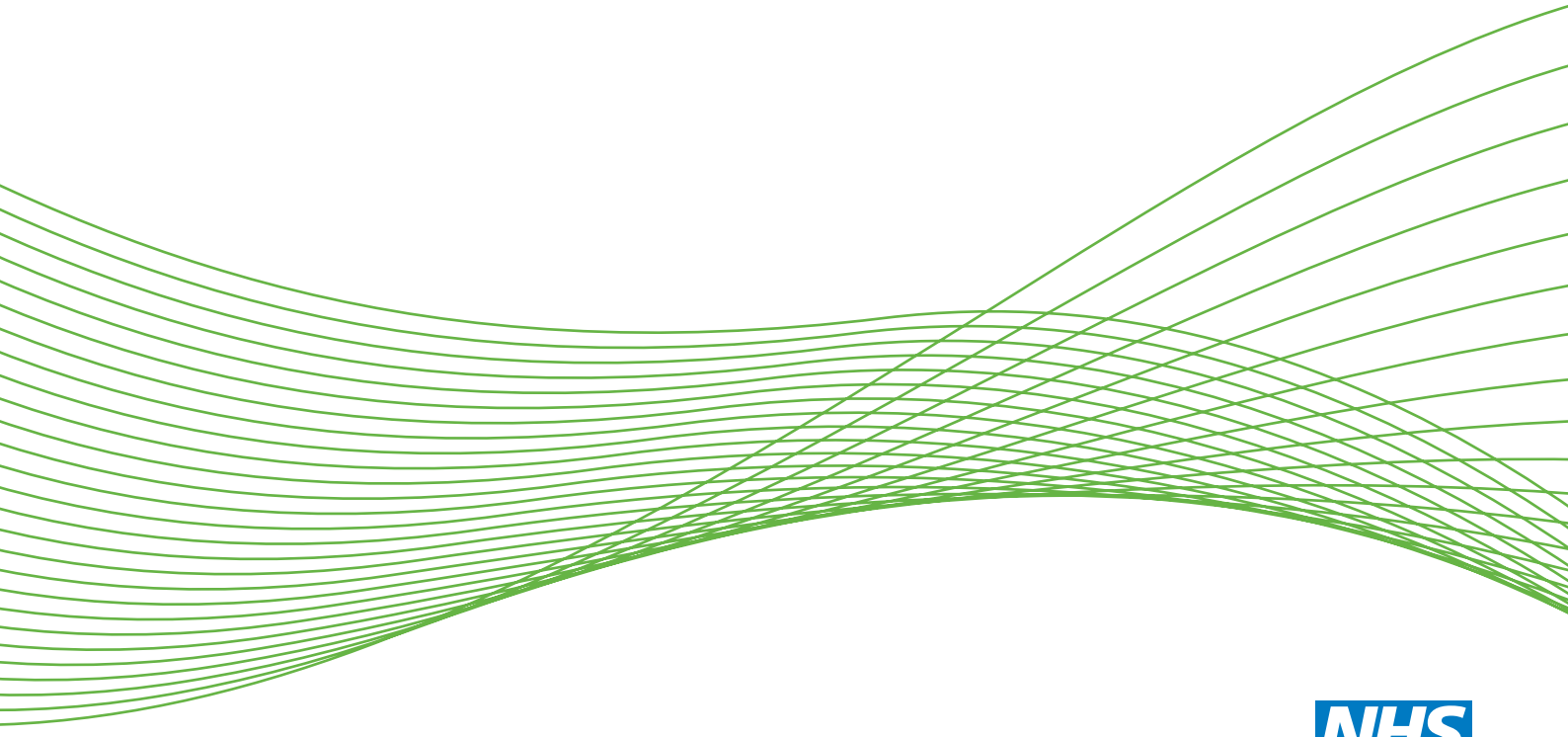
HEALTH TECHNOLOGY ASSESSMENT

VOLUME 18 ISSUE 69 DECEMBER 2014
ISSN 1366-5278

Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation

Graham Mowatt, Rodolfo Hernández, Mayret Castillo, Noemi Lois, Andrew Elders, Cynthia Fraser, Olatunde Aremu, Winfried Amoaku, Jennifer Burr, Andrew Lotery, Craig Ramsay and Augusto Azuara-Blanco



NHS
National Institute for Health Research

DOI 10.3310/hta18690

Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation

Graham Mowatt,[1] Rodolfo Hernández,[1,2] Mayret Castillo,[1] Noemi Lois,[3] Andrew Elders,[1] Cynthia Fraser,[1] Olatunde Aremu,[2] Winfried Amoaku,[4] Jennifer Burr,[5] Andrew Lotery,[6] Craig Ramsay[1] and Augusto Azuara-Blanco[3]*

[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
[3]Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK
[4]Department of Ophthalmology, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[5]Medical and Biosocial Sciences, School of Medicine, University of St Andrews, St Andrews, UK
[6]Clinical Neurosciences Research Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

*Corresponding author

Declared competing interests of authors: Andrew Lotery has received honoraria from Bayer, Novartis and Alcon and his institution has received educational grants from Novartis Pharmaceuticals. Winfried Amoaku has received personal fees from Alcon, Alimera Sciences, Allergan, Bayer, Novartis and ThromboGenics, grants from Allergan and Novartis, non-financial support from CenterVue SpA and Novartis, and other support from Pfizer.

Published December 2014
DOI: 10.3310/hta18690

This report should be referenced as follows:

Mowatt G, Hernández R, Castillo M, Lois N, Elders A, Fraser C, *et al*. Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2014;**18**(69).

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

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) 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 reviewers 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.

HTA programme

The 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 journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/57/22. The contractual start date was in February 2012. The draft report began editorial review in July 2013 and was accepted for publication in February 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation

Graham Mowatt,[1] Rodolfo Hernández,[1,2] Mayret Castillo,[1] Noemi Lois,[3] Andrew Elders,[1] Cynthia Fraser,[1] Olatunde Aremu,[2] Winfried Amoaku,[4] Jennifer Burr,[5] Andrew Lotery,[6] Craig Ramsay[1] and Augusto Azuara-Blanco[3]*

[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
[3]Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK
[4]Department of Ophthalmology, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[5]Medical and Biosocial Sciences, School of Medicine, University of St Andrews, St Andrews, UK
[6]Clinical Neurosciences Research Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

*Corresponding author a.azuara-blanco@qub.ac.uk

Background: Age-related macular degeneration is the most common cause of sight impairment in the UK. In neovascular age-related macular degeneration (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula.

Objectives: To determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected nAMD and monitoring those previously diagnosed with the disease.

