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

M Rodgers, R Hodges, J Hawkins, W Hollingworth, S Duffy, M McKibbin, M Mansfield, R Harbord, J Sterne, P Glasziou, P Whiting and M Westwood

December 2009
DOI: 10.3310/hta13600
How to obtain copies of this and other HTA programme reports

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with credit card or official purchase order)
– post (with credit card or official purchase order or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch Email: orders@hta.ac.uk
Magellan Tel: 02392 492 000
Concept House, Bell Road Fax: 02392 478 555
Basingstoke, Hants RG24 8FB, UK Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.
Colour vision testing for diabetic retinopathy: a systematic review of diagnostic accuracy and economic evaluation

M Rodgers,1* R Hodges,2 J Hawkins,2 W Hollingworth,2 S Duffy,1 M McKibbin,3 M Mansfield,4 R Harbord,2 J Sterne,2 P Glasziou,5 P Whiting2 and M Westwood1

1Centre for Reviews and Dissemination, University of York, UK
2Department of Social Medicine, University of Bristol, UK
3Department of Ophthalmology, St James’s University Hospital, Leeds, UK
4Diabetes and Thrombosis Research Group, Division of Medicine, Leeds General Infirmary, UK
5Department of Primary Care, University of Oxford, UK

*Corresponding author

Declared competing interests of authors: none

Published December 2009
DOI: 10.3310/hta13600

This report should be referenced as follows:


Health Technology Assessment is indexed and abstracted in Index Medicus/MEDLINE, Excerpta Medica/EMBASE, Science Citation Index Expanded (SciSearch®) and Current Contents®/Clinical Medicine.
NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.
Abstract

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

M Rodgers,1* R Hodges,2 J Hawkins,2 W Hollingworth,2 S Duffy,1 M McKibbin,3 M Mansfield,4 R Harbord,2 J Sterne,2 P Glasziou,5 P Whiting2 and M Westwood1

1Centre for Reviews and Dissemination, University of York, UK
2Department of Social Medicine, University of Bristol, UK
3Department of Ophthalmology, St James’s University Hospital, Leeds, UK
4Diabetes and Thrombosis Research Group, Division of Medicine, Leeds General Infirmary, UK
5Department of Primary Care, University of Oxford, UK

*Corresponding author

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.
Contents

Glossary and list of abbreviations .......... vii
Executive summary ......................... ix

1 Background ........................................ 1
   The aetiology, prevalence and diagnosis
   of diabetic retinopathy ....................... 1
   Current service provision .................... 2
   Description of technology under
   assessment ........................................ 2

2 Research questions ............................ 5
   Relevance of colour vision testing for
   diabetic retinopathy in the NHS ............. 5
   Overall aims and objectives of
   assessment ........................................ 5
   Methods for reviewing diagnostic
   accuracy ........................................... 5

3 Results of review of diagnostic accuracy 9
   Studies included in the review ............... 9
   Quality of included studies .................. 9
   Summary of test accuracy results ............. 11

4 Assessment of cost-effectiveness
evidence ........................................... 33
   Review of existing cost-effectiveness
   evidence .......................................... 33
   Independent economic assessment .......... 33

5 Survey of current practice ................. 47
   Methods ......................................... 47
   Results of the survey .......................... 47

6 Discussion ........................................ 49
   Statement of principle findings ............... 49
   Strengths and limitations of the
   assessment ....................................... 50

7 Conclusions .................................... 55
   Implications for service provision ........... 55
   Suggested research priorities ................. 55

Acknowledgements ............................ 57

References ....................................... 59

Appendix 1 Literature search strategies .. 63
Appendix 2 The QUADAS tool for
methodological assessment of diagnostic
studies .............................................. 75
Appendix 3 Data extraction tables ........... 77
Appendix 4 Table of excluded studies
with rationale ..................................... 117
Appendix 5 Online survey of screening
programme managers and clinical leads ... 129
Appendix 6 STARD checklist for reporting
of studies of diagnostic accuracy .............. 135

Health Technology Assessment reports
published to date ................................ 137

Health Technology Assessment
programme ........................................ 157
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

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

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.
**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.
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 tryglicerides and a low haematocrit level.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 guidance7,23,24 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\(^\text{25}\) 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.\(^\text{26}\)

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.\(^\text{26}\) 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.\(^\text{27}\)

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.\(^\text{27}\)

**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 defects, 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 studies31,32 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 reviews33 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.


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 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 (FNs), 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. 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

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

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 evaluated FM-100 CVT in diabetes patients.

Five of these studies compared mean error scores on the FM-100. The quality of reporting among these studies was generally low. Only one 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 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. described the patient selection criteria clearly.

**Lanthony desaturated D-15 test**

Six studies 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 participants were predominantly children and younger adults.

**Lanthony New Colour Test**

Two studies 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 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>
<thead>
<tr>
<th>Quality assessment of included studies*</th>
<th>(\text{Pseudoisochromatic plates}^a)</th>
<th>(\text{Farnsworth–Munsell 100 hue test}^b)</th>
<th>(\text{Lanthony desaturated D-15 test}^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals accounted for</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Uninterpretable results reported</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
</tr>
<tr>
<td>Clinical review bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Diagnostic review bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Test review bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Adequate reference standard execution details</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
<td>(\text{✗ ✗ ✓ ✓ ✓ ✓ ✓ ✓}^a)</td>
</tr>
<tr>
<td>Adequate test execution details</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Incorporation bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Differential verification bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Partial verification bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Disease progression bias avoided</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Appropriate reference standard</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Selection criteria described</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
<tr>
<td>Appropriate spectrum composition</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
<td>~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~</td>
</tr>
</tbody>
</table>

*Bernardczyk-Meller 2001, \(\text{Trick}^d\) 1988, \(\text{Doucet}^d\) 1991, \(\text{Maár}^d\) 2001, \(\text{Ismail}^d\) 1998, \(\text{Ayed}^d\) 1990, \(\text{Jeddi}^d\) 1994, \(\text{Greenstein}^d\) 1990, \(\text{Green}^d\) 1985, \(\text{Fong}^d\) 1999, \(\text{Baron}^d\) 1987, \(\text{Aspinall}^d\) 1983, \(\text{Sinha}^d\) 1979, \(\text{Farnsworth–Munsell 100 hue test}^d\)

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
### TABLE 2 Quality assessment of included studies* (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Appropriate spectrum composition</th>
<th>Appropriate reference described</th>
<th>Selection criteria standard</th>
<th>Appropriate reference</th>
<th>Disease progression bias avoided</th>
<th>Partial verification bias avoided</th>
<th>Differential verification bias avoided</th>
<th>Incorporation bias avoided</th>
<th>Adequate test execution details</th>
<th>Adequate reference standard execution details</th>
<th>Test review bias avoided</th>
<th>Diagnostic review bias avoided</th>
<th>Clinical review bias avoided</th>
<th>Uninterpretable results accounted for</th>
<th>Withdrawals reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mäntyjärvi 199546</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Mecca 198849</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Saracco 198050</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Lanthony New Colour Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsuo 199041</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Mecca 198849</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Mollon–Reffin Minimalist Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maár 200132</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Computerised/automated tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Alwis 199453</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Findl 200053</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Knowles 199654</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Ong 200455</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Tregear 199755</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Wong 200856</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Anomaloscopes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspinall 198356</td>
<td>?</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Mäntyjärvi 199546</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>

*a Studies appearing more than once evaluate more than one colour vision 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 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 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 evaluating the Ishihara test and one, a combination of the Ishihara and Tokyo Medical College tests (Table 3). One study did not report any outcomes for the Ishihara test and so will not be discussed further here.

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

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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{38,39} came from the ETDRS, one\textsuperscript{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\textsuperscript{38}
### TABLE 3  Key characteristics of pseudoisochromatic plate studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernardczyk-Meller 2001&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Inclusion criteria: patients for whom long-term follow-up data were available &lt;br&gt; Exclusion criteria: congenital colour vision deficiencies</td>
<td>Mean age: 17 years 100% type 1 DM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Normal vs ‘pathological’ CV test scores</td>
<td>Ophthalmoscopy &lt;br&gt; Pathological changes vs no pathological changes</td>
<td>D-15 desaturated (threshold: ‘pathological results’): TP: unclear; FP: 9; FN: unclear; TN: 21</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mirkiewicz-Sieradzka 1986&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Inclusion criteria: diabetes patients with signs of retinopathy &lt;br&gt; Exclusion criteria: patients with congenital red–green colour deficits; patients who had previously undergone photocoagulation</td>
<td>50.9% male</td>
<td>Pass vs fail (no threshold reported)</td>
<td>Ophthalmoscopy: &lt;br&gt; (I) microaneurysms and yellow spots; (II) microaneurysms, yellow spots and ‘wybroczyn’; (III) massive yellow spots; (IV) oedema &lt;br&gt; Fluorescein angiography: &lt;br&gt; (I) single leak; (II) larger leaks; (III) limited oedema; (IV) diffuse oedema</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>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) &lt;br&gt; 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)</td>
</tr>
<tr>
<td>Sinha 1979&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Inclusion criteria: diabetes patients &lt;br&gt; Exclusion criteria: patients giving the mildest indications about colour defects in family and/or growth impairment of vision</td>
<td>Mean age: 52.9 years</td>
<td>Normal colour vision; protan deficit; deutan deficit; tritan deficit</td>
<td>Slit-lamp biomicroscopy &lt;br&gt; DR vs no DR</td>
<td>Protan deficit: 0; 0; 33; 40 &lt;br&gt; Deutan deficit: 0; 0; 33; 40 &lt;br&gt; Tritan deficit: 4; 1; 29; 39</td>
<td>Protan deficit: 0 &lt;br&gt; Deutan deficit: 0 &lt;br&gt; Tritan deficit: 12%</td>
<td>Protan deficit: 100% &lt;br&gt; Deutan deficit: 100% &lt;br&gt; Tritan deficit: 100%</td>
<td>Protan deficit: 100% &lt;br&gt; deutan deficit: 100% &lt;br&gt; tritan deficit: 100%</td>
</tr>
</tbody>
</table>

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. <br> <sup>a</sup> 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 excluded patients who did not have good visual acuity and one study excluded patients with soft exudates.

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%. The reference standard in all of the diagnostic accuracy studies was used to distinguish between patients with retinopathy and those without. One of these studies made the additional distinction between those with no or background retinopathy and those with more serious retinopathy. Three studies used the reference standard to establish the grade of retinopathy in line with the Airlie House classification system. The study 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 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 evaluated the Lanthony desaturated D-15 test in patients with diabetes, all of which provided diagnostic accuracy data (Table 5).


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 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
‘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\(^4^6\)–\(^5^0\) 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\(^3^2\) reported a sensitivity of 36% and a specificity of 88%.

Of the two studies investigating DR in younger patients, one\(^4^7\) 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\(^4^6\) 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\(^4^9,5^1\) evaluated the NCT in diabetes patients (Table 6).

One study\(^4^9\) used a reference standard of combined ophthalmoscopy with fluorescein angiography, whereas the second\(^5^1\) did not specify a reference standard. Both studies aimed to differentiate between patients with and without DR. Mecca et al.\(^4^9\) defined retinopathy as the presence of at least 10 microaneurysms and small haemorrhages, whereas Matsuo et al.\(^5^1\) did not define retinopathy.

Both studies collected total error scores on the NCT, with Mecca et al.\(^4^9\) dichotomising participants as having either ‘normal colour vision’ (no errors) or ‘altered colour vision’ (any score above 0).

The study by Matsuo et al.\(^5^1\) 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.\(^4^9\) 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\(^3^2\) 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\(^3^1,5^2–5^6\) evaluated computerised CVTs in patients with diabetes (Table 8). Four of these studies evaluated variants of the SGM and one evaluated the ChromaTest\(^5^6\) (see Chapter 1, Automated/computerised tests), all of which were co-authored by developers of the system itself. A sixth study\(^5^3\) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
<th>Reference standard (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic accuracy studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayed 199037</td>
<td>Inclusion criteria: visual acuity $\geq 5/10$</td>
<td>Mean age: 44 years</td>
<td>‘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 $\geq$ participant’s age in years multiplied by two, plus 30 (axis not well defined); ‘dyschromatopsia’ if TES is $\geq$ participant’s age in years multiplied by two, plus 30 (with B-Y or R-G axis).</td>
<td>Fluorescein angiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37% male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>39% type 1 DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 198540</td>
<td>Inclusion criteria: diabetes patients attending for routine ocular screening</td>
<td>Dichotomous: abnormal TES vs normal score</td>
<td>Ophthalmoscopy</td>
<td>Dichotomous: serious vs non-serious</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: patients with soft exudates</td>
<td>Ophthalmoscopy</td>
<td>DR vs no DR</td>
<td></td>
</tr>
<tr>
<td>Jeddi 199443</td>
<td>Inclusion criteria: visual acuity 10/10</td>
<td>Categorical: normal, weak discrimination, dyschromatopsia</td>
<td>Ophthalmoscopy</td>
<td>DR vs no DR</td>
</tr>
<tr>
<td>Trick 198845</td>
<td>Inclusion criteria: DM patients with no or mild to moderate background retinopathy; visual acuity of at least 20/30 and intraocular pressure $&lt;21$ mmHg in the eye to be tested</td>
<td>Continuous/average: square root of TES (SQRT TES) and partial error scores (B-Y, R-G)</td>
<td>Conventional retinal photography</td>
<td>Dichotomous: no retinopathy vs preproliferative background retinopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: patients with macular oedema detected in either the ophthalmoscopic examination or the fundus photographs</td>
<td>Dichotomous: total/partial error score $&gt;2$ SD above the normal mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies comparing mean values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspinall 198336</td>
<td>Inclusion criteria: diabetes patients $&lt;70$ years old with normal fundi</td>
<td>Dichotomous</td>
<td>Ophthalmoscopy</td>
<td>No retinopathy vs retinopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: congenital colour vision defects; cataracts</td>
<td>Continuous/average: SQRT TES for deferred eyes is presented for each grade of macular oedema</td>
<td>Method not stated/final diagnosis</td>
<td>Graded: no macular oedema; not clinically significant macular oedema; clinically significant macular oedema</td>
</tr>
<tr>
<td>Barton 198738</td>
<td></td>
<td>Continuous/average: SQRT TES for deferred eyes is presented for each grade of macular oedema</td>
<td>Method not stated/final diagnosis</td>
<td>Graded: no macular oedema; not clinically significant macular oedema; clinically significant macular oedema</td>
</tr>
<tr>
<td>TP, FP, TN, FN</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Other outcome data</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>Abnormal colour vision: 70, 58, 25, 47</td>
<td>Abnormal colour vision: 74%</td>
<td>Abnormal colour vision: 45%</td>
<td>Abnormal colour vision with dyschromatopsia: 52%</td>
<td></td>
</tr>
<tr>
<td>Abnormal colour vision with dyschromatopsia: 46, 42, 49, 63</td>
<td>Abnormal colour vision with dyschromatopsia: 48%</td>
<td>Abnormal colour vision with weak discrimination: 26%</td>
<td>Abnormal colour vision with weak discrimination: 85%</td>
<td></td>
</tr>
<tr>
<td>Abnormal colour vision with weak discrimination: 25, 16, 70, 89</td>
<td>R-G deficits: 29, 30, 66, 75</td>
<td>R-G deficits: 31%</td>
<td>R-G deficits: 71%</td>
<td></td>
</tr>
<tr>
<td>40, 46, 22, 124</td>
<td>72%</td>
<td>66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25, 11, 13, 11</td>
<td>66%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total error score: 5, 7, 30, 15</td>
<td>Total error score: 14%</td>
<td>Total error score: 68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-Y partial error score: 4, 5, 32, 16</td>
<td>B-Y partial error score: 11%</td>
<td>B-Y partial error score: 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-G partial error score: 4, 7, 16, 30</td>
<td>R-G partial error score: 20%</td>
<td>R-G partial error score: 81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No FM-100 data reported</td>
<td></td>
</tr>
</tbody>
</table>

