met the inclusion criteria. *Table 1* shows the number of studies included per colour vision test. No relevant studies on the preferences of patients in relation to incorporating CVT were identified. Studies excluded from the review are listed in Appendix 4.

Quality of included studies

Study quality was generally poor, with the majority of studies explicitly failing to meet QUADAS criteria or reporting insufficient data to allow an assessment to be made (e.g. only one study clearly reported an appropriate patient spectrum). Other aspects of study conduct, such as justification for the selection of particular reference standards, were typically unreported. None of the included studies evaluated the reproducibility of CVT.

Pseudoisochromatic plates

Although all three studies of pseudoisochromatic plates in patients with diabetes used an appropriate

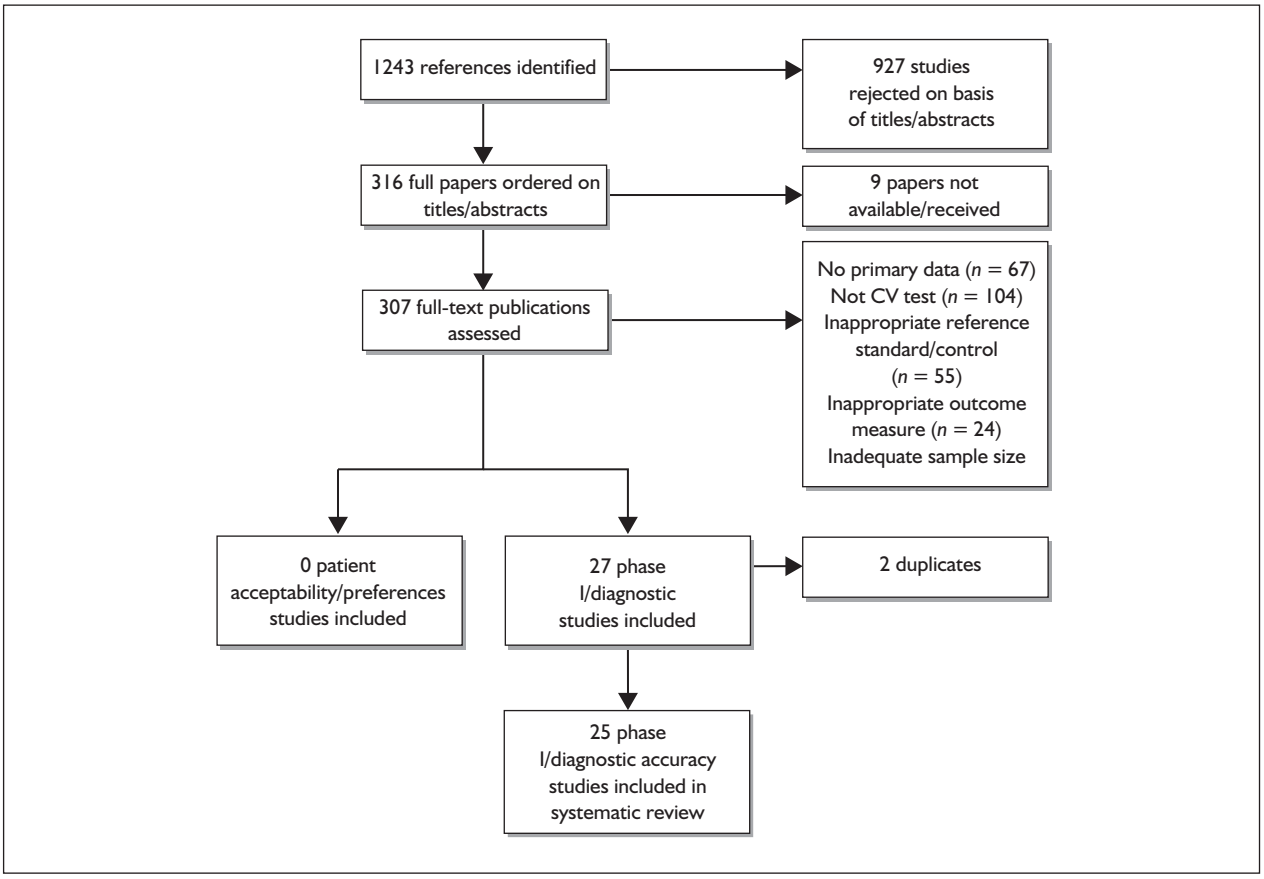

FIGURE 1 *Flow diagram showing study selection process. CV, colour vision.*

TABLE 1 *Number of studies included per colour vision test*

Colour vision test	Number of included studies (some studies evaluated more than one test)
Pseudoisochromatic plates	3
Farnsworth–Munsell 100 hue test	10
Lanthony desaturated D-15 test	6
Lanthony New Colour Test	2
Mollon–Reffin Minimalist Test	1
Automated/computerised tests	6
Anomaloscopes	2

reference standard, independent of the index test in all participants, there remained the potential for a range of biases, including those relating to patient spectrum (e.g. including only patients with established signs of retinopathy), disease progression (e.g. long or unspecified time between the index test and reference standard), clinical review (e.g. when different/additional data were available to aid diagnosis than would be available in practice) and attrition (*Table 2*).

Arrangement tests

Farnsworth–Munsell 100 hue test

A total of 10 studies[36–45] evaluated FM-100 CVT in diabetes patients.

Five[36,38,39,42,44] of these studies compared mean error scores on the FM-100. The quality of reporting among these studies was generally low. Only one[39] of the five papers had a representative spectrum of patients and reported the reference standard and index test in detail, and none of the papers reported the participant selection criteria that were used (*Table 2* and *Figure 2*).

The remaining five studies provided diagnostic accuracy data on the FM-100 test. QUADAS assessment indicated that the quality of reporting among these studies was generally poor (*Table 2*). The spectrum of patients included in each study was not representative of the general population in practice. In four studies[37,41,43,45] patients were excluded if they did not have good visual acuity, whereas one study excluded patients with soft exudates. The English National Screening Programme states that all diabetes patients should be offered retinopathy screening regardless of how good their sight is, therefore these studies are not representative of the entire population who will be offered screening in practice. Only the paper by Trick *et al.*[45] described the patient selection criteria clearly.

Lanthony desaturated D-15 test

Six studies[33,46–50] evaluated the Lanthony desaturated D-15 test in patients with diabetes. QUADAS assessment indicated that the quality of reporting among these studies was generally poor (*Table 2* and *Figure 2*). None of the studies provided any information on blinding of outcome assessors, and only one indicated whether the clinical data available during the interpretation of test results reflected that which would be available in practice. Therefore the potential for test, diagnostic and clinical review biases among this group of studies cannot be ruled out. In addition, the participant inclusion criteria applied to these studies means that their results cannot necessarily be generalised to a diabetic screening population. In two studies[46,47] participants were predominantly children and younger adults.

Lanthony New Colour Test

Two studies[49,51] evaluated the NCT in diabetes patients. The quality of reporting of both studies was poor (*Table 2*). It was not possible to distinguish poor reporting of methods from poor methodological quality, but it is likely that there were limitations in both the internal and external validity of these studies as neither adequately reported the patient spectrum or any attempts to avoid review biases.

Mollon–Reffin Minimalist Test

One study[32] evaluated the Mollon–Reffin Minimalist Test. The study was generally well reported, although no information on blinding of outcome assessors was given. In addition, only patients less than 50 years of age with

TABLE 2 *Quality assessment of included studies**

Study[a]	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Adequate test execution details	Adequate reference standard execution details	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Pseudoisochromatic plates														
Bernardczyk-Meller 2001[47]	✗	✗	?	?	✓	✓	✓	?	✗	?	?	?	✗	?
Mirkiewicz-Sieradzka 1986[57]	✗	✓	✓	?	✓	✓	✓	✗	✗	?	?	?	?	?
Sinha 1979[58]	?	✗	✓	?	✓	✓	✓	✓	?	?	?	?	?	?
Farnsworth–Munsell 100 hue test														
Aspinall 1983[36]	?	?	✓	✗	✗	?	✓	?	✗	?	?	?	?	✗
Ayed 1990[37]	?		✓	?	✓	✓	✓	✓	✗	?	?	?	✓	✓
Barton 1987[38]	?	✗	?	?	?	?	?	?	✗	?	?	?	✗	✗
Fong 1999[39]	✓	?	✓	?	✓	✓	✓	✓	✓	?	?	?	?	✓
Green 1985[40]	?	✗	✓	?	✓	✓	✓	✓	✗	?	?	?	?	✗
Greenstein 1990[41]	✗	✗	✓	?	✓	✓	✓	✓	✗	?	?	?	✓	✗
Ismail 1998[42]	?	✗	✓	?	✓	✓	✓	✓	✓	?	✓	✓	?	?
Jeddi 1994[43]	?	✗	✓	?	✓	✓	✓	✗	✗	?	?	?	?	?
Lombrail 1983[44]	✗	✗	✓	✓	✓	✓	✓	✗	✗	?	?	?	✗	✗
Trick 1988[45]	✗	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	?	✓	?
Lanthony desaturated D-15 test														
Bernardczyk-Meller 2001[47]	✗	✗	?	?	✓	✓	✓	?	✗	?	?	?	✗	?
Doucet 1991[48]	?	✓	✓	?	✓	✓	✓	✓	✓	?	?	?	✓	✓
Maár 2001[32]	✗	✓	✓	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓

continued

TABLE 2 *Quality assessment of included studies* (continued)*

Study[a]	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Adequate test execution details	Adequate reference standard execution details	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Mäntyjärvi 1995[46]	✗	?	?	?	?	?	?	✗	✗	?	?	?	✗	✓
Mecca 1988[49]	?	?	✓	?	✓	✓	✓	✓	✗	?	?	?	✓	✓
Saracco 1980[50]	?	✓	✓	?	✓	✓	✓	✗	✗	?	?	?	✗	✓
Lanthony New Colour Test														
Matsuo 1990[51]	?	?	?	?	?	?	?	✓	✗	?	?	?	✗	✗
Mecca 1988[49]	?	?	✓	?	✓	✓	✓	✓	✗	?	?	?	✓	✓
Mollon–Reffin Minimalist Test														
Maár 2001[32]	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓
Computerised/automated tests														
De Alwis 1994[52]	?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✗
Findl 2000[53]	✗	✓	✓	✓	✓	✓	✓	✓	?	?	?	✓	✗	?
Knowles 1996[54]	✗	✓	✓	✓	✓	✓	✓	?	✓	?	?	✓	✗	?
Ong 2004[31]	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	?	✓	✓
Tregear 1997[55]	?	✓	✓	?	✓	✓	✓	✓	✓	?	✓	?		✓
Wong 2008[56]	✗	✓	✓	?	✓	✓	✓	✓	✓	?	?	?	✗	✗
Anomaloscopes														
Aspinall 1983[36]	?	?	✓	✗	✗	?	✓	?	✗	?	?	?	?	✗
Mäntyjärvi 1995[46]	✗	?	?	?	?	?	?	✗	✗	?	?	?	✗	✓

a Studies appearing more than once evaluate more than one colour vision test.

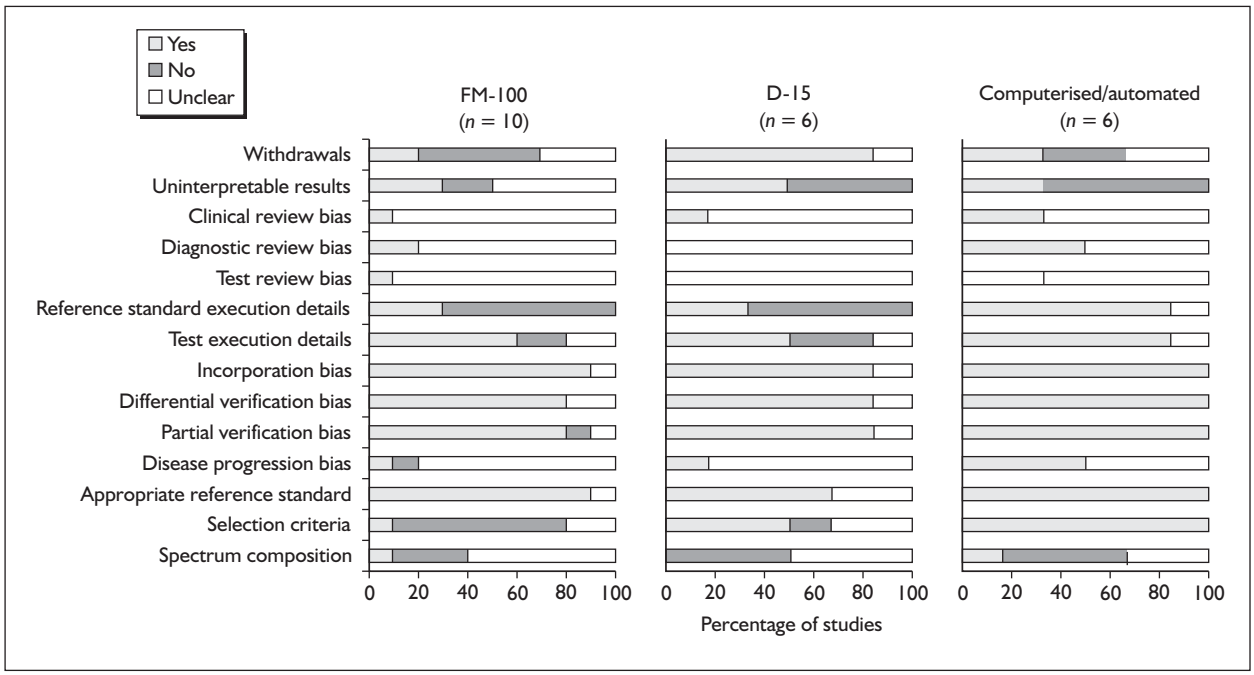

FIGURE 2 *Proportion of studies rated as yes, no or unclear for each of the QUADAS items for all tests evaluated in five or more studies. D-15, Lanthony desaturated D-15 test; FM-100, Farnsworth–Munsell 100 hue test.*

type 1 diabetes were included, thereby limiting the generalisability of the study's findings to a screening population (*Table 2*).

Automated/computerised tests

Six studies[31,52–56] evaluated computerised CVTs in patients with diabetes. The quality of reporting, as rated by QUADAS, was generally better for this group of studies than for studies evaluating other types of CVT (*Table 2* and *Figure 2*). All of the evaluations of computerised/automated tests clearly described their inclusion criteria and used an appropriate reference standard in all participants, independently of the index test. Most studies described the tests in sufficient detail to permit their replication. However, these studies were conducted within a spectrum of patients typical of that which might be seen in a screening setting (i.e. participant inclusion was restricted by age, visual acuity or other reasons excluding them from CVT investigation).

Anomaloscopes

Two studies[36,46] evaluated anomaloscopes in patients with diabetes. The quality of reporting of both studies was poor (*Table 2*).

Summary of test accuracy results

Figure 3 brings together the estimates for all of the different tests evaluated in the included studies. When more than one threshold was reported for the same test in the same study, the 'best performing' thresholds in terms of overall sensitivity and specificity are presented. Detailed results of all studies, according to type of test evaluated, are presented in subsequent sections.

Pseudoisochromatic plates

Three studies evaluated pseudoisochromatic plates in diabetes patients; two[47,57] evaluating the Ishihara test and one[58] a combination of the Ishihara and Tokyo Medical College tests (*Table 3*). One study[47] did not report any outcomes for the Ishihara test and so will not be discussed further here.

One study[57] graded retinal status according to both ophthalmoscopy and fluoroscein angiography, and the other[58] reported presence or absence of retinopathy on biomicroscopy as the reference standard. The first study[57] rated colour vision as a pass or fail on the Ishihara test; the second[58] defined patients as normal or protan-, deutan- or

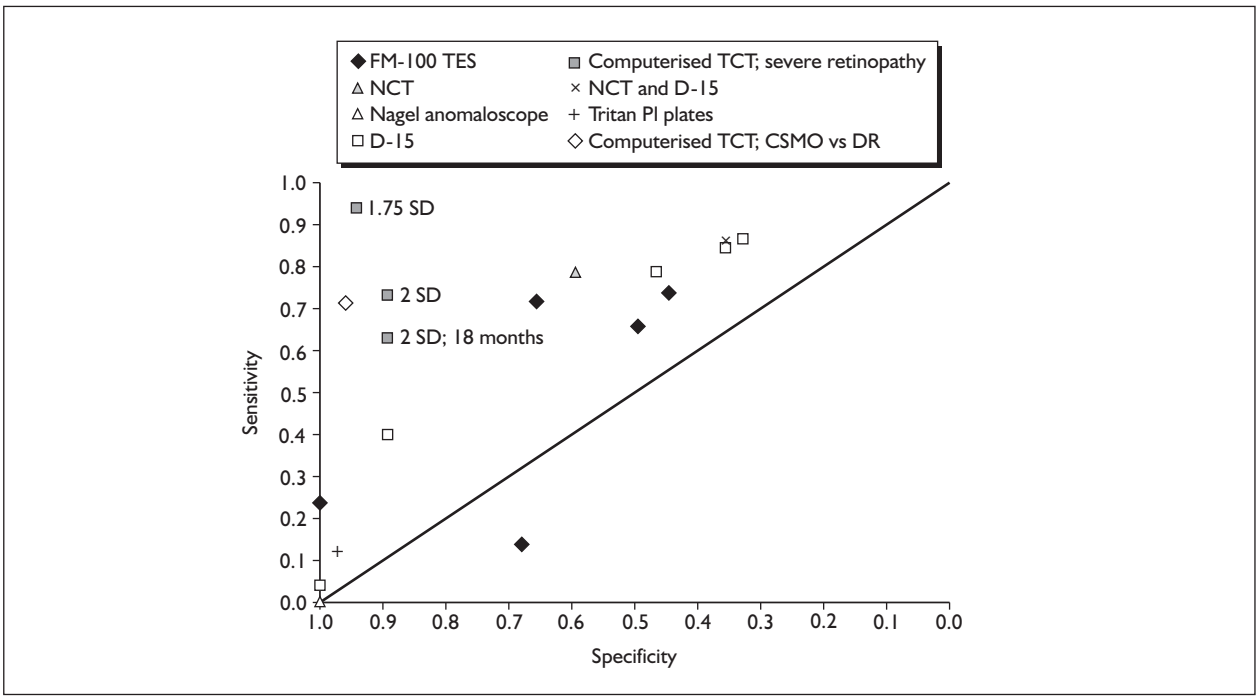

FIGURE 3 *All studies plotted in receiver operating characteristic (ROC) space (see section on quality of included studies for methodological limitations of plotted studies). 18 months, retinopathy assessed 18 months after baseline colour vision measurement; CSMO, clinically significant macular oedema; D-15, Lanthony desaturated D-15 test; DR, diabetic retinopathy; FM-100, Farnsworth–Munsell 100 hue test; NCT, Lanthony New Colour Test; PI, pseudoisochromatic; SD, diagnostic threshold in standard deviations above mean normal score; TCT, tritan contrast threshold; TES, total error score.*

tritan-deficient on the combination of the Ishihara and Tokyo Medical College tests.

For the Ishihara test, Mirkiewicz-Sieradzka *et al.*[57] reported sensitivities of 15% and 8%, respectively, for detecting the background retinopathy on ophthalmoscopy and detecting a single leak on angiography. These sensitivities increased to 88% and 82% for detecting oedema compared with ophthalmology and angiography respectively. The authors did not report sufficient data to permit the calculation of specificity values.

Sinha *et al.*[58] reported a sensitivity of 12% (95% CI 3% to 28%) and a specificity of 97.5% (95% CI 87% to 100%) in detecting retinopathy for a 'tritan-deficit' result on the combined Ishihara/Tokyo Medical College test. This equates to a positive likelihood ratio (LR+) of 4.85 (95% CI 0.57 to 41.3) and a negative likelihood ratio (LR–) of 0.90 (95% CI 0.79 to 1.03), indicating that detection of a tritan deficit on these tests cannot be reliably used to rule in or rule out retinopathy. None of the participants was shown to have a protan- or deutan-deficit result on the CVT.

Arrangement tests

Farnsworth–Munsell 100 hue test

Five studies[36,38,39,42,44] compared mean error scores on the FM-100 as opposed to investigating diagnostic accuracy (*Table 4*). One of these studies[44] reported mean FM-100 scores and standard deviations for six grades of retinopathy, reporting an overall trend towards deterioration of colour vision (i.e. higher mean error scores) with increasing retinopathy grade ($p < 0.05$). However, FM-100 scores did not differ significantly among the less severe grades. A second study[42] similarly found that FM-100 scores had some value in discriminating advanced retinopathy from no retinopathy but could not be used to detect early retinopathy. Two papers[38,39] came from the ETDRS, one[39] of which reported a significant correlation between FM-100 error score and the following factors: presence of clinically significant macular oedema (CSMO) involving the centre of the macula ($p = 0.0001$); presence of new vessels ($p = 0.0001$); presence of fluorescein leakage in centre of the macula ($p = 0.0001$); presence of cystoid changes in the centre of the macula ($p = 0.003$); and presence of focal leakage ($p = 0.002$). The second study[38]

DOI: 10.3310/hta13600

TABLE 3 *Key characteristics of pseudoisochromatic plate studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)	Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Bernardczyk-Meller 2001[47]	Inclusion criteria: patients for whom long-term follow-up data were available Exclusion criteria: congenital colour vision deficiencies	Mean age: 17 years 100% type 1 DM[a]	Normal vs 'pathological' CV test scores	Ophthalmoscopy Pathological changes vs no pathological changes	D-15 desaturated (threshold: 'pathological results'): TP: unclear; FP: 9; FN: unclear; TN: 21	Not reported	Not reported	
Mirkiewicz-Sieradzka 1986[57]	Inclusion criteria: diabetes patients with signs of retinopathy Exclusion criteria: patients with congenital red–green colour deficits; patients who had previously undergone photocoagulation	50.9% male	Pass vs fail (no threshold reported)	Ophthalmoscopy: (I) microaneurysms and yellow spots; (II) microaneurysms, yellow spots and 'wybroczyn?'; (III) massive yellow spots; (IV) oedema Fluorescein angiography: (I) single leak; (II) larger leaks; (III) limited oedema; (IV) diffuse oedema	Not reported	Not reported	Not reported	Ophthalmoscopy as reference standard (*n* pass CV test, *n* fail CV test): (I) microaneurysms and yellow spots (39 eyes, 7 eyes); (II) microaneurysms, yellow spots and 'wybroczyn' (19 eyes, 5 eyes); (III) massive yellow spots (1 eye, 2 eyes); (IV) oedema (2 eyes, 15 eyes) Angiography as reference standard (*n* pass CV test, *n* fail CV test): (I) single leak (34 eyes, 3 eyes); (II) larger leaks (25 eyes, 11 eyes); (III) limited oedema (2 eyes, 9 eyes); (IV) diffuse oedema (6 eyes in total, CV results unclear)
Sinha 1979[58]	Inclusion criteria: diabetes patients Exclusion criteria: patients giving the mildest indications about colour defects in family and/or growth impairment of vision	Mean age: 52.9 years	Normal colour vision; protan deficit; deutan deficit; tritan deficit	Slit-lamp biomicroscopy DR vs no DR	Protan deficit: 0; 0; 33; 40 Deutan deficit: 0; 0; 33; 40 Tritan deficit: 4; 1; 29; 39	Protan deficit: 0 Deutan deficit: 0 Tritan deficit: 12%	Protan deficit: 100% Deutan deficit: 100% Tritan deficit: 100%	

CV, colour vision; D-15, Lanthony desaturated D-15 test; DM, diabetes mellitus; DR, diabetic retinopathy; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.
a Authors refer to 'insulin-dependent' diabetes. We took this to mean type 1 diabetes unless stated otherwise.

briefly reported that there was no difference in mean FM-100 scores by level of retinopathy.

Five studies provided diagnostic accuracy data on the FM-100 test (*Table 4*). *Figure 4* shows results from these studies plotted in ROC space. Patient spectrums were not representative of the general population who would be screened in practice; four studies[37,41,43,45] excluded patients who did not have good visual acuity and one study excluded patients with soft exudates.[40]

Thresholds to define a positive FM-100 score varied between studies. Sensitivity ranged from 11% to 74% and specificity ranged from 45% to 100%. The study reporting a specificity of 100% reported a sensitivity of only 24%.[41] The reference standard in all of the diagnostic accuracy studies was used to distinguish between patients with retinopathy and those without. One[40] of these studies made the additional distinction between those with no or background retinopathy and those with more serious retinopathy. Three studies[40,41,43] used the reference standard to establish the grade of retinopathy in line with the Airlie House classification system. The study[40] distinguishing between those with no or background retinopathy and those with more serious retinopathy reported a sensitivity of 65% (95% CI 51% to 76%) and a specificity of 73% (95% CI 66% to 79%). One study[40] reported a LR+ of 2.38 (95% CI 1.75 to 3.24). The remaining comparisons all reported even smaller LR+, with confidence intervals incorporating 1. Therefore, the available evidence does not suggest that FM-100 testing alone could be used to rule in or rule out retinopathy in diabetes patients, or to discriminate between no or background retinopathy and more serious disease.

Lanthony desaturated D-15 test

Six studies[32,46–50] evaluated the Lanthony desaturated D-15 test in patients with diabetes, all of which provided diagnostic accuracy data (*Table 5*).

Stand-alone reference standards included ophthalmoscopy[47,48] and fluorescein angiography.[50] Combined reference standards included ophthalmoscopy with fluorescein angiography[49] and combined biomicroscopy/photography/angiography.[32] Only one study[46] did not specify a reference standard.

Although they applied different measures, most studies used the reference standard to distinguish between diabetes patients with and without retinopathy. Retinopathy, when defined, was typically characterised by the presence of microaneurysms, haemorrhages and hard exudates. One study[32] specifically evaluated the accuracy of the desaturated D-15 test in detecting 'clinically significant macular oedema' as opposed to any presence of retinopathy. Colour vision deficiency was generally defined as a 'pathological' or

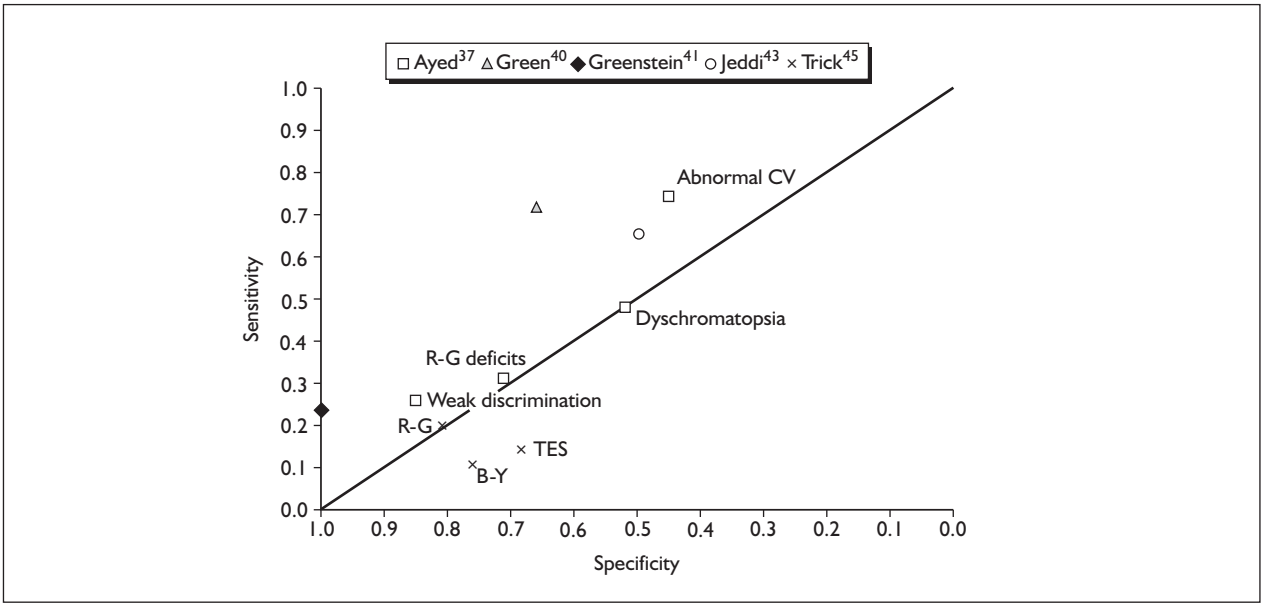

FIGURE 4 *FM-100 studies reporting 2×2 data plotted in receiver operating characteristic (ROC) space (see section on quality of included studies for methodological limitations of plotted studies). B-Y, blue-yellow partial error score; CV, colour vision; R-G, red–green partial error score; TES, total error score.*

'abnormal' desaturated D-15 score, although the specific threshold – when reported – was not consistent between studies (*Table 5*).

The studies investigating the presence or absence of retinopathy in adults with diabetes[48–50] reported sensitivities between 79% and 87% and specificities between 33% and 47% (*Figure 5*). The study evaluating the D-15 test for the detection of CSMO in adults[32] reported a sensitivity of 36% and a specificity of 88%.

Of the two studies investigating DR in younger patients, one[47] reported a specificity of 70% (95% CI 51% to 85%) in patients with a mean age of 17 years, but provided insufficient data to calculate a sensitivity value. The second study[46] administered the D-15 test in participants with a mean age of 14 years and assessed their retinopathy status 6 years later, reporting a sensitivity of 4% (95% CI 0% to 22%) and a specificity of 100% (95% CI 89% to 100%), which equates to a LR+ of 4.0 (95% CI 0.17 to 94.0) and a LR– of 0.95 (95% CI 0.85 to 1.07). On this basis there is little evidence to suggest that the D-15 test could be used to detect or predict retinopathy in young people with diabetes.

Likelihood ratios among the cross-sectional studies in adults were poor, with LR+ ranging from 1.29 to 3.87 and LR– ranging from 0.67 to 0.41, suggesting that there is little evidence to support the use of the desaturated D-15 test for detecting retinopathy in adults with diabetes. LRs were not calculable for the study investigating CSMO.

Lanthony New Colour Test

Two studies[49,51] evaluated the NCT in diabetes patients (*Table 6*).

One study[49] used a reference standard of combined ophthalmoscopy with fluorescein angiography, whereas the second[51] did not specify a reference standard. Both studies aimed to differentiate between patients with and without DR. Mecca *et al.*[49] defined retinopathy as the presence of at least 10 microaneurysms and small haemorrhages, whereas Matsuo *et al.*[51] did not define retinopathy.

Both studies collected total error scores on the NCT, with Mecca *et al.*[49] dichotomising participants as having either 'normal colour vision' (no errors) or 'altered colour vision' (any score above 0).

The study by Matsuo *et al.*[51] did not present diagnostic accuracy estimates but reported that total error scores on the NCT were significantly greater among participants with DR than in those without retinopathy ($p < 0.01$), suggesting a possible correlation between colour vision deficits and the presence of retinopathy (*Table 6*).

Mecca *et al.*[49] reported an overall sensitivity of 79% (95% CI 69% to 87%) and specificity of 60% (95% CI 48% to 72%) for the NCT. The authors reported that combining the NCT results with findings of the D-15 test (how these were combined was not clear) increased overall sensitivity (86%) but decreased specificity (36%). Both positive and negative LRs were better for NCT alone: LR+ 1.97 (95% CI 1.45 to 2.68), LR– 0.35 (95% CI 0.22 to 0.55). Although these values are slightly more promising than for some other arrangement tests, they still indicate a poor ability to rule in or rule out disease, and it should be noted that they are derived from the results of a single, small, poor-quality study.

Mollon–Reffin Minimalist Test

One study[32] evaluated the Mollon–Reffin Minimalist Test (*Table 7*).

A combination of slit-lamp biomicroscopy, retinal photography and fluorescein angiography was used to identify CSMO. An error score greater than 1 was considered a 'fail' on the Mollon-Reffin test.

Although exact numbers of patients required to calculate diagnostic accuracy measures were not reported, the authors stated that no errors were made on the protan or deutan axes by any patient. The overall sensitivity and specificity of the Mollon-Reffin test were reported to be 89% and 93% respectively. These values would suggest a LR+ of 12.7 and a LR– of 0.12. Despite the positive conclusions of this study, there is no further evidence to corroborate these findings on the diagnostic accuracy of the Mollon-Reffin test for the detection of CSMO.