Data sources: Databases searched: MEDLINE (1946 to March 2013), MEDLINE In-Process & Other Non-Indexed Citations (March 2013), EMBASE (1988 to March 2013), Biosciences Information Service (1995 to March 2013), Science Citation Index (1995 to March 2013), The Cochrane Library (Issue 2 2013), Database of Abstracts of Reviews of Effects (inception to March 2013), Medion (inception to March 2013), Health Technology Assessment database (inception to March 2013).

Review methods: Types of studies: direct/indirect studies reporting diagnostic outcomes. Index test: time domain optical coherence tomography (TD-OCT) or spectral domain optical coherence tomography (SD-OCT). Comparators: clinical evaluation, visual acuity, Amsler grid, colour fundus photographs, infrared reflectance, red-free images/blue reflectance, fundus autofluorescence imaging, indocyanine green angiography, preferential hyperacuity perimetry, microperimetry. Reference standard: fundus fluorescein angiography (FFA). Risk of bias was assessed using quality assessment of diagnostic accuracy studies, version 2. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic curves. A Markov model was developed (65-year-old cohort, nAMD prevalence 70%), with nine strategies for diagnosis and/or monitoring, and cost–utility analysis conducted. NHS and Personal Social Services perspective was adopted. Costs (2011/12 prices) and quality-adjusted life-years (QALYs) were discounted (3.5%). Deterministic and probabilistic sensitivity analyses were performed.

Results: In pooled estimates of diagnostic studies (all TD-OCT), sensitivity and specificity [95% confidence interval (CI)] was 88% (46% to 98%) and 78% (64% to 88%) respectively. For monitoring, the pooled sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. The FFA for diagnosis and nurse-technician-led monitoring strategy had the lowest cost (£39,769; QALYs 10.473) and dominated all others except FFA for diagnosis and ophthalmologist-led monitoring (£44,649; QALYs 10.575; incremental cost-effectiveness ratio £47,768). The least costly strategy had a 46.4% probability of being cost-effective at £30,000 willingness-to-pay threshold.

Limitations: Very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies reported other tests; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests.

Conclusions: Based on a small body of evidence of variable quality, OCT had high sensitivity and moderate specificity for diagnosis, and relatively high sensitivity but low specificity for monitoring. Strategies involving OCT alone for diagnosis and/or monitoring were unlikely to be cost-effective. Further research is required on (i) the performance of SD-OCT compared with FFA, especially for monitoring but also for diagnosis; (ii) the performance of strategies involving combinations/sequences of tests, for diagnosis and monitoring; (iii) the likelihood of active and inactive nAMD becoming inactive or active respectively; and (iv) assessment of treatment-associated utility weights (e.g. decrements), through a preference-based study.

Study registration: This study is registered as PROSPERO CRD42012001930.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of tables

List of figures

Glossary

Case–control study This type of study compares a group of people who have the disease and a group who do not have the disease.

Choroidal neovascularisation New blood vessels originating from the choroid. The choroid is a thin layer of connective tissue that lies between the retina and the sclera and supplies blood to the outer layers of the retina.

Diagnostic odds ratio The ratio of the odds of testing positive in those with the disease relative to the odds of testing positive in those without the disease.

Direct head-to-head study A study in which people receive both index and comparator tests (i.e. tests are evaluated in the same participants).

False negative/true negative/false positive/true positive In terms of diagnostic accuracy, indicators of index test results as compared with the reference standard: negative index test, positive reference standard/negative index test, negative reference standard/positive index test, negative reference standard/positive index test, positive reference standard.

Fundus fluorescein angiography An invasive imaging test that examines the circulation of the retina and choroid. A fluorescein dye is injected into a vein in the arm and a specialised camera photographs the dye as it passes through the blood vessels in the eye.

Index test The diagnostic test which is being evaluated.

Likelihood ratio A description of how many times more likely it is that a person with the disease will receive a particular test result than a person without the disease.

Macula The central part of the retina containing the xanthophyll pigment and two or more layers of ganglion cells. Damage to the centre of the macula, the so-called fovea, often results in loss of central vision.

Meta-analysis The quantitative pooling of data from two or more studies.

Negative predictive value The proportion of those with negative test results who do not have the disease.

Neovascular age-related macular degeneration In neovascular or 'wet' age-related macular degeneration, abnormal blood vessels grow into the macula and leak blood or fluid, leading to scarring of the macula and rapid loss of central vision.

Optical coherence tomography A non-invasive imaging technology used to obtain high resolution cross-sectional images of the retina.

Positive predictive value The proportion of those with positive test results who actually have the disease.

Randomised controlled trial A study in which people are randomly allocated to receive – or not receive – a particular treatment or intervention. This is said to be the best study type to determine effectiveness of a treatment.

Reference standard The best available test for establishing the presence or absence of the disease.

Retina The light-sensitive layer of tissue located in the back of the eye. The retina receives images via the eye's lens, converts them to electric signals and transmits them to the brain.

Sensitivity The proportion of those who actually have the disease and who are correctly identified with positive test results.

Specificity The proportion of those who actually do not have the disease and who are correctly identified with negative test results.

Visual acuity Sharpness of vision, which is tested by identifying characters on a chart from a set distance. Normal visual acuity is usually referred to as 20/20 vision, meaning the detail that a person with normal eyesight would see from 20 feet away.

Visual impairment $\leq$ 6/60 to $>$ 3/60, severe visual impairment; $\leq$ 3/60, profound visual impairment/blindness.

List of abbreviations

AMD	age-related macular degeneration
antiVEGF	antivascular endothelial growth factor
ARVO	Association for Research in Vision and Ophthalmology
BNF	*British National Formulary*
CATT	Comparison of Age-related Macular Degeneration Treatments Trials
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNV	choroidal neovascularisation
CNVM	choroidal neovascular membrane
DOR	diagnostic odds ratio
DS-ICGA	digital subtraction indocyanine green angiography
ETDRS	Early Treatment Diabetic Retinopathy Study
EVER	European Association for Vision and Eye Research
FAF	fundus autofluorescence
FFA	fundus fluorescein angiography
FN	false negative
FP	false positive
HRG	Healthcare Resource Group
HSROC	hierarchical summary receiver operating characteristic
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICG	indocyanine green
ICGA	indocyanine green angiography
IPCV	idiopathic polypoidal choroidal vasculopathy
IR	infrared reflectance
IVAN	Inhibit VEGF in Age-related choroidal Neovascularisation
LR	likelihood ratio
MARINA	Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the treatment of Neovascular Age-Related Macular Degeneration
MSAC	Medical Services Advisory Committee
nAMD	neovascular age-related macular degeneration
NIA	near-infrared autofluorescence
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCT	optical coherence tomography
PDT	photodynamic therapy
PED	pigment epithelial detachment
PHP	preferential hyperacuity perimetry
QALY	quality-adjusted life-year
QUADAS-2	quality assessment of diagnostic accuracy studies, version 2
RAP	retinal angiomatous proliferation
RCO	Royal College of Ophthalmologists
RCT	randomised controlled trial
RF	red-free image
RPE	retinal pigment epithelium
SD-OCT	spectral domain optical coherence tomography
SHTAC	Southampton Health Technology Assessments Centre
SLB	slit-lamp biomicroscopy
SLO	scanning laser ophthalmoscope