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)
### Results of review of diagnostic accuracy

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
<th>Reference standard (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fong 199939</td>
<td>Inclusion criteria: no attempt was made to eliminate cases of congenital R-G colour deficiency or other known colour vision defects</td>
<td>55% male</td>
<td>Continuous/average: SQRT TES</td>
<td>Conventional retinal photography ETDRS graded</td>
</tr>
<tr>
<td>Greenstein 199041</td>
<td>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</td>
<td>Mean age: 45.8 years 100% type I DM</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Ismail 199842</td>
<td>Exclusion criteria: any sign of cataracts on ophthalmoscopy; congenital colour deficiency; major systemic pathology other than DM</td>
<td>Mean age: 57.7 years 0% type I DM</td>
<td>Continuous/average: total and partial (B-Y axis and R-G axis) error scores were calculated; SQRT transformation was used before parametric analysis</td>
<td>Ophthalmoscopy Conventional retinal photography Graded: modified Airlie House classification: DRL10, DRL30</td>
</tr>
<tr>
<td>Lombrail 198344</td>
<td>Inclusion criteria: type 1 DM patients</td>
<td>Continuous/average: FM-100 hue score</td>
<td>Fluorescein angiography Graded: (A) no retinopathy; (B) only angiographic retinopathy; (C) background retinopathy; (D) preproliferative retinopathy; (E) proliferative retinopathy; (F) retinopathy at incurable stage</td>
<td></td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
<th>Reference standard (grading method)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fong 1999</td>
<td>Inclusion criteria: no attempt was made to eliminate cases of congenital R-G colour deficiency or other known colour vision defects</td>
<td>55% male</td>
<td>Continuous/average: SQRT TES</td>
<td>Conventional retinal photography</td>
<td>ETDRS graded</td>
<td>24%</td>
<td>100%</td>
</tr>
<tr>
<td>Greenstein 1990</td>
<td>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</td>
<td>Mean age: 45.8 years</td>
<td>100% type I DM</td>
<td>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</td>
<td>Ophthalmoscopy/conventional retinal photography/fluorescein angiography</td>
<td>Graded: modified Airlie House classification: graded levels 1 to 4</td>
<td>TES (estimated from figure): DRL10: 9.7; DRL20: 9.9; DRL30: 14.0</td>
</tr>
<tr>
<td>Ismail 1998</td>
<td>Exclusion criteria: any sign of cataracts on ophthalmoscopy; congenital colour deficiency; major systemic pathology other than DM</td>
<td>Mean age: 57.7 years</td>
<td>0% type 1 DM</td>
<td>Continuous/average: total and partial (B-Y axis and R-G axis) error scores were calculated; SQRT transformation was used before parametric analysis</td>
<td>Ophthalmoscopy</td>
<td>Conventional retinal photography</td>
<td>Graded: modified Airlie House classification: DRL10, DRL30</td>
</tr>
<tr>
<td>Lombrail 1983</td>
<td>Inclusion criteria: type 1 DM patients</td>
<td>FM-100 hue score</td>
<td>Fluorescein angiography</td>
<td>Graded: (A) no retinopathy; (B) only angiographic retinopathy; (C) background retinopathy; (D) preproliferative retinopathy; (E) proliferative retinopathy; (F) retinopathy at incurable stage</td>
<td>Comparison of multiple groups (ANOVA)</td>
<td>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)</td>
<td></td>
</tr>
</tbody>
</table>

**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
### TABLE 5  Key characteristics of D-15 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernardczyk-Meller 2001</td>
<td>Inclusion criteria: patients for whom long-term follow-up data were available</td>
<td>Mean age: 17 years</td>
<td>Normal vs ‘pathological’ CV test scores</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: congenital colour vision deficiencies</td>
<td>100% type 1 DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean diabetes duration: 7.8 years (range 3–18 years)</td>
<td></td>
</tr>
<tr>
<td>Doucet 1991</td>
<td>Exclusion criteria: people aged &gt; 65 years; visual acuity &lt; 4/10; cataract or glaucoma; known congenital dyschromatopsia; deterioration in mental functioning; using medicines that could alter colour vision</td>
<td>Mean (SD) age: 43.4 (14.4) years</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62% male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>88% type 1 DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD) diabetes duration: 134 (106) months</td>
<td></td>
</tr>
<tr>
<td>Maár 2001</td>
<td>Inclusion criteria: type 1 DM; best corrected visual acuity of at least 0.4 LogMAR (0.4 Snellen value); &lt; 50 years; no lens opacities</td>
<td>Mean age: 29.5 years</td>
<td>D-15: total colour difference score (TCDS)</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>41% male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% type 1 DM</td>
<td></td>
</tr>
<tr>
<td>Mäntyjärvi 1995</td>
<td>Inclusion criteria: schoolchildren with diabetes and healthy eyes at recruitment</td>
<td>Mean (SD) age: 14 (2) years</td>
<td>Pass/fail for each test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.3% male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD) diabetes duration: 6 (4) years</td>
<td></td>
</tr>
<tr>
<td>Mecca 1988</td>
<td>Inclusion criteria: all patients had duration &gt; 4 years; all patients had visual acuity 8/10 or better</td>
<td>Mean age: 51.1 years</td>
<td>Altered colour vision vs normal</td>
</tr>
<tr>
<td></td>
<td>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’)</td>
<td>Normal colour vision vs abnormal colour vision</td>
<td></td>
</tr>
<tr>
<td>Saracco 1980</td>
<td>Inclusion criteria: included patients with visual acuity ≥ 6/10.</td>
<td>Mean age: 51.1 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>Normal colour vision vs abnormal colour vision</td>
<td></td>
</tr>
</tbody>
</table>

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

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.
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\(^5\) additionally evaluated participants with indirect fundoscopy and retinal photography. The Findl et al. study\(^5\) 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.\(^5\) 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

---

**TABLE 6** Key characteristics of NCT studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsuo 1990(^5)</td>
<td>Inclusion criteria: visual acuity score &gt; 0.5 Exclusion criteria: participants with eyesight problems</td>
<td>Mean age: 57.4 years 54% male</td>
<td>Total error score (TES)</td>
</tr>
<tr>
<td>Mecca 1988(^4)</td>
<td>Inclusion criteria: all patients had duration &gt; 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’)</td>
<td>NCT</td>
<td>Altered colour vision (anything above zero) vs normal (no errors)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics (mean age,% male,% Type 1 DM)</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maår 2001(^3)</td>
<td>Inclusion criteria: type 1 DM; best corrected visual acuity of at least 0.4 LogMAR (0.4 Snellen value); &lt; 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</td>
<td>Mean age: 29.5 years 41% male 100% type 1 DM</td>
<td>Number of reliably identified coloured chips for each confusion line</td>
</tr>
</tbody>
</table>

D-15, Lanthony desaturated D-15 test; DM, diabetes mellitus; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.
## TABLE 6

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

## TABLE 7

<table>
<thead>
<tr>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Tritan axis; threshold error score of 1: sensitivity: 88.9%, specificity: 93.3%</td>
</tr>
<tr>
<td>Conventional retinal photography</td>
<td></td>
<td></td>
<td></td>
<td>Tritan axis; error score: CSMO (n = 10): 2.1 (0.74), no CSMO (n = 29): 1.03 (0.19)</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td></td>
<td></td>
<td></td>
<td>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; r² = 0.565)</td>
</tr>
<tr>
<td>Clinically significant macular oedema (CSMO) vs without CSMO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A total of four studies provided diagnostic accuracy data, one of which evaluated the ChromaTest study 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 participants with phakic eyes (p = 0.035). The only study reporting diagnostic accuracy data for the red–green contrast threshold indicated a sensitivity of 33% and specificity of 93% in detecting macular oedema or ischaemia (Table 8).
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 study specifically evaluated the machine’s tritan contrast threshold (TCT) test alongside retinal photography. This study reported a z-score of –1.75 (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, 95% to 97%)]. The values reported for photography alone appeared to be consistent with those reported elsewhere in the literature. 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
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 Alwis52 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.

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.
TABLE 8  Key characteristics of computerised/automated test studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Alwis 1994</td>
<td>Inclusion criteria: proven diagnosis of DM; visual acuity 6/12 or better</td>
<td>Mean age: 53.9 years</td>
<td>z-score thresholds based on standard deviations from –3.0 to 0</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>(range 18–84 years)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Findl 2000</td>
<td>Inclusion criteria: insulin-dependent type 1 diabetes patients; age &lt; 32 years; diabetes duration between 12 and 17 years</td>
<td>Mean (SD) age: 23.1</td>
<td>The threshold chrominonance of a coloured optotype without changes in luminance compared with the surrounding as a percentage</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>(4.3) years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>66% male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean diabetes duration: 12–17 years</td>
<td></td>
</tr>
<tr>
<td>Knowles 1996</td>
<td>Inclusion criteria: diabetic pseudophakes with/without retinopathy and age-matched phakic diabetic controls; pseudophakes were examined at least 3 months after cataract surgery</td>
<td>Mean age: 74.2 years</td>
<td>R-G or tritan discrimination sensitivity</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: visual acuity &lt; 6/12; previous laser eye treatment; other eye disease likely to affect CV (e.g. glaucoma/macular degeneration); significant cataract; observable posterior capsular opacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ong 2004</td>
<td>Inclusion criteria: consenting diabetes patients attending photographic screening</td>
<td>Mean age: 60.9 years</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: corrected visual acuity &lt; 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</td>
<td>21% (107/510) type 1 DM</td>
<td></td>
</tr>
<tr>
<td>Tregear 1997</td>
<td>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</td>
<td>Mean diabetes duration: 10.4 years</td>
<td>Longitudinal subgroup only: threshold scores +2 SDs above the lens equated mean</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age: 56 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30% type 1 DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD) diabetes duration: 14 years (range 1.5–60 years)</td>
<td></td>
</tr>
<tr>
<td>Reference standard (grading method)</td>
<td>TP, FP, TN, FN</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous: severe retinopathy vs non-severe retinopathy</td>
<td>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</td>
<td>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%</td>
<td>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%</td>
</tr>
<tr>
<td></td>
<td>Tritan score: 2 SD: 73%</td>
<td>Tritan score: 2 SD: 90%</td>
<td></td>
</tr>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal photography</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fundoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Airlie House classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous: no retinopathy vs background retinopathy</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous: STDR vs non-STDR</td>
<td>Any retinopathy: 24, 103, 18, 365</td>
<td>Any retinopathy: 57%</td>
<td>Any retinopathy: 78%</td>
</tr>
<tr>
<td></td>
<td>Maculopathy: 12, 30, 0, 468</td>
<td>Maculopathy: 94%</td>
<td>Maculopathy: 100%</td>
</tr>
<tr>
<td></td>
<td>STDR: 16, 26, 1, 467</td>
<td>STDR: 94%</td>
<td>STDR: 95%</td>
</tr>
<tr>
<td></td>
<td>STDR TCT + photography: 15, 2, 2, 491</td>
<td>STDR TCT + photography: 88%</td>
<td>STDR TCT + photography: 99%</td>
</tr>
<tr>
<td></td>
<td>12, 7, 7, 62</td>
<td>63%</td>
<td>90%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results of review of diagnostic accuracy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong 200874</td>
<td>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</td>
<td>Median 60 years (range 31–82 years) 0% type 1 DM</td>
<td>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)</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Study</th>
<th>Patient selection criteria</th>
<th>Clinical characteristics</th>
<th>Colour vision test (grading method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspinall 1983</td>
<td>Inclusion criteria: diabetes patients &lt; 70 years old with normal fundi Exclusion criteria: congenital colour vision defects; cataracts</td>
<td>Not stated</td>
<td>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</td>
</tr>
<tr>
<td>Mäntyjärvi 1995</td>
<td>Inclusion criteria: schoolchildren with diabetes and healthy eyes at recruitment</td>
<td>Mean age: 14 years (SD 2; range 9–19) 46.3% male Mean diabetes duration: 6 years (SD 4; range 1 month–15 years)</td>
<td>Retinopathy vs no retinopathy</td>
</tr>
</tbody>
</table>

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

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

### TABLE 9 Key characteristics of anomaloscope studies
Study Patient selection criteria

<table>
<thead>
<tr>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit-lamp biomicroscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grading according to the Early Treatment Diabetic Retinopathy Study extension of the Airlie House classification; no clinical retinopathy, NPDR and CSMO</td>
<td>TCCT detection of CSMO (NPDR used as control group): TP = 25, FP = 35, FN = 10, TN = 80</td>
<td>Sensitivity: 71% (53–83%)</td>
<td>Specificity: 71%</td>
<td>TCCT detection of CSMO (NPDR used as control group): 70% (60–78%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPDR vs no DR: 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CSMO vs NPDR: 71%</td>
</tr>
</tbody>
</table>

**Other outcome data**

- TCCT detection of CSMO (NPDR used as control group): 71% (53–83%)
- NPDR vs no DR: 30%
- CSMO vs NPDR: 71%

**Reference standard (grading method)**

<table>
<thead>
<tr>
<th>Reference standard (grading method)</th>
<th>TP, FP, TN, FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0, 0, 22, 31</td>
<td>0%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Method not stated/final diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotomous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0, 0, 22, 31</td>
<td>0%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

**Other outcome data**

- Yellow–blue colour discrimination (anomaloscope units JND) coefficient = $5.113 \times 10^{-2}$, standard error = $1.39 \times 10^{-2}$, t = 3.67
**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. 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).