Automated/computerised hue discrimination tests

Six studies[31,52–56] evaluated computerised CVTs in patients with diabetes (*Table 8*). Four of these studies evaluated variants of the SGM and one evaluated the ChromaTest[56] (see Chapter 1, Automated/computerised tests), all of which were co-authored by developers of the system itself. A sixth study[53] evaluated a similar kind of colour monitor system to measure colour contrast sensitivity, whereby the system determines the

TABLE 4 *Key characteristics of FM-100 studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)	Reference standard (grading method)
Diagnostic accuracy studies				
Ayed 1990[37]	Inclusion criteria: visual acuity ≥ 5/10	Mean age: 44 years 37% male 39% type 1 DM	'Abnormal' if TES is greater than the 95th percentile for participant's age, according to Verriest curves; 'normal' if TES is participant's age in years plus 30; 'weak discrimination' if TES is participant's age in years multiplied by two, plus 30 (axis not well defined); 'dyschromatopsia' if TES is ≥ participant's age in years multiplied by two, plus 30 (with B-Y or R-G axis).	Fluorescein angiography Graded: (1) retinopathy absent; (2) beginnings of retinopathy; (3) oedemic; (4) ischaemic with or without new vessels DR vs no DR
Green 1985[40]	Inclusion criteria: diabetes patients attending for routine ocular screening Exclusion criteria: patients with soft exudates		Dichotomous: abnormal TES vs normal score	Ophthalmoscopy Dichotomous: serious vs non-serious
Jeddi 1994[43]	Inclusion criteria: visual acuity 10/10	Mean age: 43.5 years 48% male 52% type 1 DM	Categorical: normal, weak discrimination, dyschromatopsia	Ophthalmoscopy DR vs no DR
Trick 1988[45]	Inclusion criteria: DM patients with no or mild to moderate background retinopathy; visual acuity of at least 20/30 and intraocular pressure < 21 mmHg in the eye to be tested Exclusion criteria: patients with macular oedema detected in either the ophthalmoscopic examination or the fundus photographs	Mean age: 37.2 years 68% type 1 DM	Continuous/average: square root of TES (SQRT TES) and partial error scores (B-Y, R-G) Dichotomous: total/partial error score > 2 SD above the normal mean	Conventional retinal photography Dichotomous: no retinopathy vs preproliferative background retinopathy
Studies comparing mean values				
Aspinall 1983[36]	Inclusion criteria: diabetes patients < 70 years old with normal fundi Exclusion criteria: congenital colour vision defects; cataracts		Dichotomous	Ophthalmoscopy No retinopathy vs retinopathy
Barton 1987[38]			Continuous/average: SQRT TES for deferred eyes is presented for each grade of macular oedema	Method not stated/final diagnosis Graded: no macular oedema; not clinically significant macular oedema; clinically significant macular oedema

TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Abnormal colour vision: 70, 58, 25, 47 Abnormal colour vision with dyschromatopsia: 46, 42, 49, 63 Abnormal colour vision with weak discrimination: 25, 16, 70, 89 R-G deficits: 29, 30, 66, 75	Abnormal colour vision: 74% Abnormal colour vision with dyschromatopsia: 48% Abnormal colour vision with weak discrimination: 26% R-G deficits: 31%	Abnormal colour vision: 45% Abnormal colour vision with dyschromatopsia: 52% Abnormal colour vision with weak discrimination: 85% R-G deficits: 71%	
40, 46, 22, 124	72%	66%	
25, 11, 13, 11	66%	50%	
Total error score: 5, 7, 30, 15 B-Y partial error score: 4, 5, 32, 16 R-G partial error score: 4, 7, 16, 30	Total error score: 14% B-Y partial error score: 11% R-G partial error score: 20%	Total error score: 68% B-Y partial error score: 76% R-G partial error score: 81%	
Not reported	Not reported	Not reported	No FM-100 data reported
			Comparison of scores in two groups (*t*-test; Mann–Whitney) No macular oedema ($n = 1000$), SQRT TES = 12 (SD ± 4); not clinically significant macular oedema ($n = 609$), SQRT TES = 13 (SD ± 4); clinically significant macular oedema ($n = 1248$), SQRT TES = 17 (SD ± 5)

continued

TABLE 4 *Key characteristics of FM-100 studies (continued)*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)	Reference standard (grading method)
Fong 1999[39]	Inclusion criteria: no attempt was made to eliminate cases of congenital R-G colour deficiency or other known colour vision defects	55% male	Continuous/average: SQRT TES	Conventional retinal photography ETDRS graded
Greenstein 1990[41]	Inclusion criteria: diabetes mellitus patients requiring insulin therapy; Snellen visual acuity ≥ 20/30 in the tested eye; patients showing either no sign of background retinopathy or only early background retinopathy; no history of hypertension or other metabolic disorders; no significant lens opacities or glaucoma	Mean age: 45.8 years 100% type 1 DM	Dichotomous: though not explicitly stated in the paper, a 2-SD threshold in FM-100 corrected difference score was considered a positive colour vision abnormality test result	Ophthalmoscopy/ conventional retinal photography/fluorescein angiography Graded: modified Airlie House classification: graded levels 1 to 4 Dichotomous: no retinopathy = level 1; background retinopathy ≥ level 2
Ismail 1998[42]	Exclusion criteria: any sign of cataracts on ophthalmoscopy; congenital colour deficiency; major systemic pathology other than DM	Mean age: 57.7 years 0% type 1 DM	Continuous/average: total and partial (B-Y axis and R-G axis) error scores were calculated; SQRT transformation was used before parametric analysis	Ophthalmoscopy Conventional retinal photography Graded: modified Airlie House classification: DRL10, DRL30
Lombrail 1983[44]	Inclusion criteria: type 1 DM patients		Continuous/average: FM-100 hue score	Fluorescein angiography Graded: (A) no retinopathy; (B) only angiographic retinopathy; (C) background retinopathy; (D) preproliferative retinopathy; (E) proliferative retinopathy; (F) retinopathy at incurable stage

ANOVA, analysis of variance; B-Y, blue-yellow; CSMO, clinically significant macular oedema; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; FN, false-negative; FP, false-positive; R-G, red–green; TES, total error score; TN, true-negative; TP, true-positive.

TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
			Association between clinical characteristics and outcomes (multivariate regression) Multiple linear regression for SQRT of 100 hue scores: presence of CSMO involving the centre of the macula: beta = 1.36, *p*-value = 0.0001; presence of new vessels: beta = 1.26, *p*-value = 0.0001; presence of fluorescein leakage in centre of the macula: beta = 0.48, *p*-value = 0.0001; presence of cystoid changes in the centre of the macula: beta = 0.87, *p*-value = 0.003; presence of focal leakage: beta = –0.54, *p*-value = 0.002
4, 0, 7, 13	24%	100%	
			TES (estimated from figure): DRL10: 9.7; DRL20: 9.9; DRL30: 14.0 Partial error scores: B-Y: DRL10: 6.9; DRL20: 7.8
			Comparison of multiple groups (ANOVA) Grade A (*n* = 24), mean (SD) FM-100 score: 107 (50); grade B (*n* = 15), FM-100: 144 (109); grade C (*n* = 48), FM-100: 124 (78); grade D (*n* = 12), FM-100: 182 (96); grade E (*n* = 2), FM-100: 189 (21); grade F (*n* = 2), FM-100: 234 (89)

TABLE 5 *Key characteristics of D-15 studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)
Bernardczyk-Meller 2001[47]	Inclusion criteria: patients for whom long-term follow-up data were available Exclusion criteria: congenital colour vision deficiencies	Mean age: 17 years 100% type 1 DM Mean diabetes duration: 7.8 years (range 3–18 years)	Normal vs 'pathological' CV test scores
Doucet 1991[48]	Exclusion criteria: people aged > 65 years; visual acuity < 4/10; cataract or glaucoma; known congenital dyschromatopsia; deterioration in mental functioning; using medicines that could alter colour vision	Mean (SD) age: 43.4 (14.4) years 62% male 88% type 1 DM Mean (SD) diabetes duration: 134 (106) months	Score of 0–2 given for each eye: 0 = dyschromatopsia with one or several axes; 1 = dyschromatopsia without an axis; 2 = normal (three simple inversions at any age, or four inversions/ diametrical inversions over age 45 years, or minimum of five inversions or two diametrical inversions over age 60 years)
Maár 2001[32]	Inclusion criteria: type 1 DM; best corrected visual acuity of at least 0.4 LogMAR (0.4 Snellen value); < 50 years; no lens opacities Exclusion criteria: congenital CV deficiencies; cataract; glaucoma; retinopathy, new vessels or chorioretinal scars in the macula; more than mild proliferative retinopathy; history of intraocular surgery or laser therapy	Mean age: 29.5 years 41% male 100% type 1 DM	D-15: total colour difference score (TCDS)
Mäntyjärvi 1995[46]	Inclusion criteria: schoolchildren with diabetes and healthy eyes at recruitment	Mean (SD) age: 14 (2) years 46.3% male Mean (SD) diabetes duration: 6 (4) years	Pass/fail for each test
Mecca 1988[49]	Inclusion criteria: all patients had duration > 4 years; all patients had visual acuity 8/10 or better Exclusion criteria: participants with congenital colour vision deficits; patients with maculopathy or macular oedema of mixed or proliferative retinopathy and participants with retinopathy of an advanced degenerative stage (large or numerous haemorrhages with exudate 'confluents')		Altered colour vision vs normal
Saracco 1980[50]	Inclusion criteria: included patients with visual acuity ≥ 6/10. Exclusion criteria: excluded those with congenital dyschromatism, those with retinal or general problems (unspecified) that could affect the interpretation of colour vision; diabetes patients who had had laser eye correction were also excluded	Mean age: 51.1years	Normal colour vision vs abnormal colour vision

CSMO, clinically significant macular oedema; CV, colour vision; D-15, Lanthony desaturated D-15 test; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Ophthalmoscopy Pathological changes (non-proliferative DR, preproliferative DR, cataract) vs no pathological changes	Pathological changes (non-proliferative DR, pre-proliferative DR, cataract) vs no pathological changes: TP: unclear; FP: 9; FN: unclear; TN: 21			
Fundoscopy ETDRS grading Retinopathy vs no retinopathy	26, 47, 4, 23	87%	33%	
Slit-lamp biomicroscopy Conventional retinal photography Fluorescein angiography CSMO vs without CSMO	4, 3, 6, 26	40%	90%	
Method not stated/ final diagnosis Retinopathy vs no retinopathy	1, 0, 22, 31	4%	10%	
Ophthalmoscopy Fluorescein angiography With retinopathy vs without retinopathy	72, 45, 13, 25	85%	34%	
Fluorescein angiography Dichotomous: normal (grade 0) vs pathological (grades 1, 2 and 3) Also angiography grade 0 vs grade 1	All angiography: 63, 49, 17, 43 Angiography grade 1: 42, 49, 12, 43	All angiography: 79% Angiography grade 1: 78%	All angiography: 47% Angiography grade 1: 47%	

TABLE 6 *Key characteristics of NCT studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)
Matsuo 1990[51,59]	Inclusion criteria: visual acuity score > 0.5 Exclusion criteria: participants with eyesight problems	Mean age: 57.4 years 54% male	Total error score (TES)
Mecca 1988[49]	Inclusion criteria: all patients had duration > 4 years; all patients had visual acuity ≥ 8/10 Exclusion criteria: participants with congenital colour vision deficits; patients with maculopathy or macular oedema of mixed or proliferative retinopathy and participants with retinopathy of an advanced degenerative stage (large or numerous haemorrhages with exudate 'confluents')		NCT Altered colour vision (anything above zero) vs normal (no errors)

D-15, Lanthony desaturated D-15 test; DR, diabetic retinopathy; FN, false-negative; FP, false-positive; NCT, Lanthony New Colour Test; TN, true-negative; TP, true-positive.

TABLE 7 *Key characteristics of the Mollon–Reffin Minimalist Test study*

Study	Patient selection criteria	Clinical characteristics (mean age,% male,% Type 1 DM)	Colour vision test (grading method)
Maár 2001[32]	Inclusion criteria: type 1 DM; best corrected visual acuity of at least 0.4 LogMAR (0.4 Snellen value); < 50 years; no lens opacities Exclusion criteria: congenital CV deficiencies; cataract; glaucoma; retinopathy, new vessels or chorioretinal scars in the macula; more than mild proliferative retinopathy; history of intraocular surgery or laser therapy	Mean age: 29.5 years 41% male 100% type 1 DM	Number of reliably identified coloured chips for each confusion line

D-15, Lanthony desaturated D-15 test; DM, diabetes mellitus; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

threshold chrominance of a coloured grating in which there is no change in luminance.

All six studies used slit-lamp biomicroscopy as the reference standard to ascertain retinopathy status. One study[53] additionally evaluated participants with indirect fundoscopy and retinal photography. The Findl *et al*. study[53] indicated that colour contrast sensitivity thresholds on the tritan axis significantly increased with the level of retinopathy as determined by the modified Airlie House classification ($p = 0.02$).

Knowles *et al*.,[54] however, found no significant difference in tritan discrimination using the SGM between background retinopathy and no retinopathy in patients with diabetes either with ($p = 0.6$) or without ($p = 0.3$) phakic eyes. The only significant difference in colour vision between patients with and without retinopathy reported in this study was on the red–green axis in those

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Method not stated/ final diagnosis Graded				Retinopathy: mean TES = 7.9 (SD 1.51); no retinopathy: mean TES = 3.03 (SD 0.56)
Ophthalmoscopy Fluorescein angiography With DR vs without retinopathy	NCT alone: 67, 28, 18, 42 NCT and D-15: 73, 45, 12, 25	NCT alone: 79% NCT and D-15: 86%	NCT alone: 60% NCT and D-15: 34%	

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Slit-lamp biomicroscopy Conventional retinal photography Fluorescein angiography Clinically significant macular oedema (CSMO) vs without CSMO	Not reported	Not reported	Not reported	Tritan axis; threshold error score of 1: sensitivity: 88.9%, specificity: 93.3% Tritan axis; error score: CSMO (n = 10): 2.1 (0.74), no CSMO (n = 29): 1.03 (0.19) Logistic regression: patients with CSMO had non-significantly higher total colour difference score (TCDS) on the D-15 (p = 0.345) and significantly higher Mollon–Reffin tritan score (p = 0.0015; r^2 = 0.565)

participants with phakic eyes ($p = 0.035$). The only study reporting diagnostic accuracy data for the red–green contrast threshold[55] indicated a sensitivity of 33% and specificity of 93% in detecting macular oedema or ischaemia (*Table 8*).

A total of four studies[31,52,55,56] provided diagnostic accuracy data, one of which evaluated the ChromaTest[56] and three[31,52,55] of which evaluated a variant of the SGM.

The ChromaTest study[56] included 150 patients with type 2 diabetes, 115 of whom had untreated non-proliferative diabetic retinopathy (NPDR) and 35 of whom had untreated CSMO, confirmed by slit-lamp biomicroscopy. Sensitivity and specificity of the tritan colour contrast threshold (TCCT) part of the ChromaTest for screening of CSMO in this group were 71% (95% CI 53% to 85%) and 70% (95% CI 60% to 78%) respectively. These equate to positive and negative LRs of 2.35 and 0.41 respectively. The study also reported ChromaTest

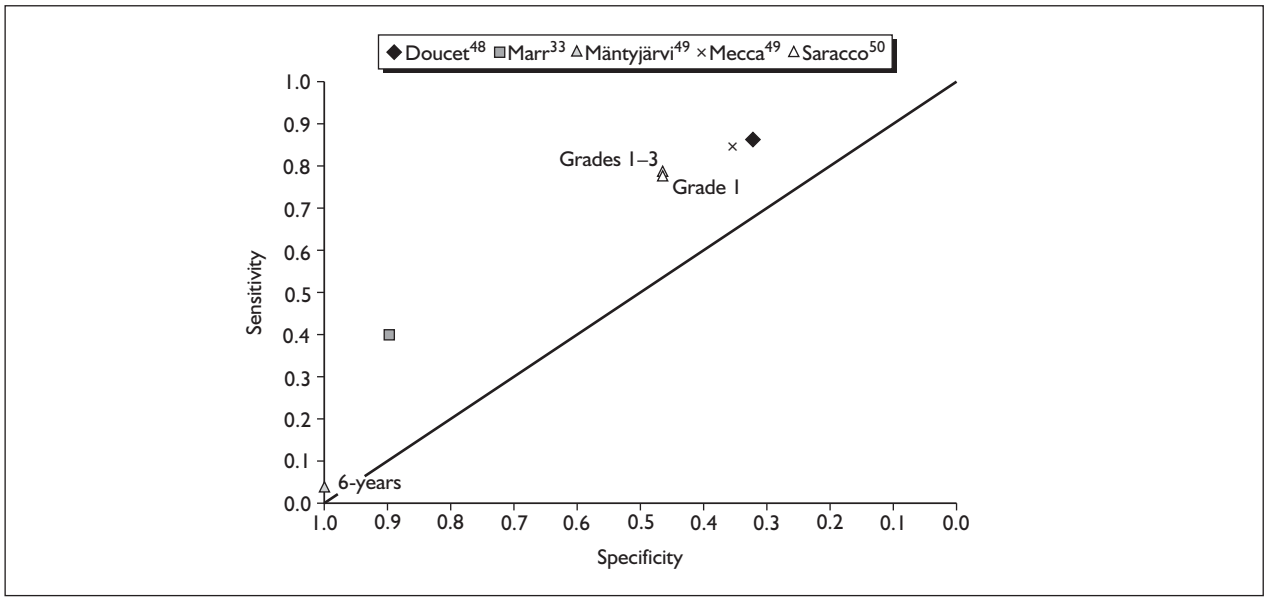

FIGURE 5 *D-15 studies reporting 2×2 data plotted in receiver operating characteristic (ROC) space (see section on quality of included studies for methodological limitations of plotted studies). Grades 1–3, all 'pathology' on angiography; grade 1, angiography grade 1 ('dry retinopathy') only; 6-years, retinopathy assessed 6 years after baseline colour vision measurement.*

scores for 30 diabetes patients without retinopathy. Using the thresholds suggested by the authors, the ChromaTest TCCT score yielded a sensitivity of 30% for distinguishing NPDR from no retinopathy and a sensitivity of 71% for distinguishing CSMO from no retinopathy. In both of these cases, the specificity of the ChromaTest was 97%. Positive and negative LRs were better for distinguishing the presence of CSMO (21.4 and 0.30 respectively) than of NPDR (9.13 and 0.72 respectively). The study's authors acknowledge that their findings may be biased (in favour of the ChromaTest) because the test was evaluated in the same data set that was used to derive positive and negative threshold levels.

One[31] of the SGM studies specifically evaluated the machine's tritan contrast threshold (TCT) test alongside retinal photography. This study reported a *z*-score of –1.75 (i.e. 1.75 standard deviations from the mean) as the optimum pass/fail criterion for distinguishing sight-threatening from non-sight-threatening retinopathy, with a sensitivity for TCT alone of 94% (95% CI 71% to 100%) and specificity of 95% (95% CI 92% to 97%). Positive and negative LRs were 17.9 (95% CI 12.1 to 26.4) and 0.06 (95% CI 0.01 to 0.42) respectively. For detecting the presence of retinopathy of any severity (anything above and including background DR), sensitivity of TCT was 57% (95% CI 41% to 72%) and specificity 78% (95% CI 74% to 82%), equating to a LR+ of 2.60 (95% CI 1.90 to 3.55) and a LR– of 0.55 (95% CI 0.39 to 0.78). Using the same threshold of $z = -1.75$ for sight-threatening CSMO, sensitivity for TCT alone was 100% (95% CI 70% to 100%) and specificity was 94% (95% CI 91% to 96%). Positive and negative LRs were 16.6 (95% CI 11.7 to 23.5) and 0 respectively. These data tend to indicate that, although TCT may be useful for ruling in higher grades of retinopathy, its performance is likely to be inadequate for the early detection of lower levels of disease.

TCT appeared to be slightly more sensitive than photography alone [94% (95% CI 69% to 100%) versus 88% (95% CI 62% to 98%)], with identical specificity [95% (95% CI for TCT, 92% to 96%; for photography, 93% to 97%). The values reported for photography alone appeared to be consistent with those reported elsewhere in the literature.[20] The authors also reported the diagnostic accuracy of TCT combined with fundus photography for detecting sight-threatening diabetic retinopathy (STDR), in which a positive test result was defined as STDR on photography and colour deficit on TCT. For combined TCT/fundus photography, sensitivity was similar to that of photography alone [88% (95% CI 64% to 99%)] and specificity increased to 100% (95% CI 99% to 100%). Combining the tests did not influence the LR– [0.12 (95% CI 0.03 to 0.43) for both combined TCT/photography and photography alone]; however, because specificity was increased to 100%, the LR+ dramatically increased from 18.9 (95% CI 12.2 to 29.2) for photography to 218 (95% CI 54.0 to 877) for the combined test. In practice, to minimise administration and travel costs, it would

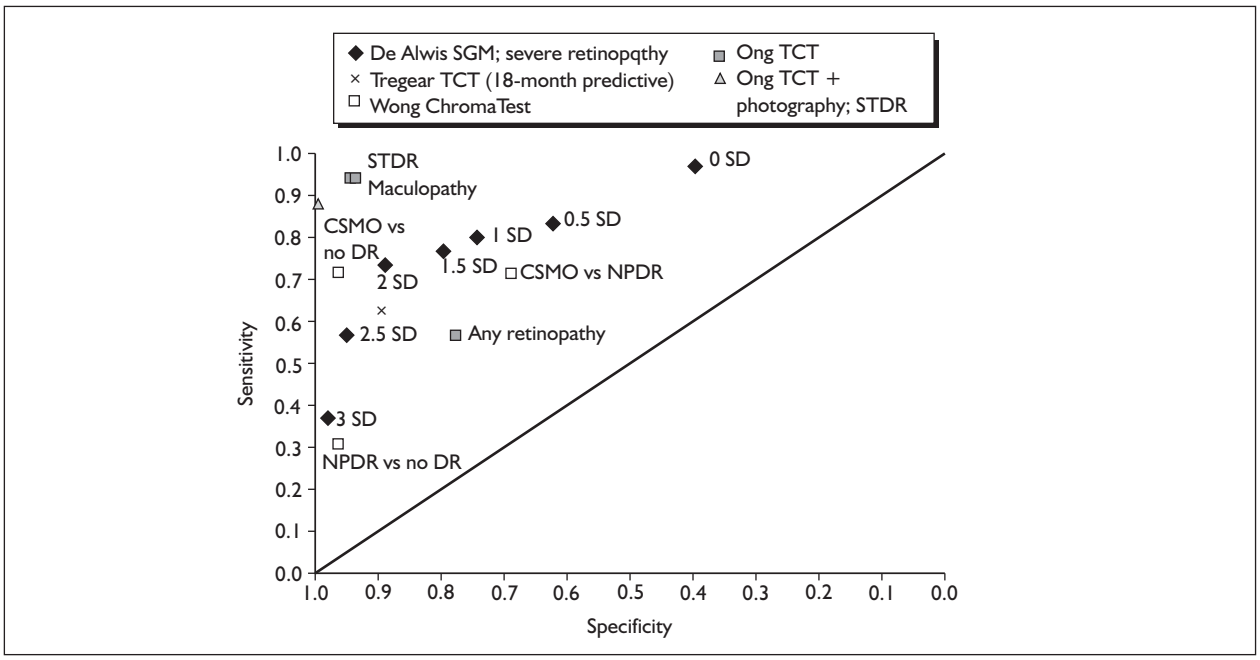

FIGURE 6 *Studies of computerised/automated tests reporting 2×2 data plotted in receiver operating characteristic (ROC) space (see section on quality of included studies for methodological limitations of plotted studies). CSMO, clinically significant macular oedema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; SD, diagnostic threshold in standard deviations above mean normal score; SGM, Sussex Gratings Machine; STDR, sight-threatening diabetic retinopathy; TCT, tritan contrast threshold.*

be most efficient to conduct CVT and photography at the same screening appointment. Given the general acceptance of retinal photography as the standard method of screening, it seems likely that, in the short term, all individuals would be screened with retinal photography and any with sight-threatening retinopathy would be referred for assessment by an ophthalmologist. Therefore, one potentially viable combination of CVT and retinal photography, not evaluated in this paper,[31,60] would be referral for assessment of any individual with sight-threatening retinopathy visualised by photography or tritan colour vision deficit. It should also be noted that, as in the ChromaTest study, the TCT thresholds used here appear to be derived from the same data set in which the test's accuracy was evaluated, thereby potentially biasing the accuracy results in favour of the TCT.

De Awis[52] reported the accuracy of a tritan pass/fail criterion for a range of thresholds: a threshold of 2 standard deviations above the mean to detect severe/advanced retinopathy had a sensitivity of 73% (95% CI 54% to 88%) and a specificity of 90% (95% CI 82% to 95%) (this provided a better balance of sensitivities and specificities than other thresholds;[52,55] *Figure 6*). Positive and negative LRs for this threshold were 7.13 (95% CI 3.92 to 13.0) and 0.30 (95% CI 0.16 to 0.54) respectively. The same threshold used to detect the broader grouping of 'moderate and severe' retinopathy had a sensitivity of 55% (95% CI 41% to 68%) and a specificity of 95% (95% CI 89% to 99%), equating to a LR+ of 12.0 (95%CI: 4.47 to 32.2) and a LR– of 0.48 (95% CI 0.36, 0.64).[52]

Tregear *et al.*[55] looked specifically at the ability of the SGM to predict macular oedema or ischaemia in a subgroup of patients who were reassessed using slit-lamp biomicroscopy 18 months after baseline TCT evaluation. At follow-up this gave a sensitivity of 63% (95% CI 38% to 84%) and a specificity of 90% (95% CI 80% to 96%). Positive and negative LRs were 6.23 (95% CI 2.85 to 13.6) and 0.41 (95% CI 0.23 to 0.74) respectively.

These data suggest that the automated TCT test might have some value in ruling in more advanced retinopathy, particularly when used in combination with retinal photography. However, it should be noted that the data for combined TCT/photography are derived from a single study with a very small number of cases with sight-threatening retinopathy, and that all of the available evaluations of the TCT were conducted in conjunction with its developers. Similarly there are no data available on the potential of this test for predicting DR.

TABLE 8 *Key characteristics of computerised/automated test studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)
De Alwis 1994[52]	Inclusion criteria: proven diagnosis of DM; visual acuity 6/12 or better Exclusion criteria: any other eye disease including glaucoma; visual acuity 6/18 or worse; previous laser treatment for retinopathy; elevated intraocular pressure in the absence of frank glaucoma	Mean age: 53.9 years (range 18–84 years)	z-score thresholds based on standard deviations from –3.0 to 0
Findl 2000[53]	Inclusion criteria: insulin-dependent type 1 diabetes patients; age < 32 years; diabetes duration between 12 and 17 years Exclusion criteria: systemic hypertension or any sign of non-diabetes-induced vascular complications; excluded patients if any ocular disease except diabetic retinopathy was evident at pre-study ophthalmic examination	Mean (SD) age: 23.1 (4.3) years 66% male Mean diabetes duration: 12–17 years	The threshold chrominance of a coloured optotype without changes in luminance compared with the surrounding expressed as a percentage
Knowles 1996[54]	Inclusion criteria: diabetic pseudophakes with/without retinopathy and age-matched phakic diabetic controls; pseudophakes were examined at least 3 months after cataract surgery Exclusion criteria: visual acuity < 6/12; previous laser eye treatment; other eye disease likely to affect CV (e.g. glaucoma/macular degeneration); significant cataract; observable posterior capsular opacity	Mean age: 74.2 years	R-G or tritan discrimination sensitivity
Ong 2004[31]	Inclusion criteria: consenting diabetes patients attending photographic screening Exclusion criteria: corrected visual acuity < 6/9; previous history of photocoagulation therapy; history of eye disease known to affect colour vision (e.g. glaucoma); signs and symptoms of significant media opacification; inability to complete the test satisfactorily	Mean age: 60.9 years 21% (107/510) type 1 DM Mean diabetes duration: 10.4 years	Using the weighted kappa coefficient of association analysis technique, the optimal pass/fail criterion to detect sight-threatening diabetic retinopathy (STDR) was z = –1.75
Tregear 1997[55]	Inclusion criteria: type 1 and type 2 diabetes patients; those taking any form of medication other than those used to control glucose levels deliberately not excluded Exclusion criteria: previous laser treatment; signs of significant lens opacification as determined by slit-lamp examination through dilated pupil; corrected visual acuity worse than 6/18	Mean age: 56 years 30% type 1 DM Mean (SD) diabetes duration: 14 years (range 1.5–60 years)	Longitudinal subgroup only: threshold scores +2 SDs above the lens equated mean

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Slit-lamp biomicroscopy Dichotomous: severe retinopathy vs non-severe retinopathy	Overall score: 3 SD: 11, 2, 19, 105; 2.5 SD: 17, 5, 13, 102; 2 SD: 22, 11, 8, 96; 1.5 SD: 23, 21, 7, 86; 1 SD: 24, 27, 6, 80; 0.5 SD: 25, 40, 5, 67; 0 SD: 29, 64, 1, 43 Tritan score: 2 SD: 22, 11, 8, 96	Overall score: 3 SD: 37%; 2.5 SD: 57%; 2 SD: 73%; 1.5 SD: 77%; 1 SD: 80%; 0.5 SD: 83%; 0 SD: 97% Tritan score: 2 SD: 73%	Overall score: 3 SD: 98%; 2.5 SD: 95%; 2 SD: 90%; 1.5 SD: 80%; 1 SD: 75%; 0.5 SD: 63%; 0 SD: 40% Tritan score: 2 SD: 90%	Right eye tritan: maculopathy grade $p < 0.001$, ischaemic grade $p < 0.005$ Left eye tritan: maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$ Right eye R-G: maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$ Left eye R-G: maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$
Slit-lamp biomicroscopy Retinal photography Fundoscopy Graded Modified Airlie House classification	Not reported	Not reported	Not reported	Level 1: 7.1% (1.7) ($n = 20$) Level 2: 7.3%, (1.9) ($n = 27$) Level 3: 10.1%, (3.0) ($n = 12$) $p = 0.02$
Slit-lamp biomicroscopy Dichotomous: no retinopathy vs background retinopathy	Not reported	Not reported	Not reported	Mean R-G discrimination sensitivity: no retinopathy: 0.610; background retinopathy: 0.789; $p = 0.035$ Mean tritan discrimination sensitivity: no retinopathy: 0.660; background retinopathy: 0.806; $p = 0.307$ Mean R-G discrimination sensitivity (controls): no retinopathy: 0.537; background retinopathy: 0.601 Mean tritan discrimination sensitivity (controls): no retinopathy: 0.786; background retinopathy: 0.823
Slit-lamp biomicroscopy Dichotomous: STDR vs non-STDR	Any retinopathy: 24, 103, 18, 365 Maculopathy: 12, 30, 0, 468 STDR: 16, 26, 1, 467 STDR TCT + photography: 15, 2, 2, 491	Any retinopathy: 57% Maculopathy: 94% STDR: 94% STDR TCT + photography: 88%	Any retinopathy: 78% Maculopathy: 100% STDR: 95% STDR TCT + photography: 99%	Mean (SD) TCT score: no retinopathy ($n = 383$): 42.5 (6.3); background retinopathy ($n = 110$): 41.7 (7.1); preproliferative retinopathy ($n = 3$): 29.6 (8.5); proliferative retinopathy ($n = 2$): 21.7 (3.3); maculopathy ($n = 12$): 24.0 (7.2)
Slit-lamp biomicroscopy Graded: no retinopathy, background, preproliferative, proliferative, maculopathy, ischaemia or maculopathy	12, 7, 7, 62	63%	90%	

continued

TABLE 8 *Key characteristics of computerised/automated test studies (continued)*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)
Wong 2008[56]	Inclusion criteria: type 2 diabetic patients with untreated NPDR and untreated CSMO Exclusion criteria: type 1 diabetes; proliferative DR; previous laser photocoagulation; current ocular pathology including infection, trauma; amblyopia; glaucoma; and/or vascular occlusion	Median 60 years (range 31–82 years) 0% type 1 DM	ChromaTest Pass/fail criterion for tritan colour contrast threshold (TCCT) given for each age group: 11.0 (30–49 years); 23.0 (50–69 years); 32.0 (70–89 years)

CSMO, clinically significant macular oedema; CV, colour vision; DM, diabetes mellitus; DR, diabetic retinopathy; FN, false-negative; FP, false-positive; NPDR, non-proliferative diabetic retinopathy; R-G, red–green; TCCT, triton colour contrast threshold; TCT, tritan contrast threshold; TN, true-negative; TP, true-positive.

TABLE 9 *Key characteristics of anomaloscope studies*

Study	Patient selection criteria	Clinical characteristics	Colour vision test (grading method)
Aspinall 1983[36]	Inclusion criteria: diabetes patients < 70 years old with normal fundi Exclusion criteria: congenital colour vision defects; cataracts	Not stated	N: normal fundus, fundi still showing no signs of retinopathy in either eye R: retinopathy, fundi showing signs, however slight, in one or both eyes
Mäntyjärvi 1995[46]	Inclusion criteria: schoolchildren with diabetes and healthy eyes at recruitment	Mean age: 14 years (SD 2; range 9–19) 46.3% male Mean diabetes duration: 6 years (SD 4; range 1 month–15 years)	Retinopathy vs no retinopathy

FN, false-negative; FP, false-positive; JND, just noticeable difference; TN, true-negative; TP, true-positive.

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Slit-lamp biomicroscopy Grading according to the Early Treatment Diabetic Retinopathy Study extension of the Airlie House classification; no clinical retinopathy, NPDR and CSMO	TCCT detection of CSMO (NPDR used as control group): TP = 25, FP = 35, FN = 10, TN = 80 Subjects with LogMAR: NPDR vs no DR: TP = 35, FP = 1, FN = 80, TN = 29, LR+ 9.13, LR– 0.72 CSMO vs no DR: TP = 25, FP = 1, FN = 10, TN = 29 CSMO vs NPDR: TP = 25, FP = 35, FN = 10, TN = 80	TCCT detection of CSMO (NPDR used as control group): 71% (53–83%) NPDR vs no DR: 30% CSMO vs NPDR: 71%	TCCT detection of CSMO (NPDR used as control group): 70% (60–78%) NPDR vs no DR: 97% CSMO vs NPDR: 70%	

Reference standard (grading method)	TP, FP, TN, FN	Sensitivity	Specificity	Other outcome data
Ophthalmoscopy Dichotomous				Yellow–blue colour discrimination (anomaloscope units JND) coefficient = 5.113×10^{-2}, standard error = 1.39×10^{-2}, t = 3.67
Method not stated/final diagnosis Dichotomous	0, 0, 22, 31	0%	100%	

Anomaloscopes

Two studies[36,46] evaluated anomaloscopes in patients with diabetes (*Table 9*).

Both studies investigated anomaloscope testing to distinguish between participants with signs of retinopathy and those without. Definitions of retinopathy were not clearly specified, and one study[46] did not specify the reference standard beyond final diagnosis.

Aspinall *et al*.[36] evaluated the Pickford–Nicolson anomaloscope and measured colour matching ratios and colour discrimination ranges for red–green, yellow–blue, and green–blue colour equations. A range of test and disease parameters was measured and analysed. Yellow–blue discrimination was found to be the best single factor for establishing retinopathy; when the population was divided at age 40 years, yellow–blue discrimination remained the best single factor in the over 40s and duration of diabetes was found to be the best factor in the under 40s.

Mäntyjärvi *et al*.[46] evaluated the traditional Nagel anomaloscope and a newer 'colour vision meter' (CVM) anomaloscope (which included a blue equation). All participants (with and without retinopathy) scored within normal limits on the Nagel anomaloscope (sensitivity of 0%, specificity of 100%), and the authors reported that mean CVM scores did not significantly differ between groups.

Neither study therefore provided evidence to support the use of these particular anomaloscopes in testing for DR.

Chapter 4

Assessment of cost-effectiveness evidence

Review of existing cost-effectiveness evidence

Methods

Search strategy

MEDLINE, EMBASE, CINAHL, NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database (HEED) were searched for economic evaluations of CVT for the diagnosis of DR. Searches were performed on 15 November 2007. The full search strategy is described in Appendix 1. In brief, the search strategy for the systematic review of CVT diagnostic accuracy was adapted by including economics search filter terms and excluding diagnostic accuracy terms. In total, after excluding duplicate articles, we identified 356 potentially relevant publications.

Results

Our search identified several economic evaluations of DR screening, including some in NHS settings.[61–63] However, there were no economic evaluations describing the cost and effects of any type of CVT for DR screening. Therefore, we reviewed the existing DR screening economic evaluations to inform parameter estimates for our independent economic assessment of CVT.

Independent economic assessment

Methods of independent economic assessment

Model structure

We developed a decision tree and Markov model to estimate the costs and effects of adding CVT to the current NSPDR using digital photography of the retina. An NHS perspective was taken for the cost-effectiveness analysis. The model was developed in Microsoft EXCEL 2000 and run with 1-year cycles for a time horizon of 50 years. The time horizon of 50 years was felt adequate to represent a lifetime horizon of the vast majority of the cohort. Half-cycle corrections have been used to improve the precision of cost-effectiveness estimates. To represent the uncertainty surrounding our base-case estimates of cost-effectiveness we used probabilistic sensitivity analyses (PSA), based on 1000 Monte Carlo second-order simulations, to estimate the possible distribution of cost-effectiveness. PSA results are presented graphically on the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC).[64]

The hypothetical cohort consisted of patients over the age of 12 years with a recorded diagnosis of diabetes, on a centralised register and invited for screening by the English NSPDR. Two models were created, one each for type 1 diabetes and type 2 diabetes.

Grading diabetes-related eye disease

Three stages of diabetes-related eye disease have been assigned based on those suggested in the English National Screening Committee (NSC) report[65] (*Table 10*). In the Markov model, the preproliferative and proliferative retinopathy states as well as maculopathy are collectively referred to as STDR as all three diagnoses follow similar referral and treatment pathways. *Table 10* also compares the NSC retinopathy grades with grades used by the ETDRS,[66] which have been used by several large epidemiological studies of disease incidence and progression.