SROC	summary receiver operating characteristic	TN	true negative
subRPE	subretinal pigment epithelium	TP	true positive
TD-OCT	time domain optical coherence tomography	VA	visual acuity
		VEGF	vascular endothelial growth factor

Plain English summary

In wet age-related macular degeneration (AMD), abnormal blood vessels develop that leak fluid and blood in the back of the eye, causing central vision to worsen rapidly (over weeks). Optical coherence tomography (OCT) is a non-invasive imaging test, widely used in the NHS, that can detect wet AMD. The more recent spectral domain OCT contains improvements over time domain OCT. OCT is usually used along with other tests, such as visual acuity. This review assessed the evidence for the usefulness of OCT in diagnosing people newly presenting with suspected wet AMD, and in determining disease activity during regular monitoring visits for those previously diagnosed with the condition. The date of the last literature searches was March 2013. Twenty-two diagnostic and eight monitoring studies were included. The evidence suggested that, for diagnosis, OCT had high sensitivity (very few people with wet AMD would be wrongly diagnosed as not having it) and moderate specificity (around one-quarter of those without wet AMD would be wrongly diagnosed as having it). For monitoring, OCT also had high sensitivity but low specificity (half of those without active disease would be wrongly diagnosed as having it). Therefore, although OCT is a sensitive test and would detect most people with wet AMD, if used as the only test to guide treatment then, potentially, a considerable number of people with inactive disease would receive treatment. However, these results should be interpreted with caution owing to the small number of studies identified and their variable quality.

Scientific summary

Background

Age-related macular degeneration is the most common cause of sight impairment in the UK. In neovascular age-related macular degeneration (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula. For patients with nAMD, it is common practice to initiate treatment with three consecutive (monthly) injections of antivascular endothelial growth factor therapy, and then the patient is reassessed to evaluate whether the disease is active or inactive. Many patients require monthly monitoring and treatment over a period of several years. Fundus fluorescein angiography (FFA), an invasive test, is considered the reference standard for detecting nAMD at initial presentation and it is also used for detecting recurrent activity at some monitoring visits. Optical coherence tomography (OCT) is a non-invasive test that can be used for detecting nAMD at initial presentation and is often used as the only imaging test for detecting recurrent activity during monitoring visits. The more recently introduced spectral domain optical coherence tomography (SD-OCT) incorporates a number of improvements over time domain optical coherence tomography (TD-OCT).

Objectives

This review aims to determine the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected nAMD and (ii) in monitoring those previously diagnosed with the disease.

Methods

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion, Health Technology Assessment database, PsycINFO, Applied Social Sciences Index and Abstracts, conference abstracts from the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the European Association for Vision and Eye Research and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered included direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity (VA), Amsler grid, colour fundus photographs, infrared reflectance, red-free images or blue reflectance, fundus autofluorescence (FAF) imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FFA.

Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the quality assessment of diagnostic accuracy studies, version 2 instrument.

The results of the individual studies were tabulated and sensitivity, specificity and their 95% confidence intervals (CIs) presented for each test or combination of tests. The presence of heterogeneity was assessed by visual examination of forest plots of sensitivity and specificity. Summary receiver operating characteristic curves were derived. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios were reported as median and 95% CI.

An economic model was developed to assess the cost-effectiveness of different strategies for diagnosis and monitoring of individuals with nAMD. Three strategies were selected for the diagnostic stage and three for the monitoring stage, giving a total of nine diagnosis–monitoring combinations.

Diagnostic strategies

(a) Stereoscopic FFA interpreted by an ophthalmologist. If positive (i.e. presence of nAMD), treat and monitor; if negative, discharge.
(b) OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
(c) VA, OCT and slit-lamp biomicroscopy (SLB) in all patients, performed/interpreted by an ophthalmologist. If positive or unclear, arrange for a FFA. If negative, discharge. This is the diagnostic strategy that best reflects standard practice.

Monitoring strategies

(a) OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear, review in 1 month's time.
(b) VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in 1 month's time. If unclear, then the ophthalmologist will arrange for a FFA. This is the monitoring strategy that best reflects standard practice.
(c) VA and OCT interpreted by a technician or nurse. If negative, review in 1 month's time. If positive or unclear, refer to an ophthalmologist for assessment (e.g. SLB and ophthalmologist interpretation of VA and SD-OCT test results). If positive, treat; if negative, review in 1 month's time; if unclear, arrange for a FFA.

The model was run for a cohort of 65-year-old men for a lifetime time horizon. A 1-month cycle length was defined. Costs were expressed in 2011–12 pounds sterling and effectiveness in quality-adjusted life-years (QALYs). Costs and QALYs were discounted at 3.5%. Cost-effectiveness analysis results were reported using incremental cost-effectiveness ratios.

Uncertainty was explored by conducting one-way sensitivity analyses, scenario analysis and probabilistic sensitivity analysis. One-way sensitivity analyses were conducted on test sensitivity and specificity for diagnosis, the probability of ophthalmologist diagnosis or monitoring having unclear results, test sensitivity and specificity for monitoring, the probability of the nurse or technician assessment being unclear, and unit costs for OCT, FFA and ranibizumab [Lucentis®, Genentech Inc. (USA)/Novartis Pharmaceutical Ltd] treatment.

In addition, three scenario analyses were tested. All of these incorporated data favouring OCT (e.g. scenario 1 included the 95% CI upper limit for OCT sensitivity and specificity for diagnosis and monitoring, with £20.90 and £139 unit costs for OCT and FFA respectively). Scenario 2 assumed a cost per treatment injection of £50 instead of £742, and scenario 3 explored the effect of monitoring patients with OCT only, within the community, with referral to secondary care only for treatment.

Results

Number and quality of studies

Twenty-two diagnostic studies (20 full text, two abstracts) enrolling 2124 people and eight (full-text) monitoring studies enrolling 463 people were included. Only full-text studies were assessed for risk of bias. For both the diagnostic and monitoring studies, the domains in which the greatest number of studies were judged to be at high risk of bias were the patient selection domain (55%, 11/20; 25%, 2/8) and flow and timing domain (40%, 8/20; 25%, 2/8).