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 (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, 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. 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. Patients are invited for screening at annual intervals. Screening is performed by a trained and accredited technician 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. However, it is currently unclear to what extent this could affect treatment and patient outcomes. There are many methods for CVT (e.g., TCT, D-15, Mollon–Reffin Minimalist Test).

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, 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. 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. study, which reported that 79% of type 1 and 77% of type 2 patients responded to the invitation and attended screening. However, estimates of response rates to retinal photography screening invitations in the UK vary widely. 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

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

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. 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). 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.
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. 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. reported diabetes-related eye disease using an adaptation of the ETDRS gradings, which we mapped to the English NSC Retinopathy Grading Standard 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 andgradable 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, 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
Background retinopathy

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 13).

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%. 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 photocoagulation80 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 STDR72,73 (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 13).

A proportion of patients with preproliferative STDR are not initially offered laser photocoagulation80 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 STDR72,73 (Table 11).
### TABLE 11

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Point estimate</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>Source</th>
<th>PSA distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening attendance:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0.79</td>
<td>0.50</td>
<td>1</td>
<td>Younis 2002</td>
<td>Uniform (0.5, 1)</td>
</tr>
<tr>
<td>Type 2</td>
<td>0.77</td>
<td>0.50</td>
<td>1</td>
<td></td>
<td>Uniform (0.5, 1)</td>
</tr>
<tr>
<td><strong>Diagnostic accuracy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Photography</strong></td>
<td></td>
<td></td>
<td></td>
<td>Ong 2004</td>
<td></td>
</tr>
<tr>
<td>Specificity no retinopathy</td>
<td>0.95</td>
<td>0.93</td>
<td>0.97</td>
<td></td>
<td>Beta (435.97, 23.89)</td>
</tr>
<tr>
<td>Specificity background retinopathy</td>
<td>0.95</td>
<td>0.93</td>
<td>0.97</td>
<td></td>
<td>Beta (435.97, 23.89)</td>
</tr>
<tr>
<td>Sensitivity STDR</td>
<td>0.88</td>
<td>0.64</td>
<td>0.99</td>
<td></td>
<td>Beta (11.49, 2.43)</td>
</tr>
<tr>
<td><strong>Photography with colour vision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity no retinopathy</td>
<td>0.90</td>
<td>0.86</td>
<td>0.94</td>
<td></td>
<td>Beta (191.25, 22.14)</td>
</tr>
<tr>
<td>Specificity background retinopathy</td>
<td>0.90</td>
<td>0.86</td>
<td>0.94</td>
<td></td>
<td>Beta (191.25, 22.14)</td>
</tr>
<tr>
<td>Sensitivity STDR</td>
<td>0.94</td>
<td>0.71</td>
<td>1</td>
<td></td>
<td>Beta (12.11, 1.71)</td>
</tr>
<tr>
<td><strong>Ophthalmologist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity no retinopathy</td>
<td>1</td>
<td>0.98</td>
<td>1</td>
<td>Assumption</td>
<td>Uniform (0.98, 1)</td>
</tr>
<tr>
<td>Specificity background retinopathy</td>
<td>1</td>
<td>0.98</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity STDR</td>
<td>1</td>
<td>0.98</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td>Younis 2002</td>
<td>Dirichlet</td>
</tr>
<tr>
<td>No retinopathy</td>
<td>0.538</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>0.365</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STDR</td>
<td>0.097</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical failure</td>
<td>0.044</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dirichlet</td>
</tr>
<tr>
<td>No retinopathy</td>
<td>0.741</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>0.234</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STDR</td>
<td>0.077</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical failure</td>
<td>0.110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>33.4</td>
<td></td>
<td></td>
<td>Younis 2002</td>
<td>Fixed</td>
</tr>
<tr>
<td>Type 2</td>
<td>64.9</td>
<td></td>
<td></td>
<td></td>
<td>Fixed</td>
</tr>
<tr>
<td><strong>Utility values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No retinopathy</td>
<td>0.83</td>
<td>0.63</td>
<td>1</td>
<td>Lloyd 2008</td>
<td>Normal (0.83, 0.10)</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>0.83</td>
<td>0.63</td>
<td>1</td>
<td></td>
<td>Normal (0.83, 0.10)</td>
</tr>
<tr>
<td>STDR</td>
<td>0.83</td>
<td>0.63</td>
<td>1</td>
<td></td>
<td>Normal (0.83, 0.10)</td>
</tr>
<tr>
<td>Blind</td>
<td>0.34</td>
<td>-0.02</td>
<td>0.70</td>
<td></td>
<td>Normal (0.34, 0.18)</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>Fixed</td>
</tr>
<tr>
<td><strong>Mortality hazard ratios (by diabetes type)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 vs no diabetes</td>
<td>3.70</td>
<td></td>
<td></td>
<td>Soedamah-Muthu 2006</td>
<td>Fixed</td>
</tr>
<tr>
<td>Type 2 vs no diabetes</td>
<td>1.93</td>
<td></td>
<td></td>
<td>Mulnier 2006</td>
<td>Fixed</td>
</tr>
</tbody>
</table>
### TABLE 11 Base-case parameter estimates, range and distribution used in the probabilistic sensitivity analysis, and data source (continued)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Point estimate</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>Source</th>
<th>PSA distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality hazard ratios (by retinopathy grade)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No retinopathy</td>
<td>Reference</td>
<td></td>
<td></td>
<td>Klein 199979</td>
<td>Lognormal (1.02, 0.34)*</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>1.02</td>
<td>0.52</td>
<td>1.99</td>
<td>Lognormal (1.02, 0.34)*</td>
<td></td>
</tr>
<tr>
<td>STDR/blind</td>
<td>1.28</td>
<td>0.62</td>
<td>2.62</td>
<td>Lognormal (1.28, 0.37)*</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment compliance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attendance at ophthalmologist</td>
<td>1</td>
<td>0.95</td>
<td>1</td>
<td>Uniform (0.95, 1)*</td>
<td></td>
</tr>
<tr>
<td>% of STDR receiving immediate photocoagulation</td>
<td>20.8%</td>
<td>10.4%</td>
<td>41%</td>
<td>Uniform (0.104, 0.410)*</td>
<td></td>
</tr>
<tr>
<td>% of preproliferative STDR (type 1) who develop proliferative STDR and have photocoagulation</td>
<td>13.5%</td>
<td>4.2%</td>
<td>22.7%</td>
<td>Uniform (0.042, 0.227)*</td>
<td></td>
</tr>
<tr>
<td>% of preproliferative STDR (type 2) who develop proliferative STDR and have photocoagulation</td>
<td>15%</td>
<td>10.2%</td>
<td>19.8%</td>
<td>Uniform (0.102, 0.198)*</td>
<td></td>
</tr>
<tr>
<td>Compliance with photocoagulation</td>
<td>1</td>
<td>0.95</td>
<td>1</td>
<td>Uniform (0.95, 1)*</td>
<td></td>
</tr>
<tr>
<td><strong>Discount rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td>3.5%</td>
<td></td>
<td></td>
<td>NICE</td>
<td>Fixed</td>
</tr>
<tr>
<td>QALYs</td>
<td>3.5%</td>
<td></td>
<td></td>
<td>Fixed</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional cost colour screening</td>
<td>£7.80</td>
<td>£3.90</td>
<td>£29</td>
<td>Uniform (£3.90, £29)*</td>
<td></td>
</tr>
<tr>
<td>Photographic screening</td>
<td>£29</td>
<td>£14.50</td>
<td>£58</td>
<td>Uniform (£14.50, £58)*</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologist appointment</td>
<td>£65</td>
<td>£32.50</td>
<td>£130</td>
<td>Uniform (£32.50, £130)*</td>
<td></td>
</tr>
<tr>
<td>Photocoagulation</td>
<td>£815</td>
<td>£407.50</td>
<td>£1630</td>
<td>Uniform (£407.50, £1630)*</td>
<td></td>
</tr>
<tr>
<td>Annual NHS cost of blindness</td>
<td>£872</td>
<td>£526</td>
<td>£1299</td>
<td>Normal (872, 197.20)d</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>NR</th>
<th>BR</th>
<th>STDR</th>
<th>Blind</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>0.9021</td>
<td>0.0809</td>
<td>0.0091</td>
<td>0.000</td>
<td>0.0074</td>
</tr>
<tr>
<td>BR</td>
<td>0</td>
<td>0.8659</td>
<td>0.1266</td>
<td>0.000</td>
<td>0.0075</td>
</tr>
<tr>
<td>STDR</td>
<td>0</td>
<td>0</td>
<td>0.8826</td>
<td>0.1080b</td>
<td>0.0095</td>
</tr>
<tr>
<td>Blind</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.9905</td>
<td>0.0095</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>NR</th>
<th>BR</th>
<th>STDR</th>
<th>Blind</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>0.8757</td>
<td>0.0789</td>
<td>0.0141</td>
<td>0.000</td>
<td>0.0312</td>
</tr>
<tr>
<td>BR</td>
<td>0</td>
<td>0.8447</td>
<td>0.1234</td>
<td>0.000</td>
<td>0.0319</td>
</tr>
<tr>
<td>STDR</td>
<td>0</td>
<td>0</td>
<td>0.8554</td>
<td>0.1046</td>
<td>0.0400</td>
</tr>
<tr>
<td>Blind</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.9600</td>
<td>0.0400</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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 photocoagulation75 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 = 44,23079) to an age and sex-matched cohort with no history of diabetes (n = 38,518,77 n = 219,79778). 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.\textsuperscript{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.\textsuperscript{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 \textit{et al.},\textsuperscript{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,\textsuperscript{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>
<thead>
<tr>
<th>TABLE 14 Garvican\textsuperscript{68} costings of photographic screening (2004) – inflated to 2007 values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost per year</strong></td>
</tr>
<tr>
<td>Administration: salaries (office manager and two part-time clerical assistants), postage, maintenance</td>
</tr>
<tr>
<td>Photography: camera (n = 4) maintenance, technician salary 3.5 WTE, storage</td>
</tr>
<tr>
<td>Grading costs: salary 1.5 WTE of ‘expert grader’</td>
</tr>
<tr>
<td>Quality assurance: consultant ophthalmologist 1–2 sessions per week, 0.5 WTE ‘expert grader’</td>
</tr>
<tr>
<td>Management: (0.5 WTE programme manager) session consultant time</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Cost per test (80% attendance)</td>
</tr>
</tbody>
</table>

WTE, whole time equivalent.

\(\text{a Because of rounding the total does not add up to the sum of the components.}\)
TABLE 15 Additional costs of FM-100 test

<table>
<thead>
<tr>
<th>Cost</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FM-100 tests (n=4)</td>
<td>£1400</td>
</tr>
<tr>
<td>Macbeth Easel lamp (n=4)</td>
<td>£560</td>
</tr>
<tr>
<td>3.5 WTE screening technicians</td>
<td>£91,000</td>
</tr>
<tr>
<td>Total</td>
<td>£92,960</td>
</tr>
<tr>
<td>Cost per test (80% attendance)</td>
<td>£7.80</td>
</tr>
</tbody>
</table>

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 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 17 Base-case results for type 2 diabetes

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

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...
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
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. 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.
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 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 STD 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 STD 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. 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 leaders 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%. 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 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).

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 sensitive.
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.\textsuperscript{92,93} There is evidence that lenses of patients with diabetes may ‘yellow’ more quickly than those in non-diabetes control subjects.\textsuperscript{92} Only one\textsuperscript{31,60} of the included studies explicitly accounted for this potential confounding factor. Some authors\textsuperscript{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). 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.
Acknowledgements

We would like to acknowledge the assistance of Dr Peter Scanlon and Donna Prentis of the National Screening Programme for Retinopathy in conducting the national survey, Dr Lionel Ripley of the University of Sussex for providing details and clarifications on published studies, and Steve Chaffey of the Department of Social Medicine, University of Bristol for project support.

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.

Roger Harbord was responsible for acquisition of data, analysis and interpretation of data, revision of the manuscript, and final approval of the version to be published.

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.
References

References


34. Cochrane Diagnostic Test Accuracy Working Group. Cochrane handbook for diagnostic test accuracy reviews. (forthcoming)


References


93. Beirne RO, McIlreavy L, Gore S, Zlatkova MB. Age-related lens yellowing per se contributes little to the increase in Farnsworth-Munsell 100 hue error scores with age. *Ophthalmic Physiol Opt* 2008;28:96.