Patient cohort

The average age of a patient with type 1 diabetes attending retinopathy screening for the first time is approximately 33 years, compared with 65 years for a patient with type 2 diabetes.[67] Because the patient age, prevalence and incidence of eye disease differ substantially between these clinical subgroups, we elected to develop a separate model for each.

Current screening

The current English national screening programme invites eligible individuals with diabetes to referral units typically based at hospitals although they can also be based in mobile units, GP surgeries or optometrists offices.[65] Patients are invited for screening at annual intervals. Screening is performed by a trained and accredited technician[68] using a digital non-mydriatic fundus 45-degree field camera with ophthalmological

grading. If screening indicates STDR then patients are referred to an ophthalmologist for further assessment and treatment planning. If screening indicates no retinopathy or background retinopathy the individual is invited back for screening at the next annual appointment (*Figure 7*). In practice, policy varies by region: in some areas individuals graded with background retinopathy may be referred to an ophthalmologist.

Colour vision testing

CVT may be a useful adjunct to current retinopathy screening methods. It is hypothesised that CVT may be able to detect nascent DR earlier than conventional photographic screening as it measures visual function as opposed to physiological findings associated with visual loss.[60] However, it is currently unclear to what extent this could affect treatment and patient outcomes. There are many methods for CVT (e.g. TCT,[31] D-15,[69] Mollon–Reffin Minimalist Test,[32] FM-100[70]).

In theory, CVT could be combined with retinal photography screening in many different ways including parallel testing (e.g. refer patient if both tests suggest eye disease) and serial testing (e.g. use the CVT to select patients for, or select the frequency of, retinal photography). Ong and colleagues,[31] in the only diagnostic accuracy study combining colour vision and retinal photography screening modalities identified by our systematic review, estimate the sensitivity and specificity of retinal photography only versus retinal photography plus CVT (TCT) with referral if both tests indicate possible eye disease or if retinal photography is ungradable in the presence of colour vision deficit.

In practice, given the acceptance of retinal photography in the NHS retinopathy screening programme, we believe that the most likely current role for CVT is in increasing the sensitivity of screening by identifying individuals with colour vision deficits who do not yet have retinopathy evident on retinal photography. Therefore, the initial structural assumption in our model is that an individual with no or background retinopathy on retinal photography but with colour vision deficit will be referred to the hospital eye clinic for a definitive diagnosis (*Figure 7*). In our model, an individual with STDR or an ungradable retinal photography result was referred to the hospital eye clinic regardless of the CVT findings. However, the CVT would be performed at the same screening appointment before the results of retinal photography were available and therefore the costs of both tests would be incurred.

Ophthalmologist diagnosis

Patients who screen positive for referable retinopathy or macular oedema are referred to an ophthalmologist for further examination using slit-lamp biomicroscopy. If the ophthalmologist confirms a diagnosis of proliferative retinopathy or macular oedema, the patient is offered laser therapy. Patients with preproliferative retinopathy are kept under ophthalmological surveillance until they either progress to proliferative retinopathy and are suitable for laser photocoagulation, or become blind or die. If the slit-lamp biomicroscopy indicates that the initial screening result was a false-positive finding, the patient will be referred back to the annual screening programme.

Treatment

Photocoagulation targets an argon laser at aneurysms or haemorrhages within the retina. Laser treatment has been shown to be effective in preventing further diabetes-related loss of vision.[71] It is assumed that individuals diagnosed with proliferative STDR are treated with laser photocoagulation and then are recalled for ophthalmological consultation annually.

Disease progression

The possible health state (Markov) transitions are depicted in *Figure 8*. We assumed that the eyesight of patients with diabetes progresses through the various stages of retinopathy, in some cases leading to blindness. Treatment of STDR with laser photocoagulation slows down the progression from STDR to blindness, but regression from more severe to less severe retinopathy or visual impairment is assumed not to occur.

Source data

Screening attendance

The base-case estimate of screening attendance rates was based on the Younis *et al.*[67] study, which reported that 79% of type 1 and 77% of type 2 patients responded to the invitation and attended screening.[72,73] However, estimates of response rates to retinal photography screening invitations in the UK vary widely.[74,75] Nearly all studies of attendance at systematic screening are based on single centres. The characteristics of patients and methods of inviting individuals for screening differ between centres accounting for the wide variability in the literature. Therefore, we varied attendance rates in the PSA over a uniform distribution between 50% and 100% (*Table 11*). In the absence of evidence to

TABLE 10 *Grades of diabetic eye disease used in the model and associated clinical pathway*

Retinopathy grade (English NSC)	Description of NSC grades	Modified ETDRS grades and descriptions	Clinical pathway
No retinopathy (R0, M0)	No visible haemorrhage or aneurysm on the fovea	Level 10: no retinopathy	Annual rescreen
Background retinopathy (R1)	Microaneurysm(s); retinal haemorrhage(s) ± any exudate not within the definition of maculopathy	Level 20 or 30: haemorrhages/ microaneurysms ETDRS STD 2A, and/or < 6 CWS	Annual rescreen
Preproliferative retinopathy (R2)	Venous beading; venous loop or reduplication; intraretinal microvascular abnormality (IRMA); multiple deep, round or blot haemorrhages	Level 40 or 50: IRMA ETDRS STD 8A, and/or two or more quadrants venous change	Refer to hospital eye service
Proliferative retinopathy (R3)	New vessels on disc (NVD); new vessels elsewhere (NVE); preretinal or vitreous haemorrhage; preretinal fibrosis ± tractional retinal detachment	≥ Level 60: fibrovascular proliferation, proliferative retinopathy. DRS high-risk characteristics	Refer to hospital eye service
Maculopathy (M1)	Exudate within 1 disc diameter (DD) of the centre of the fovea; circinate or group of exudates within the macula; retinal thickening within 1 DD of the centre of the fovea (if stereo available); any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best visual acuity of ≤ 6/12 (if no stereo)	Level 3 or 4: exudate > 1 DD from centre of macula	Refer to hospital eye service

CWS, cotton wool spot; DD, disc diameter; ETDRS, Early Treatment of Diabetic Retinopathy Study; NSC, National Screening Committee; STD, standard.

the contrary, it was assumed that the inclusion of CVT in addition to retinal photography would not alter screening attendance rates.

Diagnostic accuracy

Sensitivity and specificity data for the screening methods are shown in *Table 11*. The base-case estimates of the diagnostic accuracy of retinal photography and CVT are taken from Ong *et al.*[31] This was a prospective, comparative study of a type of CVT (TCT) compared with non-mydriatic fundus 45-degree field camera with ophthalmological grading.

In this study, 510 patients with diabetes attended a hospital-based screening centre. All patients had their eyes individually tested on the TCT followed by photographic testing in both eyes. Slit-lamp examination by an experienced ophthalmologist (considered the gold standard) was also carried out on each patient. Retinopathy grades were assessed for each test in a masked and independent manner. Ong *et al*. report that the sensitivity and specificity of retinal photography alone for the detection of STDR are 88% (15/17) and 95% (470/493) respectively. CVT alone had higher sensitivity 94% (16/17) and similar specificity 95% (467/493).[31] Ong *et al*. do not report the sensitivity and specificity of a strategy of using CVT only in patients with negative (i.e. no retinopathy or background retinopathy) retinal photography results. In the absence of this information, in the base case we assumed that the sensitivity of the combined screening strategy could increase to 94%, but specificity would be lower at 90% (assuming independence of test specificity). Therefore, CVT could potentially lead to earlier detection of DR, but would also result in more referrals to the hospital eye service. We note, however, that our estimate is based on only one study, using one type of CVT that is not readily available in clinical practice, in a very small number of patients with STDR. In sensitivity analyses we explore the thresholds of sensitivity and specificity at which CVT potentially becomes cost-effective.

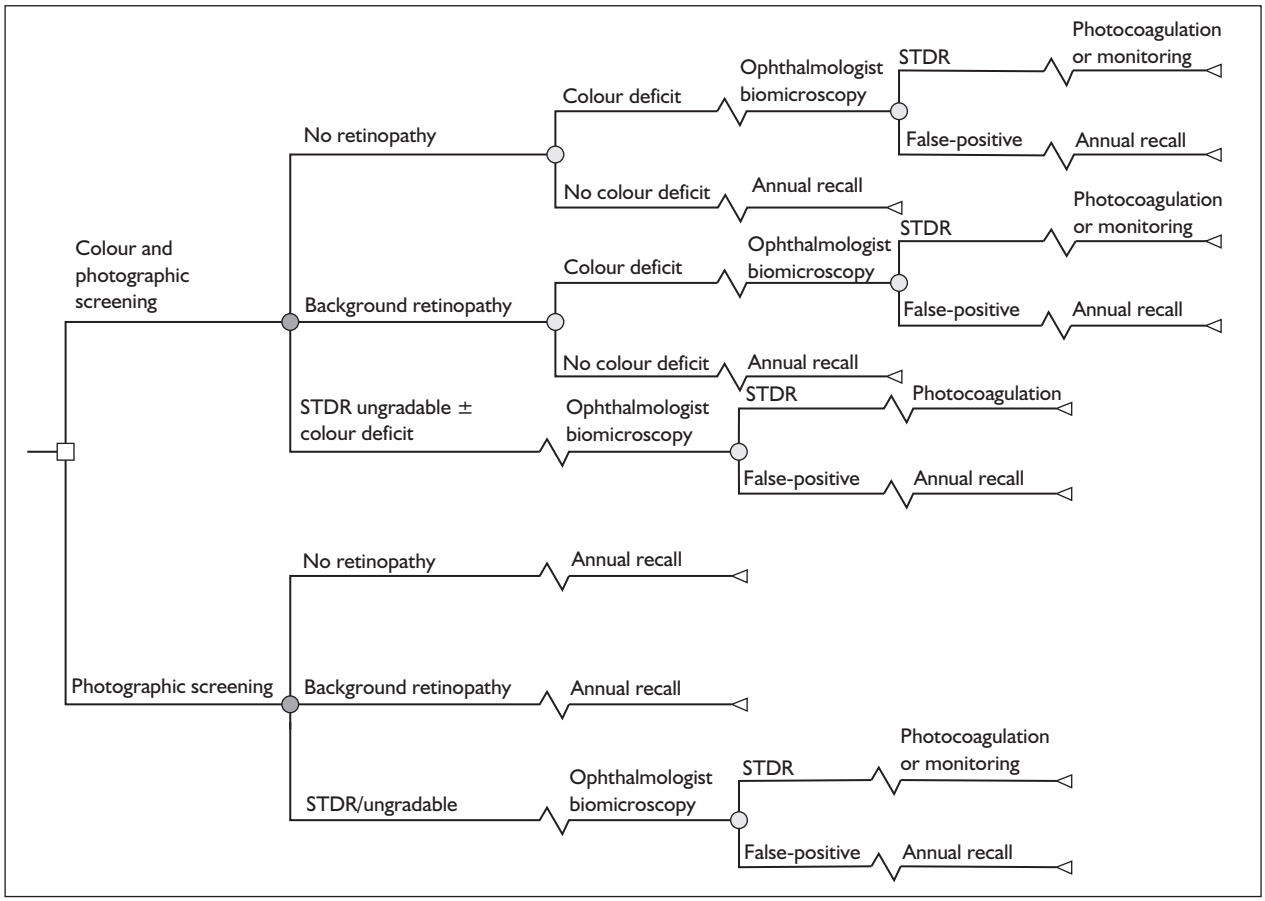

FIGURE 7 *Screening pathway. STDR, sight-threatening diabetic retinopathy.*

Because of a paucity of evidence, any potential predictive ability of including CVT in the screening workup has not been included in our modelling approach.

As slit-lamp biomicroscopy performed by an ophthalmologist is considered to be the reference standard for diagnosing diabetic eye disease, the sensitivity and specificity of this test are assumed to be 100%. In our PSA we varied this assumption by assuming a uniform distribution for both sensitivity and specificity between 98% and 100%.

Initial prevalence

The initial prevalence of diabetic eye disease in patients with type 1 and type 2 diabetes (*Table 11*) was taken from a large study of individuals attending a primary care-based DR screening programme.[67] The study was based in Liverpool and included patients with diabetes who were not under the continuing care of an ophthalmologist and who, at baseline, had not been in the systematic screening program before. Patients with type 1 ($n = 831$) and type 2 ($n = 7231$) diabetes were recruited between 1991 and 1999. Retinopathy and maculopathy were graded from dilated three-field non-stereoscopic photography by trained graders. Younis *et al.*[67] reported diabetes-related eye disease using an adaptation of the ETDRS gradings,[66] which we mapped to the English NSC Retinopathy Grading Standard[65] so that all grading definitions are consistent across the model (*Table 10*). For example, 442 out of 822 individuals (i.e. 53.8%) with type 1 diabetes and gradable biomicroscopy had no retinopathy (level 10).

Images from photographic screening may, because of technical failures, be ungradable. In these circumstances individuals are automatically referred to the hospital eye service for ophthalmologist grading. Data on the rate of technical failure have been taken from the Younis *et al.* study,[67] in which 36 out of 822 (4.4%) images were ungradable for type 1 patients and 796 out of 7231 (11%) for type 2. The higher rate of ungradable images in the type 2 population reflects

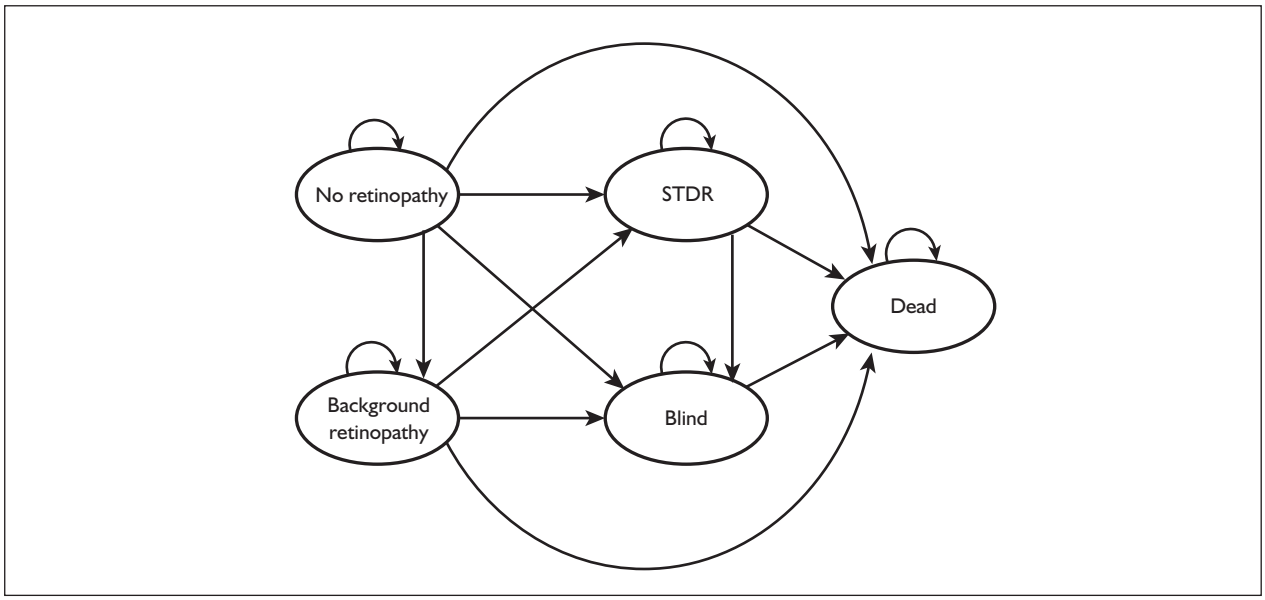

FIGURE 8 *Markov transitions. STDR, sight-threatening diabetic retinopathy.*

the older age of patients. It was assumed that ungradable images are equally likely to occur across all DR grades. The impact of uncertainty about the prevalence of retinopathy was assessed in our PSA; prevalence probabilities were assumed to follow a Dirichlet distribution based on the source data in the Younis *et al.*[67] study.

Disease transition

Annual transition rates for the progression through the various stages of DR, within a screened population, have been calculated separately for type 1 (*Table 12*) and type 2 diabetes (*Table 13*).[72,73] Type 1 ($n = 501$) and type 2 ($n = 4770$) patients from the Liverpool Diabetic Eye Study were screened at annual intervals for up to 6 years after first entering the screening programme. We converted the 6-year cumulative incidences of DR reported in the Liverpool study into annual transition probabilities using a standard conversion formula.[83] For example, the 6-year cumulative incidence of STDR in patients with type 1 diabetes and initially no retinopathy was 5.4%. This is equivalent to an annual transition probability of 0.92%.[83] These transition probabilities have been deflated to take account of transitions to mortality and blindness detailed below.

A proportion of patients with preproliferative STDR are not initially offered laser photocoagulation[80] but remain under ophthalmologist monitoring until they develop proliferative retinopathy. We used data from the Liverpool study to estimate the annual transition from preproliferative to proliferative STDR[72,73] (*Table 11*).

Data for the annual probabilities of transition to blindness from either no retinopathy or background retinopathy were taken from the economic evaluation of DR screening of Dasbach *et al.*[84] and used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Dasbach *et al* differentiated the severity of DR into high risk and low risk of progression to blindness. For our model, no retinopathy and background retinopathy have been considered equivalent to low risk in the Dasbach model.

Effectiveness of laser photocoagulation

The transition probabilities from STDR to blindness in treated and untreated patients have been taken from Odland *et al.*[71] This study was a randomised controlled trial involving 107 patients with a similar degree of STDR in both eyes, followed for 5–7 years after treatment, testing the efficacy of photocoagulation. One eye chosen at random was treated whilst the other was used as a control. In total, 77 individuals completed the 5-year follow-up. At follow-up, 44% (34/77) of eyes in the control group were legally blind compared with 13% (10/77) in the treatment group, suggesting annual transition probabilities of 10.9% and 2.7% respectively (see *Tables 12* and

TABLE 11 *Base-case parameter estimates, range and distribution used in the probabilistic sensitivity analysis, and data source*

Variables	Point estimate	Lower bound	Upper bound	Source	PSA distribution
Screening attendance:[a]					
Type 1	0.79	0.50	1	Younis 2002[67]	Uniform (0.5,1)[b]
Type 2	0.77	0.50	1		Uniform (0.5,1)[b]
Diagnostic accuracy					
Photography				*Ong 2004*[31]	
Specificity no retinopathy	0.95	0.93	0.97		Beta (435.97, 23.89)[c]
Specificity background retinopathy	0.95	0.93	0.97		Beta (435.97, 23.89)[c]
Sensitivity STDR	0.88	0.64	0.99		Beta (11.49, 2.43)[c]
Photography with colour vision					
Specificity no retinopathy	0.90	0.86	0.94		Beta (191.25, 22.14)[c]
Specificity background retinopathy	0.90	0.86	0.94		Beta (191.25, 22.14)[c]
Sensitivity STDR	0.94	0.71	1		Beta (12.11, 1.71)[c]
Ophthalmologist[a]					
Specificity no retinopathy	1	0.98	1	Assumption	Uniform (0.98, 1)[b]
Specificity background retinopathy	1	0.98	1		
Sensitivity STDR	1	0.98	1		
Prevalence[b]					
Type 1				*Younis 2002*[67]	
No retinopathy	0.538				Dirichlet[a]
Background retinopathy	0.365				
STDR	0.097				
Technical failure	0.044				
Type 2					
No retinopathy	0.741				Dirichlet[a]
Background retinopathy	0.234				
STDR	0.077				
Technical failure	0.110				
Age (years)					
Type 1	33.4			Younis 2002[67]	Fixed
Type 2	64.9				Fixed
Utility values[d]					
No retinopathy	0.83	0.63	1	Lloyd 2008[76]	Normal (0.83, 0.10)[d]
Background retinopathy	0.83	0.63	1		Normal (0.83, 0.10)[d]
STDR	0.83	0.63	1		Normal (0.83, 0.10)[d]
Blind	0.34	–0.02	0.70		Normal (0.34, 0.18)[d]
Dead	0				Fixed
Mortality hazard ratios (by diabetes type)[e]					
Type 1 vs no diabetes	3.70			Soedamah-Muthu 2006[77]	Fixed
Type 2 vs no diabetes	1.93			Mulnier 2006[78]	Fixed

TABLE 11 *Base-case parameter estimates, range and distribution used in the probabilistic sensitivity analysis, and data source (continued)*

Variables	Point estimate	Lower bound	Upper bound	Source	PSA distribution
Mortality hazard ratios (by retinopathy grade)[e]					
No retinopathy	Reference			Klein 1999[79]	
Background retinopathy	1.02	0.52	1.99		Lognormal (1.02, 0.34)[e]
STDR/blind	1.28	0.62	2.62		Lognormal (1.28, 0.37)[e]
Treatment compliance					
Attendance at ophthalmologist	1	0.95	1	Assumption	Uniform (0.95, 1)[b]
% of STDR receiving immediate photocoagulation	20.8%	10.4%	41%	Harvey 2006[80]	Uniform (0.104, 0.410)[b]
% of preproliferative STDR (type 1) who develop proliferative STDR and have photocoagulation	13.5%	4.2%	22.7%	Younis 2003[72]	Uniform (0.042, 0.227)[b]
% of preproliferative STDR (type 2) who develop proliferative STDR and have photocoagulation	15%	10.2%	19.8%	Younis 2003[73]	Uniform (0.102, 0.198)[b]
Compliance with photocoagulation	1	0.95	1	Assumption	Uniform (0.95, 1)[b]
Discount rate					
Costs	3.5%			NICE	Fixed
QALYs	3.5%				Fixed
Costs[c]					
Additional cost colour screening	£7.80	£3.90	£29	Calculated in *Table 20*	Uniform (£3.90, £29)[b]
Photographic screening	£29	£14.50	£58	Garvican 2004[68]	Uniform (£14.50, £58)[b]
Ophthalmologist appointment	£65	£32.50	£130	Garvican 2004[68]	Uniform (£32.50, £130)[b]
Photocoagulation	£815	£407.50	£1630	Garvican 2004[68]	Uniform (£407.50, £1630)[b]
Annual NHS cost of blindness	£872	£526	£1299	Clarke 2003[81]	Normal (872, 197.20)[d]

NICE, National Institute for Health and Clinical Excellence; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; STDR, sight-threatening diabetic retinopathy.
a Dirichlet distribution calculated from observed counts in source paper.[82] Upper and lower limits are interdependent.
b Uniform distribution, numbers in parentheses indicate upper and lower limit of the distribution.
c Beta distribution, numbers in parentheses indicate the alpha and beta parameters of the distribution.
d Normal distribution, numbers in parentheses indicate the mean and standard deviation.
e Lognormal distribution, numbers in parentheses indicate the mean and standard error.

TABLE 12 *Annual transition probabilities for type 1 diabetes for year 1 of the model*[a]

	NR	BR	STDR	Blind	Dead
NR	0.9021	0.0809	0.0091	0.000	0.0074
BR	0	0.8659	0.1266	0.000	0.0075
STDR	0	0	0.8826	0.1080[b]	0.0095
Blind	0	0	0	0.9905	0.0095
Death	0	0	0	0	1

BR, background retinopathy; NR, no retinopathy; STDR, sight-threatening diabetic retinopathy.
a The transition probabilities change from year to year because of the increasing annual probability of death as the cohort ages.
b In the absence of laser photocoagulation. The transition probability decreases to 0.027 when an individual receives photocoagulation treatment for the first year of the model.

TABLE 13 *Annual transition probabilities for type 2 diabetes for year 1 of the model*[a]

	NR	BR	STDR	Blind	Dead
NR	0.8757	0.0789	0.0141	0.000	0.0312
BR	0	0.8447	0.1234	0.000	0.0319
STDR	0	0	0.8554	0.1046[b]	0.0400
Blind	0	0	0	0.9600	0.0400
Death	0	0	0	0	1

BR, background retinopathy; NR, no retinopathy; STDR, sight-threatening diabetic retinopathy.
a The transition probabilities change from year to year because of the increasing annual probability of death as the cohort ages.
b In the absence of laser photocoagulation. The transition probability decreases to 0.026 when an individual receives photocoagulation treatment for the first year of the model.

13). Odland *et al.* did not differentiate between individuals with type 1 and type 2 diabetes and so, in our model, both have an identical transition probability before deflating for mortality.

Health-related quality of life

Utility values have been taken from Lloyd *et al*.[76] (*Table 11*). Utilities in this study were obtained from a group of patients with type 1 or type 2 diabetes and retinopathy in the UK ($n = 122$). Patients rated their current health using the EuroQol 5 dimensions (EQ-5D) questionnaire, which provides a single utility score [anchored at 1 (best health) and 0 (health state as bad as death)] for current health. Lloyd *et al*. found a mean utility score of 0.83 in patients with no DR and a utility score of 0.34 for patients with severe vision loss (counting fingers – hand motion). We assumed that most patients attending screening would be asymptomatic (0.83 utility score) and that the benefit of screening and treatment is through reducing the probability that a patient with STDR becomes legally blind (0.34 utility score).

Although it would have been more realistic to model differing severities of vision loss, we were unable to do so. The randomised controlled trial of photocoagulation[71] did not report results in sufficient detail to be combined with the utility scores for imperfect vision estimated by Lloyd *et al*.[76]

Mortality

Age-specific mortality rates are based on general population UK life tables (ONS, 2008, www.statistics.gov.uk/) and have been inflated to reflect the higher mortality rates of individuals with diabetes. Mortality rates gradually increase throughout the lifetime of the modelled cohort as it ages. We adjusted general population mortality rates using hazard ratios taken from Soedamah-Muthu *et al*.[77] for type 1 diabetes and Mulnier *et al*.[78] for type 2 diabetes (*Table 11*). Both studies were prospective cohort studies following patients from 1992 to 1999 matching a cohort with diabetes ($n = 7713$,[77] $n = 44{,}230$[78]) to an age and sex-matched cohort with no history of diabetes ($n = 38{,}518$,[77] $n = 219{,}797$[78]). Mortality hazard ratios between the two groups were calculated using Cox proportional hazard models. The mortality hazard ratio in type 1 diabetes was 3.7 times higher than that in the matched general population and for type 2 diabetes the hazard ratio was 1.93 times higher.

These mortality rates were then adjusted further to reflect positive correlation between the severity of diabetes-related eye disease and mortality based on Klein *et al*.[79] (*Table 11*). This was a population-based cohort study following 996 younger-onset and 1370 older-onset patients. Klein *et al*. reported the mortality hazard ratios for patients with mild retinopathy and proliferative retinopathy compared with a reference group with diabetes but no retinopathy. In our model we assumed that the relative mortality of patients with background retinopathy was equal to that of patients with 'mild retinopathy' and the mortality of patients with STDR was equal to that of patients with proliferative retinopathy. As there is no evidence to suggest that photocoagulation affects mortality, we assumed that mortality did not increase in patients with STDR who subsequently became blind.

Attendance at hospital eye clinics and compliance with therapy

Previous decision-analytical models have often assumed that 100% of patients who have positive screening results will attend the ophthalmology clinic for further diagnostic workup and, if

indicated, undergo therapy for retinopathy.[62,85,86] We have also assumed in our base case that there is 100% attendance for both, but have used a uniform distribution between 95% and 100% to assess the impact of imperfect compliance on our conclusions in the sensitivity analysis.

Costs

All current screening costs have been taken from the 2004 costings of diabetic retinal photography screening in England of Garvican.[68] That paper estimated a cost of £23 per patient on a diabetes register and £29 per patient screened if we assume an attendance rate of 80% for registered patients at screening appointments (similar to the attendance levels used in the base-case estimate). This is made with the assumption of a geographic region containing 15,000 individuals with diabetes eligible for screening and included all costs associated with equipment (e.g. cameras, eye drops), staffing, screening invitation, administration and quality assurance. A full breakdown of the costs is shown in *Table 14*.

We are not aware of any studies on the costing or resource use of any CVT in a clinical setting. To minimise administrative and patient burden, we have assumed that the CVT is conducted during the same screening appointment as the retinal photography. Therefore, administration and management costs would not increase greatly. Many of the automated CVTs, including the TCT used by Ong *et al.*,[31,60] are not commercially available. Therefore, as an example of the likely cost of CVT, we have estimated the cost of including the FM-100 test alongside retinal photography screening. We vary the cost of CVT widely in our sensitivity analysis to establish a threshold cost at which CVT might be cost-effective.

The capital cost of a FM-100 test kit is £350 (Richmond Products), and a lamp to provide the appropriate lighting costs £140 (Macbeth Lighting). It is assumed that, at most, four CVT sets and lamps would be purchased each year to be used alongside the four retinal cameras. Over time, and through use, the testing kit hues degrade; therefore, we have assumed that the kits need replacing each year. The introduction of the test would lead to an increase in staff time because of extra time spent administering the CVTs and automated recording of the results. We have made the assumption that additional staff time would be equivalent to 3.5 full-time technicians. Effectively, the introduction of CVT would double the amount of technician time compared with a screening programme based solely on retinal photography.

The extra costs associated with using the FM-100 test alongside photographic screening are presented in *Table 15*. For a geographical area of 15,000 people eligible for screening this will lead to an increased cost of £7.80 per patient screened. The FM-100 probably represents a lower bound for the cost of CVT. For automated CVTs, the equipment and maintenance costs are likely to be much higher, although technician costs could be lower.

Based on previous work,[68] the cost for a referral to an ophthalmologist is estimated to be £65 and bilateral photocoagulation costs are £815, which is made up of 1.5 treatments (average number of treatments needed per patient) and 8 outpatient follow-ups. Those who are screened as having

TABLE 14 *Garvican[68] costings of photographic screening (2004) – inflated to 2007 values*

	Cost per year
Administration: salaries (office manager and two part-time clerical assistants), postage, maintenance	£105,000
Photography: camera ($n = 4$) maintenance, technician salary 3.5 WTE, storage	£140,000
Grading costs: salary 1.5 WTE of 'expert grader'	£45,000
Quality assurance: consultant ophthalmologist 1–2 sessions per week, 0.5 WTE 'expert grader'	£30,000
Management: (0.5 WTE programme manager) session consultant time	£32,000
Total	£354,000[a]
Cost per test (80% attendance)	£29

WTE, whole time equivalent.
a Because of rounding, the total does not add up to the sum of the components.

TABLE 15 *Additional costs of FM-100 test*

	Cost
FM-100 tests ($n = 4$)	£1400
Macbeth Easel lamp ($n = 4$)	£560
3.5 WTE screening technicians	£91,000
Total	£92,960
Cost per test (80% attendance)	£7.80

FM-100, Farnsworth-Munsell 100 hue test; WTE, whole time equivalent.

preproliferative retinopathy are assumed to be recalled to an ophthalmologist annually, incurring an ophthalmologist cost of £65. This is incurred until the patient progresses to proliferative retinopathy or until they go blind or die. All patients who are blind also incur an annual cost of £872.[81] An annual ophthalmologist cost of £65 has been added to post laser photocoagulation patients to represent the cost of continued monitoring. All costs have been varied in the PSA, assuming uniform distributions from 50% to 200% of the primary estimate. This is to reflect the large uncertainties regarding the costs.

All costs have been inflated to 2007 prices using the hospital and community health services price indices. All costs and quality-adjusted life-years (QALYs) after the first year of the model have been discounted at 3.5% per annum.

Analysis

We calculated the incremental cost-effectiveness ratio (ICER) of screening using CVT as an adjunct to retinal photography versus retinal photography alone. Although there is no uniformly accepted ICER threshold defining cost-effective care, NICE[87] has cited a £20,000–30,000 per QALY threshold below which an intervention is generally accepted as cost-effective.

Results of independent economic assessment

The costs and QALYs of both current photographic screening and photographic screening with CVT, using our baseline assumptions, are shown in *Table 16* for type 1 diabetes and *Table 17* for type 2 diabetes. Adding the CVT to the screening workup adds a lifetime discounted cost of £105 per person for type 1 diabetes with a marginal increase in lifetime discounted QALYs (0.017) and years of sight (0.068). For type 2 diabetes there is an increase in cost of £177 for adding CVT with an increase in QALYs and years of sight of 0.006 and 0.022 respectively.

In all patients, CVT increases the lifetime costs per individual because of higher screening costs

TABLE 16 *Base-case results for type 1 diabetes*

	Photographic screening	Photographic screening with adjunct CVT
Percentage of patients who attend screening given a correct screening diagnosis in year 1	87.0%	83.2%
Percentage of cases of STDR identified by screening	70.1%	74.6%
Total ophthalmologist appointments (15,000 people over 50 years)	36,826	44,127
Lifetime costs[a]	£2422	£2527
Lifetime QALYs[a]	12.900	12.917
Average years of life[b]	31.185	31.185
Average years of sight[b]	21.739	21.807
ICER[a]	£6364/QALY	

CVT, colour vision testing; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-year; STDR, sight-threatening diabetic retinopathy.
a Discounted.
b Undiscounted.

TABLE 17 *Base-case results for type 2 diabetes*

	Photographic screening	Photographic screening with adjunct CVT
Percentage of patients who attend screening given a correct screening diagnosis in year 1	80.0%	77.4%
Percentage of cases of STDR identified by screening	68.9%	73%
Total ophthalmologist appointments (15,000 people over 50 years)	33,750	39,585
Lifetime costs[a]	£1049	£1226
Lifetime QALYs[a]	9.013	9.019
Average years of life[b]	16.908	16.908
Average years of sight[b]	14.111	14.133
ICER[a]	£12,432/QALY	

CVT, colour vision testing; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-year; STDR, sight-threatening diabetic retinopathy.
a Discounted.
b Undiscounted.

and also through the increase in ophthalmologist appointments and treatment because of the increased numbers of true-positives for STDR and false-positives. Overall, the proportion of patients with a correct screening diagnosis is lower when CVT is combined with retinal photography, because of the increase in false-positives. In our model, the addition of CVT increased ophthalmologist workload by approximately 7300 appointments during the lifetime of the cohort for the type 1 diabetes cohort and by 6000 appointments for the type 2 cohort.