Summary of benefits and risks

Diagnostic studies

In a meta-analysis of diagnostic studies (four TD-OCT studies) sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%) respectively.

In descriptive analyses, across the studies reporting other tests, median sensitivity was high for ICGA (93.2%, range 84.6–100.0%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0–84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

Monitoring studies

In a meta-analysis of monitoring studies (three TD-OCT, two SD-OCT studies), sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, sensitivity and specificity was 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT monitoring studies due to insufficient data. These studies reported high sensitivity of 94% and 90% but low specificity of 27% and 47%.

In the one monitoring study reporting ICGA, sensitivity of 75.9% and specificity of 88.0% was reported for detecting nAMD activity.

Summary of cost-effectiveness

The strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step ('FFA & Nurse'), had the lowest total expected cost. This strategy dominated (i.e. lower total cost and higher QALYs) all others apart from one. Diagnosis based on FFA only, followed by ophthalmologist-led monitoring ('FFA & Ophthalmologist'), had a higher total expected cost and also produced higher total expected QALYs but at a cost per additional QALY > £30,000. Moreover, the 'FFA & Nurse' strategy had a 46.5% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT alone for diagnosis or monitoring were unlikely to be cost-effective. This result seemed to be driven by the OCT low specificity that resulted in a high number of false positives (FPs).

Discussion

Strengths, limitations of the analyses and uncertainties

In terms of strengths, a systematic literature search was undertaken and non-English language studies were included. A HSROC model was applied, which takes account of the trade-off between true positives/FPs and models between-study heterogeneity. The evidence for diagnosis and monitoring was considered separately, as was the evidence for TD-OCT and SD-OCT. Regarding the economic model, multiple different pathways were developed and evaluated. In terms of limitations, very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies meeting our inclusion

criteria reported the performance of other diagnostic tests of interest; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests (performed by ophthalmologists or other health professionals).

In terms of uncertainties, there was substantial disagreement between OCT and FFA specificity, especially for monitoring. As FFA was considered the reference standard it was not possible to assess whether or not OCT might have better sensitivity or specificity than FFA. It was unclear why the specificity was lower for SD-OCT compared with TD-OCT.

The model was based on one eye status and outcomes, as this is the approach most commonly used in this health area. The so named 'one eye models' can underestimate resources used due to a proportion of nAMD individuals having active nAMD in both eyes in one particular visit. In the current model, this would increase the cost for those strategies with a higher number of FPs (i.e. lower specificity) and therefore would be unlikely to modify the general conclusions of this report. In addition, the model did not consider effects on utility due to treatment injections and frequent monitoring. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to uncertainty of the underlying condition rather than the effects of treatment injections. Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Short-time follow-up data were extrapolated to a lifetime time horizon.

Generalisability of the findings

From the populations evaluated in the primary studies, the results of this report are broadly generalisable to the NHS. One of the UK-based diagnostic studies evaluated a nurse-led, fast-track screening clinic, which may not be representative of current UK practice. In addition, 55% of the diagnostic and 25% of the monitoring studies were considered to be at risk of selection bias due to either pre-selection of participants and/or inappropriate exclusions.

Conclusions

Implications for service provision

In terms of OCT test performance, this review found that, based on a relatively small body of evidence of variable quality:

- For diagnosis of newly suspected nAMD, OCT had high sensitivity (88%) and moderate specificity (78%) (meta-analysis).
- For monitoring of those previously diagnosed with nAMD, OCT had high sensitivity (85%) but low specificity (48%) (meta-analysis).
- OCT had higher sensitivity than TD-OCT but lower specificity (monitoring studies).

The strategy that based its diagnostic decision on the results of FFA only, combined with a nurse- or technician-led stepwise approach for monitoring, had the lowest expected total cost and a 47% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT test results alone to make diagnosis and/or monitoring treatment decisions were unlikely to be a cost-effective use of resources.

There has already been a shift in the diagnostic and monitoring pathways for nAMD caused by the adoption of OCT. At the diagnostic stage, OCT is currently used in addition to FFA (reference standard), whereas for monitoring it has virtually replaced FFA, which is only used in selected circumstances. The evidence suggests that using OCT as the only test for monitoring patients with nAMD and detecting activity would, potentially, result in a substantial proportion of patients receiving treatment unnecessarily.

The continuing rise in the ageing population, with increasing numbers of people being diagnosed with nAMD and moving on to monitoring for renewed disease activity, will continue to present challenges for ophthalmology departments to have sufficient capacity to provide timely testing and treatment.

Suggested research priorities

- Regarding monitoring of nAMD, OCT is routinely used in current practice, while FFA is used only in particular scenarios. There is a substantial disagreement between OCT and FFA. There is a need to research that OCT (without FFA) is an acceptable way of detecting active nAMD and guiding treatment. As there is the theoretical possibility of OCT being better in some cases than the current reference standard, such studies might be designed to include a 'fair umpire' test, if available, to examine differences between OCT and FFA, or be designed to incorporate sufficient follow-up to assess the consequences of the tests in terms of clinical effectiveness outcomes (e.g. VA).
- Regarding diagnosis of nAMD, current practice consists of FFA (as reference standard) associated with OCT. Further research should be considered to establish the added value of OCT, and whether OCT (associated with SLB and VA) can fully replace FFA. As above, such studies might be designed to include a 'fair umpire' test, or the evaluation of the consequences of the diagnostic intervention.
- Regarding the different phenotypes of nAMD, further evidence on the diagnostic performance of OCT according to phenotype of nAMD is required.
- For both diagnosis and monitoring of nAMD, prospective studies are required to assess the diagnostic accuracy and clinical effectiveness of strategies involving possible different combinations and sequences of tests (e.g. VA, SLB, FAF imaging, OCT), including a comparison of their interpretation by ophthalmologists compared with other health professionals.
- To strengthen the evidence base used to develop the economic model, it would be important to explore the likelihood of active and inactive nAMD individuals becoming inactive or active respectively. In addition, a preference-based study to assess utility weights (e.g. decrements) associated with treatment and frequent monitoring is needed.
- Further research is needed to evaluate health status (utilities) in patients with nAMD, taking into consideration the visual function and spectrum of disease in both eyes and exploring the value added by inclusion of fellow eye information.

Study registration

This study is registered as CRD42012001930.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of health problem

Brief statement describing the health problem

Neovascular age-related macular degeneration (nAMD) causes severe visual loss and is the most common cause of blindness in persons aged > 50 years in the Western world. In recent years, there have been significant advances in the clinical management of patients with nAMD. For example, there are now effective treatments, specifically antivascular endothelial growth factor (antiVEGF), and novel diagnostic technologies, including both imaging and functional tests. Patients who are being treated for nAMD with antiVEGF require frequent and long-term follow-up for treatment to be most effective.