Appendix I

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.
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$or colour$) adj3 plate).ti,ab.
26. Mollon Reffin$.ti,ab.
27. Pease Allen$.ti,ab.
28. Giles Archer$.ti,ab.
29. Adams Desaturated,ti,ab.
30. (City University or CUCVT),ti,ab.
31. Velhagen Pfugertreident$.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. maculopathy$.ti,ab.
46. (microaneurism$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 neovascular$)).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.
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$.ti,ab.
13. (tritan or TCT).ti,ab.
15. Kojima$.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.
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$).ti,ab.
32. or/1–32
33. exp Diabetes Mellitus/
34. diabet$.ti,ab.
35. (IDDM or NIDDM or T2DM).ti,ab. ti,ab.
36. ((color$or colour$) adj blind$or deficien$or loss$or impair$).ti,ab.
37. or/33–35
38. exp 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. or/38–50
44. exp Animal Experiment/or Nonhuman/
45. (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.
46. or/53–54
47. exp Human Experiment/
48. or/55–56
49. exp Human Experiment/
50. exp Human Experiment/
51. or/55–56
52. and 51
53. or/53–54
54. or/55–56
55. and 51
56. or/55–56
57. or/33–35
58. and 51
59. or/33–35
60. and 51
61. or/33–35
62. and 51
63. or/33–35
64. and 51
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=(vision SAME test*) or ts=(visual SAME screen*) or ts=(visual SAME test*) or ts=(colour* SAME blind*) or ts=(color* SAME deficien*) or ts=(colour* SAME defect*) or ts=(colour* 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 impair*) or ts=(colour* SAME perception) or 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 cvtnet)
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 Pfugertrident*) 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=(macula* SAME edema*) or ts=(macula* SAME oedema*) or ts=(microaneuryism*) or ts=(micro aneurysm*)

CS 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 (color* 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 anomaloskop* 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/3 hemorrhag*) or (ocular* NEAR/3 haemorrhag*) or (ocular* NEAR/3 neovascular*) or (ocular* NEAR/3 leak) or (ocular* NEAR/3 perme*) or (ocular* NEAR/3 hemorrhag*) or (ocular* NEAR/3 haemorrhag*) or (ocular* NEAR/3 neovascular*) or (ocular* NEAR/3 leak) or (ocular* NEAR/3 perme*) or (ocular* NEAR/3 hemorrhag*) or (ocular* NEAR/3 haemorrhag*) or (ocular* NEAR/3 neovascular*) or (ocular* NEAR/3 bleed*) or (ocular* NEAR/3 blood*) or (intraocular* NEAR/3 hemorrhag*) 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 anomaloskop$ 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) or lanthony$ or panel(w)$(w)d(w)15 or panel$(w)d15 or d(w)15(w) 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$ or pflugertrident$ or contrast(w3)sensitivit$

s s1 OR s2 OR s3 OR s4 OR s5 and s6

s retinopathy$

s (optic$orocular$or intraocular$or macro$ or retina$(w3)(edema$or oedema$))

s maculopath$ or microaneurysm$ or micro(w) or aneurysm$ or microaneurism$ 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.

s (color test$) OR (color screen$) OR (colour test$) OR (colour screen$) OR (vision test$) OR (vision screen$) OR (vision test$) OR (vision screen$)
(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 okkuma$ 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$) OR (adams desaturated) OR (City University) OR CUCVT OR (velhagen pfugertig) OR (contrast sensitivit$)$[words] AND diabet$ OR IDDM OR NIDDM OR T2DM$[words] AND retinopath$ OR (macula$edema$) OR (macula$oedema$) OR (retina$edema$) OR (retina$oedema$) OR maculopathy$ OR microaneurysm$ OR (micro aneurysm$) OR microaneurism$ OR (micro aneurism$) OR (retina$hemorrhag$) OR (retina$haemorrhage$) OR (retina$neovascular$) OR (retina$leak) OR (retina$perme$) OR maculopath$ OR microaneurysm$ OR micro$aneurism$ OR micro$aneurisism$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak OR retina$perme$ OR retina$bleed$ OR (retina$hemorrhag$) OR (retina$haemorrhage$) OR (retina$neovascular$) OR (retina$neovascular$) OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR (retina$hemorrhag$) OR (retina$haemorrhage$) OR (retina$neovascular$) OR (retina$neovascular$) OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$ OR retina$hemorrhag$ OR retina$haemorrhage$ OR retina$neovascular$ OR retina$neovascular$ OR retina$leak$ OR retina$perme$ OR retina$bleed$.

BIOSIS (Dialog) 1926 to September Week 5 2007

Searched 5 October 2007.
325 records were retrieved.

Pascal (Dialog) 1973 to September Week 4 2007

Searched 5 October 2007.
83 records were retrieved.
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**

Searches 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 diabetics AND retinopathy
- colour AND diabetic AND retinopathy
- colour AND diabetics 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 colour
- screening 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.
AX=‘color test’ within 3 OR ‘color testing’ within 3 OR ‘color screen’ within 3 OR ‘color screening’ within 3 OR ‘color screened’ within 3 OR ‘color test’ within 3 OR ‘colour test’ within 3 OR ‘colour screening’ within 3 OR ‘colour screened’ within 3 OR ‘colour test’ within 3
AX=‘vision test’ within 3 OR ‘vision testing’ within 3 OR ‘vision screen’ within 3 OR ‘vision screening’ within 3 OR ‘vision screened’ within 3 OR ‘vision test’ within 3 OR ‘visual testing’ 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 microaneurysm or (micro aneurysm) 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’.


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/


College of Optometrists: www.college-optometrists.org/

Association of Optometrists: www.assoc-optometrists.org/


**Conference proceedings**


‘retinopathy testing’. Browsed results for potentially relevant abstracts.


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.
10. (value adj1 money).tw.
11. budget$.tw.
12. or/1–11
13. ((energy or oxygen) adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13–15
17. 12 not 16
18. Vision Screening/
19. Vision Tests/
20. exp Mass Screening/
21. screen$.ti,ab.
22. ((optic$or ocular$or intraocular$or eye$or retina$or vision$or visual$) adj2 (test$or exam$)).ti,ab.
23. Fluorescein Angiography/
24. Ophthalmoscopy/
25. Fluorophotometry/
26. Electrophoresis/
27. Retinography/
28. (fluorescence or fluorescein).ti,ab.
29. (funduscopy$or electroretin$or electro retin$or fluorophotometry$or retinoscopy$or biomicroscopy$or ophthalmoscopy$).ti,ab.
30. Photography/
31. Image Processing, Computer-Assisted/
32. Angiography/
33. (digital$or imag$or camer$or photograph$or polaroid$or angigraph$).ti,ab.
34. Ophthalmology/
35. Optometry/
36. (optometry$or optician$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.
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$)).ti,ab.
35. Fluorescence Angiography/
36. OPHTHALMOSCOPY/
37. FLUOROPHOTOMETRY/
38. ELECTRORETINOGRAPHY/
39. RETINOSCOPY/
40. (fluoresence or fluorescein).ti,ab.
41. (fundoscopy or electroretin$ or fluorophotometry or retinoscopy or biomicroscopy or ophthalmoscopy).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$)).ti,ab.
66. or/54–65
67. 30 and 49 and 53 and 66
1. exp “costs and cost analysis”/or “economic aspects of illness”/or “economic value of life”/or economics, pharmaceutical/
2. ((cost or costs or costed or costly or costing) adj (utilit$or benefit$or effective$or stud$or minimi$or analy$)).ti,ab.
3. (economic$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 aneurysm$or microaneurysm$).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 fluorescence 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
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 examination’ within 2
AX=‘vision test’ within 2 or ‘visual test’ within 2 or ‘vision exam’ 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**

<table>
<thead>
<tr>
<th>QUADAS criterion</th>
<th>Criterion met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>2. Were selection criteria clearly described?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>3. Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>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)?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>6. Did patients receive the same reference standard regardless of the index test result?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>8. Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>9. Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>10. Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>11. Were the reference standard results interpreted without knowledge of the results of the index test?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>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)?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>13. Were uninterpretable/intermediate test results reported?</td>
<td>Yes/no/unclear</td>
</tr>
<tr>
<td>14. Were withdrawals from the study explained?</td>
<td>Yes/no/unclear</td>
</tr>
</tbody>
</table>
Appendix 3

Data extraction tables
**Bibliographic details**

<table>
<thead>
<tr>
<th>Author</th>
<th>Aspinall36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1983</td>
</tr>
</tbody>
</table>

**Study characteristics**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 7 years follow-up; recruitment 1963–5, follow-up to 1972</td>
</tr>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Inclusion criteria: diabetics &lt; 70 years with normal fundi</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: congenital colour vision defects; cataracts</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>No</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Ophthalmoscopy</td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
<td>Dichotomous</td>
</tr>
<tr>
<td></td>
<td>N: normal fundus, fundi still showing no signs of retinopathy in either eye</td>
</tr>
<tr>
<td></td>
<td>R: retinopathy, fundi showing signs, however slight, in one or both eyes</td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
<td>Random/quasi-randomly selected</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
<td>FM-100</td>
</tr>
<tr>
<td></td>
<td>Anomaloscope</td>
</tr>
<tr>
<td>Colour vision grading</td>
<td>Dichotomous</td>
</tr>
</tbody>
</table>

**Participant characteristics**

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Number of participants included in study: N: n = 209; R: n = 86</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of participants included in analysis: N: n = 209; R: n = 86</td>
</tr>
</tbody>
</table>

**Age**

<table>
<thead>
<tr>
<th>Results</th>
<th>Unclear</th>
</tr>
</thead>
</table>

**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
<table>
<thead>
<tr>
<th>Bibliographic details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>How were the data collected?</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
</tr>
<tr>
<td>Patient selection criteria</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
</tr>
<tr>
<td>Reference standard</td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
</tr>
<tr>
<td>Colour vision grading</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Clinical characteristics</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

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
- 60% 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  
| Year            | 1987  
| Related papers  | Fong 1999  

### 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  
| 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

<table>
<thead>
<tr>
<th>What data/analysis is presented in the study?</th>
</tr>
</thead>
</table>
| 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 |
Appendix 3

Bibliographic details
Author Bernardczyk-Meller
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

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):

<table>
<thead>
<tr>
<th>Eye</th>
<th>Duration p &lt; 0.001</th>
<th>Age at onset p &lt; 0.001</th>
<th>Maculopathy grade p &lt; 0.001</th>
<th>Ischaemic grade p &lt; 0.005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye tritan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left eye tritan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye red–green</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left eye red–green</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes

Grading system used: 1 = no retinopathy: no lesions seen on fundoscopy; 2 = background retinopathy: maculopathy 1 and ischaemia 1; 3 = maculopathy 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Doucet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1991</td>
</tr>
</tbody>
</table>

## Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Exclusion criteria: people aged over 65 years; visual acuity &lt; 4/10; cataract or glaucoma; known congenital dyschromatopsia; deterioration in mental functioning; using medicines that could alter colour vision</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>No</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Other: fundoscopy</td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
<td>Graded</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
<td>D-15; presented under luminance of 500 lux</td>
</tr>
<tr>
<td>Colour vision grading</td>
<td>Categorical</td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
</tbody>
</table>

## Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Number of participants included in study: 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.36 (14.4) years (range 16–65 years)</td>
</tr>
<tr>
<td>Sex</td>
<td>62% male</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>88% insulin-dependent DM</td>
</tr>
<tr>
<td>Mean (SD) diabetes duration</td>
<td>133.74 (105.76) months (range 1 month to 39 years)</td>
</tr>
<tr>
<td>Mean (SD) HbA1c levels</td>
<td>11.38% (3.41%) (range 5.4–28.8%)</td>
</tr>
<tr>
<td>12 patients had a normal result (57.5%)</td>
<td></td>
</tr>
<tr>
<td>Other relevant clinical measures: tested creatinine clearance, nocturnal microalbuminuria and peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

*continued*
### Results

Were groups comparable in terms of demographic and clinical characteristics?

Unclear

What data/analysis is presented in the study?

Diagnostic data \((2 \times 2; \text{sensitivity, specificity})\)

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 \((p < 0.001)\)
<table>
<thead>
<tr>
<th><strong>Bibliographic details</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
<td>Findl53</td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>2000</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Study characteristics</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Cross-sectional</td>
<td></td>
</tr>
<tr>
<td><strong>How were the data collected?</strong></td>
<td>Retrospectively</td>
<td></td>
</tr>
<tr>
<td><strong>Were participants recruited consecutively?</strong></td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td><strong>Patient selection criteria</strong></td>
<td>Inclusion criteria: insulin dependent type I diabetics; age &lt; 32 years; diabetes duration between 12 and 17 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Does the study include a control group of non-diabetics?</strong></td>
<td>Yes; 25 age-matched healthy control subjects: 17 males; mean age 23.8 years</td>
<td></td>
</tr>
<tr>
<td><strong>Reference standard</strong></td>
<td>Slit-lamp biomicroscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conventional retinal photography: colour fundus photography of seven fields</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined methods: fundoscopy, biomicroscopy and retinal photography</td>
<td></td>
</tr>
<tr>
<td><strong>Retinopathy grading</strong></td>
<td>Graded</td>
<td></td>
</tr>
<tr>
<td>(reference standard)</td>
<td>Modified Airlie House classification</td>
<td></td>
</tr>
<tr>
<td><strong>For which eye was retinopathy assessed?</strong></td>
<td>Left</td>
<td></td>
</tr>
<tr>
<td><strong>Colour vision test(s)</strong></td>
<td>Computerised/automated method</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Colour vision grading</strong></td>
<td>Continuous/average</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The threshold chrominance of a coloured optotype without changes in luminance compared with the surrounding expressed as a percentage</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Participant characteristics</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>Number of participants included in study: overall: n = 59; level 1: n = 20; level 2: n = 27; level 3: n = 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of participants included in analysis: overall: n = 59; level 1: n = 20; level 2: n = 27; level 3: n = 12</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>66% male</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td>Overall 100% insulin dependent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes duration: overall range 12–17 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) LogMAR or Snellen visual acuity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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
- **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
- **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

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
### Bibliographic details

**Author** Green

**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.

### 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 ($2 \times 2$; sensitivity, specificity)

- Number of eyes: $TP = 40$; $FP = 46$; $FN = 22$; $TN = 124$; sens. $= 72$%; spec. $= 66$%
Comparison of multiple groups (analysis of variance):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
<th>Number of Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No retinopathy</td>
<td>TES = 59;</td>
<td>TES = 115;</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>TES = 31;</td>
<td></td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>TES = 24;</td>
<td></td>
</tr>
<tr>
<td>Exudative maculopathy</td>
<td>TES = 12</td>
<td></td>
</tr>
<tr>
<td>Polarity assessment</td>
<td>TES = 15;</td>
<td>TES = 28;</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>Polarity assessment = 15;</td>
<td></td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>Polarity assessment = 8;</td>
<td></td>
</tr>
<tr>
<td>Exudative maculopathy</td>
<td>Polarity assessment = 3;</td>
<td></td>
</tr>
<tr>
<td>Abnormally high 100 hue test TES</td>
<td>No retinopathy n = 19;</td>
<td></td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>n = 14;</td>
<td></td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>n = 14;</td>
<td></td>
</tr>
<tr>
<td>Exudative maculopathy</td>
<td>n = 12;</td>
<td></td>
</tr>
</tbody>
</table>
### Bibliographic details