CVT increases the number of lifetime QALYs and years of sight by increasing the number of patients with STDR who ultimately receive an ophthalmologist appointment and treatment. In total, 74.6% of patients with type 1 diabetes and STDR are correctly identified by CVT combined with retinal photography, compared with 70.1% of the same patients screened with retinal photography alone. A similar increase in true-positives is evident in patients with type 2 diabetes. The results of the base-case analysis show an

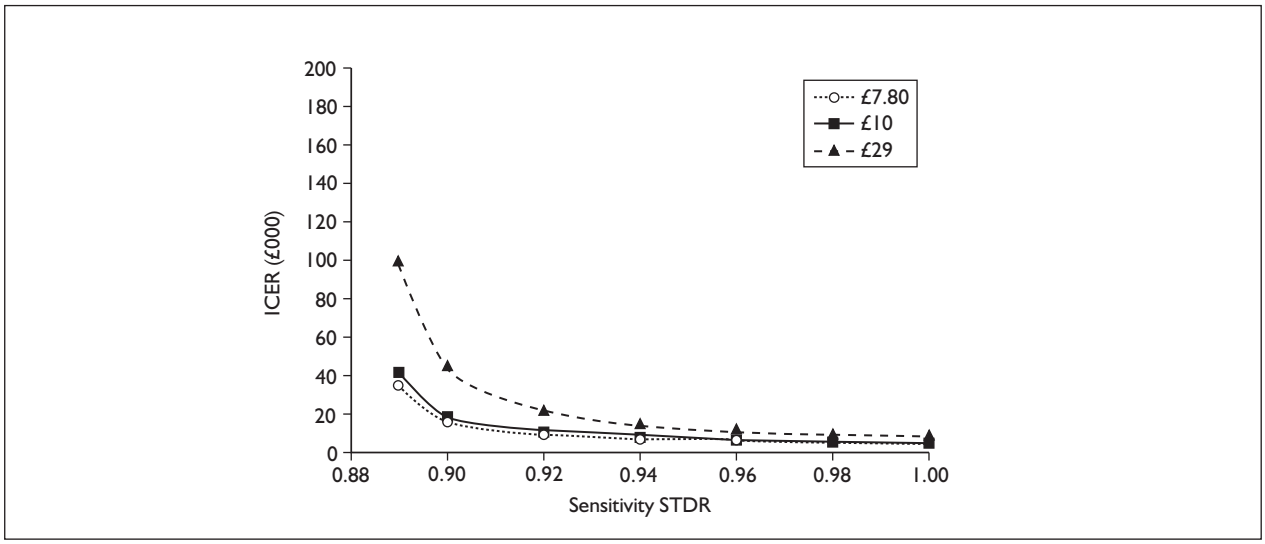

FIGURE 9 *Two-way threshold analysis of the sensitivity and cost of colour vision testing for sight-threatening diabetic retinopathy (STDR) versus the incremental cost-effectiveness ratio (ICER) (type 1 diabetes).*

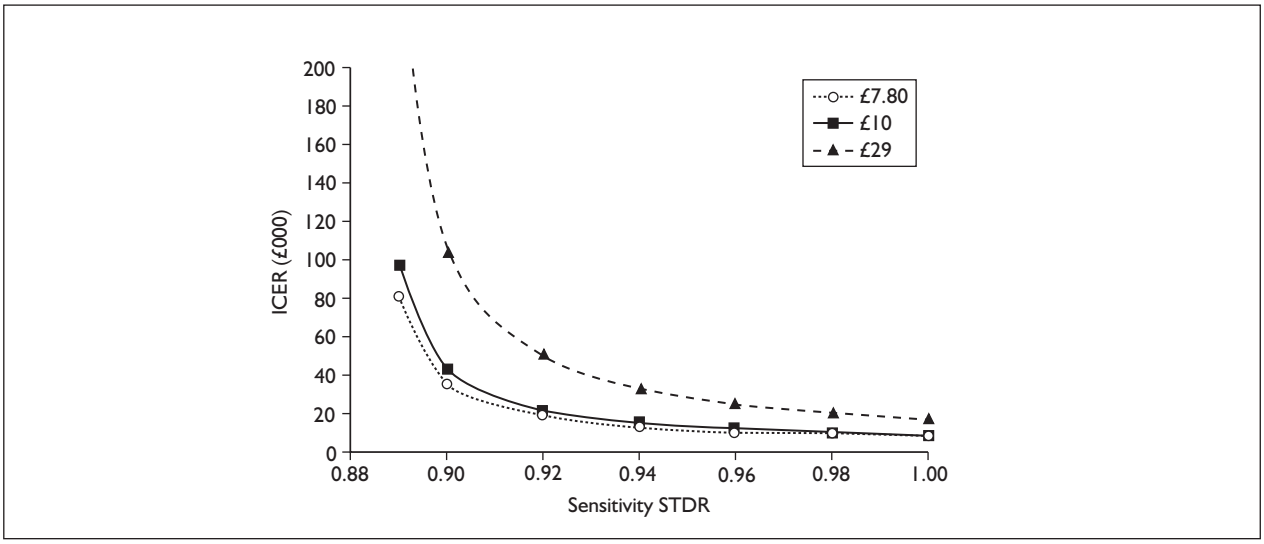

FIGURE 10 *Two-way threshold analysis of the sensitivity and cost of colour vision testing for sight-threatening diabetic retinopathy (STDR) versus the incremental cost-effectiveness ratio (ICER) (type 2 diabetes).*

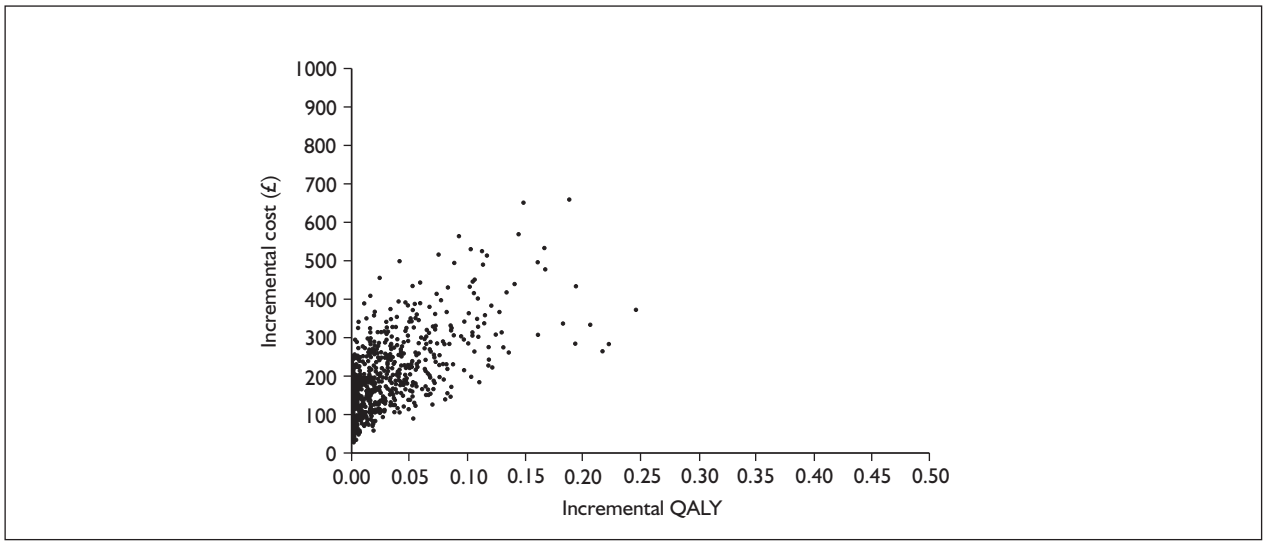

FIGURE 11 *Cost-effectiveness plane – type 1 diabetes.*

ICER of £6364 per QALY and £12,432 per QALY for type 1 and type 2 diabetes respectively. This suggests that the addition of CVT in the screening workup can be cost-effective (i.e. below £20,000 per QALY) if the additional testing method adequately increases sensitivity and is relatively inexpensive.

Threshold/scenario analysis

Figures 9 and *10* depict the impact of different levels of sensitivity of CVT on the ICER, keeping all other base-case estimates constant. The ICER rises sharply as the sensitivity of combined CVT and retinal photography falls towards 0.88 (the sensitivity of retinal photography alone). However, because CVT screening is relatively cheap and photocoagulation is effective at reducing progression to blindness, the sensitivity of CVT and retinal photography screening has to fall to 0.896 (type 1 diabetes) or 0.916 (type 2 diabetes) before the ICER for type 1 diabetes exceeds the £20,000 threshold.

At an additional cost of CVT testing of £29, doubling the overall cost of the screening workup, the ICER still remains below the £20,000 threshold for our base case of 94% sensitivity for STDR in type 1 diabetes (*Figure 9*). However at this cost a small reduction in sensitivity below the base case

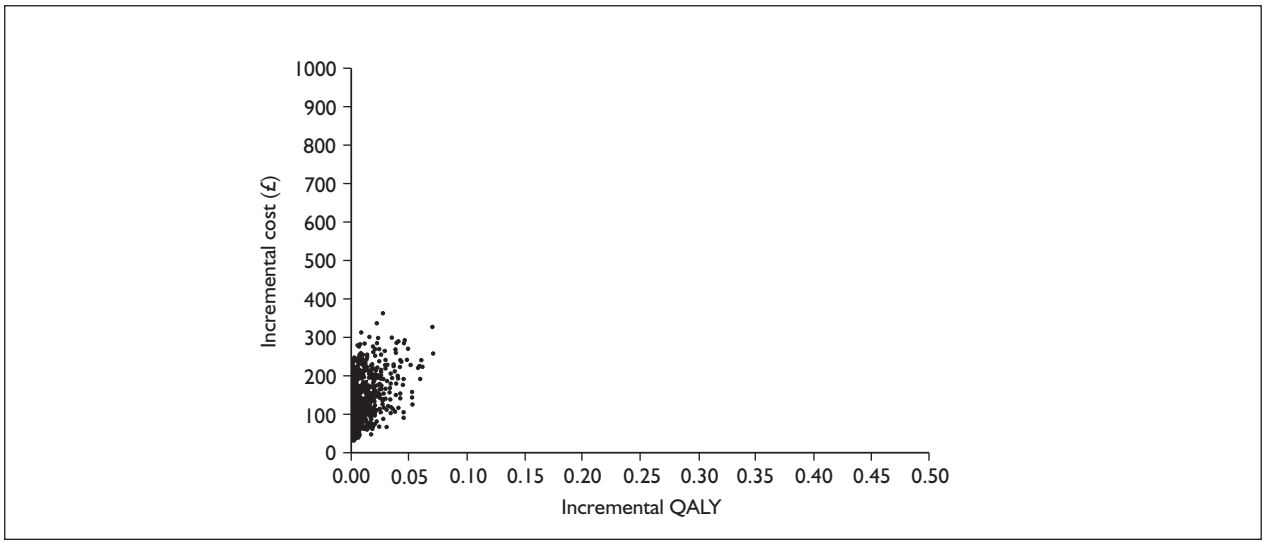

FIGURE 12 *Cost-effectiveness plane – type 2 diabetes.*

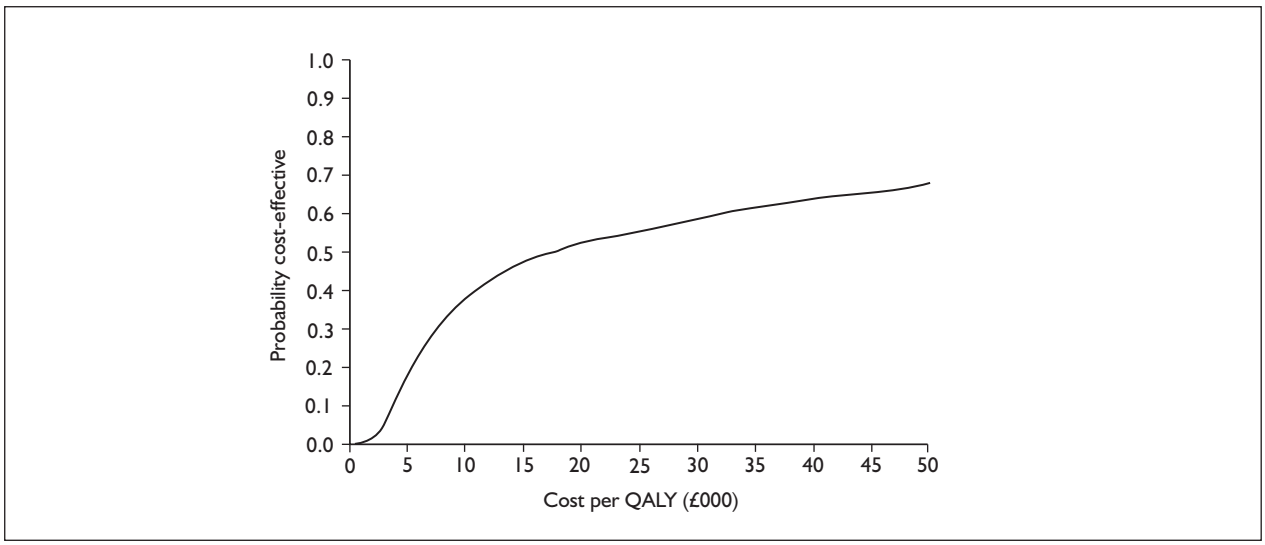

FIGURE 13 *Cost-effectiveness acceptability curve – type 1 diabetes.*

94% (0.924 for type 1 diabetes) would render the use of CVT not cost-effective. If CVT costs £29, the ICER for type 2 diabetes is not below the £20,000 threshold unless the sensitivity is increased to 0.984 (*Figure 10*).

Probabilistic sensitivity analysis

The cost-effectiveness planes in *Figures 11* and *12* show that, under our structural assumptions, the inclusion of CVT in screening always results in increased costs and is as effective or more effective than retinal photography screening alone. This is because the results of CVT only affect the management of patients with negative retinal photography screening results, in effect increasing the sensitivity and reducing the specificity of screening. The increased sensitivity leads to increased effectiveness, but the cost of the CVT itself and the additional ophthalmologist visits because of reduced specificity lead to increased costs overall. The increased number of false-positive cases referred to the ophthalmologist may also increase unnecessary anxiety, although this is difficult to quantify and is not included in our QALY calculations. The uncertainty about whether CVT is more accurate than current retinal photography screening, because of the paucity of diagnostic accuracy studies, is depicted by

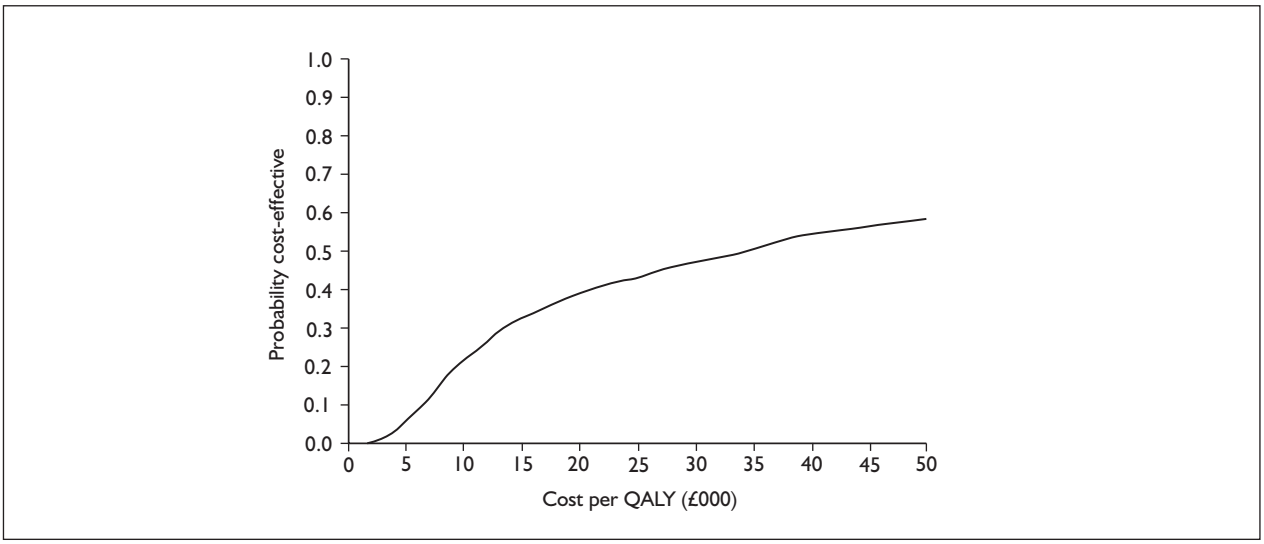

FIGURE14 Cost-effectiveness *acceptability curve – type 2 diabetes.*

the number of points that lie on or very close to the vertical axis (where the CVT strategy is not effective).

The CEACs (*Figures 13* and *14*) derived from the PSA indicate a 52.9% probability (type 1) or 39% probability (type 2) that the addition of CVT to retinal photography will be cost-effective at a cost per QALY threshold of £20,000. The fact that the probability of cost-effectiveness depicted in the CEACs never increases beyond 70%, no matter how much society is willing to pay for a QALY, reflects the considerable uncertainty that CVT combined with retinal photography is more sensitive than retinal photography alone. If CVT combined with retinal photography is not more sensitive, it is unlikely to be effective or cost-effective in improving patient outcomes.

Chapter 5

Survey of current practice

Methods

The aim of the survey was to determine which tests are currently used in the detection and management of DR, over and above the requirements of the national screening programme, to gather views of practitioners on the potential role of CVT.

The English NSC was set up to provide advice, support and facilitation to strategic health authorities, primary care trusts and local programmes implementing systematic DR screening programmes. The aim of the programme is to reduce the risk of sight loss among people with diabetes, by the prompt identification and effective treatment of sight-threatening retinopathy, at the appropriate stage during the disease process.[88] We consulted the NSC for their input before survey development, and contacted national screening programme clinical leads and project managers through the committee.

The survey was created using the online software Survey Monkey (www.surveymonkey.com/). A link to the online survey was sent to the target respondents.

Questionnaire specification

Participants were asked general identification questions, which geographical region they were from and how many primary care trusts are covered by their local programme. Participants were then asked to select from several options the primary methods of retinal screening that their programme currently uses and if any additional tests are routinely used. The following questions concerned who receives the additional tests, be it all patients screened or a specific subgroup. An open question at the end of the survey asked respondents to list and give details on any screening tests that they felt deserved to be a future research priority (see Appendix 5).

When composing the survey we avoided the use of leading questions that might prompt respondents to discuss colour vision specifically. A combination of tick box and open questions were used when appropriate.

Sample selection and data collection

All NSPDR clinical leads and project managers at 96 local programme centres in England were invited to take part in the online survey. These participants were contacted via the NSC. To maximise the response rate, potential participants were sent a reminder email 1 month after receiving the initial survey.

Data analysis

The survey data were cleaned and deduplicated to remove multiple responses from the same individual. Proportions were calculated across different responses.

Results of the survey

Clinical leads and project managers from 48 of a possible 96 centres responded to the survey, giving a response rate of 50%. Respondents were evenly spread over the geographical regions of England. The southwest had the highest proportion of respondents (18.9%) and Yorkshire and the Humber had the smallest (5.7%).

The National Service Framework for diabetes was set up to ensure that all patients with diabetes were offered retinopathy screening by December 2007. Therefore it was anticipated that respondent centres would have at least one method of screening for all patients in the local area covered by their programme. The results show that retinal photography is the primary method of screening used in all of the responding local DR screening programmes, and that none of these local programmes routinely uses CVT, nor is it used for research purposes. In total, 2% of respondents reported contrast sensitivity, 6% slit-lamp biomicroscopy and 2% ophthalmoscopy as other routinely used tests.

Only 8% of the respondents believed that CVT should be a future research priority for the NSPDR. These respondents were from Lincolnshire, Nottingham, Shropshire and Southampton. Although CVT is not high on the research agenda of many of the clinical leads or programme managers, it is interesting to note that optical coherence tomography was listed by 32% of the respondents as being a test that should be a future research priority. An optical coherence tomography scan is an optical analogue of ultrasound imaging, which uses low coherence interferometry to acquire cross-sectional images of the retina.[89]

Chapter 6
Discussion

Statement of principal findings

Clinical evaluation

Quantity and quality of evidence

The limited available evidence on the diagnostic accuracy of CVT in DR is generally of poor methodological quality. With a few exceptions, the potential for multiple biases could not be excluded. For example, spectrum of disease is an important consideration in the evaluation of diagnostic accuracy, yet on the QUADAS evaluation only one included study met the 'appropriate spectrum composition' criterion. In addition, the majority of studies excluded groups of patients (i.e. those with poorer visual acuity) that form part of the typical diabetes screening population, thereby limiting the generalisability of these findings to a screening context.

Pseudoisochromatic plates

A very small amount of poorly reported evidence is available on the diagnostic accuracy of pseudoisochromatic plates. Ishihara plates are not designed to detect tritan defects, and the available evidence suggests that they are of little value in screening for DR.

Arrangement tests

A small number of studies show a correlation between FM-100 score and degree or stage of retinopathy; however, diagnostic accuracy estimates were highly variable and no consistent cut-off value for FM-100 score was identified among the included studies. Even for the detection of more advanced retinopathy, accuracy estimates were poor, which suggests that FM-100 alone would not be useful as a screening tool for the detection of DR.

Although diagnostic accuracy estimates in adults with diabetes were more consistent across studies of the D-15 than across those of the FM-100, specificities were generally low and, on the basis of the available evidence, the D-15 alone does not appear to be a promising screening tool for the detection of DR.

The NCT showed little promise as a screening test and, although a single study reported promising results for the Mollon–Reffin Minimalist Test in detecting CSMO, no data were available on its ability to detect less severe forms of retinopathy. In addition, this test is not currently commercially available.

Computerised/automated tests

Of the six studies evaluating computerised or automated CVTs, four focused on tritan testing using the ChromaTest or variants of the SGM. Specificities were generally good for detecting more advanced retinopathy and CSMO, although sensitivities were more variable. As with the surface arrangement tests, these methods appear less sensitive and specific in detecting milder forms of retinopathy. In one study, the combination of positive results on both TCT and retinal photography produced an extremely high positive likelihood ratio for the detection of sight-threatening retinopathy, but did not appear to improve the ability of retinal photography alone to rule out disease. The optimal performance thresholds reported for these tests were derived from the data collected in the evaluation, thereby potentially biasing the diagnostic accuracy results in favour of the test. It should also be noted that these studies were all conducted in collaboration with the developers of the ChromaTest/SGM tests; there is no independent evaluative evidence available.

Anomaloscopes

Although generally considered the gold standard for detecting (typically red–green) colour deficiencies, the evidence on anomaloscopes was limited in both quality and quantity. The two available studies gave conflicting findings, one reporting that yellow–blue discrimination was the best single predictive factor of retinopathy and the other reporting no differences in anomaloscope performance between diabetes patients with and without retinopathy. Therefore these methods cannot currently be recommended as a tool for screening for DR.

Economic evaluation

The results of the base-case analysis give an ICER of £6364 and £12,432 for type 1 and type 2 diabetes, respectively, suggesting that the addition of CVT to the screening workup can be cost-effective if it adequately increases sensitivity (compared with retinal photography alone) and is relatively inexpensive.

However, as noted in the systematic review of diagnostic accuracy, the direct evidence on diagnostic accuracy of CVT alone is scant and studies evaluating the accuracy of combining CVT with retinal photography are even more rare. Therefore the results of our base-case analysis indicate what CVT might achieve if larger, independent diagnostic accuracy studies confirm the preliminary findings of Ong *et al.*[31,60] that it can increase the sensitivity of retinal photography alone. Our PSA highlighted the uncertainty in the literature on the diagnostic accuracy of CVT. There is still a substantial probability that CVT is not diagnostically accurate enough to be either an effective or a cost-effective addition to current screening methods.

Survey

Our survey of national screening programme clinical leads and project managers indicated the following:

- retinal photography is universally employed as the primary method for retinal screening
- a small minority of local programmes also incorporate slit-lamp biomicroscopy and contrast sensitivity testing
- no centres responding to the survey reported using CVT as part of their retinopathy programme, and few considered CVT to be a research priority
- a substantial proportion of respondents considered optical coherence tomography to be a research priority.

Strengths and limitations of the assessment

Clinical evaluation

We searched a wide range of electronic databases and other sources to identify relevant studies for the systematic review. However, despite using a search strategy designed for maximum sensitivity, only a small amount of evidence on CVT in diabetes was found. We included relevant studies regardless of language of publication or publication status to avoid publication and language biases; 32% ($n = 8$) of studies were published in a language other than English and 20% ($n = 5$) were not full-length peer-reviewed journal articles. Although not as straightforward to assess as for intervention studies, publication bias can be an issue for reviews of diagnostic accuracy studies. We therefore excluded studies including very small numbers of patients. To obtain the maximum available evidence, we included phase I-type studies measuring the correlation of CVT scores with retinopathy status, as well as studies measuring diagnostic accuracy. Nevertheless, only a total of 25 relevant studies fulfilled criteria for inclusion in the systematic review. The majority of these studies were relatively old, with 79% ($n = 19$) being published at least 10 years before this report and 38% ($n = 9$) being published at least 20 years ago.

To prevent errors or bias in the selection, quality assessment and data extraction of studies, two reviewers undertook each of these processes independently. We used the validated QUADAS criteria to assess study quality, although, in many cases, when studies failed QUADAS criteria it was impossible to determine which had clear methodological flaws and which failed because of poor reporting of methods.

As the included studies were highly heterogeneous, it was considered inappropriate to statistically pool their findings. We therefore presented the results in a narrative synthesis, according to the test evaluated, with sensitivities and specificities plotted in ROC space for illustration. ROC plots provide an easy to interpret visual summary of all of the studies included in a review. They enable the reader to assess quickly the variability between studies, the accuracy of the test and whether there appears to be a threshold effect, without the potentially misleading effect of pooling using a summary ROC when there is significant between-study heterogeneity. In addition, we provided the corresponding likelihood ratios, as these allow clinicians to calculate post-test probabilities of disease from pretest probabilities. It should be noted, however, that the number of studies included for each CVT was small, and not all studies reported data to allow the calculation of diagnostic accuracy estimates.

Economic evaluation

The economic evaluation is strengthened by the recent publication of several large epidemiological studies[67,72,73,90] detailing the prevalence and incidence of DR in the UK population eligible for screening.

The main limitations of the economic evaluation relate to the lack of evidence on the diagnostic accuracy of CVT and the cost-effectiveness of photocoagulation therapy. Diagnostic accuracy data on CVT were taken from one paper that looked at TCT, a test that has seldom been used in a clinical setting. Only 17 patients in this study had STDR and therefore the confidence intervals surrounding the estimate for sensitivity are wide, resulting in the wide range in cost-effectiveness estimates found in our PSA. Although this paper did report the sensitivity and specificity of CVT and retinal photography combined, it did not directly evaluate the accuracy of CVT in patients with no STDR evident on screening retinal photography. Therefore, we had to make assumptions about the independence of CVT and retinal photography tests in order to estimate the sensitivity and specificity of CVT combined with retinal photography in our analysis. For these reasons, the cost-effectiveness results describe what CVT could achieve if these initial diagnostic accuracy results are confirmed in larger studies examining different ways of combining the results of CVT and retinal photography.

No detailed costings of any type of CVT were identified. Furthermore, many types of CVT used in research settings are not available commercially, making cost estimation difficult. We included a wide range of costs in our sensitivity analysis to address this limitation and recognise the likely cost differences between relatively simple colour arrangement tests and more technically complex computer-based tests. In fact, our results did not vary greatly at plausible test costs (from £7.80 to £29). Nevertheless, before any type of CVT could be included in routine screening, it would be important to precisely measure the fixed and variable costs of implementation.

The effectiveness of treatment is important in analysing the cost-effectiveness of systematic screening programmes. Treatment efficacy for our model was taken from a randomised controlled trial published in 1984.[71] If treatment has improved over time then results from this paper will underestimate the effectiveness of photocoagulation as used in clinical settings today. More recent trials are not available as this treatment is now the standard of care. The randomised trial also did not report any details on the incremental costs of photocoagulation or any generic outcome that could be used to calculate QALYs. Therefore, we estimated costs and patient utility scores based on observational data collected in other studies. This limitation, which is common in decision-analysis models, could lead to bias in our conclusions if photocoagulation is more or less cost-effective than estimated.

Survey of current practice

To ensure the relevance of the survey and to contact an appropriate sample population, we approached the English NSC who consulted on the content of the survey and contacted all of the programme managers and clinical leads in England. Further attempts to maximise response were made by keeping the survey brief and providing it online, as well as sending a brief follow-up reminder to potential responders. Ultimately, these efforts resulted in a response rate of 50%, higher than typically achieved in postal and email surveys. No further attempts were made to contact the 50% who did not respond. There would be potential for bias in the findings of the survey if the non-responders were systematically different from the responders on factors that might influence their responses. We considered this unlikely in this case but, as the possibility cannot be entirely ruled out, appropriate caution must be exercised when interpreting the findings of the survey. The phrasing of the survey introduction and questions was specifically designed to avoid unduly biasing responses in favour of, or against, CVT.

Uncertainties

There are several CVTs (e.g. Harvey–Rand–Ritter and tritan-based pseudoisochromatic plates) that have been developed but not evaluated in the context of detecting or predicting retinopathy in patients with diabetes. Consequently, direct conclusions cannot be drawn about the diagnostic accuracy of these tests.

The NSC has developed a list of criteria for the viability, effectiveness and appropriateness of a screening programme. These criteria relate to the condition and test of interest, the available

treatments and the proposed screening programme itself. As a national retinopathy screening programme has already been implemented, only the subset of criteria relating to the test is relevant to the appropriateness of CVT in DR. The first of these criteria states that any potential screening test should be simple, safe, precise and validated. Most of the tests evaluated in the review were both relatively safe and simple to conduct (although scoring and interpretation of the non-automated arrangement tests can be relatively complex). As discussed previously, not all CVTs have been validated and, for those that have, data on their precision are limited and/or heterogeneous.

The second criterion states that the distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. When more than one study evaluated the same CVT, cut-offs used to define a positive result varied considerably and the method to establish these cut-offs was rarely reported.

The NSC criteria state that the test should be acceptable to the screening population. However, our extensive search found no evidence on this issue. In the context of introducing CVT as a component of screening for DR, patient concerns, if any, might relate to the potential additional time required for attending screening appointments. Patients may also be concerned about the consequences of any false-positive results, such as additional follow-up appointments.

The final NSC criterion mandates that there should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to these individuals. In our model, patients who screen positive for referable retinopathy or macular oedema are referred to an ophthalmologist for further examination using slit-lamp biomicroscopy. If the ophthalmologist confirms the diagnosis of preproliferative retinopathy, proliferative retinopathy or macular oedema, the patient is offered laser therapy. If the slit-lamp biomicroscopy indicates that the initial screening result was a false-positive finding, the patient will be referred back to the annual screening programme.

The available evidence suggests that CVT alone would not be sufficiently accurate to screen for DR. Unlike mydriatic retinal photography, CVT has not consistently been shown to have sensitivity values exceeding 80%.[20] If CVT was to be used in retinopathy screening, this would most likely be as an adjunct to the existing programme, which is based on retinal photography. However, the only available direct evidence on the combination of retinal photography and CVT comes from a single study[31,60] and would require confirmation from further studies before CVT could be considered an effective adjunct in retinal screening.

There is insufficient evidence to draw any clear conclusions on the ability of CVT to predict the risk of future DR among patients without evidence of retinal damage at assessment. The value of any test to predict DR depends upon the availability and effectiveness of strategies to act on a positive result to prevent or delay the occurrence of clinically significant retinopathy. Such strategies might include more intensive monitoring of metabolic control and blood pressure among patients identified as being at risk. In the absence of data on the predictive value of CVT, there is currently little to support this approach for opportunistic detection of early-stage DR in primary care, as incipient retinopathy is screened for on an annual basis.

Our survey of local retinopathy screening programmes showed that there is limited interest in CVT as an adjunct to retinal photography as a screening tool. However, some respondents did report an interest in optical coherence tomography. The evaluation of optical coherence tomography was outside the scope of this report, but its role in detecting DR is the subject of an HTA-funded research project (ongoing at the time of publication).[89,91]

As stated previously, restricted inclusion criteria mean that some kinds of patients who would be seen routinely in DR screening were excluded from the majority of studies, thereby limiting the generalisability of their findings.

The primary uncertainty in the economic evaluation related to how CVT could be incorporated into a screening programme currently using retinal photography. As described previously in this report, the test could be used in parallel with retinal photography or serially to filter patients before or after retinal photography. The stage at which the test is incorporated will determine which diagnostic properties are most crucial. For example, if the objective was to avoid the need for patients to undergo retinal photography, the test would need to be highly sensitive. Alternatively, if a test was used to confirm a positive result on retinal photography, it would need to be highly

specific. The diagnostic accuracy studies identified in our review provided little guidance on this vital issue. Most studies evaluated the accuracy of CVT in isolation and did not explore whether it would improve the sensitivity and specificity of current screening methods. In consultation with clinical colleagues on our research team, we developed a structural model (*Figure 7*) describing how CVT might be incorporated into current screening. Based on this structural model we were able to estimate cost-effectiveness. However, if CVT is considered a potentially useful adjunct to the current screening programme, there will clearly be a need for further evaluations in large cohorts who are eligible for screening, demonstrating how it can be combined with retinal photography to improve diagnostic accuracy, targeting of treatment and patient outcomes.

There is also likely to be clinical variation in the treatment of patients with STDR identified by screening, which cannot be adequately represented by a decision-analysis model. Some patients at the early stages of STDR may not receive laser photocoagulation immediately after ophthalmologist confirmation of the disease. Instead, a period of close monitoring may occur until treatment is deemed suitable. It is therefore possible that a screening test such as CVT, which may detect some cases of STDR earlier, merely prolongs the time spent under ophthalmological monitoring without reducing the time until definitive therapy. If this is the case, our model would overestimate the cost-effectiveness of adding CVT to current screening. We did not identify any studies examining the therapeutic impact of CVT and therefore we did not quantify this uncertainty in the model.

Other relevant factors

The majority of CVTs developed to detect acquired colour vision defects such as DR do so by evaluating tritan colour deficits. However, there has been some debate as to whether the performance of participants on tritan-based colour vision tests might be influenced by age-related lens yellowing.[92,93] There is evidence that lenses of patients with diabetes may 'yellow' more quickly than those in non-diabetes control subjects.[92] Only one[31,60] of the included studies explicitly accounted for this potential confounding factor. Some authors[93] have suggested that iris colour and macular pigment density should also be taken into consideration when interpreting CVT performance. None of these variables was explicitly addressed in the evidence identified in this review.

Assessment of factors relevant to the NHS and other parties

The current NHS screening programme is based on providing people with diabetes the opportunity for annual retinal screening, predominantly based on retinal photography. Any changes in the structure or delivery of the DR screening programme need to take into account several factors, including the likely ongoing increase in the prevalence of diabetes corresponding to the increased prevalence of obesity and an aging population. The relative costs and benefits of any potentially competing adjunct tests (e.g. CVT versus optical coherence tomography) need to be considered explicitly. Should any future evidence support the use of CVT, this will need to be sufficiently robust to impact on clinical opinion, which at present does not appear to consider CVT worthy of further attention in a screening context.

Chapter 7
Conclusions

Implications for service provision

- There is insufficient evidence to support the use of CVT alone as a method of screening for retinopathy in patients with diabetes. The evidence that is available is limited in quantity and is of generally poor quality.
- Pseudoisochromatic plates, anomaloscopes and colour arrangement tests (including FM-100, D-15 and NCT) all showed unacceptably poor diagnostic accuracy estimates for screening for milder forms of retinopathy (the Exeter Standards of the British Diabetic Association require screening levels of at least 80% sensitivity and 95% specificity).[21] These estimates generally improved for advanced forms of retinopathy, but remained poor.
- A single study reported that sensitivity and specificity for detecting advanced retinopathy exceeded 90% for certain variations on the automated SGM when combined with retinal photography such that presence of disease was defined as failure of both tests; this represents a small, but not statistically significant, improvement in sensitivity over retinal photography alone. However, this single study was conducted by the test developers and the technology has not been independently evaluated. As for CVT alone, the available evidence on combination testing is extremely limited.
- If these initial results on diagnostic accuracy for the automated SGM are confirmed in larger independent studies then the addition of CVT to current screening using retinal photography could be cost-effective. However, better quality diagnostic accuracy studies directly comparing the incremental value of CVT in addition to retinal photography are needed before drawing conclusions on cost-effectiveness.
- There is no published evidence on patient preferences in relation to colour vision screening for DR.
- Retinal photography is universally employed as the primary method for retinal screening by centres responding to a survey of current practice; none used CVT.