The current reference standard for diagnosis of nAMD is fundus fluorescein angiography (FFA)[1] which may also be used to monitor the activity of the disease after treatment. However, FFA is time-consuming, invasive and requires expert interpretation. Optical coherence tomography (OCT) is now widely used for the diagnosis and management of nAMD. OCT is non-invasive, safer and more straightforward to do and interpret than FFA. OCT may help clinicians to provide a more cost-effective service for people with nAMD by potentially replacing the current reference standard of FFA and helping to distinguish between those patients with active disease requiring treatment and those whose disease is not active at a particular point in time and who do not require treatment. OCT might also lead to efficiencies by allowing other categories of health professionals to become involved in the diagnosis and monitoring of patients.

Aetiology, pathology and prognosis

Neovascular age-related macular degeneration is a pathological process in which new blood vessels arising from the choroid breach the normal tissue barriers and come to lie within the subretinal pigment epithelium (subRPE) and/or subretinal spaces. These new vessels, commonly referred to as choroidal neovascularisation (CNV) or choroidal neovascular membrane (CNVM), leak fluid, lipids and blood, elicit an inflammatory response and, as part of their natural history, undergo a scarring process, all of which has a deleterious effect on the visual cells of the retina (photoreceptors), leading to central loss of vision. Besides CNV, there are two other recognised phenotypes of nAMD: (1) retinal angiomatous proliferation (RAP) in which vascular complex seems to arise de novo from the retinal circulation, or results from CNV anastomosing with the retinal circulation; and (2) intrachoroidal/subRPE aneurysmal dilatation(s) of the choroidal vasculature, known as idiopathic polypoidal choroidal vasculopathy (IPCV).[2] These phenotypes may occur in isolation or be mixed with other phenotypes.[3]

The onset of nAMD results in progressive and unremitting loss of central vision in the affected eye, with rare exceptions in cases of IPCV in which spontaneous improvement may be observed. A number of studies have shown that extrafoveal CNV will grow towards the fovea. Once foveal involvement has occurred, CNV will expand and involve ever-increasing areas of the macula. Thus, the majority of eyes will experience acute visual loss, either moderate [defined as a doubling of the visual angle which equates to a three-line worsening on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) chart] or severe (defined as a quadrupling of the visual angle and which equates to a six-line worsening on the ETDRS VA chart). However, some patients with a fellow eye with good vision will not notice any such changes despite the onset of neovascularisation.

Neovascular age-related macular degeneration is now treated with repeated intraocular injections of drugs designed to antagonise vascular endothelial growth factor (antiVEGF). This will stabilise sight in most patients (≈90%) and will improve vision in a smaller group (≈30%) during the first 2 years of treatment.[1] Long-term (beyond 3–4 years) outcomes from randomised controlled trials (RCTs) using antiVEGF are, however, not available. These drugs are administered monthly (often with a mandated minimum of three injections for the first 3 months, and thereafter depending on whether or not active nAMD is present) as intraocular injections until the macula is rendered fluid free. When the disease becomes quiescent, treatment is stopped and patients are monitored for relapse, with treatment being restarted if needed, by monthly intraocular injections based on findings of VA checks, clinical examination and OCT. FFA is typically used to confirm the diagnosis of nAMD prior to initiating antiVEGF therapy, but it is used only in selected circumstances for monitoring activity of nAMD after treatment. Relapse of nAMD is unpredictable and can occur within weeks, months or even years after stopping treatment.

Epidemiology, incidence and prevalence

The prevalence of all forms of age-related macular degeneration (AMD) (including neovascular and atrophic AMD), which affects more than 600,000 people in the UK, is expected to rise by a quarter to nearly 756,000 by 2020. The estimated number of individuals with nAMD in the UK for 2011 is 368,000 and will increase substantially due to the ageing population.[4–6] Estimates of incidence of nAMD in the UK suggest that there are between 13,000 and 37,000 new cases annually.[5] The National Institute for Health and Care Excellence (NICE) guidance on ranibizumab [Lucentis®, Genentech Inc. (USA)/Novartis Pharmaceutical Ltd] and pegaptanib (Macugen®, Pfizer Ltd) for the treatment of age-related macular degeneration (AMD) (issued 2008 and modified 2012) estimated that there were about 26,000 new cases of nAMD in the UK each year.[7] Many of these individuals will require monthly monitoring and treatment for several years. Relevant risk factors include age, cigarette smoking, nutritional factors, cardiovascular diseases and genetic markers, including genes regulating complement, lipid, angiogenic and extracellular matrix pathways.

Impact of health problem

Significance for patients in terms of ill-health (burden of disease); significance for the NHS

Age-related macular degeneration is the most common cause of blindness and partial sighted registration in the UK.[1] As the incidence of AMD increases with age, the burden of disease to the NHS and society is expected to increase with an ageing population. Furthermore, loss of vision contributes to a psychological ill-health (depression, emotional distress) and reduced quality of life.

Ophthalmology accounts for 10% (5 million per year) of all outpatient attendances to the NHS and AMD accounts for 15% of all ophthalmology outpatient attendances.[1] Loss of VA is associated with a profound impairment of quality of life. Visual loss increases the risk of frequent falls. Depression and visual hallucinations (Charles Bonnet syndrome) are frequent accompaniments of severe central vision loss. Patients with Charles Bonnet syndrome (associated with visual loss) and their family members should be informed that visual symptoms are not unusual and are not a sign of psychosis or mental deterioration.

Measurement of disease

The spectrum of disease may be classified according to the reduction of VA (e.g. mild, moderate or severe). In addition to this spectrum of disease, during monitoring of patients undergoing treatment with antiVEGF drugs, it is important to determine whether or not the disease is active. Disease activity is typically determined with imaging technologies, mainly FFA and OCT.

Current service provision

Management of disease

Diagnosis of neovascular age-related macular degeneration and care pathway

Typically, patients with possible AMD present to primary care (optometrists or general practitioners) with non-specific symptoms (such as reduced, blurred and distorted vision). Some patients do not report symptoms and are diagnosed at routine eye examination. Clinical examination of the retina reveals typical changes associated with AMD such as drusen and irregularities in the appearance of the retinal pigment epithelium (RPE), most commonly in both eyes. However, the presence of a neovascular component may be difficult to detect clinically, especially early on in the course of its development. The diagnostic pathway for nAMD and the management of patients with known disease include imaging technologies (*Figure 1*).