<table>
<thead>
<tr>
<th>Author</th>
<th>Greenstein(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1990</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Inclusion criteria: DM patients requiring insulin therapy; Snellen visual acuity $\geq 20/30$ 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</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>Yes ($n = 14$); mean age $38$ years $\pm 11.6$ years (range 23–61 years)</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Ophthalmoscopy</td>
</tr>
<tr>
<td>Conventional retinal photography</td>
<td></td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td></td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
<td>Dichotomous</td>
</tr>
<tr>
<td>No retinopathy level 1: $n = 7$; background retinopathy level 2: $n = 17$</td>
<td></td>
</tr>
<tr>
<td>Graded</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
<td>Right</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
<td>FM-100</td>
</tr>
<tr>
<td>FM-100-hue test under standard illuminant C lighting conditions</td>
<td></td>
</tr>
<tr>
<td>Colour vision grading</td>
<td>Dichotomous</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

### Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>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 &gt; level 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean age overall: 45.8 years $\pm 13.9$ years (range 24–68 years)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>100% insulin-dependent DM</td>
</tr>
<tr>
<td></td>
<td>Mean duration of insulin therapy: 18.2 years $\pm 9.1$ years (range 7–40 years)</td>
</tr>
<tr>
<td></td>
<td>Mean age at onset of diabetes: 27.6 years $\pm 14.7$ years (range 8–54 years)</td>
</tr>
</tbody>
</table>
### Results

| Were groups comparable in terms of demographic and clinical characteristics? | Unclear |
| What data/analysis is presented in the study? | Diagnostic data ($2 \times 2$; 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Jeddi*43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1994</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up</td>
<td>18 months (range 12–24 months)</td>
</tr>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Patient selection criteria

| Inclusion criteria          | visual acuity 10/10 |

### Does the study include a control group of non-diabetics?

| No |

### Reference standard

<table>
<thead>
<tr>
<th>Ophthalmoscopy</th>
</tr>
</thead>
</table>

| All tests given every 6 months |
| Other: fundoscopy; visual field test |

### Colour vision test(s)

<table>
<thead>
<tr>
<th>FM-100</th>
</tr>
</thead>
</table>

| All tests given every 6 months |

### Colour vision grading

<table>
<thead>
<tr>
<th>Categorical</th>
</tr>
</thead>
</table>

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 included in study: 60 |
| Number of participants included in analysis: 60 |

| Mean: 43.5 years (range 24–63 years) |
| 48% male |

| 52% insulin-dependent DM |
| Mean diabetes duration: 10 years (range 1–18 years) |

### Results

| Unclear |

<p>| Were groups comparable in terms of demographic and clinical characteristics? |</p>
<table>
<thead>
<tr>
<th><strong>What data/analysis is presented in the study?</strong></th>
<th><strong>Diagnostic data</strong> (2 × 2; sensitivity, specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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%</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>There is colour vision impairment in 50% of people without retinopathy on angiography and 65% of people with retinopathy</td>
<td></td>
</tr>
<tr>
<td>An increase in CV error scores or individualisation of an axis was noted in 36% of cases without retinopathy and 34% with background retinopathy</td>
<td></td>
</tr>
<tr>
<td>Overall, 37% of patients made mistakes in reading colours</td>
<td></td>
</tr>
</tbody>
</table>
### Bibliographic details

**Author**  
Lombrail

**Year**  
1983

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Inclusion criteria: insulin dependent diabetics</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>No</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Fluorescein angiography</td>
</tr>
</tbody>
</table>

#### Retinopathy grading (reference standard)

- 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

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

### 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)

\[ F = 2.42, p < 0.05 \]
<table>
<thead>
<tr>
<th>Bibliographic details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>How were the data collected?</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
</tr>
<tr>
<td>Patient selection criteria</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
</tr>
<tr>
<td>Reference standard</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retinopathy grading (reference standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotomous</td>
</tr>
<tr>
<td>Clinically significant macular oedema (CSMO) vs without CSMO</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

| For which eye was retinopathy assessed? | Random/quasi-randomly selected |

<table>
<thead>
<tr>
<th>Colour vision test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-15</td>
</tr>
<tr>
<td>Other: Mollon–Reffin Minimalist Test version 6.0</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colour vision grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous/average</td>
</tr>
<tr>
<td>D-15: total colour difference score (TCDS)</td>
</tr>
<tr>
<td>Mollon–Reffin: number of reliably identified coloured chips for each confusion line</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
</tbody>
</table>

*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 ($2 \times 2$; 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

**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

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were groups comparable in terms of demographic and clinical characteristics?</td>
<td>Unclear</td>
</tr>
<tr>
<td>What data/analysis is presented in the study?</td>
<td>Diagnostic data ($2 \times 2$; sensitivity, specificity)</td>
</tr>
<tr>
<td>TP, FP, FN, TN calculated from text (no thresholds reported):</td>
<td></td>
</tr>
<tr>
<td>a. Desaturated D-15: TP = 0, FP = 7, FN = 0, TN = 47</td>
<td></td>
</tr>
<tr>
<td>b. D-15: TP = 0, FP = 0, FN = 0, TN = 54</td>
<td></td>
</tr>
<tr>
<td>c. Nagel anomaloscope: TP = 0, FP = 0, FN = 0, TN = 54</td>
<td></td>
</tr>
<tr>
<td>2. Follow-up (1993):</td>
<td></td>
</tr>
<tr>
<td>a. Desaturated D-15: TP = 1, FP = 0, FN = 22, TN = 31</td>
<td></td>
</tr>
<tr>
<td>b. D-15: TP = 1, FP = 0, FN = 22, TN = 31</td>
<td></td>
</tr>
<tr>
<td>c. Nagel anomaloscope: TP = 0, FP = 0, FN = 23, TN = 31</td>
<td></td>
</tr>
<tr>
<td>d. CVM anomaloscope: not calculable (no significant difference between groups)</td>
<td></td>
</tr>
</tbody>
</table>

### 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.
<table>
<thead>
<tr>
<th>Bibliographic details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Year</td>
</tr>
<tr>
<td>Related papers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>How were the data collected?</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
</tr>
<tr>
<td>Patient selection criteria</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
</tr>
<tr>
<td>Reference standard</td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
</tr>
<tr>
<td>Colour vision grading</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were groups comparable in terms of demographic and clinical characteristics?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What data/analysis is presented in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of scores in two groups (t-test; Mann–Whitney)</td>
</tr>
<tr>
<td>Retinopathy: mean TES = 7.9 (SD 1.51); no retinopathy: mean TES = 3.03 (SD 0.56) (p &lt; 0.01)</td>
</tr>
<tr>
<td>Association between clinical characteristics and outcomes (multivariate regression)</td>
</tr>
<tr>
<td>NCT score was positively correlated with duration of diabetes (p &lt; 0.05) and HbA1c (p &lt; 0.02), but negatively correlated with coefficient variation of R–R interval in electrocardiography (an index for autonomic neuropathy, p &lt; 0.02)</td>
</tr>
</tbody>
</table>
### Bibliographic details

<table>
<thead>
<tr>
<th>Author</th>
<th>Mecca49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1988</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
| 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       | Dichotomous |
| (reference standard)      | 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?

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic data (2 × 2: sensitivity, specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-15, 18–45 group</td>
<td>TP = 31, TN = 20, FP = 15, FN = 9</td>
</tr>
<tr>
<td>D-15, 46–75 group</td>
<td>TP = 41, TN = 5, FP = 30, FN = 4</td>
</tr>
<tr>
<td>D-15, overall</td>
<td>TP = 72, TN = 25, FP = 45, FN = 13</td>
</tr>
<tr>
<td>NCT, 18–45 group</td>
<td>TP = 32, TN = 25, FP = 10, FN = 8</td>
</tr>
<tr>
<td>NCT, 46–75 group</td>
<td>TP = 35, TN = 17, FP = 18, FN = 10</td>
</tr>
<tr>
<td>NCT, overall</td>
<td>TP = 67, TN = 42, FP = 28, FN = 18</td>
</tr>
<tr>
<td>NCT + D-15 combined</td>
<td>(threshold: impaired CV on one or both tests): TP = 73; TN = 25; FP = 45; FN = 12</td>
</tr>
</tbody>
</table>

Comparison of scores in two groups (t-test; Mann–Whitney)

<table>
<thead>
<tr>
<th></th>
<th>NCT scores:</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–45 group: without</td>
<td>without retinopathy 0.69 (1.18); with retinopathy 2.40 (1.58)</td>
</tr>
<tr>
<td>46–75 group: without</td>
<td>without retinopathy 1.60 (1.87); with retinopathy 3.24 (2.14)</td>
</tr>
</tbody>
</table>

Chi-squared values (retinopathy vs no retinopathy):

<table>
<thead>
<tr>
<th></th>
<th>D-15 18–45 group: 9.446, p &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-15 46–75 group:</td>
<td>0.574, p = not significant</td>
</tr>
<tr>
<td>NCT 18–45 group:</td>
<td>20.037, p &lt; 0.001</td>
</tr>
<tr>
<td>NCT 46–75 group:</td>
<td>6.113, p &lt; 0.05</td>
</tr>
</tbody>
</table>
### Bibliographic details

<table>
<thead>
<tr>
<th>Author</th>
<th>Mirkiewicz-Sieradzka57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1986</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Inclusion criteria: diabetic patients with signs of retinopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: patients with congenital red–green colour deficits; patients who had previously undergone photocoagulation</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>No</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Ophthalmoscopy</td>
</tr>
<tr>
<td></td>
<td>Fluorescein angiography</td>
</tr>
<tr>
<td>Retinopathy grading</td>
<td>Graded</td>
</tr>
<tr>
<td>(reference standard)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ophthalmoscopy:</td>
</tr>
<tr>
<td></td>
<td>I. Microaneurysms and yellow spots</td>
</tr>
<tr>
<td></td>
<td>II. Microaneurysms, yellow spots and ('wybroczyn')?</td>
</tr>
<tr>
<td></td>
<td>III. Massive yellow spots</td>
</tr>
<tr>
<td></td>
<td>IV: Oedema</td>
</tr>
<tr>
<td></td>
<td>Angiography:</td>
</tr>
<tr>
<td></td>
<td>I: Single leak</td>
</tr>
<tr>
<td></td>
<td>II: Larger leaks</td>
</tr>
<tr>
<td></td>
<td>III: Limited oedema</td>
</tr>
<tr>
<td></td>
<td>IV: Diffuse oedema</td>
</tr>
</tbody>
</table>

### Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants included in study: 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Range 20–78 years</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>50.9% male</td>
</tr>
<tr>
<td>Results</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Were groups comparable in terms of demographic and clinical characteristics?</td>
</tr>
<tr>
<td>What data/analysis is presented in the study?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Notes</td>
</tr>
</tbody>
</table>
### Bibliographic details

<table>
<thead>
<tr>
<th>Author</th>
<th>Ong31,60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2004</td>
</tr>
<tr>
<td>Related papers</td>
<td>Ong 200340</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

**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 experienced 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

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Number of participants included in study: 510 (STDR 17, NSTDR 493)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of participants included in analysis: 510 (STDR 17, NSTDR 493)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (SD): STDR: 60.4 (11.3) years; NSTDR: 60.9 (13.9) years ((p &gt; 0.5))</td>
</tr>
</tbody>
</table>
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 x 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 < 0.001) 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 < 0.001; 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Saracco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1980</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>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</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>No</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Fluorescein angiography</td>
</tr>
<tr>
<td>Retinopathy grading (reference standard)</td>
<td>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)</td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
<td>D-15</td>
</tr>
<tr>
<td>Colour vision grading</td>
<td>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</td>
</tr>
</tbody>
</table>
### Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Number of participants included in study: 88 (172 eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of participants included in analysis: 88 (172 eyes)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean: 51.12 years</td>
</tr>
<tr>
<td></td>
<td>0–20 years: 8 eyes; 20–40 years: 31 eyes; 40–60 years: 76 eyes; 60+ years: 57 eyes</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Mean (SD) LogMAR or Snellen visual acuity</td>
</tr>
<tr>
<td></td>
<td>Myopia (at least 2 dioptres): 17 people (34 eyes)</td>
</tr>
<tr>
<td></td>
<td>Other relevant clinical measures: 22 people (40 eyes) beginnings of cataracts</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Were groups comparable in terms of demographic and clinical characteristics?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>What data/analysis is presented in the study?</td>
<td>Diagnostic data $(2 \times 2)$; sensitivity, specificity</td>
</tr>
<tr>
<td></td>
<td>Normal vs pathology: $TP = 63, FP = 49, FN = 17, TN = 43$</td>
</tr>
<tr>
<td></td>
<td>Angiographic grade 0 vs 1: $TP = 42, FP = 49, FN = 12, TN = 43$</td>
</tr>
</tbody>
</table>
**Bibliographic details**

**Author**  Sinha

**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

**Retinopathy grading (reference standard)**  Dichotomous

**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 \((2 \times 2; \text{sensitivity, specificity})\)
- 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
<table>
<thead>
<tr>
<th><strong>Bibliographic details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
</tr>
<tr>
<td><strong>Year</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Study characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>How were the data collected?</strong></td>
</tr>
<tr>
<td><strong>Were participants recruited consecutively?</strong></td>
</tr>
<tr>
<td><strong>Patient selection criteria</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td><strong>Does the study include a control group of non-diabetics?</strong></td>
</tr>
<tr>
<td><strong>Reference standard</strong></td>
</tr>
<tr>
<td>Slit-lamp biomicroscopy</td>
</tr>
<tr>
<td>Dilated with 1% tropicamide</td>
</tr>
<tr>
<td><strong>Retinopathy grading (reference standard)</strong></td>
</tr>
<tr>
<td>No retinopathy: no evidence of retinopathy can be seen clinically</td>
</tr>
<tr>
<td>Background: characterised by the development of microaneurysms, superficial and deep retinal haemorrhages and the formation of hard exudates</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Maculopathy: clinically significant macular oedema as characterised by the ETDRS group, characterised by thickening of the retina within 500 ( \mu )m of the centre of the macula, the presence of hard exudates associated with retinal thickening within 500 ( \mu )m 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</td>
</tr>
<tr>
<td><strong>For which eye was retinopathy assessed?</strong></td>
</tr>
<tr>
<td><strong>Colour vision test(s)</strong></td>
</tr>
<tr>
<td>Computerised/automated method</td>
</tr>
<tr>
<td>SGM; set up to produce low spatial frequency equiluminant, sinusoidal gratings on a high-resolution colour monitor that were randomly tritan or red–green</td>
</tr>
<tr>
<td><strong>Colour vision grading</strong></td>
</tr>
<tr>
<td>Continuous/average</td>
</tr>
<tr>
<td>(1) Tritan contrast threshold (TCT) and (2) red–green contrast threshold (RGCT)</td>
</tr>
<tr>
<td>Dichotomous</td>
</tr>
<tr>
<td>Longitudinal subgroup only: threshold scores +2 SDs above the lens-equated mean</td>
</tr>
</tbody>
</table>

continued
### Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>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</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>30% insulin-dependent type I diabetics</td>
</tr>
<tr>
<td></td>
<td>Overall mean duration: 14 years (range 1.5–60 years)</td>
</tr>
</tbody>
</table>