Suggested research priorities

- A total of 32% of survey respondents considered optical coherence tomography to be a research priority. CVT was not identified as a research priority by survey respondents. Therefore, optical coherence tomography may be a greater priority for future research than CVT. An ongoing HTA-funded study is investigating the value of adding optical coherence tomography to retinal photography to identify macular oedema.
- Information about the sensitivity and specificity of CVT alone, which is the focus of most previous studies, is less useful than estimates of the diagnostic accuracy of CVT combined with retinal photography as this is the most likely mode of use in the NHS. Uncertainties in the CVT literature could be resolved by further research evaluating the addition of different CVT modalities to retinal photographic screening, either to improve accuracy of detection or to establish any predictive ability. Any such study would have to be conducted prospectively, in a sample generalisable to the wider screening population, be independent of the test developers, account for the potential effects of lens yellowing, iris colour and macular pigment density alongside other clinical factors, and follow STARD reporting guidelines for reporting diagnostic accuracy studies.
- Ideally, as well as measuring diagnostic accuracy, any future studies of screening for DR should consider the consequences of positive and negative results in terms of costs, subsequent treatment/prevention options and participant outcomes.
- Activity-based cost analyses detailing the resource use of the various manual and automated CVT strategies are also necessary. These studies should estimate the capital and labour costs of implementing CVT in typical primary care trust diabetes populations.

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Contribution of authors

Mark Rodgers, Rebecca Hodges, James Hawkins and Will Hollingworth were responsible for conception and design, acquisition of data, analysis and interpretation of data, drafting and revision of the manuscript, and final approval of the version to be published.

Steven Duffy was responsible for conception and design, acquisition of data, interpretation of data, drafting and revision of the manuscript, and final approval of the version to be published.

Martin McKibbin and Michael Mansfield were responsible for analysis and interpretation of data, revision of the manuscript, and final approval of the version to be published.

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Jonathan Sterne was responsible for conception and design, interpretation of data, revision of the manuscript, and final approval of the version to be published.

Paul Glasziou was responsible for conception and design, interpretation of data, revision of the manuscript, and final approval of the version to be published

Penny Whiting and Marie Westwood were responsible for conception and design, interpretation of data, revision of the manuscript, and final approval of the version to be published.

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Appendix 1

Literature search strategies

Systematic review search strategies

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID gateway) 1950 to September Week 3 2007

Searched 4 October 2007.
643 records were retrieved in MEDLINE and 6 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Color Vision Defects/
2. Color Perception/
3. Color Perception Tests/
4. Vision Screening/
5. Vision Tests/
6. Contrast Sensitivity/
7. ((color$or colour$or vision or visual) adj3 (test$or screen$)).ti,ab.
8. ((color$or colour$) adj3 (blind$or deficien$or defect$or loss or impair$or perception)).ti,ab.
9. (monochromatopsia or achromatopsia or deutan or protan).ti,ab.
10. anomaloscop$.ti,ab.
11. pseudoisochromatic$.ti,ab.
12. hue$discrimination$.ti,ab.
13. lantern$.ti,ab.
14. (tritan or TCT).ti,ab.
15. Ishihara$.ti,ab.
16. Kojima$.ti,ab.
17. Ohkuma$.ti,ab.
18. Matsubara$.ti,ab.
19. Dvorine$.ti,ab.
20. cvtmet.ti,ab.
21. (Hardy Rand Rittler$or AOHRR or AO H-R-R).ti,ab.
22. Lanthony$.ti,ab.
23. (panel d 15 or panel d15 or d 15 panel or d15 panel).ti,ab.
24. Farnsworth$.ti,ab.
25. ((color$or colour$) adj plate).ti,ab.
26. Mollon Reffin$.ti,ab.
27. Pease Allen$.ti,ab.
28. Giles Archer$.ti,ab.
29. Adams Desaturated.ti,ab.
30. (City University or CUCVT).ti,ab.
31. Velhagen Pflugertrident$.ti,ab.
32. (contrast adj3 sensitivit$).ti,ab.
33. or/1–32
34. exp Diabetes Mellitus/
35. diabet$.ti,ab.
36. (IDDM or NIDDM or T2DM).ti,ab.
37. or/34–36
38. 33 and 37
39. exp Diabetic Retinopathy/
40. retinopath$.ti,ab.
41. exp Macular Degeneration/
42. Retinal Hemorrhage/
43. Retinal Neovascularization/
44. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
45. maculopath$.ti,ab.
46. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.
47. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
48. or/39–47
49. 38 and 48
50. Animals/
51. Humans/
52. 50 not (50 and 51)
53. 49 not 52

EMBASE (OVID gateway) 1980 to 2007 Week 39

Searched 4 October 2007.
419 records were retrieved.

1. Color Vision Defect/
2. Color Vision/
3. Color Vision Test/
4. Vision Test/
5. Color Blindness/
6. Contrast Sensitivity/
7. ((color$or colour$or vision or visual) adj3 (test$or screen$)).ti,ab.
8. ((color$or colour$) adj3 (blind$or deficien$or defect$or loss or impair$or perception)).ti,ab.
9. (monochromatopsia or achromatopsia or deutan or protan).ti,ab.
10. anomaloscop$.ti,ab.
11. pseudoisochromatic$.ti,ab.
12. hue$discrimination$.ti,ab.
13. lantern$.ti,ab.
14. (tritan or TCT).ti,ab.
15. Ishihara$.ti,ab.

16. Kojima$.ti,ab.
17. Ohkuma$.ti,ab.
18. Matsubara$.ti,ab.
19. Dvorine$.ti,ab.
20. cvtmet.ti,ab.
21. (Hardy Rand Rittler$or AOHRR or AO H-R-R).ti,ab.
22. Lanthony$.ti,ab.
23. (panel d 15 or panel d15 or d 15 panel or d15 panel).ti,ab.
24. Farnsworth$.ti,ab.
25. ((color$or colour$) adj plate).ti,ab.
26. Mollon Reffin$.ti,ab.
27. Pease Allen$.ti,ab.
28. Giles Archer$.ti,ab.
29. Adams Desaturated.ti,ab.
30. (City University or CUCVT).ti,ab.
31. Velhagen Pflugertrident$.ti,ab.
32. (contrast adj3 sensitivit$).ti,ab.
33. or/1–32
34. exp Diabetes Mellitus/
35. diabet$.ti,ab.
36. (IDDM or NIDDM or T2DM).ti,ab.).ti,ab.
37. or/34–36
38. 33 and 37
39. exp Retinopathy/
40. retinopath$.ti,ab.
41. Retina Maculopathy/
42. Retina Edema/
43. Retina Hemorrhage/
44. Retina Neovascularization/
45. Retina Macula Degeneration/
46. Microaneurysm/
47. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
48. maculopath$.ti,ab.
49. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.
50. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
51. or/39–50
52. 38 and 51
53. Animal/or Animal Experiment/or Nonhuman/
54. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
55. or/53–54
56. exp Human/or Human Experiment/
57. 55 not (55 and 56)
58. 52 not 57

CINAHL (OVID gateway) 1982 to September Week 4 2007

Searched 4 October 2007.
115 records were retrieved.

1. Color Perception/
2. Color Perception Tests/
3. Color Vision Defects/
4. Vision Screening/
5. Vision Tests/
6. ((color$or colour$or vision or visual) adj3 (test$or screen$)).ti,ab.
7. ((color$or colour$) adj3 (blind$or deficien$or defect$or loss or impair$or perception)).ti,ab.
8. (monochromatopsia or achromatopsia or deutan or protan).ti,ab.
9. anomaloscop$.ti,ab.
10. pseudoisochromatic$.ti,ab.
11. hue$discrimination$.ti,ab.
12. lantern$.ti,ab.
13. (tritan or TCT).ti,ab.
14. Ishihara$.ti,ab.
15. Kojima$.ti,ab.
16. Ohkuma$.ti,ab.
17. Matsubara$.ti,ab.
18. Dvorine$.ti,ab.
19. cvtmet.ti,ab.
20. (Hardy Rand Rittler$or AOHRR or AO H-R-R).ti,ab.
21. Lanthony$.ti,ab.
22. (panel d 15 or panel d15 or d 15 panel or d15 panel).ti,ab.
23. Farnsworth$.ti,ab.
24. ((color$or colour$) adj plate).ti,ab.
25. Mollon Reffin$.ti,ab.
26. Pease Allen$.ti,ab.
27. Giles Archer$.ti,ab.
28. Adams Desaturated.ti,ab.
29. (City University or CUCVT).ti,ab.
30. Velhagen Pflugertrident$.ti,ab.
31. (contrast adj3 sensitivit$).ti,ab.
32. or/1–31
33. exp Diabetes Mellitus/
34. diabet$.ti,ab.
35. (IDDM or NIDDM or T2DM).ti,ab.
36. or/33–35
37. 32 and 36
38. Diabetic Retinopathy/
39. retinopath$.ti,ab.
40. Macular Degeneration/
41. Eye Hemorrhage/
42. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
43. maculopath$.ti,ab.
44. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.

45. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
46. or/38–45
47. 37 and 46

Science Citation Index (Web of Science) 1900 to 30 September 2007
Searched 4 October 2007.
463 records were retrieved.

TS=(color* SAME test*) or TS=(color* SAME screen*) or TS=(colour* SAME test*) or TS=(colour* SAME screen*) or TS=(vision SAME test*) or TS=(vision SAME screen*) or TS=(visual SAME test*) or TS=(visual SAME screen*)
TS=(color* SAME blind*) or TS=(color* SAME deficien*) or TS=(color* SAME defect*) or TS=(color* SAME loss*) or TS=(color* SAME impair*) or TS-(color* SAME perception) or TS=(colour* SAME blind*) or TS=(colour* SAME deficien*) or TS=(colour* SAME defect*) or TS=(colour* SAME loss*) or TS=(colour* SAME impair*) or TS=(colour* SAME perception)
TS=(monochromatopsia or achromatopsia or deutan or protan)
TS=(anomaloscop* or pseudoisochromatic*) or TS=(hue* discrimination*) or TS=(lantern* or tritan or TCT or Ishihara* or Kojima* or Ohkuma* or Matsubara* or Dvorine* or cvtmet)
TS=(Hardy Rand Rittler*) or TS=(AOHRR or AO H-R-R or Lanthony*) or TS=(panel d 15) or TS=(panel d15) or TS=(d 15 panel) or TS=(d15 panel) or TS=(Farnsworth*)
TS=(color* plate) or TS=(colour* plate) or TS=(Mollon Reffin*) or TS=(Pease Allen*) or TS=(Giles Archer*) or TS=(Adams Desaturated) or TS=(City University) or TS=(CUCVT) or TS=(Velhagen Pflugertrident*) or TS=(contrast SAME sensitivit*)
#1 or #2 or #3 or #4 or #5 or #6
TS=(diabet* or IDDM or NIDDM or T2DM)
#7 and #8
TS=(retinopath*) or TS=(macula* SAME edema*) or TS=(macula* SAME oedema*) or TS=(retina* SAME edema*) or TS=(retina* SAME oedema*) or TS=(optic* SAME edema*) or TS=(ocular* SAME edema*) or TS=(optic* SAME oedema*) or TS=(ocular* SAME oedema*)or TS=(intraocular* SAME edema*) or TS=(intraocular* SAME oedema*) or TS=(maculopath*) or TS=(microaneurysm*) or TS=(micro aneurysm*) or TS=(microaneurism*) or TS=(micro aneurism*) or TS= (retina* SAME hemorrhag*) or TS=(retina* SAME haemorrhage*) or TS=(retina* SAME neovascular*) or TS=(retina* SAME leak*) or TS=(retina* SAME perme*) or TS=(retina* SAME bleed*) or TS= (eye* SAME hemorrhag*) or TS=(eye* SAME haemorrhage*) or TS=(eye* SAME neovascular*) or TS=(eye* SAME leak*) or TS=(eye* SAME perme*) or TS=(eye* SAME bleed*)
TS= (ocular* SAME hemorrhag*) or TS=(ocular* SAME haemorrhage*) or TS=(ocular* SAME neovascular*) or TS=(ocular* SAME leak*) or TS=(ocular* SAME perme*) or TS=(ocular SAME bleed*) or TS= (intraocular* SAME hemorrhag*) or TS=(intraocular* SAME haemorrhage*) or TS=(intraocular* SAME neovascular*) or TS=(intraocular* SAME leak*) or TS=(intraocular* SAME perme*) or TS=(intraocular* SAME bleed*) or TS= (optic* SAME hemorrhag*) or TS=(optic* SAME haemorrhage*) or TS=(optic* SAME neovascular*) or TS=(intraocular* SAME leak*) or TS=(optic* SAME perme*) or TS=(optic* SAME bleed*)
#10 or #11
#9 and #12
TS=(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys)
#13 NOT #14

CDSR and CENTRAL (Cochrane Library) 2007 Issue 3
Searched 4 October 2007.
38 reviews were retrieved in CDSR and 84 records in CENTRAL.

#1 MeSH descriptor Color Vision Defects explode all trees
#2 MeSH descriptor Color Perception explode all trees
#3 MeSH descriptor Color Perception Tests explode all trees
#4 MeSH descriptor Vision Screening explode all trees
#5 MeSH descriptor Vision Tests explode all trees
#6 MeSH descriptor Contrast Sensitivity explode all trees
#7 (color* NEAR/3 test*) or (colour* NEAR/3 test*) or (color* NEAR/3 screen*) or (colour* NEAR/3 screen*) or (vision NEAR/3 test*) or (vision NEAR/3 screen*) or (visual NEAR/3 test*) or (visual NEAR/3 screen*)
#8 (color* NEAR/3 blind*) or (color* NEAR/3 deficien*) or (color* NEAR/3 defect*) or (color* NEAR/3 loss) or (color* NEAR/3

impair*) or (colour* NEAR/3 blind*) or (colour* NEAR/3 deficien*) or (colour* NEAR/3 defect*) or (colour* NEAR/3 loss) or (colour* NEAR/3 impair*)
#9 monochromatopsia or achromatopsia or deutan or protan or anomaloscop* or pseudoisochromatic* or "hue* discrimination*" or lantern* or tritan or TCT
#10 ishihara* or kojima* or ohkuma* or matsubara* or dvorine* or cvtmet or "hardy rand rittler*" or AOHRR or AO H-R-R or lanthony* or "panel d 15" or "panel d15" or "d 15 panel" or "d15 panel" or farnsworth* or "color* plate" or "colour* plate" or "mollon reffin*" or "pease allen*" or "giles archer*" or "adams desaturated" or "City University" or CUCVT or "velhagen pflugertrident*" or (contrast NEAR/3 sensitivit*)
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Diabetes Mellitus explode all trees
#13 (diabet* or IDDM or NIDDM or T2DM)
#14 (#12 OR #13)
#15 (#11 AND #14)
#16 MeSH descriptor Diabetic Retinopathy explode all trees
#17 (retinopath*)
#18 MeSH descriptor Macular Degeneration explode all trees
#19 MeSH descriptor Retinal Hemorrhage explode all trees
#20 MeSH descriptor Retinal Neovascularization explode all trees
#21 (macula* NEAR/3 edema*) or (macula* NEAR/3 oedema*) or (retina* NEAR/3 edema*) or (retina* NEAR/3 oedema*) or (optic* NEAR/3 edema*) or (optic NEAR/3 oedema*) or (ocular* NEAR/3 edema*) or (ocular* NEAR/3 oedema*) or (intraocular* NEAR/3 edema*)
#22 (maculopath* or microaneurysm* or "micro aneurysm*" or microaneurism* or "micro aneurism*" or (retina* NEAR/3 hemorrhag*) or (retina* NEAR/3 haemorrhag*) or (retina* NEAR/3 neovascular*) or (retina* NEAR/3 leak) or (retina* NEAR/3 perme*) or (eye* NEAR/3 hemorrhag*) or (eye* NEAR/3 haemorrhag*) or (eye* NEAR/3 neovascular*) or (eye* NEAR/3 leak) or (eye* NEAR/3 perme*) or (ocular* NEAR/3hemorrhag*) or (ocular* NEAR/3 haemorrhag*) or (ocular* NEAR/3 neovascular*) or (ocular* NEAR/3 leak*) or (ocular* NEAR/3 perme*) or (ocular* NEAR/3 bleed*) or (intraocular* NEAR/3hemorrhag*) or (intraocular* NEAR/3 haemorrhag*) or (intraocular* NEAR/3 neovascular*) or (intraocular* NEAR/3 leak*) or (intraocular* NEAR/3 perme*) or (intraocular* NEAR/3 bleed*)
#23 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 (#15 AND #23)

DARE and HTA (CRD internal databases) 1994 to September 2007

Searched 4 October 2007.
0 records were retrieved in DARE and 1 record was retrieved in HTA.

s (color$or colour$or vision or visual)(w3)(test$or screen$)
s (color$or colour$)(w3)(blind$or deficien$or defect$or loss or impair$or perception)
s monochromatopsia or achromatopsia or deutan or protan or anomaloscop$or pseudoisochromatic$or hue$(w)discrimination$or lantern$or tritan or TCT
s ishihara$or kojima$or ohkuma$or matsubara$or dvorine$or cvtmet or hardy(w)rand(w)rittler$or AOHRR or AO(w)H(w)R(w)R or lanthony$or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or farnsworth$or (color$or colour$)(w)plate or mollon(w)reffin$or pease(w)allen$or giles(w)archer$or adams(w)desaturated or City(w)University or CUCVT or velhagen(w)pflugertrident$or contrast(w3)sensitivit$
s s1 OR s2 OR s3 OR s4
s diabet$or IDDM or NIDDM or T2DM
s s5 and s6
s retinopath$
s (optic$or ocular$or intraocular$or macula$or retina$)(w3)(edema$or oedema$)
s maculopath$or microaneurysm$or micro(w)aneurysm$or microaneurism$or micro(w)aneurism$or (ocular$or intraocular$or optic$or retina$or eye$)(w3)(hemorrhag$or haemorrhag$or neovascular$or leak or perme$or bleed$or neo(w)vascular$)
s s8 OR s9 OR s10
s s7 AND s11

LILACS (Birme Virtual Health Library) 1982 to September 2007

Searched 4 October 2007.
1 record was retrieved.

(color test$) OR (color screen$) OR (colour test$) OR (colour screen$) OR (vision test$) OR

(vision screen$) OR (visual test$) OR (visual screen$) OR (color blind$) OR (colour blind$) OR monochromatopsia OR achromatopsia OR deutan OR protan OR anomaloscop$OR pseudoisochromatic$OR (hue$discrimination$) OR lantern$or tritan OR TCT OR ishihara$OR kojima$OR ohkuma$OR matsubara$OR dvorine$OR cvtmet OR (hardy rand rittler$) OR AOHRR OR lanthony$OR (panel d 15) OR (panel d15) OR (d 15 panel) OR (d15 panel) OR farnsworth$OR (color plate) OR (colour plate) OR (mollon reffin$) OR (pease allen$) OR (giles archer$) OR (adams desaturated) OR (City University) OR CUCVT OR (velhagen pflugertrident$) OR (contrast sensitivit$)[words]
AND
diabet$OR IDDM OR NIDDM OR T2DM[words]
AND
retinopath$OR (macula$edema$) OR (macula$oedema$) OR (retina$edema$) OR (retina$oedema$) OR maculopath$OR microaneurysm$OR (micro aneurysm$) OR microaneurism$OR (micro aneurism$) OR (retina$hemorrag$) OR (retina$haemorrhage$) OR (retina$neovascular$) OR (retina$leak) OR (retina$perme$) OR (eye$hemorrhag$) OR (eye$haemorrhag$) OR (eye$neovascular$) OR (eye$leak) OR (eye$perme$)[words]

BIOSIS (Dialog) 1926 to September Week 5 2007
Searched 5 October 2007.
325 records were retrieved.

s (color? or colour? or vision or visual)(3n)(test or tests or testing or tested or screen or screens or screening or screened)
s (color? or colour?)(3n)(blind or blindness or deficient or deficiency or defect or defects or defection or loss or impair or impaired or impairment or perception)
s monochromatopsia or achromatopsia or deutan or protan
s anomaloscop? or pseudoisochromatic? or hue(w) discrimination? or lantern? or tritan or TCT or Ishihara? or Kojima? or ohkuma? or Matsubara? or Dvorine? or cvtmet or Hardy(w)Rand(w)Rittler? or AOHRR or Lanthony? or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or Farnsworth? or color?(w)plate or colour?(w) plate or Mollon(w)Reffin? or Pease(w)Allen? or Giles(w)Archer? or Adams(w)Desaturated or City(w)University or CUCVT or Velhagen(w) Pflugertrident? or contrast(3n)sensitivit?
s s1:s4
s diabet? or IDDM or NIDDM or T2DM
s retinopath? or macula?(3n)edema? or macula?(3n)oedema? or retina?(3n)edema? or retina?(3n)oedema? or optic?(3n)edema? or optic?(3n)oedema? or ocular?(3n)edema? or ocular?(3n)oedema? or intraocular?(3n)edema? or intraocular?(3n)oedema? or maculopath? or microaneurysm? or micro(w)aneurysm? or microaneurism? or micro(w)aneurism? or retina?(3n)hemorrhag? or retina?(3n) haemorrhage? or retina?(3n)neovascular? or retina?(3n)leak or retina?(3n)perme? or eye?(3n) hemorrhag? or eye?(3n)haemorrhag? or eye?(3n) neovascular? or eye?(3n)leak or eye?(3n)perme? or ocular?(3n)hemorrhag? or ocular?(3n)haemorrhag? or ocular?(3n)neovascular? or ocular?(3n)leak? or ocular?(3n)perme? or ocular?(3n)bleed? or intraocular?(3n)hemorrhag? or intraocular?(3n) haemorrhag? or intraocular?(3n)neovascular? or intraocular?(3n)leak? or intraocular?(3n)perme? or intraocular?(3n)bleed? or optic?(3n)hemorrhag? or optic?(3n)haemorrhag? or optic?(3n)neovascular? or optic?(3n)leak? or optic?(3n)perme? or optic?(3n)bleed?
s s5 and s6 and s7

Pascal (Dialog) 1973 to September Week 4 2007
Searched 5 October 2007.
83 records were retrieved.

s (color? or colour? or vision or visual)(3n)(test or tests or testing or tested or screen or screens or screening or screened)
s (color? or colour?)(3n)(blind or blindness or deficient or deficiency or defect or defects or defection or loss or impair or impaired or impairment or perception)
s monochromatopsia or achromatopsia or deutan or protan
s anomaloscop? or pseudoisochromatic? or hue(w) discrimination? or lantern? or tritan or TCT or Ishihara? or Kojima? or ohkuma? or Matsubara? or Dvorine? or cvtmet or Hardy(w)Rand(w)Rittler? or AOHRR or Lanthony? or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or Farnsworth? or color?(w)plate or colour?(w) plate or Mollon(w)Reffin? or Pease(w)Allen? or Giles(w)Archer? or Adams(w)Desaturated or City(w)University or CUCVT or Velhagen(w) Pflugertrident? or contrast(3n)sensitivit?
s s1:s4
s diabet? or IDDM or NIDDM or T2DM
s retinopath? or macula?(3n)edema? or macula?(3n)oedema? or retina?(3n)edema? or retina?(3n)oedema? or optic?(3n)edema? or optic?(3n)oedema? or ocular?(3n)edema? or

ocular?(3n)oedema? or intraocular?(3n)edema? or intraocular?(3n)oedema? or maculopath? or microaneurysm? or micro(w)aneurysm? or microaneurism? or micro(w)aneurism? or retina?(3n)hemorrhag? or retina?(3n) haemorrhage? or retina?(3n)neovascular? or retina?(3n)leak or retina?(3n)perme? or eye?(3n) hemorrhag? or eye?(3n)haemorrhag? or eye?(3n) neovascular? or eye?(3n)leak or eye?(3n)perme? or ocular?(3n)hemorrhag? or ocular?(3n)haemorrhag? or ocular?(3n)neovascular? or ocular?(3n)leak? or ocular?(3n)perme? or ocular?(3n)bleed? or intraocular?(3n)hemorrhag? or intraocular?(3n) haemorrhag? or intraocular?(3n)neovascular? or intraocular?(3n)leak? or intraocular?(3n)perme? or intraocular?(3n)bleed? or optic?(3n)hemorrhag? or optic?(3n)haemorrhag? or optic?(3n)neovascular? or optic?(3n)leak? or optic?(3n)perme? or optic?(3n)bleed?
s s5 and s6 and s7

Dissertation Abstracts (Dialog)
1861 to July 2007
Searched 5 October 2007.
4 records were retrieved.

s (color? or colour? or vision or visual)(3n)(test or tests or testing or tested or screen or screens or screening or screened)
s (color? or colour?)(3n)(blind or blindness or deficient or deficiency or defect or defects or defection or loss or impair or impaired or impairment or perception)
s monochromatopsia or achromatopsia or deutan or protan
s anomaloscop? or pseudoisochromatic? or hue(w) discrimination? or lantern? or tritan or TCT or Ishihara? or Kojima? or ohkuma? or Matsubara? or Dvorine? or cvtmet or Hardy(w)Rand(w)Rittler? or AOHRR or Lanthony? or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or Farnsworth? or color?(w)plate or colour?(w) plate or Mollon(w)Reffin? or Pease(w)Allen? or Giles(w)Archer? or Adams(w)Desaturated or City(w)University or CUCVT or Velhagen(w) Pflugertrident? or contrast(3n)sensitivit?
s s1:s4
s diabet? or IDDM or NIDDM or T2DM
s retinopath? or macula?(3n)edema? or macula?(3n)oedema? or retina?(3n)edema? or retina?(3n)oedema? or optic?(3n)edema? or optic?(3n)oedema? or ocular?(3n)edema? or ocular?(3n)oedema? or intraocular?(3n)edema? or intraocular?(3n)oedema? or maculopath? or microaneurysm? or micro(w)aneurysm? or microaneurism? or micro(w)aneurism? or retina?(3n)hemorrhag? or retina?(3n) haemorrhage? or retina?(3n)neovascular? or retina?(3n)leak or retina?(3n)perme? or eye?(3n) hemorrhag? or eye?(3n)haemorrhag? or eye?(3n) neovascular? or eye?(3n)leak or eye?(3n)perme? or ocular?(3n)hemorrhag? or ocular?(3n)haemorrhag? or ocular?(3n)neovascular? or ocular?(3n)leak? or ocular?(3n)perme? or ocular?(3n)bleed? or intraocular?(3n)hemorrhag? or intraocular?(3n) haemorrhag? or intraocular?(3n)neovascular? or intraocular?(3n)leak? or intraocular?(3n)perme? or intraocular?(3n)bleed? or optic?(3n)hemorrhag? or optic?(3n)haemorrhag? or optic?(3n)neovascular? or optic?(3n)leak? or optic?(3n)perme? or optic?(3n)bleed?
s s5 and s6 and s7

Inside Conferences (Dialog)
1993 to 3 October 2007
Searched 5 October 2007.
0 records were retrieved.

s (color? or colour? or vision or visual)(3n)(test or tests or testing or tested or screen or screens or screening or screened)
s (color? or colour?)(3n)(blind or blindness or deficient or deficiency or defect or defects or defection or loss or impair or impaired or impairment or perception)
s monochromatopsia or achromatopsia or deutan or protan
s anomaloscop? or pseudoisochromatic? or hue(w) discrimination? or lantern? or tritan or TCT or Ishihara? or Kojima? or ohkuma? or Matsubara? or Dvorine? or cvtmet or Hardy(w)Rand(w)Rittler? or AOHRR or Lanthony? or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or Farnsworth? or color?(w)plate or colour?(w) plate or Mollon(w)Reffin? or Pease(w)Allen? or Giles(w)Archer? or Adams(w)Desaturated or City(w)University or CUCVT or Velhagen(w) Pflugertrident? or contrast(3n)sensitivit?
s s1:s4
s diabet? or IDDM or NIDDM or T2DM
s retinopath? or macula?(3n)edema? or macula?(3n)oedema? or retina?(3n)edema? or retina?(3n)oedema? or optic?(3n)edema? or optic?(3n)oedema? or ocular?(3n)edema? or ocular?(3n)oedema? or intraocular?(3n)edema? or intraocular?(3n)oedema? or maculopath? or microaneurysm? or micro(w)aneurysm? or microaneurism? or micro(w)aneurism? or retina?(3n)hemorrhag? or retina?(3n) haemorrhage? or retina?(3n)neovascular? or retina?(3n)leak or retina?(3n)perme? or eye?(3n) hemorrhag? or eye?(3n)haemorrhag? or eye?(3n)

neovascular? or eye?(3n)leak or eye?(3n)perme? or ocular?(3n)hemorrhag? or ocular?(3n)haemorrhag? or ocular?(3n)neovascular? or ocular?(3n)leak? or ocular?(3n)perme? or ocular?(3n)bleed? or intraocular?(3n)hemorrhag? or intraocular?(3n)haemorrhag? or intraocular?(3n)neovascular? or intraocular?(3n)leak? or intraocular?(3n)perme? or intraocular?(3n)bleed? or optic?(3n)hemorrhag? or optic?(3n)haemorrhag? or optic?(3n)neovascular? or optic?(3n)leak? or optic?(3n)perme? or optic?(3n)bleed?
s s5 and s6 and s7

NTIS (National Technical Information Service) (US Department of Commerce) 1990 to September 2007
Searched 5 October 2007.
0 records were retrieved.

Each line searched separately:

color test diabetic [With all of the words]
color test diabetes [With all of the words]
color testing diabetic [With all of the words]
color testing diabetes [With all of the words]
color screen diabetic [With all of the words]
color screen diabetes [With all of the words]
color screening diabetic [With all of the words]
color screening diabetes [With all of the words]
colour test diabetic [With all of the words]
colour test diabetes [With all of the words]
colour testing diabetic [With all of the words]
colour testing diabetes [With all of the words]
colour screen diabetic [With all of the words]
colour screen diabetes [With all of the words]
colour screening diabetic [With all of the words]
colour screening diabetes [With all of the words]
color retinopathy diabetes [With all of the words]
color retinopathy diabetic [With all of the words]
colour retinopathy diabetes [With all of the words]
colour retinopathy diabetic [With all of the words]

ReFer (Research Findings electronic Register) (ReFer website) September 2007
Searched 5 October 2007.
0 records were retrieved.

Each line searched separately:

color AND diabetic AND retinopathy
color AND diabetes AND retinopathy
colour AND diabetic AND retinopathy
colour AND diabetes AND retinopathy

ClinicalTrials.gov (US National Library of Medicine) September 2007
Searched 5 October 2007.
0 records were retrieved.

Each line searched separately:

color, diabetic, retinopathy
color, diabetes, retinopathy
colour, diabetic, retinopathy
colour, diabetes, retinopathy

Current Controlled Trials (MetaRegister of Current Controlled Trials – mRCT) September 2007
Searched 5 October 2007.
0 records were retrieved.

Each line searched separately:

retinopathy AND colour
retinopathies AND colour
retinopathy AND color
retinopathies AND color
screening AND color
screen AND color
screening AND colour
screen AND colour

ClinicalStudyResults.org (ClinicalStudyResults website) September 2007
5 October 2007.
0 records were retrieved.

Each line searched separately:

color, diabetes, retinopathy
retinopathy
retinopathies

ClinicalTrialResults.org (Clinical Trial Results website) September 2007
5 October 2007.
0 records were retrieved.

Each line searched separately:

retinopathy
retinopathies

NHS EED (CRD internal databases) 1994 to September 2007
5 October 2007.
0 records were retrieved.

s (color$or colour$or vision or visual)(w3)(test$or screen$)
s (color$or colour$)(w3)(blind$or deficien$or defect$or loss or impair$)
s monochromatopsia or achromatopsia or deutan or protan or anomaloscop$or pseudoisochromatic$or hue$(w)discrimination$or lantern$or tritan or TCT
s ishihara$or kojima$or ohkuma$or matsubara$or dvorine$or cvtmet or hardy(w)rand(w)rittler$or AOHRR or AO(w)H(w)R(w)R or lanthony$or panel(w)d(w)15 or panel(w)d15 or d(w)15(w)panel or d15(w)panel or farnsworth$or (color$or colour$)(w)plate or mollon(w)reffin$or pease(w)allen$or giles(w)archer$or adams(w)desaturated or City(w)University or CUCVT or velhagen(w)pflugertrident$or contrast(w3)sensitivit$
s s1 OR s2 OR s3 OR s4
s diabet$or IDDM or NIDDM or T2DM
s s5 and s6
s retinopath$
s (optic$or ocular$or intraocular$or macula$or retina$)(w3)(edema$or oedema$)
s maculopath$or microaneurysm$or micro(w)aneurysm$or microaneurism$or micro(w)aneurism$or (ocular$or intraocular$or optic$or retina$or eye$)(w3)(hemorrhag$or haemorrhag$or neovascular$or leak or perme$or bleed$or neo(w)vascular$)
s s8 OR s9 OR s10
s s7 AND s11

HEED (Wiley online) September 2007

5 October 2007.
2 records were retrieved.

AX='color test' within 3 OR 'color testing' within 3 OR 'color tests' within 3 OR 'color screen' within 3 OR 'color screening' within 3 OR 'color screened' within 3 OR 'colour test' within 3 OR 'colour testing' within 3 OR 'colour tests' within 3 OR 'colour screen' within 3 OR 'colour screening' within 3 OR 'colour screened' within 3
AX='vision test' within 3 OR 'vision testing' within 3 OR 'vision tests' within 3 OR 'vision screen' within 3 OR 'vision screening' within 3 OR 'vision screened' within 3 OR 'visual test' within 3 OR 'visual testing' within 3 OR 'visual tests' within 3 OR 'visual screen' within 3 OR 'visual screening' within 3 OR 'visual screened' within 3
CS=1 or 2
AX=diabetes or diabetic or IDDM or NIDDM or T2DM
AX=retinopathy or retinopathies or (macular edema) or (macular oedema) or (retina edema) or (retina oedema) or (macular edemas) or (macular oedemas) or (retina edemas) or (retina oedemas) or maculopathy or microaneurysm or (micro aneurysm) or microaneurism or (micro aneurism) or (retina hemorrhage) or (retina haemorrhage) or (eye hemorrhage) or (eye haemorrhage)
CS=3 and 4 and 5

Internet sites searched

Websites were browsed (publications and research) and searched using a variety of combinations of the following terms: 'colour vision screening', 'color vision screening', 'colour vision', 'color vision', 'colour screening', 'color screening', 'retinopathy', 'diabetes', 'diabetic'.