According to current guidelines from the Royal College of Ophthalmologists (RCO),[1] FFA interpreted by an ophthalmologist is the method of choice and reference standard test to diagnose nAMD. Occasionally, indocyanine green angiography (ICGA) is associated with FFA as part of the reference standard when particular phenotypes of nAMD are suspected, including RAP and IPCV (see above). FFA is an invasive and time-consuming procedure, entailing the injection of a dye into a peripheral vein by a nurse and a trained photographer to undertake the test (obtain the images of the CNV, RAP, IPCV lesions). In addition to FFA, current guidelines recommend using OCT at diagnosis. Owing to recent developments in technology, it is possible that in some cases OCT might be superior to FFA in detecting nAMD (*Table 1*).

Treatment and monitoring of neovascular age-related macular degeneration

When active nAMD is confirmed, treatment with antiVEGF therapy is initiated.[8,9] For all patients with nAMD it is common practice to use three consecutive (monthly) intravitreal injections of antiVEGF therapy, and then the patient is reassessed to evaluate whether or not the disease is active (i.e., neovascularisation leaking fluid/blood at the macula) or inactive (*Figure 2*). For this purpose, both FFA and OCT may be used, although the latter more often than the former, according to the guidelines of the RCO.[1] Studies that have a large influence in current practice used VA and OCT at

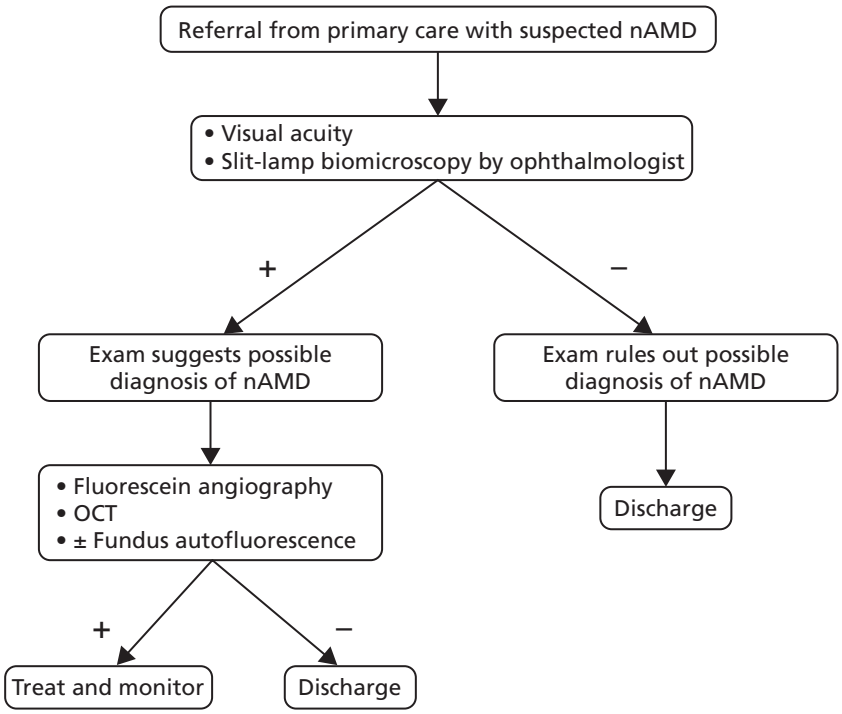


FIGURE 1 Current diagnostic pathway of nAMD.

TABLE 1 Apparent features of OCT and FFA for nAMD

Features	OCT (index test)	FFA (reference standard)
Accuracy	High?	Reference standard
Invasiveness	Non-invasive	Invasive
Knowledge and skills needed to interpret	Moderate	High
Interpretable	Most tests	Nearly all tests
Cost	Low to moderate	Moderate
Side effects	None	Allergy (rarely anaphylactic shock)

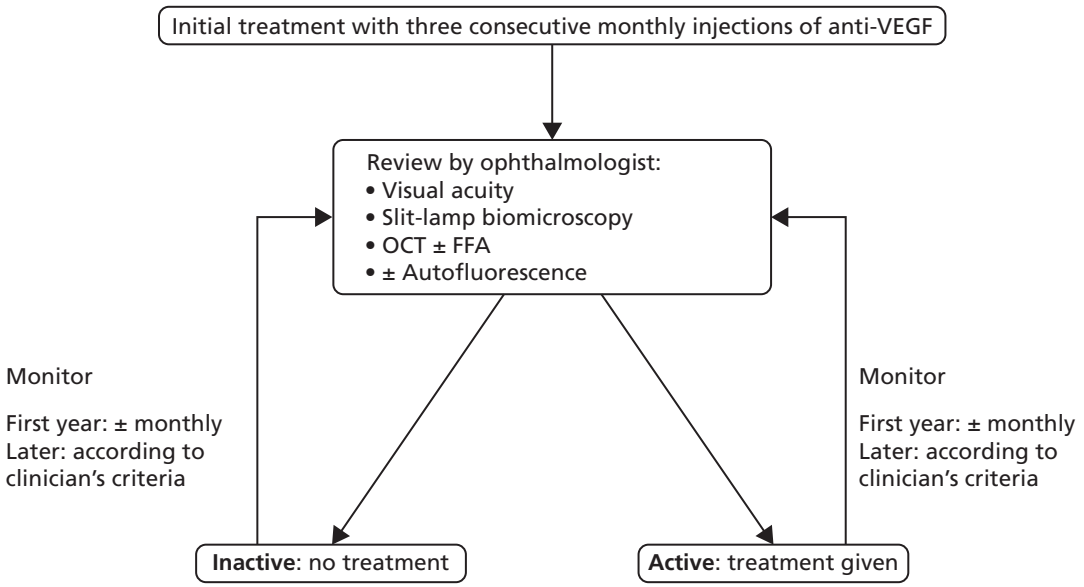


FIGURE 2 Current monitoring pathway of nAMD.

monthly intervals and FFA at quarterly intervals to decide on the need for retreatment. In some units, OCT is the only test performed to determine activity of the neovascular process in clinical practice; in some centres FFA is performed in selected cases during the monitoring phase. Other technologies such as fundus autofluorescence (FAF) may also be used at baseline and at variable intervals during the follow-up of these patients as areas of atrophy in the RPE (difficult to detect clinically but easily observed on autofluorescence images) could be associated with fluid in the retina in the absence of active nAMD.