### Results

**Were groups comparable in terms of demographic and clinical characteristics?**

Unclear

**What data/analysis is presented in the study?**

Diagnostic data ($2 \times 2$; 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Trick15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1988</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cross-sectional</th>
</tr>
</thead>
<tbody>
<tr>
<td>How were the data collected?</td>
<td>Prospectively</td>
</tr>
<tr>
<td>Were participants recruited consecutively?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Patient selection criteria</td>
<td>Inclusion criteria: DM patients with no or mild to moderate background retinopathy; visual acuity of at least 20/30 and intraocular pressure &lt; 21 mmHg in the eye to be tested. Exclusion criteria: patients with macular oedema detected in either the ophthalmoscopic examination or the fundus photographs</td>
</tr>
<tr>
<td>Does the study include a control group of non-diabetics?</td>
<td>Yes: n = 35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Conventional retinal photography Seven-field fundus photographs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy grading (reference standard)</td>
<td>Dichotomous No retinopathy vs preproliferative background retinopathy (grade 1a to grade 1b lesions according to the modified Airlie House classification)</td>
</tr>
<tr>
<td>For which eye was retinopathy assessed?</td>
<td>Random/quasi-randomly selected Monocular test but no details on how the eye was selected</td>
</tr>
<tr>
<td>Colour vision test(s)</td>
<td>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</td>
</tr>
<tr>
<td>Colour vision grading</td>
<td>Continuous/average Square root of total error score (TES) and partial error scores (blue-yellow, red–green) Dichotomous Total/partial error score &gt; 2 SD above the normal mean</td>
</tr>
</tbody>
</table>

### Participant characteristics

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Number of participants included in study: no retinopathy: n = 37; background retinopathy: n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD): no retinopathy 36.9 (11.1) years; background retinopathy 37.9 (8.6) years</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>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)</td>
</tr>
</tbody>
</table>
### 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

**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
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 ($2 \times 2$; 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 $\geq 0.1$, 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adab P. (1996) Screening for sight-threatening eye disease. Cost-effectiveness of screening modalities must be determined</td>
<td>1</td>
</tr>
<tr>
<td>Adams AJ. (1982) Chromaticity and luminosity changes in glaucoma and diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Apostol S, Carstocea B. (1994) [Color vision in diabetics]</td>
<td>1</td>
</tr>
<tr>
<td>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</td>
<td>2</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Banford D, North RV, Dolben J, Butler G, Owens DR. (1994) Longitudinal study of visual functions in young insulin-dependent diabetics</td>
<td>4</td>
</tr>
<tr>
<td>Barca L, Vaccari G. (1978) Diabetic retinopathy and colour discrimination under various illuminants</td>
<td>1</td>
</tr>
<tr>
<td>Bensinger RE. (1992) Color vision and color vision testing</td>
<td>1</td>
</tr>
<tr>
<td>Birbeck JA. (1972) Studies of colour vision in juvenile diabetes [meeting abstract]</td>
<td>1</td>
</tr>
<tr>
<td>Birch J. (1993) Diagnosis of defective colour vision</td>
<td>1</td>
</tr>
<tr>
<td>Birch J, Chisholm IA, Kinear P, Marre M, Pinckers AJLG, Pokorny J, et al. (1979) Acquired colour vision defects</td>
<td>1</td>
</tr>
<tr>
<td>Bischoff P. (1993) [Frequency of ophthalmological examinations in diabetic retinopathy]</td>
<td>2</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Bresnick GH, Condit RS, Palta M, Korth K, Groo A, Syrjala S. (1985)</td>
<td>2, 4</td>
</tr>
<tr>
<td>Association of hue discrimination loss and diabetic retinopathy</td>
<td></td>
</tr>
<tr>
<td>A screening approach to the surveillance of patients with diabetes</td>
<td></td>
</tr>
<tr>
<td>for the presence of vision-threatening retinopathy</td>
<td></td>
</tr>
<tr>
<td>Prevalence of diabetic eye disease in an inner city population</td>
<td></td>
</tr>
<tr>
<td>the Liverpool Diabetic Eye Study</td>
<td></td>
</tr>
<tr>
<td>Bronte-Stewart JM, Cant JS, Craig JO. (1984)</td>
<td>3, 4</td>
</tr>
<tr>
<td>Colour vision in young diabetics</td>
<td></td>
</tr>
<tr>
<td>A high uptake eye and foot screening service for an urban population</td>
<td></td>
</tr>
<tr>
<td>Bucher MB, Leuenberger PM, Roth A. (1983) [Diabetes and color vision]</td>
<td>3</td>
</tr>
<tr>
<td>Buckingham TJ, Young SA. (1993) Changes in retinal function</td>
<td>2</td>
</tr>
<tr>
<td>with duration of diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>quality improvement project</td>
<td></td>
</tr>
<tr>
<td>Buxton MJ, Sculpher MJ, Ferguson BA, Humphreys JE, Altmann JF,</td>
<td>2</td>
</tr>
<tr>
<td>Spiegelhalter DJ, et al. (1991) Screening for treatable diabetic</td>
<td></td>
</tr>
<tr>
<td>retinopathy: a comparison of different methods</td>
<td></td>
</tr>
<tr>
<td>Cameron BL. (2002) Making diabetes management routine: how often</td>
<td>1, 2</td>
</tr>
<tr>
<td>do you and your patients screen for complications?</td>
<td></td>
</tr>
<tr>
<td>methodologies in practice</td>
<td></td>
</tr>
<tr>
<td>Cathelineau G, Villatte-Cathelineau B, Lombrail P. (1986) [Color</td>
<td>1</td>
</tr>
<tr>
<td>vision and diabetes]</td>
<td></td>
</tr>
<tr>
<td>Cirillo D, Gonfiantini E, De Grandis D, Bongiovanni L, Robert JJ,</td>
<td>2</td>
</tr>
<tr>
<td>and adolescents</td>
<td></td>
</tr>
<tr>
<td>Clark JB, Grey RH, Lim KK, Burns-Cox CJ. (1994)</td>
<td>2</td>
</tr>
<tr>
<td>Loss of vision before ophthalmic referral in blind and partially</td>
<td></td>
</tr>
<tr>
<td>sighted diabetics in Bristol</td>
<td></td>
</tr>
<tr>
<td>Collier A, Mitchell JD, Clarke BF. (1985) Visual evoked potential</td>
<td>2, 5</td>
</tr>
<tr>
<td>and contrast sensitivity function in diabetic retinopathy</td>
<td></td>
</tr>
<tr>
<td>Hue discrimination loss and retinopathy severity in diabetes</td>
<td></td>
</tr>
<tr>
<td>mellitus [meeting abstract]</td>
<td></td>
</tr>
<tr>
<td>zone in diabetic retinopathy: quantitative vs qualitative assessment</td>
<td></td>
</tr>
<tr>
<td>Cranston IC. (2002) Bexley diabetes retinal screening programme</td>
<td>1</td>
</tr>
<tr>
<td>Crognale MA, Switkes E, Rabin J, Schneck ME, Haegerstrom-Portnoy G,</td>
<td>1, 5</td>
</tr>
<tr>
<td>Adams AJ. (1993) Application of the spatiochromatic visual evoked</td>
<td></td>
</tr>
<tr>
<td>potential to detection of congenital and acquired color-vision</td>
<td></td>
</tr>
<tr>
<td>deficiencies</td>
<td></td>
</tr>
<tr>
<td>et al. (1997) A 3–19 year follow up study on diabetic retinopathy</td>
<td></td>
</tr>
<tr>
<td>in patients diagnosed in childhood and treated with conventional</td>
<td></td>
</tr>
<tr>
<td>therapy</td>
<td></td>
</tr>
<tr>
<td>Dain SJ. (2004) Clinical colour vision tests</td>
<td>1</td>
</tr>
<tr>
<td>Dain SJ, Saunders JE. (1987) F-M 100 hue total error scores have</td>
<td>1, 3</td>
</tr>
<tr>
<td>discrete values</td>
<td></td>
</tr>
<tr>
<td>color vision in patients with type 1 diabetes</td>
<td></td>
</tr>
<tr>
<td>retinopathy in children and adolescents with type 1 diabetes</td>
<td></td>
</tr>
<tr>
<td>Davies NP, Morland AB. (2002) Chromatic and achromatic spectral</td>
<td>3, 5</td>
</tr>
<tr>
<td>sensitivity in diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>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</td>
<td>2</td>
</tr>
<tr>
<td>Erb C, Fahlke M. (2006) [Colour vision and acquired colour vision disturbances. I. basic aspects]</td>
<td>1</td>
</tr>
<tr>
<td>Farber ME, Lotshaw RR. (1986) Screening for diabetic retinopathy contrast sensitivity function [meeting abstract]</td>
<td>4</td>
</tr>
<tr>
<td>Faria de Abreu JR, Neves F, Reis J. (1981) [Functional retinal abnormalities in diabetic patients with no retinopathy]</td>
<td>5</td>
</tr>
<tr>
<td>Farnsworth D. (1957) The Farnsworth-Munsell 100-hue test manual</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Gerkowicz M. (1989) [Color vision in patients with juvenile-onset diabetes mellitus]</td>
<td>4</td>
</tr>
<tr>
<td>Ginsberg AP. (1984) A new contrast sensitivity vision test chart</td>
<td>2</td>
</tr>
<tr>
<td>Giusti C. (2002) Novel diagnostic and therapeutic approaches to the diabetic retinopathy</td>
<td>1</td>
</tr>
<tr>
<td>Gunduz K, Arden GB, Perry S. (1988) Color-contrast thresholds are elevated in mild disease though other color tests give normal results [meeting abstract]</td>
<td>1</td>
</tr>
<tr>
<td>Hampson S. (2001) Experience of setting up a retinal screening service</td>
<td>2</td>
</tr>
<tr>
<td>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</td>
<td>3</td>
</tr>
<tr>
<td>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</td>
<td>3, 4</td>
</tr>
<tr>
<td>Heitz R, Heitz-Wackermann RM. (1987) [The Haguenau automatized Farnsworth 100 hue test]</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Karadeniz S, Kir N, Yilmaz MT, Ongor E, Dincag N, Baar D, et al. (1996) Alteration of visual function in impaired glucose tolerance</td>
<td>3</td>
</tr>
<tr>
<td>Kinnear PR. (1970) Proposals for scoring and assessing the 100-hue test</td>
<td>1</td>
</tr>
<tr>
<td>Kinnear PR, Aspinall PA, Lakowski R. (1972) The diabetic eye and colour vision</td>
<td>4</td>
</tr>
<tr>
<td>Kitano S. (2005) &quot;Grading of diabetic retinopathy from non-stereoscopic color fundus photographs: relationship to fluorescein angiography findings and three-year prognosis&quot;</td>
<td>2</td>
</tr>
<tr>
<td>Klemperer I, Yassur Y. (1987) [Contrast sensitivity in testing visual functions in diabetics]</td>
<td>1</td>
</tr>
<tr>
<td>Knudsen LL, Andersen CU, Lervang HH, Vad J. (2002) [Screening for diabetic retinopathy in the County of North Jutland]</td>
<td>2</td>
</tr>
<tr>
<td>Krasny J, Cihelkova I, Dominek Z, Soucek P, Tresevlova 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</td>
<td>2</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Lagerlof O. (1978) Quantitative assessment of acquired colour vision deficiency in maculopathy</td>
<td>1</td>
</tr>
<tr>
<td>Lagerlof O. (1999) [To test color vision is also important]</td>
<td>1</td>
</tr>
<tr>
<td>Lakowski R, Aspinall PA, Kinnear PR. (1972) Association between colour vision losses and diabetes mellitus</td>
<td>4</td>
</tr>
<tr>
<td>Lanthony P. (1978) The new color test</td>
<td>1</td>
</tr>
<tr>
<td>Lee SC. (1997) Screening for early diabetic retinopathy by a high resolution computer vision system [meeting abstract]</td>
<td>1</td>
</tr>
<tr>
<td>Leid J, Gastaud P, Vola JL. (1985) [Diagnostic and prognostic significance of chromatic syndromes in diabetes]</td>
<td>1</td>
</tr>
<tr>
<td>Liska V. (1999) [Contrast sensitivity in type 1 diabetics without symptoms of diabetic retinopathy]</td>
<td>2</td>
</tr>
<tr>
<td>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</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion*</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Maberley DAL, Koushik A, Cruess AF. (2002) Factors associated with missed eye examinations in a cohort with diabetes</td>
<td>2</td>
</tr>
<tr>
<td>MacCuish AC. (1993) Early detection and screening for diabetic retinopathy</td>
<td>1</td>
</tr>
<tr>
<td>Mailath L. (1972) The AN-59 anomaloscope in the research of acquired colour vision deficiencies</td>
<td>5</td>
</tr>
<tr>
<td>Mäntyjärvi M. (1987) Screening of colour vision defects in diabetic patients</td>
<td>3</td>
</tr>
<tr>
<td>Mäntyjärvi M. (1989) Colour vision and dark adaptation in diabetic patients after photocoagulation</td>
<td>2, 3</td>
</tr>
<tr>
<td>Mäntyjärvi M. (1992) Screening of diabetics who read incorrectly colour-dependent glucose test-strips</td>
<td>3, 4</td>
</tr>
<tr>
<td>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)</td>
<td>3</td>
</tr>
<tr>
<td>Mollon JD, Pokorny J, Knoblauch K. (2003) Normal and defective colour vision</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusiona</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Navuluri RB. (2000) Diabetic retinopathy screening among Hispanics in Lea County New Mexico</td>
<td>2</td>
</tr>
<tr>
<td>New Zealand Health Technology Assessment. (1998) Colour vision screening; a critical appraisal of the literature</td>
<td>2</td>
</tr>
<tr>
<td>Nguyen QD, Do DV. (2003) Diabetic retinopathy: an overview for non-ophthalmologists</td>
<td>1</td>
</tr>
<tr>
<td>Parker JA. (1979) Farnsworth 100 hue scoring for acquired color vision deficiencies by weighted functions</td>
<td>3</td>
</tr>
<tr>
<td>Pinckers A, Cruysberg JR. (1986) Farnsworth-Munsell 100-hue test and lightness discrimination test</td>
<td>1</td>
</tr>
<tr>
<td>Pokorny J, Smith VC. (1986) Eye disease and color defects</td>
<td>1</td>
</tr>
<tr>
<td>Pokorny J, Smith VC, Verriest G, Pinckers A. (1979) Congenital and acquired colour vision defects</td>
<td>1</td>
</tr>
<tr>
<td>Porta M, Kohnert E. (1991) Screening for diabetic retinopathy in Europe</td>
<td>1</td>
</tr>
<tr>
<td>Regan D, Neima D. (1983) Low-contrast letter charts as a test of visual function</td>
<td>2</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Scase MO, Foster DH, Honan WP, Heron JR, Guilford MC, Scarpello JHB. (1990) Abnormalities in hue discrimination revealed with very brief stimuli in diabetes mellitus and in optic neuritis</td>
<td>5</td>
</tr>
<tr>
<td>Schoenfeld ER, Greene JM, Wu SY, Leske MC. (2001) Patterns of adherence to diabetes vision care guidelines: baseline findings from the Diabetic Retinopathy Awareness Program</td>
<td>2</td>
</tr>
<tr>
<td>Shin YJ, Park KH, Hwang JM, Wee WR, Lee JH. (2007) A new color vision test to differentiate congenital and vision defects</td>
<td>3</td>
</tr>
<tr>
<td>Shiraishi H, Shimizu K, Ohta Y. (1989) [Color vision under different luminosity in various fundus diseases]</td>
<td>4</td>
</tr>
<tr>
<td>Shotliff K, Moore D, Dimock J, Feher MD. (2004) Screening for diabetic retinopathy – false-positives do occur (it could be Shagreene)</td>
<td>2, 5</td>
</tr>
<tr>
<td>Simader E, Kreissig I, Turmer KH, Reinauer KM. (1995) [Importance of color vision testing in diabetic patients]</td>
<td>5</td>
</tr>
<tr>
<td>Singer DE, Nathan DM, Fogel HA, Schachat AP. (1992) Screening for diabetic retinopathy</td>
<td>1</td>
</tr>
<tr>
<td>Soto-Pedre E, Hernaez-Ortega MC, Pinies JA. (2007) Duration of diabetes and screening coverage for retinopathy among patients with type 2 diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Spafford MM, Lovasik JV. (1986) Clinical evaluation of ocular and visual functions in insulin-dependent juvenile diabetics</td>
<td>3</td>
</tr>
<tr>
<td>Squirell DM, Talbot JF. (2003) Screening for diabetic retinopathy</td>
<td>1</td>
</tr>
<tr>
<td>Stefansson E. (2004) Man vs machine: is technology a blessing or a barrier in screening for diabetic eye disease?</td>
<td>1</td>
</tr>
<tr>
<td>Taylor WO. (1974) Problems in performance and interpretation of Farnsworth's 100-hue test</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Tong L, Carkeet A. (2001) A new colour vision arrangement test to detect functional changes in diabetic macular oedema</td>
<td>1</td>
</tr>
<tr>
<td>Turner K, Bodmer C. (2004) Improving retinopathy screening: are we meeting the NSF target?</td>
<td>2</td>
</tr>
<tr>
<td>Usku D, Atmaca LS. (1992) Farnsworth–Munsell 100-hue test for patients with diabetes mellitus</td>
<td>4</td>
</tr>
<tr>
<td>Verriest G. (1963) Further studies on acquired deficiency of color discrimination</td>
<td>3</td>
</tr>
<tr>
<td>Verriest G. (1980) Colour deficiencies V</td>
<td>1</td>
</tr>
<tr>
<td>Vingrys AJ, King-Smith PE. (1988) A quantitative scoring technique for panel tests of colour vision</td>
<td>3</td>
</tr>
<tr>
<td>Weiss H, Zwas F, McKinnon P. (1979) Spectral sensitivity measurements in early diabetic retinopathy [meeting abstract]</td>
<td>1</td>
</tr>
</tbody>
</table>
### Appendix 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zwas F, Weiss H, McKinnon P. (1980) Spectral sensitivity measurements in early diabetic retinopathy</td>
<td>1</td>
</tr>
</tbody>
</table>