MedlinePlus: www.nlm.nih.gov/medlineplus/medlineplus.html
intute: www.intute.ac.uk/
National Library for Health (NLH) Diabetes Specialist Library: www.library.nhs.uk/diabetes/
National Library for Health (NLH) Screening Specialist Library: www.library.nhs.uk/screening/
National Screening Programme for Sight-threatening Diabetic Retinopathy: www.nscretinopathy.org.uk/
British Association for Retinal Screeners: www.eyescreening.org.uk/
Diabetes UK: www.diabetes.org.uk/
American Diabetic Association (US): www.diabetes.org/home.jsp
Royal College of Ophthalmologists: www.rcophth.ac.uk/
American Academy of Ophthalmology (US): www.aao.org/
College of Optometrists: www.college-optometrists.org/
Association of Optometrists: www.assoc-optometrists.org/
National Eye Institute (US): www.nei.nih.gov/

Conference proceedings

American Academy of Ophthalmology annual meeting (1999–2006) (www.aao.org/meetings/annual_meeting/) – Searchable archive available: posters 1999–2006; programs 2001–6. Searched using various combinations of the following terms: 'color', 'colour', 'color vision', 'colour vision' and 'retinopathy'.

American Diabetic Association Annual Scientific Sessions (2003–7) (www.diabetes.org/for-health-professionals-and-scientists/profed.jsp) – Searchable archive available: 2003–7. Searched using various combinations of the following terms: 'color vision', 'colour vision', 'retinopathy screening' and

'retinopathy testing'. Browsed results for potentially relevant abstracts.

European Association for the Study of Diabetes annual meeting (2001–7) (www.easd.org/) – Abstracts available in a variety of PDF, web page and searchable formats: 2001–7. Browsed/searched: 'color', 'colour', 'retinopathy'.

Royal College of Ophthalmologists Annual Congress (2004–7) (www.rcophth.ac.uk/scientific/) – Abstracts available in PDF format: 2004–7. Browsed PDFs using search facility: 'color', 'colour', 'retinopathy'.

Search alerts

Search alerts were set up in MEDLINE and EMBASE to run every time the databases were updated (usually weekly). The following strategy was used:

(colo?r vision and retinopathy).ti,ab.

Search alerts were also created in the following journals:

American Journal of Ophthalmology (http://archopht.ama-assn.org/) – Alert criteria: Title or Abstract: (color or colour) and vision and retinopathy.
British Journal of Ophthalmology (http://bjo.bmj.com/) – Alert criteria: Title or Abstract: (color or colour) and vision and retinopathy.
Clinical and Experimental Ophthalmology (www.blackwell-synergy.com/loi/ceo) – Alert criteria: Full text: (color or colour) and vision and retinopathy.
Diabetes (http://diabetes.diabetesjournals.org/) – Alert criteria: Anywhere: (color or colour) and vision and retinopathy.
Diabetes Care (http://care.diabetesjournals.org/) – Alert criteria: Anywhere: (color or colour) and vision and retinopathy
Diabetic Medicine (www.blackwell-synergy.com/toc/dme/0/0) – Alert criteria: Full text: (color or colour) and vision and retinopathy
Investigative Ophthalmology and Visual Science (www.iovs.org/) – Alert criteria: Title or Abstract: (color or colour) and vision and retinopathy.
Ophthalmology (www.sciencedirect.com/science/journal/01616420) – Alert criteria: Title-Abstr-Key: ((color or colour) and vision and retinopathy)

Economics search strategies

Diabetic retinopathy screening (economic/cost) search strategies

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID gateway) 1950 to November Week 1 2007

15 November 2007.
209 records were retrieved in MEDLINE and 5 in MEDLINE In-Process & Other Non-Indexed Citations.

1. economics/
2. exp "costs and cost analysis"/
3. economics, dental/
4. exp "economics, hospital"/
5. economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. (economic$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
9. (expenditure$not energy).tw.
10. (value adj1 money).tw.
11. budget$.tw.
12. or/1–11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13–15
17. 12 not 16
18. Vision Screening/
19. Vision Tests/
20. exp Mass Screening/
21. screen$.ti,ab.
22. ((optic$or ocular$or intraocular$or eye$or retina$or vision$or visual$) adj2 (test$or exam$)).ti,ab.
23. Fluorescein Angiography/
24. Ophthalmoscopy/
25. Fluorophotometry/
26. Electroretinography/
27. Retinoscopy/
28. (fluoresence or fluorescein).ti,ab.
29. (fundoscop$or electroretin$or electro retin$or fluorophotometr$or retinoscop$or biomicroscop$or ophthalmoscop$).ti,ab.
30. Photography/
31. Image Processing, Computer-Assisted/
32. Angiography/
33. (digital$or imag$or camer$or photograph$or polaroid$or angiograph$).ti,ab.
34. Ophthalmology/
35. Optometry/
36. (optomet$or optician$or ophthalm$).ti,ab.
37. or/18–36

38. exp Diabetes Mellitus/
39. diabet$.ti,ab.
40. (IDDM or NIDDM or T2DM).ti,ab.
41. or/38–40
42. exp Diabetic Retinopathy/
43. retinopath$.ti,ab.
44. exp Macular Degeneration/
45. Retinal Hemorrhage/
46. Retinal Neovascularization/
47. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
48. maculopath$.ti,ab.
49. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.
50. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
51. or/42–50
52. 17 and 37 and 41 and 51
53. Animals/
54. Humans/
55. 53 not (53 and 54)
56. 52 not 55

EMBASE (OVID gateway)
1980 to 2007 Week 45
Searched 15 November 2007.
240 records were retrieved.

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. exp PHARMACOECONOMICS/
5. or/1–4
6. (econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6–9
11. 5 or 10
12. (metabolic adj cost).ti,ab.
13. ((energy or oxygen) adj cost).ti,ab.
14. ((energy or oxygen) adj expenditure).ti,ab.
15. or/12–14
16. 11 not 15
17. editorial.pt.
18. note.pt.
19. letter.pt.
20. or/17–19
21. 16 not 20
22. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
23. exp animal/
24. Nonhuman/
25. or/22–24
26. exp human/
27. exp human experiment/
28. 26 or 27
29. 25 not (25 and 28)
30. 21 not 29
31. exp vision test/
32. exp SCREENING/
33. screen$.ti,ab.
34. ((eye$or retina$or vision$or visual$) adj2 (test$or exam$)).ti,ab.
35. Fluorescence Angiography/
36. OPHTHALMOSCOPY/
37. FLUOROPHOTOMETRY/
38. ELECTRORETINOGRAPHY/
39. RETINOSCOPY/
40. (fluoresence or fluorescein).ti,ab.
41. (fundoscop$or electroretin$or fluorophotometr$or retinoscop$or biomicroscop$or ophthalmoscop$).ti,ab.
42. PHOTOGRAPHY/
43. digital imaging/or image processing/
44. Retina Angiography/
45. (digital$or imag$or camer$or photograph$or polaroid$or angiograph$).ti,ab.
46. OPHTHALMOLOGY/
47. OPTOMETRY/
48. (optomet$or optician$or ophthalm$).ti,ab.
49. or/31–48
50. exp Diabetes Mellitus/
51. diabet$.ti,ab.
52. (IDDM or NIDDM or T2DM).ti,ab.
53. or/50–52
54. exp Retinopathy/
55. retinopath$.ti,ab.
56. Retina Maculopathy/
57. Retina Edema/
58. Retina Hemorrhage/
59. Retina Neovascularization/
60. Retina Macula Degeneration/
61. Microaneurysm/
62. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
63. maculopath$.ti,ab.
64. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.
65. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
66. or/54–65
67. 30 and 49 and 53 and 66

CINAHL (OVID gateway) 1982 to November Week 2 2007

Searched 15 November 2007.
24 records were retrieved.

1. exp "costs and cost analysis"/or "economic aspects of illness"/or "economic value of life"/or economics, pharmaceutical/
2. ((cost or costs or costed or costly or costing) adj (utilit$or benefit$or effective$or stud$or minimi$or analys$)).ti,ab.
3. (economic$or pharmacoeconomic$or price$or pricing).ti,ab.
4. (expenditure$not energy).ti,ab.
5. (value adj1 money).ti,ab.
6. budget$.ti,ab.
7. or/1–6
8. exp Vision Tests/
9. exp Health Screening/
10. screen$.ti,ab.
11. ((eye$or retina$or vision$or visual$) adj2 (test$or exam$)).ti,ab.
12. OPHTHALMOSCOPY/
13. (fluoresence or fluorescein).ti,ab.
14. (fundoscop$or electroretin$or fluorophotometr$or retinoscop$or biomicroscop$or ophthalmoscop$).ti,ab.
15. PHOTOGRAPHY/
16. Digital Imaging/
17. Image Processing, Computer Assisted/
18. Angiography/
19. (digital$or imag$or camer$or photograph$or polaroid$or angiograph$).ti,ab.
20. OPHTHALMOLOGY/
21. OPTOMETRY/
22. (optomet$or optician$or ophthalm$).ti,ab.
23. or/8–22
24. exp Diabetes Mellitus/
25. diabet$.ti,ab.
26. (IDDM or NIDDM or T2DM).ti,ab.
27. or/24–26
28. Diabetic Retinopathy/
29. Macular Degeneration/
30. Eye Hemorrhage/
31. ((optic$or ocular$or intraocular$or macula$or retina$) adj3 (edema$or oedema$)).ti,ab.
32. maculopath$.ti,ab.
33. (microaneurism$or micro aneurism$or microaneurysm$or micro aneurysm$).ti,ab.
34. ((ocular$or intraocular$or optic$or retina$or eye$) adj3 (hemorrhag$or haemorrhag$or neovascular$or leak$or perme$or bleed$or neo vascular$)).ti,ab.
35. or/28–34
36. 7 and 23 and 27 and 35

NHS EED (CRD internal databases) 1994 to October 2007

Searched 15 November 2007.
41 records were retrieved.

s screen$
s screening/xti
s (eye$or retina$or vision$or visual$)(w2)(test$or exam$)
s fluoresence or fluorescein
s fundoscop$or electroretin$or fluorophotometr$or retinoscop$or biomicroscop$or ophthalmoscop$
s digital$or imag$or camer$or photograph$or polaroid$or angiograph$
s optomet$or optician$or ophthalm$
s s1 or s2 or s3 or s4 or s5 or s6 or s7
s diabet$or IDDM or NIDDM or T2DM
s retinopath$
s (optic$or ocular$or intraocular$or macula$or retina$)(w3)(edema$or oedema$)
s maculopath$or microaneurysm$or micro(w) aneurysm$or microaneurism$or micro(w) aneurism$or (ocular$or intraocular$or optic$or retina$or eye$)(w3)(hemorrhag$or haemorrhag$or neovascular$or leak or perme$or bleed$or neo(w) vascular$)
s s10 OR s11 OR s12
s s8 AND s9 AND s13
HEED (Wiley online). 2007/Nov. 15th November 2007.
64 records were retrieved.
AX=screen or screened or screening
AX='eye test' within 2 or 'eye exam' within 2 or 'eye examination' within 2
AX='retina test' within 2 or 'retinal test' within 2 or 'retina exam' within 2 or 'retinal exam' within 2 or 'retina examination' within 2 or 'retinal examination' within 2
AX='vision test' within 2 or 'visual test' within 2 or 'vision exam' within 2 or 'visual exam' within 2 or 'vision examination' within 2 or 'visual examination' within 2
AX=fluoresence or fluorescein or s fundoscopy or electroretinography or fluorophotometry or retinoscopy or biomicroscopy or ophthalmoscopy or ophthalmoscope
AX=digital or image or imaging or camera or photograph or polaroid or angiography
AX=optometrist or optician or ophthalmologist
CS=1 or 2 or 3 or 4 or 5 or 6 or 7
AX=diabetes or diabetic or IDDM or NIDDM or T2DM
AX=retinopathy

AX=(macular edema) or (macular oedema) or (retinal edema) or (retinal oedema) or (macular edemas) or (macular oedemas) or (retinal edemas) or (retinal oedemas)	AX=maculopathy or microaneurysm or (micro aneurysm) or microaneurism or (micro aneurism) CS=10 or 11 or 12 CS=8 and 9 and 13

Appendix 2

The QUADAS tool for methodological assessment of diagnostic studies

	QUADAS criterion	Criterion met?
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes/no/unclear
2.	Were selection criteria clearly described?	Yes/no/unclear
3.	Is the reference standard likely to correctly classify the target condition?	Yes/no/unclear
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests (i.e. under 1 month)?	Yes/no/unclear
5.	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes/no/unclear
6.	Did patients receive the same reference standard regardless of the index test result?	Yes/no/unclear
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes/no/unclear
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes/no/unclear
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes/no/unclear
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/no/unclear
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/no/unclear
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice (i.e. duration of diabetes, hypertension, renal disease, HbA1c, smoking, visual acuity)?	Yes/no/unclear
13.	Were uninterpretable/intermediate test results reported?	Yes/no/unclear
14.	Were withdrawals from the study explained?	Yes/no/unclear

Appendix 3

Data extraction tables

Bibliographic details	
Author	Aspinall[36]
Year	1983
Study characteristics	
Study design	Longitudinal Over 7 years follow-up; recruitment 1963–5, follow-up to 1972
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: diabetics < 70 years with normal fundi Exclusion criteria: congenital colour vision defects; cataracts
Does the study include a control group of non-diabetics?	No
Reference standard	Ophthalmoscopy
Retinopathy grading (reference standard)	Dichotomous N: normal fundus, fundi still showing no signs of retinopathy in either eye R: retinopathy, fundi showing signs, however slight, in one or both eyes
For which eye was retinopathy assessed?	Random/quasi-randomly selected Patients' preferred eye
Colour vision test(s)	FM-100 Anomaloscope
Colour vision grading	Dichotomous
Participant characteristics	
Number of participants	Number of participants included in study: N: $n = 209$; R: $n = 86$ Number of participants included in analysis: N: $n = 209$; R: $n = 86$
Age	
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Association between clinical characteristics and outcomes (multivariate regression): Yellow–blue colour discrimination (anomaloscope units JND) coefficient = 5.113×10^{-2}, standard error = 1.39×10^{-2}, t = 3.67 The single variable with the greatest discriminating power between the two groups was colour discrimination along the yellow–blue axis Following division of the population into two groups at 40 years, duration was found to be the best single predictive parameter for the under 40s and yellow–blue colour discrimination was the best single predictive parameter for the over 40s (see *Figures 1* and *2*) The model, which also includes blood glucose control, duration of diabetes, proteinuria and colour discrimination, has a negative predictive value of 0.82 and a positive predictive value of 0.54

Bibliographic details	
Author	Ayed[37]
Year	1990
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: visual acuity ≥ 5/10
Does the study include a control group of non-diabetics?	No
Reference standard	Fluorescein angiography
Retinopathy grading (reference standard)	Graded 1. Retinopathy absent 2. Beginnings of retinopathy 3. Oedemic 4. Ischaemic with or without new vessels
For which eye was retinopathy assessed?	Both
Colour vision test(s)	FM-100; presented under luminance of 600 lux
Colour vision grading	Continuous/average Total error score (TES) Dichotomous 'Abnormal' if TES is greater than the 95th percentile for participants age, according to Verriest curves Categorical 1. 'Normal' if TES is ≤ participant's age in years plus 30 2. 'Weak discrimination' if TES is ≤ participant's age in years multiplied by two, plus 30 (axis not well defined) 3. 'Dyschromatopsia' if TES is ≥ participant's age in years multiplied by two, plus 30 (with blue-yellow or red–green axis)
Participant characteristics	
Number of participants	Number of participants included in study: 100 (200 eyes) Number of participants included in analysis: 100 (200 eyes)
Age	Mean: 44 years (range 14–70 years)
Sex	37% male
Clinical characteristics	39% insulin-dependent DM Mean diabetes duration: 9 years (range 3–22 years) Other relevant clinical measures: tested urinary and blood glucose; data not reported

continued

Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) 1. Retinopathy absent (105 eyes) – abnormal CV in 55% of cases (40% with dyschromatopsia, 15% with 'weak discrimination'); 29% also have red–green deficits 2. Beginnings of retinopathy (53 eyes) – abnormal CV in 63% of cases (30% with dyschromatopsia, 33% with 'weak discrimination'); 22% also have red–green deficits 3. Oedemic (20 eyes) – abnormal CV in 85% of cases (70% with dyschromatopsia, 15% with 'weak discrimination'); 52% also have red–green deficits 4. Ischaemic with or without new vessels (22 eyes) – abnormal CV in 91% of cases (73% with dyschromatopsia, 18% with 'weak discrimination'); 30% also have red–green deficits Association between clinical characteristics and outcomes (multivariate regression): 80% of participants aged 30+ years and 52.5% of participants aged < 30 years had colour vision impairment 63% of patients with 10 years' duration of DM, 69% of patients with 10–20 years' duration, and 75% of patients with 20+ years' duration had CV impairment 61% CV impairment in well-controlled diabetes and 69% in poorly controlled diabetes
Notes	36% of patients made errors on reading urinary glucose dipsticks, and 31% made errors on blood glucose dipsticks. All of these patients were found to have dyschromatopsia on the FM-100 30% of patients had different CV results for each eye The authors concluded that colour vision impairment is frequent in DM and can occur in the absence of retinopathy

Bibliographic details	
Author	Barton[38]
Year	1987
Related papers	Fong 1999[39]
Study characteristics	
Study design	Cross-sectional
Does the study include a control group of non-diabetics?	No
Reference standard	Method not stated/final diagnosis
Retinopathy grading (reference standard)	Graded No macular oedema; not clinically significant macular oedema; clinically significant macular oedema
For which eye was retinopathy assessed?	Unclear
Colour vision test(s)	FM-100
Colour vision grading	Continuous/average Square root of total error score (SQRT TES) for deferred eyes is presented for each grade of macular oedema
Participant characteristics	
Number of participants	Number of participants included in study: no macular oedema: *n* = 1000; not clinically significant macular oedema: *n* = 609; clinically significant macular oedema: *n* = 1248 Number of participants included in analysis: no macular oedema: *n* = 1000; not clinically significant macular oedema: *n* = 609; clinically significant macular oedema: *n* = 1248
Results	
What data/analysis is presented in the study?	Comparison of scores in two groups (*t*-test; Mann–Whitney): No macular oedema (*n* = 1000), SQRT TES = 12 (SD ±4) Not clinically significant macular oedema (*n* = 609), SQRT TES = 13(SD ±4) Clinically significant macular oedema (*n* = 1248), SQRT TES = 17(SD ±5) Association between clinical characteristics and outcomes (multivariate regression): No difference in mean SQRT TES by level of retinopathy or sex

Bibliographic details	
Author	Bernardczyk-Meller[47]
Year	2001
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	No
Patient selection criteria	Inclusion criteria: patients for whom long-term follow-up data were available Exclusion criteria: congenital colour vision deficiencies
Does the study include a control group of non-diabetics?	No
Reference standard	Ophthalmoscopy
Retinopathy grading (reference standard)	Dichotomous Pathological changes (non-proliferative DR, preproliferative DR, cataract) vs no pathological changes
For which eye was retinopathy assessed?	Both
Colour vision test(s)	D-15, saturated and desaturated Ishihara plates
Colour vision grading	Dichotomous Normal vs 'pathological' CV test scores
Participant characteristics	
Number of participants	Number of participants included in study: 38 Number of participants included in analysis: 38
Age	17 years (range 7–27 years)
Clinical characteristics	100% insulin-dependent DM Mean diabetes duration: 7.8 years (range 3–18 years)
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) D-15 desaturated (threshold: 'pathological results'): TP = unclear; FP = 9; FN = unclear; TN = 21

Bibliographic details	
Author	De Alwis[52]
Year	1993
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: proven diagnosis of DM; visual acuity 6/12 or better Exclusion criteria: any other eye disease including glaucoma; visual acuity 6/18 or worse; previous laser treatment for retinopathy; elevated intraocular pressure in the absence of frank glaucoma
Does the study include a control group of non-diabetics?	Yes ($n = 69$)
Reference standard	Slit-lamp biomicroscopy Dilation of pupil; 90-dioptre fundus examination lens; 5 of 7 fields examined
Retinopathy grading (reference standard)	Dichotomous Severe retinopathy (maculopathy grade 4 and/or ischaemic grade 4) vs non-severe retinopathy (anything below maculopathy grade 4 and/or ischaemic grade 4)
For which eye was retinopathy assessed?	Both
Colour vision test(s)	Computerised/automated method Chromatic contrast sensitivity test (Sussex Grating Machine); computer-automated, television-based machine; red–green and tritan axes tested; performed at a distance of 2 m at an angle of 5 degrees to retina
Colour vision grading	Dichotomous *z*-score thresholds based on standard deviations from –3.0 to 0
Participant characteristics	
Number of participants	Number of participants included in study: non-severe retinopathy: $n = 107$; severe retinopathy: $n = 30$ Number of participants included in analysis: non-severe retinopathy: $n = 107$; severe retinopathy: $n = 30$
Age	Mean overall: 53.9 years (range 18–84 years)
Results	
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) –3.0 SD: TP $n = 11$, FP $n = 2$, TN $n = 105$, FN $n = 19$, sens.= 37%, spec.= 98% –2.5 SD: TP $n = 17$, FP $n = 5$, TN $n = 102$, FN $n = 13$, sens.= 57%, spec.= 95% –2.0 SD: TP $n = 22$, FP $n = 11$, TN $n = 96$, FN $n = 8$, sens.= 73%, spec.= 90% –1.5 SD: TP $n = 23$, FP $n = 21$, TN $n = 86$, FN $n = 7$, sens.= 77%, spec.= 80% –1.0 SD: TP $n = 24$, FP $n = 27$, TN $n = 80$, FN $n = 6$, sens.= 80%, spec.= 75% –0.5 SD: TP $n = 25$, FP $n = 40$, TN $n = 67$, FN $n = 5$, sens.= 83%, spec.= 63% 0 SD: TP $n = 29$, FP $n = 64$, TN $n = 43$, FN $n = 1$, sens.= 97%, spec.= 40%

continued

	Association between clinical characteristics and outcomes (multivariate regression): Right eye tritan: duration $p < 0.001$, age at onset $p < 0.001$, maculopathy grade $p < 0.001$, ischaemic grade $p < 0.005$ Left eye tritan: duration $p < 0.001$, age at onset $p < 0.001$, maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$ Right eye red–green: duration $p < 0.001$, age at onset $p < 0.185$, maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$ Left eye red–green: duration $p < 0.002$, age at onset $p < 0.002$, maculopathy grade $p < 0.001$, ischaemic grade $p < 0.002$
Notes	Grading system used: 1 = no retinopathy: no lesions seen on fundoscopy; 2 = background retinopathy: maculopathy 1 and ischaemia 1; 3 = maculopathy: ischaemia 1 and maculopathy 2–4; 4 = ischaemia: maculopathy 1 and ischaemia 2–4; 5 = mixed disease: maculopathy 2–4 and ischaemia 2–4 Each eye was assigned a diagnostic code consisting of two digits, the first corresponding to the maculopathy grade and the second to the ischaemia grade. No retinopathy and background retinopathy were combined into one group

Bibliographic details	
Author	Doucet[48]
Year	1991
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Exclusion criteria: people aged over 65 years; visual acuity < 4/10; cataract or glaucoma; known congenital dyschromatopsia; deterioration in mental functioning; using medicines that could alter colour vision
Does the study include a control group of non-diabetics?	No
Reference standard	Other: fundoscopy
Retinopathy grading (reference standard)	Graded ETDRS grading: 0: no retinopathy or one or two microaneurysms; 1: background retinopathy; 2: preproliferative retinopathy; 3: proliferative retinopathy
Colour vision test(s)	D-15; presented under luminance of 500 lux
Colour vision grading	Categorical Score of 0–2 given for each eye: 0 = dyschromatopsia with one or several axes; 1 = dyschromatopsia without an axis; 2 = normal (three simple inversions at any age, or four inversions/diametrical inversions over age 45 years, or minimum of five inversions or two diametrical inversions over age 60 years)
Participant characteristics	
Number of participants	Number of participants included in study: 100
	Number of participants included in analysis: 100
Age	43.36 (14.4) years (range 16–65 years)
Sex	62% male
Clinical characteristics	88% insulin-dependent DM
	Mean (SD) diabetes duration: 133.74 (105.76) months (range 1 month to 39 years)
	Mean (SD) HbA1c levels: 11.38% (3.41%) (range 5.4–28.8%) 12 patients had a normal result (57.5%)
	Other relevant clinical measures: tested creatinine clearance, nocturnal microalbuminuria and peripheral neuropathy

continued

Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) ETDRS grading: 0: no retinopathy or one or two microaneurysms: $n = 70$ 1: background retinopathy: $n = 14$ 2: preproliferative retinopathy: $n = 3$ 3: proliferative retinopathy: $n = 13$ 26/30 with DR had dyschromatopsia on D-15; 47/70 without DR had dyschromatopsia on D-15 ($p < 0.01$) Association between clinical characteristics and outcomes (multivariate regression): Numbers were small but authors noted a relationship between severity of retinopathy and FM-100 score 29/73 with dyschromatopsia on D-15 also have peripheral neuropathy; 8/27 without dyschromatopsia on D-15 have peripheral neuropathy ($p < 0.01$) Electrophysiology scores were significantly lower in the dyschromatopsia group (76.78, SD 38.35) than in the non-dyschromatopsia group (115.68, SD 35.85) ($p < 0.001$) Within non-DR patients, no significant difference in peripheral neuropathy between those with and those without dyschromatopsia Within DR patients, significant difference in peripheral neuropathy between those with (17/26) and those without (1/4)dyschromatopsia; however, the mean electrophysiological score was not significantly different Overall, patients with dyschromatopsia were significantly older ($p < 0.05$), with more alcohol problems ($p < 0.05$), more peripheral neuropathy ($p < 0.05$), more microalbuminuria ($p < 0.01$) and more hypertension ($p < 0.001$)

Bibliographic details	
Author	Findl[53]
Year	2000
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Retrospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: insulin dependent type I diabetics; age < 32 years; diabetes duration between 12 and 17 years
	Exclusion criteria: excluded patients with systemic hypertension or any sign of non-diabetes-induced vascular complications; excluded patients if any ocular disease except DR was evident at prestudy ophthalmic examination
Does the study include a control group of non-diabetics?	Yes; 25 age-matched healthy control subjects: 17 males; mean age 23.8 years
Reference standard	Slit-lamp biomicroscopy
	Conventional retinal photography: colour fundus photography of seven fields
	Combined methods: fundoscopy, biomicroscopy and retinal photography
Retinopathy grading (reference standard)	Graded Modified Airlie House classification
For which eye was retinopathy assessed?	Left
Colour vision test(s)	Computerised/automated method
	Colour contrast sensitivity along tritan axis investigated using a computer graphics device and a colour monitor system; the threshold chrominance of a coloured optotype without changes in luminance compared with the surrounding is determined
Colour vision grading	Continuous/average
	The threshold chrominance of a coloured optotype without changes in luminance compared with the surrounding expressed as a percentage
Participant characteristics	
Number of participants	Number of participants included in study: overall: $n = 59$; level 1: $n = 20$; level 2: $n = 27$; level 3: $n = 12$
	Number of participants included in analysis: overall: $n = 59$; level 1: $n = 20$; level 2: $n = 27$; level 3: $n = 12$
Age	Mean (SD): overall 23.1 (4.3) years; level 1: 22.9 (4.2) years; level 2: 23.7 (4.5) years; level 3: 22.1 (4.0) years
Sex	66% male
Clinical characteristics	Overall 100% insulin dependent
	Diabetes duration: overall range 12–17 years
	Mean (SD) LogMAR or Snellen visual acuity
	Snellen best-corrected visual acuity: level 1: 20/20 in all; level 2: 20/20 in all; level 3: 20/20 in 7, 20/25 in 5
	Mean (SD) fasting blood glucose: level 1: 121.3 (57.9) mg/100 ml; level 2: 164.3 (67) mg/100 ml; level 3: 194.8 (84.4) mg/100 ml

continued

	Mean (SD) HbA1c levels: level 1: 7.7% (1.1%); level 2: 8.5% (1.0%); level 3: 10.7% (1.5%)
	Other relevant clinical measures:
	Systolic blood pressure: level 1: 127.9 (7.1) mmHg; level 2: 121.1 (10.5) mmHg; level 3: 124.8 (8.0) mmHg
	Diastolic blood pressure: level 1: 66.3 (12.1) mmHg; level 2: 60.6 (10.1) mmHg; level 3: 60.0 (7.3) mmHg
	Pulse rate: level 1: 72.4 (11.4) bpm; level 2: 73.4 (11.2) bpm; level 3: 74.3 (10.5) bpm
Results	
Were groups comparable in terms of demographic and clinical characteristics?	No; plasma glucose levels ($p = 0.012$) and HbA1c values ($p < 0.001$) were higher in the more advanced stages of DR
What data/analysis is presented in the study?	Comparison of multiple groups (analysis of variance):
	Level 1: 7.1% (1.7), $n = 20$; level 2: 7.3% (1.9), $n = 27$; level 3: 10.1% (3.0), $n = 12$ ($p = 0.02$)

Bibliographic details	
Author	Fong[39]
Year	1999
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: no attempt was made to eliminate cases of congenital red–green colour deficiency or other known colour vision defects
Does the study include a control group of non-diabetics?	No
Reference standard	Conventional retinal photography Stereoscopic fundus photographs of the seven standard fields taken with a 30-degree fundus camera
Retinopathy grading (reference standard)	Graded ETDRS extension of the modified Airlie House classification: group A: eyes without macular oedema; group B: macular oedema not clinically significant; group C: eyes with clinically significant macular oedema with centre of macular not involved; group D: clinically significant macular oedema with centre of the macula involved
For which eye was retinopathy assessed?	Random/quasi-randomly selected One eye was selected but no details on which eye or how it was selected
Colour vision test(s)	FM-100 Conducted under the illumination of a Macbeth Easel lamp at a distance of 30 cm with the subjective near refraction placed in a trial frame
Colour vision grading	Continuous/average Square root of total error score (SQRT TES)
Participant characteristics	
Number of participants	Number of participants included in study: group A: $n = 825$; group B: $n = 557$; group C: $n = 469$; group D: $n = 850$ Number of participants included in analysis: group A: $n = 825$; group B: $n = 557$; group C: $n = 469$; group D: $n = 850$
Sex	Overall 55% male
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Association between clinical characteristics and outcomes (multivariate regression) Multiple linear regression for SQRT 100 hue scores: Age: beta = 0.11, p-value = 0.0001; type 2 diabetes: beta = 0.45, p-value = 0.0001; presence of CSMO involving the centre of the macula: beta = 1.36, p-value = 0.0001; presence of new vessels: beta = 1.26, p-value = 0.0001; presence of fluorescein leakage in centre of the macula: beta = 0.48, p-value = 0.0001; presence of cystoid changes in the centre of the macula: beta = 0.87, p-value = 0.003; presence of focal leakage: beta = –0.54, p-value = 0.002 Non-significant factors: gender, body mass index, duration of diabetes, urine glucose, urine protein, serum creatinine, HbA1c, cholesterol, haematocrit, haemoglobin, diastolic blood pressure, effort at diabetic control, years of cigarette smoking

continued

Bibliographic details	
Author	Green[40]
Year	1985
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: diabetics attending for routine ocular screening Exclusion criteria: patients with soft exudates
Does the study include a control group of non-diabetics?	Yes ($n = 16$)
Reference standard	Ophthalmoscopy
Retinopathy grading (reference standard)	Dichotomous Serious (proliferative and exudative maculopathy) vs non-serious (no DR and background retinopathy) Graded Group NR: no retinopathy; group B: background retinopathy; group P: proliferative retinopathy; group E: exudative maculopathy
For which eye was retinopathy assessed?	Both, monocularly performed on both eyes
Colour vision test(s)	FM-100 Test performed under illuminant C lighting conditions at an illumination level of approx. 200 lux in a VeriVide light cabinet and with no time limit
Colour vision grading	Dichotomous Abnormal total error score (TES) vs normal score. Abnormal defined as outside the 95th percentile as defined by Verriest *et al.*[94]
Participant characteristics	
Number of participants	Number of participants included in study: Serious: $n = 36$; non-serious: $n = 90$ Normal: $n = 3$; no retinopathy: $n = 19$; background retinopathy: $n = 11$; proliferative retinopathy: $n = 14$; exudative maculopathy: $n = 12$ Number of participants included in analysis: Serious: $n = 36$; non-serious: $n = 90$ Normal: $n = 3$; no retinopathy: $n = 19$; background retinopathy: $n = 11$; proliferative retinopathy: $n = 14$; exudative maculopathy: $n = 12$
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) Number of eyes: TP = 40; FP = 46; FN = 22; TN = 124; sens. = 72%; spec. = 66%

	Comparison of multiple groups (analysis of variance): Number of patients: no retinopathy TES = 59; background retinopathy TES = 31; proliferative retinopathy TES = 24; exudative maculopathy TES = 12 Number of patients: no retinopathy polarity assessment = 59; background retinopathy polarity assessment = 15; proliferative retinopathy polarity assessment = 8; exudative maculopathy polarity assessment = 3 Number of patients with abnormally high 100 hue test TES: no retinopathy *n* = 19; background retinopathy *n* = 11; proliferative retinopathy *n* = 14; exudative maculopathy *n* = 12 Number of eyes: no retinopathy TES = 115; background retinopathy TES = 55; proliferative retinopathy TES = 42; exudative maculopathy TES = 20 Number of eyes: no retinopathy polarity assessment = 115; background retinopathy polarity assessment = 28; proliferative retinopathy polarity assessment = 13; exudative maculopathy polarity assessment = 5 Number of eyes with abnormally high 100 hue test TES: no retinopathy *n* = 28; background retinopathy *n* = 18; proliferative retinopathy *n* = 21; exudative maculopathy *n* = 19

Bibliographic details	
Author	Greenstein[41]
Year	1990
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: DM patients requiring insulin therapy; Snellen visual acuity ≥ 20/30 in the tested eye; patients showing either no sign of background retinopathy or only early background retinopathy; no history of hypertension or other metabolic disorders; no significant lens opacities or glaucoma
Does the study include a control group of non-diabetics?	Yes ($n = 14$); mean age 38 years ± 11.6 years (range 23–61 years)
Reference standard	Ophthalmoscopy Conventional retinal photography Fluorescein angiography
Retinopathy grading (reference standard)	Dichotomous No retinopathy level 1: $n = 7$; background retinopathy level 2: $n = 17$ Graded Modified Airlie House classification: level 1: normal fundus; level 2: one or more microaneurysms only; level 3: microaneurysms with one or more other non-proliferative lesions present of mild to moderate degree; level 4: microaneurysms with one or more other non-proliferative lesions present of severe degree
For which eye was retinopathy assessed?	Right
Colour vision test(s)	FM-100 FM-100-hue test under standard illuminant C lighting conditions
Colour vision grading	Dichotomous Although not explicitly stated in the paper we have applied a 2 SD threshold in FM-100 age-corrected difference score for a positive colour vision abnormality test result
Participant characteristics	
Number of participants	Number of participants included in study: level 1: $n = 7$; level > 1–2: $n = 8$; level > 2–3: $n = 6$; level > 3–4: $n = 3$; no background retinopathy is level 1 and background retinopathy > level 1 Number of participants included in analysis: level 1: $n = 7$; level > 1–2: $n = 8$; level > 2–3: $n = 6$; level > 3–4: $n = 3$; no background retinopathy is level 1 and background retinopathy > level 1
Age	Mean age overall: 45.8 years ± 13.9 years (range 24–68 years)
Clinical characteristics	100% insulin-dependent DM Mean duration of insulin therapy: 18.2 years ± 9.1 years (range 7–40 years) Mean age at onset of diabetes: 27.6 years ± 14.7 years (range 8–54 years)

Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) FM-100 hue test assuming a positive result at a threshold of 2 SD in age-corrected difference score: TP = 4; FP = 0; FN = 13; TN = 7
Notes	We have assumed that ±2 SD difference in FM-100 score difference is a positive test result for background retinopathy. We have applied this to the results in *Figure 1*

Bibliographic details	
Author	Jeddi[43]
Year	1994
Study characteristics	
Study design	Longitudinal Mean follow-up 18 months (range 12–24 months)
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: visual acuity 10/10
Does the study include a control group of non-diabetics?	No
Reference standard	Ophthalmoscopy All tests given every 6 months Other: fundoscopy; visual field test
Colour vision test(s)	FM-100 All tests given every 6 months
Colour vision grading	Categorical 1. 'Normal' if TES is ≤ participant's age in years plus 30 2. 'Weak discrimination' if TES is ≤ participant's age in years multiplied by two, plus 30 (axis not well defined) 3. 'Dyschromatopsia' if TES is ≥ participant's age in years multiplied by two, plus 30 (with blue-yellow or red–green axis)
Participant characteristics	
Number of participants	Number of participants included in study: 60 Number of participants included in analysis: 60
Age	Mean: 43.5 years (range 24–63 years)
Sex	48% male
Clinical characteristics	52% insulin-dependent DM Mean diabetes duration: 10 years (range 1–18 years)
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear

What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) Of patients with normal fundoscopy (*n* = ?), 27% had signs of retinopathy on angiography. On angiography, 38/60 patients had beginnings of retinopathy. At follow-up, retinopathy appeared in 9% of cases and got worse, developing into the preproliferative form, in 10.5% Visual field was altered in 35% of cases: 32% of patients without retinopathy on angiography and 37% of patients with retinopathy. On follow-up, appearance of new 'scotomes parafoveolaires' in 27% of patients without retinopathy and 24% with background retinopathy Colour vision was abnormal in 57% of participants: weak discrimination with most areas in the blue-yellow axis in 22%, dyschromatopsia of the blue-yellow axis in 35%. In 10% of cases there is also red–green dyschromatopsia There is colour vision impairment in 50% of people without retinopathy on angiography and 65% of people with retinopathy An increase in CV error scores or individualisation of an axis was noted in 36% of cases without retinopathy and 34% with background retinopathy Overall, 37% of patients made mistakes in reading colours

Bibliographic details	
Author	Lombrail[44]
Year	1983
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: insulin dependent diabetics
Does the study include a control group of non-diabetics?	No
Reference standard	Fluorescein angiography
Retinopathy grading (reference standard)	Graded Grade A: no retinopathy; grade B: only angiographic retinopathy (at least two microaneurysms at the posterior pole); grade C: background retinopathy; grade D: preproliferative retinopathy (presence of oedema or ischaemia); grade E: proliferative retinopathy (retinal or preretinal neovascularisation); grade F: retinopathy at incurable stage
For which eye was retinopathy assessed?	Unclear
Colour vision test(s)	FM-100
Colour vision grading	Continuous/average FM-100 hue score
Participant characteristics	
Number of participants	Number of participants included in study: overall: 103; grade A: 24; grade B: 15; grade C: 48; grade D: 12; grade E: 2; grade F: 2 Number of participants included in analysis: overall: 103; grade A: 24; grade B: 15;grade C: 48; grade D: 12; grade E: 2; grade F: 2
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Comparison of multiple groups (analysis of variance) Grade A: $n = 24$, mean (SD) FM-100 score = 107 (50); grade B: $n = 15$, FM-100 = 144 (109); grade C: $n = 48$, FM-100 = 124 (78); grade D: $n = 12$, FM-100 = 182 (96); grade E: $n = 2$, FM-100 = 189 (21); grade F: $n = 2$, FM-100 = 234 (89) $F = 2.42$, $p < 0.05$

Bibliographic details	
Author	Maár[32]
Year	2001
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: type I DM; best corrected visual acuity of at least 0.4 LogMAR (0.4 Snellen value); < 50 years of age; no lens opacities
	Exclusion criteria: congenital CV deficiencies; cataract; glaucoma; retinopathy, new vessels or chorioretinal scars in the macula; more than mild proliferative retinopathy; history of intraocular surgery or laser therapy
Does the study include a control group of non-diabetics?	No
Reference standard	Slit-lamp biomicroscopy
	Conventional retinal photography
	Fluorescein angiography
Retinopathy grading (reference standard)	Dichotomous
	Clinically significant macular oedema (CSMO) vs without CMSO
	Biomicroscopic findings were graded using the ETDRS criteria; fundal photographs were graded using the modified Airlie House classification; angiograms were classified using the ETDRS fluorescein angiogram grading form
For which eye was retinopathy assessed?	Random/quasi-randomly selected
Colour vision test(s)	D-15
	Other: Mollon–Reffin Minimalist Test version 6.0
	Contains set of grey chips of varying lightness that serve as background chips, a set of coloured probe chips and an orange demonstration chip. Five grey chips are placed randomly on black Plexiglass. To these the examiner first adds the orange chip, which does not lie on any confusion line, mixes it with the grey chips and invites the patient to identify the 'coloured chip' by touching with a pointer. If the patient successfully identifies the orange chip, the examiner draws a probe chip from the middle of the protan, deutan or tritan series. After correct identification of this probe, the examiner then moves inwards along the confusion line and presents the least saturated chip; if, on the other hand, the response to the first protan probe is incorrect, the examiner moves outwards to the most saturated chip
Colour vision grading	Continuous/average
	D-15: total colour difference score (TCDS)
	Mollon–Reffin: number of reliably identified coloured chips for each confusion line
Participant characteristics	
Number of participants	Number of participants included in study: overall: 39; CMSO: 10; no CMSO: 29
	Number of participants included in analysis: overall: 39; CMSO: 10; no CMSO: 29
Age	Mean (SD): overall: range 17–47 years; CMSO: 33.7 (7.75) years; no CMSO: 28.07 (5.67) years
Sex	Overall 41% male

continued

Clinical characteristics	% insulin dependent: overall: 100%; CMSO: 100%; no CMSO: 100%
	Mean (SD) diabetes duration: overall: not stated; CMSO: 22.8 (7.00) years; no CMSO: 12.31 (7.22) years
	Mean (SD) LogMAR or Snellen visual acuity: overall LogMAR: not stated; CMSO: 0.07 (2.01); no CMSO: –0.6 (0.17)
	Mean (SD) HbA1c levels: overall: not stated; CMSO: 6.94 (0.68); no CMSO: 7.93 (1.04)
	Other relevant clinical measures
	Duration of intensive insulin treatment (years): CMSO: 6.22 (2.33); no CMSO: 5.95 (3.40)
Results	
Were groups comparable in terms of demographic and clinical characteristics?	No
	Duration of diabetes was significantly longer in patients with CMSO ($p = 0.0003$) and more severe retinopathy ($p < 0.0001$). Visual acuity was poorer in the CMSO group ($p = 0.692$)
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity)
	D-15 (TCDS of 116.9): sensitivity: 36%; specificity: 88%
	Mollon–Reffin (tritan axis; threshold error score of 1): sensitivity: 88.9%; specificity: 93.3%
	Values were estimated using chi-squared test
	Comparison of scores in two groups (*t*-test; Mann–Whitney)
	D-15 (TCDS): CSMO ($n = 10$): 144.8 (23.34); no CSMO ($n = 29$): 132.23 (28.44)
	Mollon–Reffin (tritan axis; error score): CSMO ($n = 10$): 2.1 (0.74); no CSMO ($n = 29$): 1.03 (0.19)
	There were no errors on the Mollon–Reffin protan or deutan axes by any patient
	Association between clinical characteristics and outcomes (multivariate regression)
	Logistic regression: patients with CSMO had non-significantly higher TCDS on the D-15 ($p = 0.345$) and significantly higher Mollon–Reffin tritan score ($p = 0.0015$; $r^2 = 0.565$)
Notes	Authors' conclusions:
	The Mollon–Reffin Minimalist Test version 6.0 may be useful as part of the screening and follow-up for macular oedema in young patients with juvenile onset diabetes. The use of blue-yellow colour vision tests without examination of the lens in diabetic patients older than 30 years is inadvisable

Bibliographic details	
Author	Mäntyjärvi[46]
Year	1995
Study characteristics	
Study design	Longitudinal, cross-sectional Patients were assessed for both CV and retinopathy at follow-up
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: diabetic schoolchildren with healthy eyes at recruitment
Does the study include a control group of non-diabetics?	No
Reference standard	Method not stated/final diagnosis
Retinopathy grading (reference standard)	Dichotomous Retinopathy vs no retinopathy
For which eye was retinopathy assessed?	Unclear
Colour vision test(s)	D-15 Lanthony desaturated Anomaloscope; Nagel anomaloscope was administered at baseline and at follow-up; colour vision meter 712 anomaloscope (CVM) was administered at follow-up only
Colour vision grading	Dichotomous Pass/fail for each test
Participant characteristics	
Number of participants	Number of participants included in study: overall: 54; DR at follow-up: 23; no DR at follow-up: 31 Number of participants included in analysis: overall: 54; DR at follow-up: 23; no DR at follow-up: 31
Age	Mean (SD): at recruitment: 14 (2) years (range 9–19 years)
Sex	46.3% male
Clinical characteristics	Mean (SD) diabetes duration: 6 (SD 4) years (range 1 month to 15 years)

continued

Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) TP, FP, FN, TN calculated from text (no thresholds reported): 1. Baseline (1987): a. Desaturated D-15: TP = 0, FP = 7, FN = 0, TN = 47 b. D-15: TP = 0, FP = 0, FN = 0, TN = 54 c. Nagel anomaloscope: TP = 0, FP = 0, FN = 0, TN = 54 2. Follow-up (1993): a. Desaturated D-15: TP = 1, FP = 0, FN = 22, TN = 31 b. D-15: TP = 1, FP = 0, FN = 22, TN = 31 c. Nagel anomaloscope: TP = 0, FP = 0, FN = 23, TN = 31 d. CVM anomaloscope: not calculable (no significant difference between groups)
Notes	Authors' conclusion: No predictive signs of DR could be found with the CV tests, nor could these tests distinguish between DR and non-DR children

Bibliographic details	
Author	Matsuo[51]
Year	1990
Related papers	Matsuo 1988[59]
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: visual acuity score > 0.5 Exclusion criteria: participants with eyesight problems
Does the study include a control group of non-diabetics?	Yes
Reference standard	Method not stated/final diagnosis
Retinopathy grading (reference standard)	Graded
For which eye was retinopathy assessed?	Both
Colour vision test(s)	Other: Lanthony New Colour Test (NCT): 15 component colour arrangement test
Colour vision grading	Continuous/average Total error score (TES)
Participant characteristics	
Number of participants	Number of participants included in study: total: 56; retinopathy: 20; no retinopathy: 36
Age	Mean (SD): 57.4 (1.7) years
Sex	54% male
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Comparison of scores in two groups (*t*-test; Mann–Whitney) Retinopathy: mean TES = 7.9 (SD 1.51); no retinopathy: mean TES = 3.03 (SD 0.56) ($p < 0.01$) Association between clinical characteristics and outcomes (multivariate regression) NCT score was positively correlated with duration of diabetes ($p < 0.05$) and HbA1c ($p < 0.02$), but negatively correlated with coefficient variation of R–R interval in electrocardiography (an index for autonomic neuropathy, $p < 0.02$)

Bibliographic details	
Author	Mecca[49]
Year	1988
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: all patients had duration greater than 4 years; all patients had visual acuity 8/10 or better Exclusion criteria: participants with congenital colour vision deficits; patients with maculopathy or macular oedema of mixed or proliferative retinopathy and participants with retinopathy of an advanced degenerative stage (large or numerous haemorrhages with exudate 'confluents')
Does the study include a control group of non-diabetics?	Yes: 80 non-diabetics, aged 18–75 years, all of whom had 10/10 vision and no alterations of the anterior segment, back of the eye or intraocular pressure
Reference standard	Ophthalmoscopy Fluorescein angiography
Retinopathy grading (reference standard)	Dichotomous With retinopathy (with at least 10 microaneurysms and small haemorrhages and exudates that are non-'confluents') vs without retinopathy
For which eye was retinopathy assessed?	Right
Colour vision test(s)	D-15 Presented under luminance of 500 lux Other: Lanthony New Colour Test (NCT): conducted under luminance of 250 lux. Scored on the number of errors in each series multiplied by the saturation of the colour. Tested four figures, which together constituted the total score for the examined eye
Colour vision grading	Continuous/average NCT: error scores Dichotomous D-15: altered colour vision vs normal NCT: altered colour vision (anything above zero) vs normal (no errors)
Participant characteristics	
Number of participants	Number of participants included in study: 155 Number of participants included in analysis: 155
Age	Mean (SD) Participants were divided into two groups: those aged 18–45 years and those aged 46–75 years Without retinopathy: 18–45 group: 30.1 (8.5) years; 46–75 group: 61.4 (7.0) years With retinopathy: 18–45 group: 35.6 (8.4) years; 46–75 group: 61.1 (6.9) years
Clinical characteristics	Mean (SD) diabetes duration Without retinopathy: 18–45 group: 9.6 (4.9) years; 46–75 group: 9.8 (4.4) years With retinopathy: 18–45 group: 17.4 (5.2) years; 46–75 group: 12.1 (5.0) years

Results	
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) D-15, 18–45 group: TP = 31, TN = 20, FP = 15, FN = 9 D-15, 46–75 group: TP = 41, TN = 5, FP = 30, FN = 4 D-15, overall: TP = 72, TN = 25, FP = 45, FN = 13 NCT, 18–45 group: TP = 32, TN = 25, FP = 10, FN = 8 NCT, 46–75 group: TP = 35, TN = 17, FP = 18, FN = 10 NCT, overall: TP = 67, TN = 42, FP = 28, FN = 18 NCT + D-15 combined overall (threshold: impaired CV on one or both tests): TP = 73; TN = 25; FP = 45; FN = 12 Comparison of scores in two groups (*t*-test; Mann–Whitney) NCT scores: 18–45 group: without retinopathy 0.69 (1.18); with retinopathy 2.40 (1.58) 46–75 group: without retinopathy 1.60 (1.87); with retinopathy 3.24 (2.14) Chi-squared values (retinopathy vs no retinopathy): D-15 18–45 group: 9.446, $p < 0.01$ D-15 46–75 group: 0.574, p = not significant NCT 18–45 group: 20.037, $p < 0.001$ NCT 46–75 group: 6.113, $p < 0.05$

Bibliographic details	
Author	Mirkiewicz-Sieradzka[57]
Year	1986
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: diabetic patients with signs of retinopathy
	Exclusion criteria: patients with congenital red–green colour deficits; patients who had previously undergone photocoagulation
Does the study include a control group of non-diabetics?	No
Reference standard	Ophthalmoscopy
	Fluorescein angiography
Retinopathy grading (reference standard)	Graded
	Ophthalmoscopy:
	I. Microaneurysms and yellow spots
	II. Microaneurysms, yellow spots and ('wybroczyn'?)
	III. Massive yellow spots
	IV: Oedema
	Angiography:
	I: Single leak
	II: Larger leaks
	III: Limited oedema
	IV: Diffuse oedema
For which eye was retinopathy assessed?	Unclear
Colour vision test(s)	Ishihara plates
Colour vision grading	Dichotomous
	Pass vs fail (no threshold reported)
Participant characteristics	
Number of participants	Number of participants included in study: 51
Age	Range 20–78 years
Sex	50.9% male

Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) Ophthalmoscopy as reference standard (*n* pass CV, *n* fail CV): I. Microaneurysms and yellow spots (39 eyes, 7 eyes) II. Microaneurysms, yellow spots and 'wybroczyn' (19 eyes, 5 eyes) III. Massive yellow spots (1 eye, 2 eyes) IV: Oedema (2 eyes, 15 eyes) Angiography as reference standard (*n* pass CV, *n* fail CV): I: Single leak (34 eyes, 3 eyes) II: Larger leaks (25 eyes, 11 eyes) III: Limited oedema (2 eyes, 9 eyes) IV: Diffuse oedema (6 eyes in total, CV results unclear)
Notes	The authors concluded that small ophthalmoscopic changes and little leakage on the angiographic picture of the macular region are connected with colour disturbances in 15% and 8% of eyes respectively. The authors do not provide data at the level of patient

Bibliographic details	
Author	Ong[31,60]
Year	2004
Related papers	Ong 2003[60]
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: consenting diabetic patients attending photographic screening
	Exclusion criteria: corrected visual acuity worse than 6/9; previous history of photocoagulation therapy; history of eye disease known to affect colour vision (e.g. glaucoma); signs and symptoms of significant media opacification; inability to complete the test satisfactorily
Does the study include a control group of non-diabetics?	Yes: 'lens-equated' control subjects: $n = 310$; mean (SD) age: 48 (19.1) years
Reference standard	Slit-lamp biomicroscopy
	Examinations conducted by an experience ophthalmologist
Retinopathy grading (reference standard)	Dichotomous
	Retinopathy stage was graded using the European staging protocol and then dichotomised into 'sight-threatening diabetic retinopathy' (STDR; includes preproliferative retinopathy, proliferative retinopathy, maculopathy) or 'non-sight-threatening diabetic retinopathy' (NSTDR; includes no retinopathy and background retinopathy)
For which eye was retinopathy assessed?	Random/quasi-randomly selected
Colour vision test(s)	Computerised/automated method
	Tritan contrast threshold (TCT) test: computerised cathode ray tube (CRT)-based technique – participants are scored on their ability to distinguish vertical, sinusoidal, low spatial frequency and standardised equiluminent gratings from a uniform background; chromaticity of the gratings is changed along a tritan confusion axis
Colour vision grading	Continuous/average
	z-score: To account for the accelerated lens yellowing experienced by diabetics, standardised scores were obtained from a randomly selected eye of 310 non-diabetic control participants. The TCT scores from the diabetic participants and 'lens-equated' control subjects were used to calculate an overall z-score for the diabetic participants. A negative z-score indicates that a patient's tritan vision is still worse than normal, even when both age and lens yellowing have been taken into account
	Dichotomous
	Using the weighted kappa coefficient of association analysis technique, the optimal pass/fail criterion to detect STDR was $z = -1.75$. This threshold was used to dichotomise patients into pass/fail on the TCT test
Participant characteristics	
Number of participants	Number of participants included in study: 510 (STDR 17, NSTDR 493)
	Number of participants included in analysis: 510 (STDR 17, NSTDR 493)
Age	Mean (SD): STDR: 60.4 (11.3) years; NSTDR: 60.9 (13.9) years ($p > 0.5$)

Clinical characteristics	21% insulin dependent (107/510) Mean (SD) diabetes duration: STDR: 11.8 (6.9) years; NSTDR: 10.4 (8.6) years ($p = 0.43$) Mean (SD) LogMAR or Snellen visual acuity Snellen log values: STDR: 0.1 (0.11); NSTDR: 0.06 (0.09) ($p = 0.13$) Mean (SD) HbA1c levels: STDR: 9.8 (1.6); NSTDR: 8.1 (2.2) ($p = 0.02$) Other relevant clinical measures: Urinary albumin counts (ml/l): STDR: 28.2 (28.7); NSTDR: 26 (47.6) ($p = 0.19$)
Results	
Were groups comparable in terms of demographic and clinical characteristics?	No; STDR patients had significantly worse HbA1c levels than NSTDR patients
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) 1. TCT only: TP = 16, TN = 467, FP = 26, FN = 1 2. Fundus photography only: TP = 15, FP = 23, FN = 2, TN = 470 3. TCT and photography (failed both tests): TP = 15, FP = 2, FN = 2, TN = 491 4. TCT plus photography for patients who failed the TCT: TP = 15, FP = 2, FN = 2, TN = 491 5. Photography plus TCT for patients who failed photography: TP = 15, FP = 2, FN = 2, TN = 491 There were a total of 21 unassessable photographs. These were counted as positives (2 true-positives and 19 false-positives) Comparison of scores in two groups (*t*-test; Mann–Whitney) Significantly worse TCT ($p < 0.0001$) and HbA1c ($p = 0.02$) in patients with STDR than in those with NSTDR (Mann–Whitney U). Best corrected visual acuity was worse, duration of diabetes was longer and urinary albumin counts were higher in the STDR group, but these differences were not significant (Mann–Whitney U) STDR patients have significantly abnormal TCTs compared with 'lens-equated' control subjects ($p < 0.0001$; Mann–Whitney U). No significant differences in TCT were found between NSTDR patients and 'lens-equated' control subjects Comparison of multiple groups (analysis of variance) Mean (SD) TCT score: no retinopathy ($n = 383$): 42.5 (6.3); background retinopathy ($n = 110$): 41.7 (7.1); preproliferative retinopathy ($n = 3$): 29.6 (8.5); proliferative retinopathy ($n = 2$): 21.7 (3.3); maculopathy ($n = 12$): 24.0 (7.2) Association between clinical characteristics and outcomes (multivariate regression) Pearson correlation analysis found significant correlations between age and TCT ($p < 0.0001$), age and diabetes duration ($p < 0.001$), and age and HbA1c ($p < 0.001$). None of the other variables showed significant correlation with TCT (HbA1c: $p > 0.4$; urinary albumin counts: $p > 0.1$; duration of diabetes: $p > 0.8$) Logistic regression showed TCT ($p < 0.001$) and HbA1c ($p = 0.018$) significantly correlated with the presence of STDR, but not with duration of diabetes, urinary albumin counts or log best corrected visual acuity
Notes	The authors concluded that TCT had a higher sensitivity and was more cost-effective than fundus photography. They also concluded that adding the TCT test to fundus photography can also significantly improve the overall performance in screening for STDR

Bibliographic details	
Author	Saracco[50]
Year	1980
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Unclear
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: included patients with visual acuity ≥ 6/10 Exclusion criteria: excluded those with congenital dyschromatism and those with retinal or general problems (unspecified) that could affect the interpretation of colour vision; diabetic patients who had had laser eye correction were also excluded
Does the study include a control group of non-diabetics?	No
Reference standard	Fluorescein angiography
Retinopathy grading (reference standard)	Dichotomous Normal (grade 0) vs pathological (grades 1, 2 and 3) Also angiography grade 0 vs grade 1 Graded 0. Normal angiography 1. 'Dry' retinopathy (microaneurysms, small haemorrhaging, areas of capillary obliteration, but no evidence of leaks) 2. Exudative retinopathy (oedema, with leaks) 3. Proliferative retinopathy (any stage)
For which eye was retinopathy assessed?	Unclear
Colour vision test(s)	D-15
Colour vision grading	Dichotomous Normal colour vision (grades 0 and 1) vs abnormal colour vision (grades 2c, 2d and 3) Categorical Grades: 0. Normal 1. 'Permutations' (more than two inversions of the hues) 2a. With protan 2b. Deutan axis 2c. Tritan axis 2d. 'Tetartan' axis 3. Dyschromatopsia without an axis

Participant characteristics	
Number of participants	Number of participants included in study: 88 (172 eyes)
	Number of participants included in analysis: 88 (172 eyes)
Age	Mean: 51.12 years
	0–20 years: 8 eyes; 20–40 years: 31 eyes; 40–60 years: 76 eyes; 60+ years: 57 eyes
Clinical characteristics	Mean (SD) LogMAR or Snellen visual acuity
	Myopia (at least 2 dioptres): 17 people (34 eyes)
	Other relevant clinical measures: 22 people (40 eyes) beginnings of cataracts
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity)
	Normal vs pathology: TP = 63, FP = 49, FN = 17, TN = 43
	Angiographic grade 0 vs 1: TP = 42, FP = 49, FN = 12, TN = 43

Bibliographic details	
Author	Sinha[58]
Year	1979
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: diabetics
	Exclusion criteria: patients giving the mildest indications about colour defects in family and/or growth impairment of vision
Does the study include a control group of non-diabetics?	Yes: $n = 40$
Reference standard	Slit-lamp biomicroscopy
	Biomicroscopy
Retinopathy grading (reference standard)	Dichotomous
	Diabetics with DR vs diabetics without DR
For which eye was retinopathy assessed?	Both; each eye was tested on two occasions and the results averaged
Colour vision test(s)	Ishihara plates
	Other: Ishihara charts and Tokyo Medical College colour vision charts
Colour vision grading	Categorical
	Normal colour vision; protan deficit; deutan deficit; tritan deficit
Participant characteristics	
Number of participants	Number of participants included in study: non-DR: $n = 40$; DR: $n = 33$
	Number of participants included in analysis: non-DR: $n = 40$; DR: $n = 33$
Age	Mean: non-DR: 51.2 years; DR: 55 years
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity)
	TP = 4, FP = 1, FN = 29, TN = 39, sens. = 12%, spec. = 97.5%
	This result is for tritan deficits vs normal. No participants had a protan or deutan defect CV result

Bibliographic details	
Author	Tregear[55]
Year	1997
Study characteristics	
Study design	Longitudinal, cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: type I and type II diabetics; diabetics taking any form of medication other than those used to control glucose levels deliberately not excluded Exclusion criteria: previous laser treatment; signs of significant lens opacification as determined by slit-lamp examination through dilated pupil; corrected visual acuity worse than 6/18
Does the study include a control group of non-diabetics?	Yes: $n = 347$ lens-equated control subjects
Reference standard	Slit-lamp biomicroscopy Dilated with 1% tropicamide
Retinopathy grading (reference standard)	Graded No retinopathy: no evidence of retinopathy can be seen clinically Background: characterised by the development of microaneurysms, superficial and deep retinal haemorrhages and the formation of hard exudates Preproliferative: five or more cotton wool spots on the fundus, presence of white vessels, venous bleeding and venous loops, features associated with severe background retinopathy such as widespread blotchy dark haemorrhages Proliferative: presence of new blood vessels at the optic disc (elsewhere on the retina if more than half a disc diameter in size, less than half a disc diameter associated with vitreous haemorrhage) or by vitreous haemorrhage anywhere Maculopathy: clinically significant macular oedema as characterised by the ETDRS group, characterised by thickening of the retina within 500 μm of the centre of the macula, the presence of hard exudates associated with retinal thickening within 500 μm of the macula, and a zone of retinal thickening one disc area or larger in size within a disc diameter of the centre of the macula
For which eye was retinopathy assessed?	Random/quasi-randomly selected
Colour vision test(s)	Computerised/automated method SGM; set up to produce low spatial frequency equiluminant, sinusoidal gratings on a high-resolution colour monitor that were randomly tritan or red–green
Colour vision grading	Continuous/average (1) Tritan contrast threshold (TCT) and (2) red–green contrast threshold (RGCT) Dichotomous Longitudinal subgroup only: threshold scores +2 SDs above the lens-equated mean

continued

Participant characteristics	
Number of participants	Number of participants included in study: no retinopathy: *n* = 87; background retinopathy: *n* = 116; preproliferative: *n* = 26; proliferative: *n* = 13; maculopathy: *n* = 63; total: *n* = 305
	Number of participants included in analysis: no retinopathy: *n* = 87; background retinopathy: *n* = 116; preproliferative: *n* = 26; proliferative: *n* = 13; maculopathy: *n* = 63; total: *n* = 305
Age	Mean (SD): no retinopathy: 52.09 (16.89) years; background retinopathy: 55.10 (14.95) years; preproliferative: 63.04 (14.39) years; proliferative: 53.92 (18.72) years; maculopathy: 62.32 (11.94) years
Clinical characteristics	30% insulin-dependent type I diabetics
	Overall mean duration: 14 years (range 1.5–60 years)
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Unclear
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity)
	Ability to predict macular oedema or ischaemia (longitudinal data from subgroup of 87 patients with background DR, followed up at 18 months): (1) TCT: TP = 12, FP = 7, FN = 7, TN = 62; (2) RGCT: TP = 6, FP = 5, FN = 12, TN = 64
	Comparison of multiple groups (ANOVA)
	Main cross-sectional study results:
	No retinopathy RGCT: mean 0.45, SD 0.17, variance 0.03
	Background RGCT: mean 0.57, SD 0.24, variance 0.06
	Maculopathy RGCT: mean 0.81, SD 0.29, variance 0.08
	Preproliferative RGCT: mean 0.73, SD 0.19, variance 0.08
	Proliferative RGCT: mean 0.88, SD 0.34, variance 0.12
	Main cross-sectional study results
	No retinopathy TCT: mean 0.55, SD 0.17, variance 0.05
	Background TCT: mean 0.74, SD 0.29, variance 0.09
	Maculopathy TCT: mean 1.14, SD 0.31, variance 0.09
	Preproliferative TCT: mean 1.05, SD 0.26, variance 0.07
	Proliferative TCT: mean 1.13, SD 0.31, variance 0.09

Bibliographic details	
Author	Trick[45]
Year	1988
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: DM patients with no or mild to moderate background retinopathy; visual acuity of at least 20/30 and intraocular pressure < 21 mmHg in the eye to be tested Exclusion criteria: patients with macular oedema detected in either the ophthalmoscopic examination or the fundus photographs
Does the study include a control group of non-diabetics?	Yes: $n = 35$
Reference standard	Conventional retinal photography Seven-field fundus photographs
Retinopathy grading (reference standard)	Dichotomous No retinopathy vs preproliferative background retinopathy (grade 1a to grade 1b lesions according to the modified Airlie House classification)
For which eye was retinopathy assessed?	Random/quasi-randomly selected Monocular test but no details on how the eye was selected
Colour vision test(s)	FM-100 Administered monocularly under standard illuminant C (Macbeth Easel lamp) lighting conditions with no time limit imposed. The order of presentation of the boxes was varied randomly between patients
Colour vision grading	Continuous/average Square root of total error score (TES) and partial error scores (blue-yellow, red–green) Dichotomous Total/partial error score > 2 SD above the normal mean
Participant characteristics	
Number of participants	Number of participants included in study: no retinopathy: $n = 37$; background retinopathy: $n = 20$ Number of participants included in analysis: no retinopathy: $n = 37$; background retinopathy: $n = 20$
Age	Mean (SD): no retinopathy 36.9 (11.1) years; background retinopathy 37.9 (8.6) years
Clinical characteristics	Overall 68% insulin dependent Mean diabetes duration: retinopathy: 8.1 years (range 1–45 years); background retinopathy: 16 years (range 2–33 years) Mean (SD) fasting blood glucose: no retinopathy: 203.2 (73.9); background retinopathy: 236.0 (84.2) Mean (SD) HbA1c levels: no retinopathy 8.5 (1.8); background retinopathy: 9.2 (1.7)

continued

Results	
Were groups comparable in terms of demographic and clinical characteristics?	No; groups are comparable in all characteristics other than diabetes duration. The average duration of diabetes was 8.1 years (range 1–45 years) in the group without DR and 16 years (range 2–33 years) for the patients with background retinopathy
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) TES: TP = 5, FP = 7, FN = 15, TN = 30 Blue-yellow: TP = 4, FP = 5, FN = 16, TN = 32 Red–green: TP = 4, FP = 7, FN = 30, TN = 16 Comparison of multiple groups (ANOVA) No retinopathy: square root TES 9.69 (4.16), blue-yellow error 7.6, red–green error 6.25 Background retinopathy: square root TES 11.33 (4.23), blue-yellow error 8.75, red–green error 7.5 No difference in square root TES between no retinopathy and background retinopathy diabetics ($t = 1.42$, $df = 55$, $p > 0.15$) Association between clinical characteristics and outcomes (multivariate regression) HbA1c correlated with square root TES ($r = 0.30$, $df = 55$, $p < 0.05$) but duration of diabetes and blood glucose did not
Notes	We calculated mean error score for blue-yellow and red–green from *Figure 1*

Bibliographic details	
Author	Wong[56]
Year	2008
Study characteristics	
Study design	Cross-sectional
How were the data collected?	Prospectively
Were participants recruited consecutively?	Unclear
Patient selection criteria	Inclusion criteria: type 2 diabetic patients with untreated non-proliferative DR and untreated clinically significant macular oedema (CSMO); cataract and pseudophakia were not excluded as both are more common in diabetics and exclusion would have limited the usefulness of the ChromaTest screening Exclusion criteria: type 1 diabetes; proliferative DR; previous laser photocoagulation; current ocular pathology including infection, trauma; amblyopia; glaucoma; and/or vascular occlusion
Does the study include a control group of non-diabetics?	No
Reference standard	Slit-lamp biomicroscopy Dilated fundoscopy with slit-lamp biomicroscopy and 78 D lens was performed by a specialist registrar
Retinopathy grading (reference standard)	Graded Grading according to the ETDRS extension of the Airlie House classification: no clinical retinopathy, non-proliferative diabetic retinopathy (NPDR) and CSMO
For which eye was retinopathy assessed?	Unclear Text says that both eyes were tested but the results are for 150 eyes from 150 patients?
Colour vision test(s)	Computerised/automated method ChromaTest: the subject is seated at a fixed distance from the monitor so that the alphabetical letter displayed on the computer screen subtends a constant angle on the retina. The letter size creates an image that tests the central 6.5 degrees of the retina. The letters are displayed on a background of equiluminance. The operator has no influence on the contrast of the test letter given. The computer finds the end point of the test by a modified binary search method; if a response is correct, on the next presentation the colour difference between letter and background is halved; if the response is incorrect, the colour contrast is doubled
Colour vision grading	Dichotomous Pass/fail criterion for tritan colour contrast threshold (TCCT) given for each age group: 11.0 (30–49 years); 23.0 (50–69 years); 32.0 (70–89 years) Pass/fail criterion for protan colour contrast threshold (PCCT) not given
Participant characteristics	
Number of participants	Number of participants included in study: no clinical retinopathy: $n = 30$; NPDR: $n = 115$; CSMO: $n = 35$ Number of participants included in analysis: no clinical retinopathy: $n = 30$; NPDR: $n = 115$; CSMO: $n = 35$
Age	Median age of all groups: 60 years (range 31–82 years)
Sex	% male not stated

continued

Clinical characteristics	% insulin dependent not stated Median duration of diabetes: 16.0 years Best corrected LogMAR visual acuity (BCVA) median for NPDR = 0.2; BCVA median for CSMO = 0.2; interquartile range for visual acuity NPDR = 0.20; interquartile range for visual acuity CSMO = 0.30
Results	
Were groups comparable in terms of demographic and clinical characteristics?	Yes
What data/analysis is presented in the study?	Diagnostic data (2×2; sensitivity, specificity) TCCT detection of CSMO (NPDR used as control group): TP = 25, FP = 35, FN = 10, TN = 80, sens. = 71% (95% CI 53% to 83%), spec. = 70% (95% CI 60% to 78%) ($p < 0.0001$) Subjects with LogMAR BCVA ≥ 0.1, sens. to detect CSMO improves to 75% (95% CI 47–91%) and spec. to 85% (95% CI 67% to 89%) ($p = 0.0002$) Subjects with CSMO with central macular thickening, sens. to detect CSMO improves to 83.3% (95% CI 58% to 96%) ($p < 0.0001$) NPDR vs no DR: TP = 35, FP = 1, FN = 80, TN = 29, sens. = 30%, spec. = 97%, LR+ 9.13, LR– 0.72 CSMO vs no DR: TP = 25, FP = 1, FN = 10, TN = 29, sens. = 71%, spec. = 97%, LR+ 21.43, LR– 0.30 CSMO vs NPDR: TP = 25, FP = 35, FN = 10, TN = 80, sens. = 71%, spec. = 70%, LR+ 2.35, LR– 0.41 Comparison of scores in two groups (*t*-test; Mann–Whitney) Median PCCT for NPDR = 3.9%, CSMO = 5.6%; Wilcoxon Rank sum test $p = 0.01$ PCCT difference between no DR and NPDR: $p = 0.15$; no DR and CSMO: $p = 0.002$ Median TCCT for NPDR = 15.4%, CSMO = 29.6%; Wilcoxon Rank sum test $p = 0.0002$ TCCT difference between no DR and NPDR: $p < 0.001$; no DR and CSMO: $p < 0.001$