If fluid is not seen intraretinally or subretinally, further treatment is not given and the patient is followed thereafter regularly. The timing of follow-up visits is variable, typically every 4 weeks for the first year, extending the intervals after the second year. Varying intervals have been proposed, such as 'treat and extend' strategy, where if there is no active disease, no treatment is given and the monitoring intervals are progressively extended. If the disease is judged to be active, further injections of antiVEGF are given. Either a single injection or three injections are administered if activity is detected on follow-up and then the patient returns to the monthly monitoring scheme. The possibility of using VA (without imaging tests) as the only test to guide treatment during monitoring (i.e. treatment would be given if there is a loss of five or more letters from best previously observed VA) has been modelled using data from published trials for nAMD.[10] The authors concluded that an individualised VA-guided regimen could sustain visual outcomes and improve cost-effectiveness compared with current regimes.

Current service cost

Table 2 shows an estimation of unit costs associated with current diagnosis and monitoring care pathways. A first referral visit to a hospital eye service will involve an eye examination and is costed at £106. In addition, OCT and FFA tests can be indicated, with the overall cost for the first visits ascending to £274.71. A follow-up monitoring visit can involve a face-to-face attendance with an ophthalmologist and an OCT test only (£131). However, if a FFA is indicated, the monitoring visit will cost £248.27. Without doubt, the major cost category is given by the treatment cost. There are two possible antiVEGF treatments: ranibizumab and bevacizumab (Avastin®, Roche) at £742.17 and £50 per injection respectively. NICE guidelines advocate for the use of ranibizumab unless individual sight is heavily deteriorated. It should be noted that special cost arrangements are in place and a reduced cost for ranibizumab is agreed under a Patient Access Scheme negotiated between the manufacturer and the Department of Health. Under this agreement, the cost of ranibizumab to the UK NHS (confidential) is significantly lower than the list price given above. The cost of bevacizumab is based on that of a compounded product as supplied by different compounding pharmacies in the UK.

Variation in service and/or uncertainty about best practice

Once nAMD has been diagnosed, monotherapy with an antiVEGF drug (administered into the vitreous) is the current standard of care. Ranibizumab is highly effective and recommended by current guidelines. Bevacizumab remains unlicensed in the UK although its use worldwide reflects the fact that it is much cheaper than ranibizumab (as currently supplied for intravitreal administration) with similar efficacy.[8,9]

Retinal imaging with OCT before and after intravitreal administration of antiVEGF therapy is regularly used.[13] Following antiVEGF therapy a reduction of intraretinal and subretinal fluid is typically observed, often with rapid unification of the retinal layers and improvement/restoration of the anatomical contours. This anatomical improvement is often accompanied by improvements in VA.

The ultimate treatment goal when nAMD has already developed is to achieve restoration of central vision and prevent visual loss with normal or near normal foveal and macular anatomy. Complete cessation of exudation can result in good unification of the tissue layers, but most patients report difficulty with reading small print and other visually demanding tasks, even when tissue contours have been apparently restored. High-resolution OCT scans obtained after antiVEGF treatment show persistent abnormalities of the outer retina even though the tissues appear to be fluid free. In cases where localised atrophy and fibrosis have already occurred, considerable impairment of central visual function can remain, despite the achievement of a fluid free macula.

TABLE 2 Diagnosis and monitoring costs associated with nAMD health care

	Unit costs (£, 2011–12)		
Intervention	Diagnosis	Monitoring	Source
Ophthalmologist visit	£106.18	£79.74	*NHS Reference Costs 2011–12*[11] (Ophthalmology – consultant led: first attendance or follow-up non-admitted face to face)
FFA	£117.26	£117.26	*NHS Reference Costs 2011–12*[11] (HRG BZ23Z minor vitreous retinal procedures)
OCT	£51.27	£51.27	*NHS Reference Costs 2011–12*[11] (HRG RA23Z ultrasound scan, less than 20 minutes)
Medication ranibizumab		£742.17	Ranibizumab. Source: BNF[12] (accessed 9 May 2013) [Lucentis® (Novartis) solution for intravitreal injection, ranibizumab 10 mg/ml, net price 0.23-ml vial = £742.17]
Medication bevacizumab		£50.00	As supplied by compounding pharmacies. Manufacturer's list price not applicable

BNF, *British National Formulary*; HRG, Healthcare Resource Group.

Patients who have been treated with antiVEGF therapy should be examined at regular intervals. Although most clinicians will use OCT for monitoring patients with nAMD, there is probably large variability on the tests used (e.g. biomicroscopy of the fundus, FFA and fundus photography).

As explained above, patients treated with antiVEGF injection should receive injections monthly for the first 3 months and, thereafter, should be monitored monthly. If active nAMD is present, treatment should be continued, and if there is no active exudative AMD, observation at monthly intervals is recommended. The use of technologies, including OCT, FFA and FAF during the follow-up of these patients is variable as it depends on clinical findings, the judgement of the treating ophthalmologist and the clinical pathways established at different centres. The workload associated with such contemporary AMD services is significant and is expected to increase, as the best outcomes are achieved with monthly follow-up visits. It is expected that these follow-up visits may continue for as long as 4 years or longer. The pressure on resources and service delivery in the AMD clinics is expected to become even more intense as many patients cannot be discharged, and there is a need to accommodate new incident cases. The regular monthly follow-up for AMD patients under treatment, in order to maintain efficacy, is demanding. This situation is likely to be further aggravated by the impending treatments with intravitreal therapies of macular oedema secondary to diabetic retinopathy and retinal vein occlusion. As such, the problem seems more acute than was originally envisaged, and is expected to get worse. It has been suggested engaging non-medical staff (optometrists, nurses, technicians) to undertake some of the duties in the AMD clinic in order to increase capacity. Such roles include clinical assessments, especially retreatment decision-making.

Relevant national guidelines, including National Service Frameworks

Subsequent to the technology appraisal and issuing of guidance by NICE, ranibizumab has been widely adopted as the treatment of choice for subfoveal nAMD in the UK.[7] However, the high cost of ranibizumab, along with the positive clinical experience with bevacizumab, has stimulated a debate on whether or not bevacizumab could be used in practice.

In the UK, guidelines for the management and treatment of nAMD were published by the RCO in 2009 (and in 2013 were undergoing revision).[1] According to the RCO guidelines, FFA interpreted by an ophthalmologist is the method of choice and reference standard test to diagnose nAMD. Occasionally, ICGA is associated with FFA as part of the reference standard when particular phenotypes of nAMD are suspected, including RAP and IPCV. In addition to FFA, current guidelines recommend using OCT at diagnosis. During follow-up and monitoring of disease activity, after treatment the current guidelines recommend the use of OCT mainly, and FFA at the discretion of the clinician.

Description of technologies under assessment

Reference standard: fundus fluorescein angiography

Fundus fluorescein angiography is currently the reference standard for diagnosing CNV in AMD. A fluorescein angiogram is a sequence of images captured of the fundus over a 10-minute period after injection of the non-toxic dye fluorescein isothiocyanate into a suitable peripheral vein.