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
Appendix 5

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast sensitivity</td>
<td></td>
</tr>
<tr>
<td>Ocular coherence tomography (OCT)</td>
<td></td>
</tr>
<tr>
<td>Colour vision testing</td>
<td></td>
</tr>
<tr>
<td>Other (previously specified)</td>
<td></td>
</tr>
</tbody>
</table>

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)
* 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

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item number</th>
<th>Item number</th>
<th>On page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title/Abstract/Keywords</td>
<td>1</td>
<td>Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity')</td>
<td>iii</td>
</tr>
<tr>
<td>Introduction</td>
<td>2</td>
<td>State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups</td>
<td>5</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>3</td>
<td>The study population: The inclusion and exclusion criteria, setting and locations where data were collected</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>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)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>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)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>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)</td>
<td>6</td>
</tr>
<tr>
<td>Test methods</td>
<td>7</td>
<td>The reference standard and its rationale (Reference standard inclusion criteria)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>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)</td>
<td>6, Appendix 3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>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)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>The number, training and expertise of the persons executing and reading the index tests and the reference standard (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>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)</td>
<td>6, Table 2, Figure 2</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals) (Data analysis)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Methods for calculating test reproducibility, if carried out</td>
<td>N/A</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>14</td>
<td>When study was performed, including beginning and end dates of recruitment (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms) (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>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)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td>Test results</td>
<td>17</td>
<td>Time interval between the index tests and the reference standard, and any treatment administered in between (Quality assessment)</td>
<td>Table 2, Figure 2</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>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)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Any adverse events from performing the index tests or the reference standard (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td>Estimates</td>
<td>21</td>
<td>Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals) (Data extraction and results)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>How indeterminate results, missing data and outliers of the index tests were handled (Data extraction)</td>
<td>Appendix 3</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if carried out (Results)</td>
<td>ROC plots</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Estimates of test reproducibility, if carried out</td>
<td>N/A</td>
</tr>
<tr>
<td>Discussion</td>
<td>25</td>
<td>Discuss the clinical applicability of the study findings</td>
<td>49–53</td>
</tr>
</tbody>
</table>
Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
  By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
  A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
  A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
  A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.

No. 6
Systematic review of outpatient services for chronic pain control.
  By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: a systematic review.

No. 8
Routine preoperative testing: a systematic review of the evidence.
  By Munro J, Booth A, Nicholl J.

No. 9
Systematic review of the effectiveness of laxatives in the elderly.
  By Petticrew M, Watt I, Sheldon T.

No. 10
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
  A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down’s syndrome.
  A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
  By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.

No. 4

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
  By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, et al.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
  By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
  A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
  By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
  By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
  By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
  By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
  By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
  A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prosthesis.

Volume 3, 1999
No. 1
Informed decision making: an annotated bibliography and systematic review.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

No. 4

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

No. 13
‘Early warning systems’ for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Griev R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds.

No. 18
What role for statins? A review and economic model.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kaulka S, et al.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenn AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
Volume 4, 2000

No. 1  The estimation of marginal time preference in a UK-wide sample (TEMPUS) project. A review by Cairns JA, van der Pol MM.


No. 3  Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. By Davies SC, Cronin E, Gill M, Greening P, Hickman M, Normand C.

No. 4  Community provision of hearing aids and related audiology services. A review by Reeves DJ, Alborz A, Hickson FS, Bamford J M.

No. 5  False-negative results in screening programmes: systematic review of impact and implications. By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6  Costs and benefits of community postnatal support workers: a randomised controlled trial. By Morrell C J, Spilby H, Stewart P, Walters S, Morgan A.

No. 7  Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness. By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, et al.

No. 8  An introduction to statistical methods for health technology assessment. A review by White SJ, Ashby D, Brown PJ.

No. 9  Disease-modifying drugs for multiple sclerosis: a rapid and systematic review. By Clegg A, Bryant J, Milne R.


No. 11  Cost and outcome implications of the organisation of vascular services. By Michaels J, Brazier E, Palfreyman S, Shacklely P, Slack R.


No. 17  A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18  Liquid-based cytology in cervical screening: a rapid and systematic review. By Payne N, Chilcott J, McGoogan E.


No. 20  Routine referral for radiography of patients presenting with low back pain: is patients’ outcome influenced by GPs’ referral for plain radiography? By Kerry S, Hilton S, Patel S, Dunlas D, Rink E, Lord J.

No. 21  Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. By O’Meara S, Callum N, Majid M, Sheldon T.

No. 22  Using routine data to complement and enhance the results of randomised controlled trials. By Lewsey JD, Leyland AH, Murray GD, Boddy FA.


No. 24  Outcome measures for adult critical care: a systematic review. By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, et al.

No. 25  A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding. By Fairbank L, O’Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26  Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review. By Parkes J, Bryant J, Milne R.


No. 30  A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina. By McDonagh MS, Bachmann LM, Gold S, Kleijnen J, ter Riet G.
No. 31  A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.  By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32  Intrathecal pumps for giving opioids in chronic pain: a systematic review.  By Williams JE, Louw G, Towlerton G.

No. 33  Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.  By Shepherd J, Waugh N, Hewitson P.

No. 34  A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.  By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.


No. 36  A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.  By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37  Systematic review of treatments for atopic eczema.  By Hoare C, Li Wan Po A, Williams H.

No. 38  Bayesian methods in health technology assessment: a review.  By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.


No. 40  A systematic review of treatments for severe psoriasis.  By Griffiths CEM, Clark CM, Chalmers RG, Li Wan Po A, Williams HC.

Volume 5, 2001


No. 3  Equity and the economic evaluation of healthcare.  By Sassi F, Archard L, Le Grand J.

No. 4  Quality-of-life measures in chronic diseases of childhood.  By Eiser C, Morse R.


No. 9  Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.  By Callum N, Nelson EA, Flemming K, Sheldon T.


No. 11  Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.  By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12  Statistical assessment of the learning curves of health technologies.  By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.


No. 16  How to develop cost-conscious guidelines.  By Eccles M, Mason J.

No. 17  The role of specialist nurses in multiple sclerosis: a rapid and systematic review.  By De Broe S, Christopher F, Waugh N.


No. 19  The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.  By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 21  Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.

No. 22  The measurement and monitoring of surgical adverse events.
  By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23  Action research: a systematic review and guidance for assessment.
  By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24  A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.

No. 25  A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
  By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26  Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.

No. 27  The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.

No. 28  A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
  By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29  Superseded by a report published in a later volume.

No. 30  The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
  By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31  Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.

No. 32  A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
  By Clegg A, Scott DA, Sidiou M, Hewiston P, Waugh N.

No. 33  Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
  By Brooks ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34  Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
  By David AS, Adams C.

No. 35  A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.

No. 36  Cost analysis of child health surveillance.
  By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1  A study of the methods used to select review criteria for clinical audit.
  By Hearshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2  Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.

No. 3  Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin’s lymphoma: a systematic review and economic evaluation.

No. 4  A systematic review of discharge arrangements for older people.

No. 5  The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
  By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6  The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
  By O’Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7  The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.

No. 8  Promoting physical activity in South Asian Muslim women through ‘exercise on prescription’.
  By Carroll B, Ali N, Azam N.

No. 9  Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.

No. 10  A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
  By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11  Screening for gestational diabetes: a systematic review and economic evaluation.
  By Scott DA, Loveman E, McIntyre I, Waugh N.

No. 12  The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.

No. 13  The clinical effectiveness of trastuzumab for breast cancer: a systematic review.

No. 14  The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
No. 15  A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
   By Vale L, Wyness L, McCormack K, McKenzie I, Brazzelli M, Stears SC.

No. 16  The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
   By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, et al.

No. 17  A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
   By Cummins C, Connock M, Fry-Smith A, Burl A.

No. 18  Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.

   By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, et al.

No. 20  Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
   By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21  The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
   By Jobanputra P, Barton P, Bryan S, Burl A.

No. 22  A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
   By Kaltenhaier E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23  A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
   By Forbes C, Wilby J, Richardson G, Sculptor M, Mather L, Reimmsa R.

No. 24  A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.

No. 25  A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.

No. 26  A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolitic and neuroprotective therapy for acute ischaemic stroke in the NHS.

No. 27  A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.

No. 28  Clinical effectiveness and cost– consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
   By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29  Treatment of established osteoporosis: a systematic review and cost–utility analysis.
   By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30  Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.

No. 31  Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.

No. 32  The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.

No. 33  The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
   By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34  A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.

No. 35  A systematic review of the costs and effectiveness of different models of paediatric home care.

Volume 7, 2003

No. 1  How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
   By Egger M, Juni P, Bartlett C, Holenstein F, Sterne J.

No. 2  Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.

No. 3  Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
   By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burl A.

No. 4  A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.

No. 5  Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.

No. 6  The cost-effectiveness of screening for Helicobacter pylori to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women’s preferences in the management of menorrhagia.

No. 9
Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

No. 11
First and second trimester antenatal screening for Down’s syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.

No. 14
Prostate Testing for Cancer and Treatment (Protect) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, et al.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GJ, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21

No. 22
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chikcott J, Brennan A, Booth A, Karron J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Alsibai S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chikcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capcitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.
Volume 8, 2004

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of meticillin-resistant Staphylococcus aureus: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, et al.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Humm A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAI, Delaney BC, Barton PM, Deeks JJ, et al.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.

No. 4
A systematic review of the role of bisphosphonates in metastastic disease.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capetitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Siddhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.

No. 12
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Pylllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREIN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MCG, Vale L, Scott NW, Campbell MK, et al.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.
No. 19  
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment ofmania associated with bipolar affective disorder.  

No. 20  
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.  

No. 21  
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health promotion.  

No. 22  
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.  
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23  
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.  
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24  
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.  

No. 25  
Development and validation of methods for assessing the quality of diagnostic accuracy studies.  
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26  
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.  

No. 27  
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28  
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29  
VenUS E: a randomised controlled trial of two types of bandage for treating venous leg ulcers.  
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30  
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.  

No. 31  
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.  
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32  
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.  

No. 33  
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.  
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34  
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.  

No. 35  
Coronary artery stents: a rapid systematic review and economic evaluation.  

No. 36  
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.  