Appendix 4

Table of excluded studies with rationale

Study	Reason for exclusion[a]
Abraham FA, Haimovitz J, Berezin M. (1988) The photopic and scotopic visual thresholds in diabetics without diabetic retinopathy	2, 5
Adab P. (1996) Screening for sight-threatening eye disease. Cost-effectiveness of screening modalities must be determined	1
Adams AJ. (1982) Chromaticity and luminosity changes in glaucoma and diabetes	3
Adams AJ, Huie K, Schefrin BE, Bresnick GH, Zisman F. (1986) A simple clinical test of blue cone sensitivity in early eye disease	2, 3, 5
Adams AJ, Schefrin B, Huie K. (1987) New clinical color threshold test for eye disease	1
Afrashi F, Erakgun T, Kose S, Ardic K, Mente J. (2003) Blue-on-yellow perimetry vs achromatic perimetry in type 1 diabetes patients without retinopathy	4, 5
Agardh E, Agardh CD, Hansson-Lundblad C. (1993) The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy	2
Agardh E, Agardh CD, Koul S, Torffvit O. (1994) A four-year follow-up study on the incidence of diabetic retinopathy in older onset diabetes mellitus	2
Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA. (2006) The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy	2
Alexander MM, Canning CR. (1995) A telephone study of diabetic retinopathy and the diabetes miniclinic in general practice: a regional study in Wessex	2
Anderson RM, Wolf FM, Musch DC, Fitzgerald JT, Johnson MW, Nwankwo RB, *et al.* (2002) Conducting community-based, culturally specific, eye disease screening clinics for urban African Americans with diabetes	2
Anderson S, Broadbent DM, Swain JYS, Vora JP, Harding SP. (2003) Ambulatory photographic screening for diabetic retinopathy in nursing homes	2
Apostol S, Carstocea B. (1994) [Color vision in diabetics]	1
Arden G, Gunduz K, Perry S. (1988) Color vision testing with a computer graphics system: preliminary results	5
Arden GB, Gündüz K, Perry S. (1988) Color vision testing with a computer graphics system: preliminary results	3
Arden GB, Wolf JE, Tsang Y. (1998) Does dark adaptation exacerbate diabetic retinopathy? Evidence and a linking hypothesis	3
Arend O, Remky A, Evans D, Stüber R, Harris A. (1997) Contrast sensitivity loss is coupled with capillary dropout in patients with diabetes	2
Ariyasu RG, Lee PP, Linton KP, LaBree LD, Azen SP, Siu AL. (1996) Sensitivity, specificity and predictive values of screening tests for eye conditions in a clinic-based population	2
Arun CS, Ngugi N, Lovelock L, Taylor R. (2003) Effectiveness of screening in preventing blindness due to diabetic retinopathy	2
Author not found. (1992) Screening guidelines for diabetic retinopathy. American College of Physicians, American Diabetes Association, and American Academy of Ophthalmology	1
Bachmann MO, Nelson SJ. (1998) Impact of diabetic retinopathy screening on a British district population: case detection and blindness prevention in an evidence-based model	1

Study	Reason for exclusion[a]
Bailey CC, Sparrow JM. (2001) Visual symptomatology in patients with sight-threatening diabetic retinopathy	2
Baker R, Grimshaw G, Thompson JR, Wilson A. (1999) Services for diabetic retinopathy screening in England and Wales: a survey of ophthalmologists	2
Banford D, North RV, Dolben J, Butler G, Owens DR. (1994) Longitudinal study of visual functions in young insulin-dependent diabetics	4
Bangstad HJ, Brinchmann-Hansen O, Hultgren S, Dahl-Jorgensen K, Hanssen KF. (1994) Impaired contrast sensitivity in adolescents and young type 1 (insulin-dependent) diabetic patients with microalbuminuria	2
Barca L, Vaccari G. (1978) Diabetic retinopathy and colour discrimination under various illuminants	1
Barton FB, Bresnick GH, Knatterud GL, Fisher MR, Early Treatment Diabetic Retinopathy Study Research Group. (1988) Classification of Farnsworth-Munsell 100-hue test results by pattern of error scores [meeting abstract]	4
Barton FB, Fong DS, Knatterud GL, Group ER. (2004) Classification of Farnsworth-Munsell 100-hue test results in the Early Treatment Diabetic Retinopathy Study	4
Basch CE, Walker EA, Howard CJ, Schmoon H, Zybert P. (1999) The effect of health education on the rate of ophthalmic examinations among African Americans with diabetes mellitus	2
Bensinger RE. (1992) Color vision and color vision testing	1
Benson WH, Farber ME. (1988) Clinical screening for diabetic retinopathy using Lanthony's desaturated D-15 [meeting abstract]	4
Bernardczyk-Meller J, Kielczewska-Mrozikiewicz D, Meller M, Pecold K. (2000) [Diagnostics of the early retinal and optic nerve changes in long-standing type 1 diabetes mellitus]	1
Bernardczyk-Meller J, Siwiec-Prociska J, Stankiewicz W, Fichna P, Pecold K, Korman E. (2004) [Influence of Eqb 761 on the function of the retina in children and adolescent with long lasting diabetes mellitus – preliminary report]	5
Birbeck JA. (1972) Studies of colour vision in juvenile diabetes [meeting abstract]	1
Birch J. (1993) Diagnosis of defective colour vision	1
Birch J. (1997) Acquired tritanopia in diabetic maculopathy	3, 5
Birch J, Ariffin AE, Kurtz A. (1991) Colour vision screening for the detection of diabetic retinopathy	3
Birch J, Chisholm IA, Kinear P, Marre M, Pinckers AJLG, Pokorny J, *et al*. (1979) Acquired colour vision defects	1
Birch J, Dain SJ. (1987) An averaging method for the interpretation of the Farnsworth-Munsell 100-Hue Test. II. Colour vision defects acquired in diabetic retinopathy	3
Bischoff P. (1993) [Frequency of ophthalmological examinations in diabetic retinopathy]	2
Bonvin ER, Dosso AA, Baglivo E. (1994) Contrast sensitivity in diabetics with and without background retinopathy [meeting abstract]	2
Booth AJ, Sinclair NE, Clover A, Luff AJ, Leatherdale A, Newsom RSB. (2004) Does retinal screening improve the visual outcome of diabetic maculopathy treatment?	2
Boucher MC, Nguyen QT, Angioi K. (2005) Mass community screening for diabetic retinopathy using a nonmydriatic camera with telemedicine	2
Bowman KJ. (1982) A method for quantitative scoring of the Farnsworth panel D-15	3
Brash PD, Ripley L, De Alwis D, Tooke JE. (1995) Tritan colour vision impairment is evident in the pre-diabetic state [meeting abstract]	3, 5

Study	Reason for exclusion[a]
Bresnick GH, Condit RS, Palta M, Korth K, Groo A, Syrjala S. (1985) Association of hue discrimination loss and diabetic retinopathy	2, 4
Bresnick GH, Mukamel DB, Dickinson JC, Cole DR. (2000) A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy	2
Broadbent DM, Scott JA, Vora JP, Harding SP. (1999) Prevalence of diabetic eye disease in an inner city population: the Liverpool Diabetic Eye Study	2
Bronte-Stewart JM, Cant JS, Craig JO. (1984) Colour vision in young diabetics	3, 4
Bryant VM, Wilson A, Jones TH, Hague RV. (1999) A high uptake eye and foot screening service for an urban population	2
Bucher MB, Leuenberger PM, Roth A. (1983) [Diabetes and color vision]	3
Buckingham TJ, Young SA. (1993) Changes in retinal function with duration of diabetes mellitus	2
Buonaccorso KM. (1999) Diabetic retinopathy screening: a clinical quality improvement project	2
Buxton MJ, Sculpher MJ, Ferguson BA, Humphreys JE, Altman JF, Spiegelhalter DJ, *et al.* (1991) Screening for treatable diabetic retinopathy: a comparison of different methods	2
Cameron BL. (2002) Making diabetes management routine: how often do you and your patients screen for complications?	1, 2
Cathelineau G, Cathelineau BV. (1991) Diabetic retinopathy: methodologies in practice	2
Cathelineau G, Villatte-Cathelineau B, Lombrail P. (1986) [Color vision and diabetes]	1
Cirillo D, Gonfiantini E, De Grandis D, Bongiovanni L, Robert JJ, Pinelli L. (1984) Visual evoked potentials in diabetic children and adolescents	2
Clark JB, Grey RH, Lim KK, Burns-Cox CJ. (1994) Loss of vision before ophthalmic referral in blind and partially sighted diabetics in Bristol	2
Collier A, Mitchell JD, Clarke BF. (1985) Visual evoked potential and contrast sensitivity function in diabetic retinopathy	2, 5
Condit R, Bresnick G, Korth K, Mattson D, Syrjala S. (1982) Hue discrimination loss and retinopathy severity in diabetes mellitus [meeting abstract]	1, 4
Conrath J, Giorgi R, Raccah D, Ridings B. (2005) Foveal avascular zone in diabetic retinopathy: quantitative vs qualitative assessment	2
Cranston IC. (2002) Bexley diabetes retinal screening programme	1
Crognale MA, Switkes E, Rabin J, Schneck ME, Haegerstrom-Portnoy G, Adams AJ. (1993) Application of the spatiochromatic visual evoked potential to detection of congenital and acquired color-vision deficiencies	1, 5
d'Annunzio G, Malvezzi F, Vitali L, Barone C, Giacchero R, Klersy C, *et al.* (1997) A 3–19 year follow up study on diabetic retinopathy in patients diagnosed in childhood and treated with conventional therapy	2
Dain SJ. (2004) Clinical colour vision tests	1
Dain SJ, Saunders JE. (1987) F-M 100 hue total error scores have discrete values	1, 3
Daley ML, Watzke RC, Riddle MC. (1987) Early loss of blue-sensitive color vision in patients with type 1 diabetes	3, 5
Danne T, Kordonouri O, Enders I, Hövener G. (1998) Monitoring for retinopathy in children and adolescents with type 1 diabetes	1, 2
Davies NP, Morland AB. (2002) Chromatic and achromatic spectral sensitivity in diabetes mellitus	3, 5

Study	Reason for exclusion[a]
Davies R, Roderick P, Canning C, Brailsford S. (2002) The evaluation of screening policies for diabetic retinopathy using simulation	1, 2
De Marco R, Capasso L, Magli A, Franzese A, Gasparini N, Ambrosio G. (1996) Measuring contrast sensitivity in aretinopathic patients with insulin dependent diabetes mellitus	2
Deb-Joardar N, Germain N, Thuret G, Garcin AF, Manoli P, Defreyn A, *et al.* (2007) Systematic screening for diabetic retinopathy with a digital fundus camera following pupillary dilatation in a university diabetes department	2
Del Beato P, Tanzilli P, Giusti C, Pannarale L, Vingolo EM. (1995) Acquired dyschromatopsia in diabetes without diabetic retinopathy [meeting abstract]	4
Della Sala S, Bertoni G, Somazzi L, Stubbe F, Wilkins AJ. (1985) Impaired contrast sensitivity in diabetic patients with and without retinopathy: a new technique for rapid assessment	2
Dhanesha U, Gilchrist J, Miles D, Bradford N, Weatherill J. (1991) Loss of visual function associated with microalbuminuria in diabetes mellitus: a pilot study	2
Di Leo MA, Caputo S, Falsini B, Porciatti V, Greco AV, Ghirlanda G. (1994) Presence and further development of retinal dysfunction after 3-years follow-up in IDDM patients without angiographically documented vasculopathy	2
Di Leo MA, Caputo S, Falsini B, Porciatti V, Minnella A, Greco AV, *et al.* (1992) Nonselective loss of contrast sensitivity in visual system testing in early type 1 diabetes	2
Dickson PR, McCarty CA, Keeffe JE, Baxter R, Harper CA, Taylor HR. (1996) Diabetic retinopathy: examination practices and referral patterns of general practitioners	2
Doucet J, Chassagne P, Poutrain JR, Ozenne G, Denis P, Bercoff E, *et al.* (1992) [Dyschromatopsia: a manifestation of diabetic neuropathy]	4
Doucet J, Chassagne P, Trivalle C, Ozenne G, Retout A, Parain D, *et al.* (1994) [Dyschromatopsia: manifestation or epiphenomenon in the course of diabetic neuropathy]	3
Drum B, Armaly MF, Huppert WE. (1987) Sources of short wavelength sensitivity loss in glaucoma	3
Dunn NR, Bough P. (1996) Standards of care of diabetic patients in a typical English community	2
Elia Y. (2004) Is poor glucose control associated with colour vision deficiencies before retinopathy in pre-teen children with type 1 diabetes?	5
Elliott M, Plehwe W, Kearns M, Yue DK, Turtle JR. (1988) Visual contrast sensitivity in diabetes using a simple screening test [meeting abstract]	2
Erb C, Fahle M. (2006) [Colour vision and acquired colour vision disturbances. I. basic aspects]	1
Esbester M. (2002) The Portsmouth retinopathy screening scheme	1
Facey K, Cummins E, Macpherson K, Morris A, Reay L, Slattery J. (2002) Organisation of services for diabetic retinopathy screening. *Health Technology Assessment Report 1*	1, 2
Farber ME, Lotshaw RR. (1986) Screening for diabetic retinopathy contrast sensitivity function [meeting abstract]	4
Faria de Abreu JR, Neves F, Reis J. (1981) [Functional retinal abnormalities in diabetic patients with no retinopathy]	5
Farnsworth D. (1957) The Farnsworth-Munsell 100-hue test manual	1
Feigl B, Brown B, Lovie-Kitchin J, Swann P. (2005) Monitoring retinal function in early age-related maculopathy: visual performance after 1 year	3
Feitosa-Santana C, Oiwa NN, Paramei GV, Bimler D, Costa MF, Lago M, *et al.* (2006) Color space distortions in patients with type 2 diabetes mellitus	3, 5
Fendrick AM, Javitt JC, Chiang YP. (1992) Cost-effectiveness of the screening and treatment of diabetic retinopathy. What are the costs of underutilization?	1, 2

Study	Reason for exclusion[a]
Fong DS, Gottlieb J, Ferris FL, III, Klein R. (2001) Understanding the value of diabetic retinopathy screening	1
Fontana M, Verriest G. (1986) Modification by fluoangiography of color vision in diabetic patients	3
Foster DT, Wylie-Rosett J, Walker EA. (1996) Local survey of optometrists about dilated fundoscopic examinations for patients with diabetes: making use of phone book yellow-page listings	2
Foulds WS, McCuish A, Barrie T, Green F, Scobie IN, Ghafour IM, *et al*. (1983) Diabetic retinopathy in the west of Scotland: its detection and prevalence and the cost-effectiveness of a proposed screening programme	2
Fristrom B. (1998) Peripheral and central colour contrast sensitivity in diabetes	5
Gartaganis SP, Psyrojannis AJ, Koliopoulos JX, Mela EK. (2001) Contrast sensitivity function in patients with impaired oral glucose tolerance	2
Garvican L, Clowes J, Gillow T. (2000) Preservation of sight in diabetes: developing a national risk reduction programme	2
Gatling W, Howie AJ, Hill RD. (1995) An optical practice-based diabetic eye screening programme	2
Gerkowicz M. (1989) [Color vision in patients with juvenile-onset diabetes mellitus]	4
Ghafour IM, Foulds WS, Allan D. (1984) Short-term effect of slit-lamp illumination and argon laser light on visual function of diabetic and non-diabetic subjects	3
Ghafour IM, Foulds WS, Allan D, McClure E. (1982) Contrast sensitivity in diabetic subjects with and without retinopathy	2
Gillibrand WP, Broadbent DM, Swain JY, Harding SP, Vora JP. (2000) Knowledge levels of diabetic eye disease in people with diabetes: results of a descriptive survey	2
Ginsberg AP. (1984) A new contrast sensitivity vision test chart	2
Ginsburg AP, Cannon MW. (1983) Comparison of three methods for rapid determination of threshold contrast sensitivity	3
Giusti C. (2001) Lanthony 15-Hue Desaturated Test for screening of early color vision defects in uncomplicated juvenile diabetes	3, 5
Giusti C. (2002) Novel diagnostic and therapeutic approaches to the diabetic retinopathy	1
Glenn S. (2000) Risk factors screening and treatment of diabetic eye disease	1
Gruben C, Zrenner E. (1990) Contrast sensitivity loss in early diabetic retinopathy [meeting abstract]	2
Gualtieri M, Nishi M, Lago M, Ventura DF. (2005) Color discrimination and chromatic contrast sensitivity assessed in type 2 diabetic patients without retinopathy	3, 5
Gunduz K, Arden GB, Perry S. (1988) Color-contrast thresholds are elevated in mild disease though other color tests give normal results [meeting abstract]	1
Hampson S. (2001) Experience of setting up a retinal screening service	2
Hardy KJ, Fisher C, Heath P, Foster DH, Scarpello JH. (1995) Comparison of colour discrimination and electroretinography in evaluation of visual pathway dysfunction in aretinopathic IDDM patients	3
Hardy KJ, Lipton J, Scase MO, Foster DH, Scarpello JH. (1992) Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas	3
Hardy KJ, Scarpello JH, Foster DH. (1995) Relation between blood glucose control over 3 months and colour discrimination in insulin dependent diabetic patients without retinopathy	3, 4
Harvey JN, Craney L, Nagendran S, Ng CS. (2006) Towards comprehensive population-based screening for diabetic retinopathy: operation of the North Wales diabetic retinopathy screening programme using a central patient register and various screening methods	2
Heitz R, Heitz-Wackermann RM. (1987) [The Haguenau automatized Farnsworth 100 hue test]	1

Study	Reason for exclusion[a]
Hellstedt T, Kaaja R, Teramo K, Immonen I. (1997) Contrast sensitivity in diabetic pregnancy	2
Henricsson M, Nyström L, Blohmé G, Ostman J, Kullberg C, Svensson M, *et al.* (2003) The incidence of retinopathy 10 years after diagnosis in young adult people with diabetes	2
Hood DC, Benimoff NI, Greenstein VC. (1984) The response range of the blue-cone pathways: a source of vulnerability to disease	2, 3
Howes SC, Caelli T, Mitchell P. (1982) Contrast sensitivity in diabetics with retinopathy and cataract	2, 5
Ichikawa H, Hukami K, Tanabe S. (1983) Standard pseudoisochromatic plates. 2. For acquired color vision defects	2
Immonen IJ, Hellstedt T, Teramo K, Kaaja R. (1996) Contrast sensitivity during pregnancy in diabetics with minimal retinopathy [meeting abstract]	2
James M, Turner DA, Broadbent DM, Vora J, Harding SP. (2000) Cost effectiveness analysis of screening for sight threatening diabetic eye disease	2
Javitt JC, Aiello LP. (1996) Cost-effectiveness of detecting and treating diabetic retinopathy	1, 2
Javitt JC, Canner JK, Frank RG, Steinwachs DM, Sommer A. (1990) Detecting and treating retinopathy in patients with type 1 diabetes mellitus. A health policy model	2
Karadeniz S, Kir N, Yilmaz MT, Ongor E, Dinccag N, Baar D, *et al.* (1996) Alteration of visual function in impaired glucose tolerance	3
Kawasaki K, Yonemura K, Yokogawa Y, Saito N, Kawakita S. (1986) Correlation between ERG oscillatory potential and psychophysical contrast sensitivity in diabetes	2
Kergoat H, Lovasik JV. (1991) Accommodative performance for chromatic targets in diabetes mellitus: a preliminary report	5
Kessel L, Alsing A, Larsen M. (1999) Diabetic vs non-diabetic colour vision after cataract surgery	5
Khosla PK, Talwar D, Tewari HK. (1991) Contrast sensitivity changes in background diabetic retinopathy	2
Kinnear PR. (1970) Proposals for scoring and assessing the 100-hue test	1
Kinnear PR, Aspinall PA, Lakowski R. (1972) The diabetic eye and colour vision	4
Kitano S. (2005) [Grading of diabetic retinopathy from non-stereoscopic color fundus photographs: relationship to fluorescein angiography findings and three-year prognosis]	2
Klein BE, Davis MD, Segal P, Long JA, Harris WA, Haug GA, *et al.* (1984) Diabetic retinopathy: assessment of severity and progression	2
Klein R, Klein BE, Moss SE. (1990) The Wisconsin epidemiologic study of diabetic retinopathy: an update	2
Klemperer I, Yassur Y. (1987) [Contrast sensitivity in testing visual functions in diabetics]	1
Knudsen LL, Andersen CU, Lervang HH, Vad J. (2002) [Screening for diabetic retinopathy in the County of North Jutland]	2
Krasny J, Cihelkova I, Dominek Z, Soucek P, Treslova L, Lebl J, *et al.* (2007) [Contrast sensitivity and fluorescein angiography in evaluating the ocular changes in the relation to the diabetes mellitus type 1 compensation in young adult patients	2
Kristensen JK, Sandbaek A, Bro F, Lassen JF, Lauritzen T. (2004) Routine screening for diabetic eye complications in a population based cohort of 4.438 persons with type 2 diabetes in a Danish county	2
Kumari Rani P, Raman R, Manikandan M, Mahajan S, Paul PG, Sharma T. (2006) Patient satisfaction with tele-ophthalmology vs ophthalmologist-based screening in diabetic retinopathy	2
Kurtenbach A, Erb C, Adler M, Born B. (2001) Colour vision in diabetics tested by the Farnsworth–Munsell 28-hue desaturated test	5
Kurtenbach A, Flogel W, Erb C. (2002) Anomaloscope matches in patients with diabetes mellitus	5
Kurtenbach A, Schiefer U, Neu A, Zrenner E. (1999) Development of brightness matching and colour vision deficits in juvenile diabetics	3, 5

Study	Reason for exclusion[a]
Kurtenbach A, Schiefer U, Neu A, Zrenner E. (1999) Preretinopic changes in the colour vision of juvenile diabetics	5
Kurtenbach A, Schiefer U, Zrenner E, Neu A. (1997) Juvenile diabetics and the colour vision meter	5
Kurtenbach A, Wagner U, Neu A, Schiefer U, Ranke MB, Zrenner E. (1994) Brightness matching and colour discrimination in young diabetics without retinopathy	5
Lagerlof O. (1978) Quantitative assessment of acquired colour vision deficiency in maculopathy	1
Lagerlof O. (1999) [To test color vision is also important]	1
Lakowski R, Aspinall PA, Kinnear PR. (1972) Association between colour vision losses and diabetes mellitus	4
Lanthony P. (1978) The new color test	1
Lee SC. (1997) Screening for early diabetic retinopathy by a high resolution computer vision system [meeting abstract]	1
Lee SJ, McCarty CA, Sicari C, Livingston PM, Harper CA, Taylor HR, *et al.* (2000) Recruitment methods for community-based screening for diabetic retinopathy	2
Lee SJ, Sicari C, Harper CA, Livingston PM, McCarty CA, Taylor HR, *et al.* (2000) Examination compliance and screening for diabetic retinopathy: a 2-year follow-up study	2
Leese G, Broadbent D, Harding S, Vora J. (1995) Screening for diabetic retinopathy. Approaching 90% sensitivity with new techniques	1
Leese GP, Broadbent DM, Harding SP, Vora JP. (1996) Detection of sight threatening diabetic eye disease	1
Leese GP, Morris AD, Swaminathan K, Petrie JR, Sinharay R, Ellingford A, *et al.* (2005) Implementation of national diabetes retinal screening programme is associated with a lower proportion of patients referred to opthalmology	2
Leid J, Gastaud P, Vola J. (1982) Resultats d'examens de la vision color ée chez les diabétiques avec ou sans rétinopathie	1
Leid J, Gastaud P, Vola JL. (1985) [Diagnostic and prognostic significance of chromatic syndromes in diabetes]	1
Leid J, Leid V. (1990) [Medical management of diabetic retinopathy. Pathophysiologic rationale. Time-course of color vision impairment and angiography in patients treated for one year]	4
Liska V. (1999) [Contrast sensitivity in type 1 diabetics without symptoms of diabetic retinopathy]	2
Liska V, Dostalek M. (1999) Are contrast sensitivity functions impaired in insulin dependent diabetics without diabetic retinopathy?	2
Livingston PM, McCarty CA, Woods CA, Harper AC, Keeffe JE, Taylor HR. (1998) Use of focus groups to identify health promotion strategies for the early detection of diabetic retinopathy	2
Livingston PM, Wood CA, Butler M, Oh J, Keefe JE, Taylor HR. (1998) General practitioners are the most important conveyors of information to their patients regarding diabetic retinopathy	1
Lobefalo L, Verdesca G, D'Antonio E, Verrotti A, Rancitelli L, Mancini A, *et al.* (1996) [Chromatic perimetry in diabetics without retinopathy]	3, 5
Lobefalo L, Verrotti A, Mastropasqua L, Chiarelli F, Della Loggia G, Morgese G, *et al.* (1998) Colour and achromatic perimetry in diabetic children without retinopathy	3, 5
Lobefalo L, Verrotti A, Mastropasqua L, Della Loggia G, Cherubini V, Morgese G, *et al.* (1998) Blue-on-yellow and achromatic perimetry in diabetic children without retinopathy	4, 5
Lopez M, Martin R, Martinez R, Garcia J, Sanchez R, Lopez I, *et al.* (2002) What is the cause of the impaired color vision in diabetic patients? [meeting abstract]	4
Lutz M, Bresinck GH. (1989) Diabetic retinopathy and visual field sensitivity assessed with color perimetry [meeting abstract]	5

Study	Reason for exclusion[a]
Maberley D, Walker H, Koushik A, Cruess A. (2003) Screening for diabetic retinopathy in James Bay, Ontario: a cost-effectiveness analysis	2
Maberley DAL, Koushik A, Cruess AF. (2002) Factors associated with missed eye examinations in a cohort with diabetes	2
MacCuish AC. (1993) Early detection and screening for diabetic retinopathy	1
Mackie SW, Barrie T, Maccuish AC, Walsh G. (1993) Measurement of contrast sensitivity in patients with diabetic retinopathy using the Pelli–Robson chart [meeting abstract]	2
Mailath L. (1972) The AN-59 anomaloscope in the research of acquired colour vision deficiencies	5
Maione M, Bontempelli G, Scoccianti L, Righi I. (1985) [Color vision and diabetes. Hue test results in reexamination after 5 yr]	3
Maione M, Graziosi P, Scoccianti L, Righi I, Bontempelli G, La Medica A. (1987) [Contrast sensitivity for coloured gratings in diabetic retinopathy]	4
Malagola R, Gargiulo P, Giusti C, Bosco D, Pannarale L, Scalfati M, *et al*. (1994) Screening of early color-vision defects in insulin-dependent diabetic-patients with background retinopathy [meeting abstract]	4
Maliszewski M, Dennis C, DeCoste KC. (1988) Prevention, detection and treatment of diabetic eye disease: an overview and demonstration project	2
Mäntyjärvi M. (1987) Screening of colour vision defects in diabetic patients	3
Mäntyjärvi M. (1989) Colour vision and dark adaptation in diabetic patients after photocoagulation	2, 3
Mäntyjärvi M. (1992) Screening of diabetics who read incorrectly colour-dependent glucose test-strips	3, 4
Mäntyjärvi M. (1993) Colour vision in diabetic patients after photocoagulation treatment. A five-year follow-up	3, 5
Mäntyjärvi M, Nielikainen S, Osmoviita J, Myohanen T. (1988) [Diabetes and color vision]	1
Marmion VJ. (1977) The results of a comparison of the hundred hue test and static color perimetry in diabetic retinopathy (short description of methods and results)	3
Mastropasqua L, Lobefalo L, Carpineto P, Ciancaglini M, Calogiuri MT, Verrotti A, *et al*. (1994) Study of color discrimination in insulin-dependent mellitus diabetes	3
McCarlie J, Alexander G, Sommerville J, McGettrick P, MacPherson N, Collier A. (1999) Use of collaborative audit to assist local implementation of the SIGN guideline for prevention of visual impairment in diabetes	2
Mittl R, Jindra LF, Zemon V, Ng E, Peralta M. (1989) Contrast sensitivity testing in patients with diabetic maculopathy [meeting abstract]	2
Mollon JD, Pokorny J, Knoblauch K. (2003) Normal and defective colour vision	1
Montori VM. (2001) Review: mydriatic retinal photography is the most effective test for detecting diabetic retinopathy. Commentary on Hutchinson A, McIntosh A, Peters J, O'Keefe C, Khunti K, Baker R, *et al*. Effectiveness of screening and monitoring tests for diabetic retinopathy	1
Mortlock KE, Chiti Z, North RV, Drasdo N, Owens DR. (2003) L/M and S-cone ERGs in subjects with no or early diabetic retinopathy [meeting abstract]	3, 4
Moss SE, Klein R, Klein BE. (1995) Factors associated with having eye examinations in persons with diabetes	2
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Weiss H, Zwas F, McKinnon P. (1979) Spectral sensitivity measurements in early diabetic retinopathy [meeting abstract]	1
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Study	Reason for exclusion[a]
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Yamamoto S, Kamiyama M, Nitta K, Yamada T, Hayasaka S. (1996) Selective reduction of the S cone electroretinogram in diabetes	5
Younis N, Broadbent DM, James M, Harding SP, Vora JP. (2002) Current status of screening for diabetic retinopathy in the UK	1
Zisman F, Adams AJ. (1982) Spectral sensitivity of cone mechanisms in juvenile diabetics [meeting abstract]	1
Zwas F, Weiss H, McKinnon P. (1980) Spectral sensitivity measurements in early diabetic retinopathy	1

a Reason for exclusion: 1 – no primary data; 2 – inappropriate intervention; 3 – no reference standard/not phase I; 4 – inappropriate outcome; 5 – sample size inadequate.

Appendix 5

Online survey of screening programme managers and clinical leads

1. Introduction

We have been commissioned by the Health Technology Assessment programme to conduct a comprehensive overview of methods used in testing for retinopathy in people with diabetes.

In order to ensure that project outputs are relevant to service providers and decision makers, we are collecting information from local leads for retinopathy screening on what testing strategies are currently in use, over and above the requirements of the National Screening Programme for Diabetic Retinopathy. We would also like your views on testing strategies which should be prioritized for future research funding.

We would therefore be grateful if you could spare the time to complete the following short questionnaire. All responses will be used for research purposes only.

Name

Designation

Local Programme Name

Geographical region of local screening programme

- ☐ East Midlands
- ☐ East of England
- ☐ London
- ☐ North East
- ☐ North West
- ☐ South East
- ☐ South West
- ☐ West Midlands
- ☐ Yorkshire and the Humber
- ☐ Northern Ireland
- ☐ Scotland
- ☐ Wales

Number of PCTs covered by local programme

2. Default Section

What is the primary method of retinal screening in your local programme?

- ☐ Retinal photography
- ☐ Direct ophthalmoscopy

* **Within your local programme, are any additional tests used, which are not required by the National Screening Programme for Diabetic Retinopathy?**

- ◯ Yes
- ◯ No

3.

What additional screening methods are currently used (either as part of routine clinical practice or research)?

- [ ] Contrast sensitivity
- [ ] Ocular coherence tomography (OCT)
- [ ] Colour vision testing
- [ ] Other

Please briefly describe the specific test(s) used.

4.

Are any of these tests routinely included in screening assessments?

- ◯ Yes
- ◯ No

If 'yes', please specify which ones.

- [ ] Contrast sensitivity
- [ ] Ocular coherence tomography (OCT)
- [ ] Colour vision testing
- [ ] Other (please specify)

Details/comments

5.

Are any of these tests used only in a research context?

- ◯ Yes
- ◯ No

If 'yes', please specify which ones.

- [ ] Contrast sensitivity
- [ ] Ocular coherence tomography (OCT)
- [ ] Colour vision testing
- [ ] Other (please specify)

Details/comments

6.

In which patients are the previously identified tests used?

	Patients receiving test
Contrast sensitivity	
Ocular coherence tomography (OCT)	
Colour vision testing	
Other (previously specified)	

If limited to a subgroup, please give details

7.

What is the clinical purpose of including the additional test or tests?

Contrast sensitivity	
Ocular coherence tomography (OCT)	
Colour vision testing	
Other (previously specified)	

8.

On what basis was the decision to introduce the additional test or tests made? (e.g. journal article, advice from colleague(s), clinical research interest)

Contrast sensitivity	
Ocular coherence tomography (OCT)	
Colour vision testing	
Other (previously specified)	

9.

*** Please state/describe any areas, relating to future testing strategy for the National Screening Programme for Diabetic Retinopathy, which you consider should be research priorities.**

- [ ] Contrast sensitivity
- [ ] Ocular coherence tomography (OCT)
- [ ] Colour vision testing
- [ ] Other (please specify)
- [ ] None

Details/comment

Appendix 6

STARD checklist for reporting of studies of diagnostic accuracy

Section and topic	Item number		On page number
Title/Abstract/Keywords	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity')	iii
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	5
Methods			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected	6
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard? (Participant inclusion criteria)	6
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected (Study design inclusion criteria)	6
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)? (Study design inclusion criteria)	6
Test methods	7	The reference standard and its rationale (Reference standard inclusion criteria)	6
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard (Data extraction)	6, Appendix 3
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard (Data analysis)	7
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard (Data extraction)	Appendix 3
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers (Quality assessment)	6, *Table 2*, *Figure 2*
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals) (Data analysis)	7
	13	Methods for calculating test reproducibility, if carried out	N/A

Results			
Participants	14	When study was performed, including beginning and end dates of recruitment (Data extraction)	Appendix 3
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms) (Data extraction)	Appendix 3
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended) (Data extraction)	Appendix 3 Study flow diagram p. 9
Test results	17	Time interval between the index tests and the reference standard, and any treatment administered in between (Quality assessment)	*Table 2*, *Figure 2*
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition (Data extraction)	Appendix 3
	19	A cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard (Data extraction)	Appendix 3
	20	Any adverse events from performing the index tests or the reference standard (Data extraction)	Appendix 3
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals) (Data extraction and results)	Appendix 3
	22	How indeterminate results, missing data and outliers of the index tests were handled (Data extraction)	Appendix 3
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if carried out (Results)	ROC plots
	24	Estimates of test reproducibility, if carried out	N/A
Discussion	25	Discuss the clinical applicability of the study findings	49–53

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By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

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Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

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The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

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Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

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A review of near patient testing in primary care.
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Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
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We look forward to hearing from you.

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