No. 37  
Rituximab (MabThera) for aggressive non-Hodgkin’s lymphoma: systematic review and economic evaluation.  
By Knight C, Hind D, Brewer N, Abbott V.

No. 38  
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.  
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al.

No. 39  
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.  
By Shepherd J, Brodfin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40  
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.  
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al.

No. 41  
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.  
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, et al.

No. 42  
Involving South Asian patients in clinical trials.  
By Hussain-Gambles M, Leese B, Akin K, Brown J, Mason S, Tovey P.

No. 43  
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.  
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44  
Identification and assessment of ongoing trials in health technology assessment reviews.  

No. 45  
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine.  
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.
No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knee: a randomised controlled trial and health economic analysis.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.

No. 4
Randomised evaluation of alternative electroosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenefine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champing J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al.

No. 8
Lay public’s understanding of equipoise and randomisation in randomised controlled trials.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEM-QOL) and an evaluation of current methodology.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.

No. 12
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BHE, Barton E, Pearmain P, Bryan S, Hyde C.

No. 13
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.

No. 14
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.

No. 15
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lopramine.

No. 16
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.

No. 17
A randomised controlled comparison of alternative strategies in stroke care.
By Kafra L, Evans A, Perez J, Knupp M, Swift C, Donaldson N.

No. 18
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woolskynowycz M, Rogers S, Taylor-Adams S, Vincent C.

No. 19
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 20

No. 21
A systematic review and economic evaluation of alendronate, etidronate, risendronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.
No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

No. 25
Imatinib for the treatment of patients with unrespectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

No. 26
Indirect comparisons of competing interventions.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for eczema: a systematic review and economic evaluation.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Mathies Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants’ and professionals’ preferences in randomised controlled trials.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty, and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
No. 48  Systematic review of effectiveness of different treatments for childhood retinoblastoma.

No. 49  Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

No. 50  The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

Volume 10, 2006

No. 1  The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease.

No. 2  FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranwick G, Forbes J.

No. 3  The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

No. 4  A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

No. 5  Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dandar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6  Systematic review and evaluation of methods of assessing urinary incontinence.

No. 7  The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.

No. 8  Surveillance of Barrett’s oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9  Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

No. 10  Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11  Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.

No. 12  A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

No. 13  Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

No. 14  The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, et al.


No. 17  Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, et al.

No. 18  Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

No. 19  Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.

No. 20  A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry’s disease and mucopolysaccharidosis type 1.

No. 21  Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22  Pressure relieving support surfaces: a randomised evaluation.
No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher’s disease: a systematic review.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, et al.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hills G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).

No. 41
The clinical and cost-effectiveness of oxaliplatin and capcitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Panderl A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bows IR, Collins K, Walters SJ, McDonagh AJG.

No. 44

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.

No. 48
Evaluation of the ventricular assist device programme in the UK.
No. 49

No. 50
A systematic review and economic evaluation.

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisozone for the treatment of hormone-refractory metastatic prostate cancer.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

No. 4
The clinical effectiveness and cost-effectiveness of stromium ranelate for the prevention of osteoprotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

No. 23
Systematic review of the effectiveness of preventing and treating Staphylococcus aureus carriage in reducing peritoneal catheter-related infections.
No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O’Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al.
152

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECA trial.

No. 50
Evaluation of diagnostic tests when there is no gold standard: A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hamney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.

No. 2
‘Cut down to quit’ with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.

No. 4
By Charlesworth G, Shepstone L, Wilson E, Thalhanay M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterecomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.

No. 7
The use of economic evaluations in NHS decision making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveyman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta, agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta agonists for the treatment of chronic asthma in children under the age of 12 years.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlson J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/ faecal incontinence: a comparative evaluation of key product categories.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.

No. 31
The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The reflux trial.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wenzt R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.

No. 36
Immunophrophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burris A.
No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amitriptyline, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no 67): a systematic review and economic evaluation.

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, et al., on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.

No. 20
Systematic review of respite care in the frail elderly.

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREEhold for AntiDepressant response) study.

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

No. 27
Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.

No. 28
A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin’s lymphoma.

Bortezomib for the treatment of multiple myeloma patients.

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.

Erlotinib for the treatment of relapsed non-small cell lung cancer.

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.
No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The POoNTER trial.

No. 31
The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.
By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, et al., on behalf of the 3CPO study investigators.

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.
By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

No. 35
Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.

No. 36
Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.

No. 37
A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.

No. 38
The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.
By Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, Anderson R.

No. 39
Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.
By Parker SG, Oliver P, Pennington M, Bond J, Jagger C, Enderby PM, et al.

No. 40
Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis

No. 41
The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.

No. 42
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.

No. 43
Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.

No. 44
The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.

Suppl. 2
Gemcitabine for the treatment of metastatic breast cancer.
By Jones J, Takeda A, Tan SC, Cooper K, Loveman E, Clegg A.

Varenicline in the management of smoking cessation: a single technology appraisal.
By Hind D, Tappenden P, Peters J, Kenjegalieva K.

Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal.
By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.

Omalizumab for the treatment of severe persistent allergic asthma.

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma.
By Boland A, Bagust A, Hockenhull J, Davis H, Chiu F, Dickson R.

Adalimumab for the treatment of psoriasis.
By Turner D, Picot J, Cooper K, Loveman E.

Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal.
By Holmes M, C Carroll C, Papiaoannou D.

Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal.

Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.
By Bond M, Hoyle M, Moxham T, Napier M, Anderson R.

No. 45
Vitamin K to prevent fractures in older women: systematic review and economic evaluation.
By Stevenson M, Lloyd-Jones M, Papiaoannou D.

No. 46
The effects of biofeedback for the treatment of essential hypertension: a systematic review.
By Greenhalgh J, Dickson R, Dundar Y.

No. 47
A randomised controlled trial of the use of acidovir and/or prednisolone for the early treatment of Bell’s palsy: the BELLS study.

Suppl. 3
Lapatinib for the treatment of HER2-overexpressing breast cancer.
By Jones J, Takeda A, Picot J, von Keyserlingk C, Clegg A.

Infliximab for the treatment of ulcerative colitis.
By Hyde C, Bryan S, Juarez-Garcia A, Andronis I, Fry-Smith A.
Rimonabant for the treatment of overweight and obese people.

Telbivudine for the treatment of chronic hepatitis B infection.
   By Hartwell D, Jones J, Harris P, Cooper K.

Entecavir for the treatment of chronic hepatitis B infection.
   By Shepherd J, Gospodarevskaya E, Frampton G, Cooper, K.

Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal.
   By Stevenson M, Pandor A.

Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal.
   By Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E.

Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck.

Mifamurtide for the treatment of osteosarcoma: a single technology appraisal.
   By Pandor A, Fitzgerald P, Stevenson M, Papaioannou D.

Ustekinumab for the treatment of moderate to severe psoriasis.
   By Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A.

No. 48
Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model.

No. 49
Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation.

No. 50
Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoeconomic and qualitative study.

No. 51
ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening.

No. 52
The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation.

No. 53
Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks’ gestation (TOPS).

No. 54
Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.

No. 55
VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers.

No. 56
A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial.

No. 57
Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice.
   By Kai J, Ulph F, Cullinan T, Qureshi N.

No. 58
Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation.

No. 59
Development of a toolkit and glossary to aid in the adaptation of health technology assessment (HTA) reports for use in different contexts.
   By Chase D, Rosten C, Turner S, Hicks N, Milne R.
Prioritisation Strategy Group

Chair,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Dr Bob Coates,
Consultant Advisor, NETSCC, HTA

Dr Andrew Cook,
Consultant Advisor, NETSCC, HTA

Dr Peter Davidson,
Director of Science Support, NETSCC, HTA

Professor Robin E Fermer,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Dr Nick Hicks,
Director of NHS Support, NETSCC, HTA

Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), Department of Health, London

Ms Lynn Kerridge,
Chief Executive Officer, NETSCC and NETSCC, HTA

Dr Ruairidh Milne,
Director of Strategy and Development, NETSCC

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Ruairidh Milne,
Director of Strategy and Development, NETSCC

Ms Pamela Young,
Specialist Programme Manager, NETSCC, HTA

HTA Commissioning Board

Programme Director,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Deputy Chair,
Dr Andrew Farmer,
Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Ann Ashburn,
Professor of Rehabilitation and Head of Research, Southampton General Hospital

Professor Deborah Ashby,
Professor of Medical Statistics, Queen Mary, University of London

Professor John Cairns,
Professor of Health Economics, London School of Hygiene and Tropical Medicine

Professor Peter Croft,
Director of Primary Care Sciences Research Centre, Keele University

Professor Nicky Cullum,
Director of Centre for Evidence-Based Nursing, University of York

Professor Jenny Donovan,
Professor of Social Medicine, University of Bristol

Professor Steve Halligan,
Professor of Gastrointestinal Radiology, University College Hospital, London

Professor Freddie Handys,
Professor of Urology, University of Sheffield

Professor Allan House,
Professor of Liaison Psychiatry, University of Leeds

Dr Martin J Landray,
Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford

Professor Stuart Logan,
Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter and Plymouth

Dr Rafael Perera,
Lecturer in Medical Statistics, Department of Primary Health Care, University of Oxford

Professor Ian Roberts,
Professor of Epidemiology & Public Health, London School of Hygiene and Tropical Medicine

Professor Mark Sculpher,
Professor of Health Economics, University of York

Professor Helen Smith,
Professor of Primary Care, University of Brighton

Professor Kate Thomas,
Professor of Complementary & Alternative Medicine Research, University of Leeds

Professor David John Torgerson,
Director of York Trials Unit, University of York

Professor Hywel Williams,
Professor of Dermato-Epidemiology, University of Nottingham

Observers

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council
## Diagnostic Technologies & Screening Panel

### Members

<table>
<thead>
<tr>
<th>Chair, Professor Paul Glasziou, Professor of Evidence-Based Medicine, University of Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride</td>
</tr>
<tr>
<td>Professor Glyn Eblyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales</td>
</tr>
<tr>
<td>Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford</td>
</tr>
<tr>
<td>Professor Paul D Griffiths, Professor of Radiology, University of Sheffield</td>
</tr>
<tr>
<td>Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford</td>
</tr>
<tr>
<td>Dr Susanne M Ludgate, Medical Director, Medicines &amp; Healthcare Products Regulatory Agency, London</td>
</tr>
<tr>
<td>Dr Anne Mackie, Director of Programmes, UK National Screening Committee</td>
</tr>
<tr>
<td>Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital</td>
</tr>
<tr>
<td>Mr Stephen Pilling, Director, Centre for Outcomes, Research &amp; Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London</td>
</tr>
<tr>
<td>Mrs Una Rennard, Service User Representative</td>
</tr>
<tr>
<td>Dr Philip Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne</td>
</tr>
<tr>
<td>Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital</td>
</tr>
<tr>
<td>Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE</td>
</tr>
<tr>
<td>Ms Dawn Talbot, Service User Representative</td>
</tr>
<tr>
<td>Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds</td>
</tr>
<tr>
<td>Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary</td>
</tr>
</tbody>
</table>

### Observers

<table>
<thead>
<tr>
<th>Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board</td>
</tr>
<tr>
<td>Dr Ursula Wells, Principal Research Officer, Department of Health</td>
</tr>
</tbody>
</table>

---

## Pharmaceuticals Panel

### Members

<table>
<thead>
<tr>
<th>Chair, Professor Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Peter Elton, Director of Public Health, Bain Primary Care Trust</td>
</tr>
<tr>
<td>Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London</td>
</tr>
<tr>
<td>Mrs Barbara Greggains, Service User Representative</td>
</tr>
<tr>
<td>Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority</td>
</tr>
<tr>
<td>Dr Dyfrig Hughes, Reader in Pharmacoepidemiology and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University</td>
</tr>
<tr>
<td>Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre</td>
</tr>
<tr>
<td>Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia</td>
</tr>
<tr>
<td>Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham</td>
</tr>
<tr>
<td>Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge</td>
</tr>
<tr>
<td>Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester</td>
</tr>
<tr>
<td>Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd</td>
</tr>
<tr>
<td>Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool</td>
</tr>
<tr>
<td>Mr David Symes, Service User Representative</td>
</tr>
<tr>
<td>Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines &amp; Healthcare Products Regulatory Agency</td>
</tr>
</tbody>
</table>

### Observers

<table>
<thead>
<tr>
<th>Ms Kay Pattison, Section Head, NHS R&amp;D Programme, Department of Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health</td>
</tr>
<tr>
<td>Dr Heike Weber, Programme Manager, Medical Research Council</td>
</tr>
<tr>
<td>Dr Ursula Wells, Principal Research Officer, Department of Health</td>
</tr>
</tbody>
</table>

---

Current and past membership details of all HTA programme ‘committees’ are available from the HTA website (www.hta.ac.uk)
Therapeutic Procedures Panel

Members

Chair, Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust
Deputy Chair, Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry
Professor Jane Barlow, Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry
Ms Maree Barnett, Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill, Service User Representative
Mrs Anthea De Barton-Watson, Service User Representative
Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London
Professor Steve Goodacre, Professor of Emergency Medicine, University of Sheffield
Professor Christopher Griffiths, Professor of Primary Care, Barts and The London School of Medicine and Dentistry
Mr Paul Hilton, Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne
Professor Nicholas James, Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital
Dr Peter Martin, Consultant Neurologist, Addenbrooke’s Hospital, Cambridge

Observers
Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health
Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts, Clinical Trials Manager, Medical Research Council
Professor Tom Walley, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool
Dr Ursula Wells, Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair, Dr Edmund Jessop, Medical Adviser, National Specialist, National Commissioning Group (NCG), London
Deputy Chair, Dr David Pencheon, Director, NHS Sustainable Development Unit, Cambridge
Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson, General Practitioner, Parkway Medical Centre, Newcastle upon Tyne
Professor Mike Kelly, Director, Centre for Public Health Excellence, NICE, London
Dr Chris McCall, General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset
Ms Jeannett Martin, Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton, Locum Consultant in Public Health Medicine, Bristol Primary Care Trust
Miss Nicky Mullany, Service User Representative
Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine
Professor Ken Stein, Senior Clinical Lecturer in Public Health, University of Exeter

Observers
Ms Christine McGuire, Research & Development, Department of Health

Dr Caroline Stone, Programme Manager, Medical Research Council

Dr Kieran Sweeney, Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth
Professor Carol Tannahill, Glasgow Centre for Population Health
Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick Medical School, Coventry
Current and past membership details of all HTA programme ‘committees’ are available from the HTA website (www.hta.ac.uk).
Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.