Neovascular lesions are classified by their location with reference to the foveal avascular zone – extrafoveal, juxtafoveal or subfoveal. Lesions lying more than 200 μm from fixation are defined as extrafoveal and may also be described as juxtafoveal or subfoveal when immediately adjacent to or involving the geometric centre of the fovea respectively. Neovascular lesions located away from the macula are termed peripheral and those around the optic nerve juxtapapillary. A more refined classification of the neovascular lesion is obtained by describing the composition of the exudative lesion after stereoscopic review of the entire sequence of the angiogram. The exudative lesion is defined as the area occupied by the neovascular complex, any associated blood, thick exudate and pigment epithelial detachments (PEDs) that are contiguous to the neovascular complex and obscure its margins. The neovascular complex can, therefore, consist of RAP, CNV and IPCV.

The classification of nAMD lesions is based on the temporal and spatial features of the patterns of fluorescence as observed on the FFA. CNV lesions are classified according to their location relative to the fovea (see above), and pattern of fluorescein angiographic leakage. The majority of CNVs occur subfoveally.

Classic choroidal neovascularisation

Classic CNV is said to be present when an area of well-delineated hyperfluorescence appears in the early phases of the FFA, usually before seconds have elapsed following injection of the fluorescent dye into a peripheral vein. Most commonly, classic CNV represents new vessels that have breached the RPE and lie in the subretinal space. Sometimes a typical lacy pattern of hyperfluorescence is observed in the very early phase of the angiogram which corresponds to the vascular profiles before the fluorescein has leaked out of these vessels and obscured the margins. Classic CNV also leaks aggressively and hence there is considerable pooling of fluorescein dye in the subretinal space in late frames of the angiogram.

Occult choroidal neovascularisation

Occult CNV, as its name suggests, refers to the presence of leakage without clear evidence of neovascular profiles in the early angiographic images. Two types of occult leakage are recognised. The first is a characteristic stippled hyperfluorescence which occurs early and is located at the level of the RPE. The RPE layer is elevated and in the later phases of the angiogram there is increasing hyperfluorescence and pooling of dye in the subretinal pigment epithelial space. The pattern of leakage suggests new vessels between Bruch's membrane and the RPE and it is therefore considered to be a fibrovascular PED. The second pattern of occult leakage is a more diffuse hyperfluorescence with poorly demarcated boundaries which occurs late in the angiographic phase, generally after 2 minutes have elapsed since injection of dye. There is no corresponding hyperfluorescence in the early frames and there is shallow elevation of the RPE. This type of leakage is referred to as late leakage of indeterminate origin. Many lesions are mixed showing combinations of classic and occult features. It is now common practice to classify lesions by presence or absence of classic and/or occult CNV. In the absence of any occult CNV, lesions are termed classic with no occult (100% classic) and conversely occult with no classic (0% classic).

When CNV is mixed, the lesion is classified by the proportion of classic. When the lesion is composed primarily of classic CNV (i.e. classic > 50%), it is termed predominantly classic. When there is 1–49% classic, the lesions are termed minimally classic.

Retinal angiomatous proliferation

One type of neovascularisation that has been well recognised by the use of high-speed video angiography using the scanning laser ophthalmoscope (SLO) is the RAP lesion. RAP is seen commonly as a round area of intraretinal telangiectatic, dilated blood vessels located juxta- or extrafoveally. On viewing stereo pairs of images, the vessels are often seen to turn sharply from the inner retina towards the choroidal interface. Except in early stages, RAPs are associated with PEDs. They leak and hence the adjacent retina is usually disrupted with cystoid spaces. ICGA is a helpful test to determine the presence of RAP.

Idiopathic polypoidal choroidal vasculopathy

Polyps are seen as focal, round areas of abnormal dilated choroidal vessels, often associated with large areas of lipid deposition and haemorrhage. The presence of haemorrhagic PED is highly suggestive of the presence of this phenotype. These are best visualised by ICGA.

Optical coherence tomography

Optical coherence tomography was developed at the Michigan Institute of Technology, MI, USA in 1991. It is a light-wave-based technology producing cross-sectional images of the retina with scan rates and resolution parameters that have greatly improved over the last 10 years. OCT is a non-invasive, non-contact visual test that requires around 5–10 minutes to assess both eyes.[14] From the investigator's point of view, it is user friendly (e.g. OCT is easier to do than FFA), typically undertaken by trained medical

photographers or ophthalmic imaging technicians, and interpreted by ophthalmologists. Automated analysis can also be used.

There are two main types of OCT system. The earlier time domain optical coherence tomography (TD-OCT) system, available from 1995, had an image rate of 100–400 scans per second and provided information for a limited view of the retina by taking six scans radially-oriented 30 degrees from each other with a resolution in the range of 10 to 20 µm.[14] The newer system, spectral domain optical coherence tomography (SD-OCT), has been available since 2006. Improvements with this system include (i) a faster scan speed of approximately 27,000 scans per second, (ii) the ability to scan larger areas of the retina by taking several horizontal line scans such that there are no 'missed areas', (iii) increased resolution at 5 µm, and (iv) 'real time registration', which was not previously available with TD-OCT.[14] The real-time registration feature enables the identification of specific anatomical locations on the retina, against which subsequent tests may be evaluated, which is of particular importance in the monitoring of patients.[14] Compared with TD-OCT, the faster scan speed of SD-OCT enables the collection of additional information on larger regions of the retina and eliminates image distortion arising from patient movement, while the improved resolution allows for a clearer and more distinguishable view of retinal layers, with the possibility of detecting earlier signs of disease.[14]

Identification of important subgroups

There are different subgroups of patients with nAMD. They are diagnosed according to FFA findings and are described above. Subgroup classification depends on the location (extra-, juxta- and subfoveal) and type of neovascularisation (classic and occult CNV, RAP, and IPCV), which could be mixed in different combinations. Although the initial treatment is similar for all subgroups (with antiVEGF therapy), the natural history and progression after treatment are different. It is also possible that the performance of diagnostic technologies may be different among subtypes of nAMD. OCT is not currently used in isolation to identify subgroups.

Current usage in the NHS

Both FFA and OCT are currently used in the NHS to diagnose and monitor patients with nAMD. They are recommended technologies to provide standard care. FFA is essential for diagnosis of the condition. Regarding monitoring, FFA is less commonly used than OCT.

Anticipated costs associated with intervention

Table 3 presents an estimation of the number of visits in a lifetime of the population. Based on census, nAMD prevalence and Interim Life Table data, it is possible to estimate the number of visits for the population lifetime. Calculations in *Table 3* are for England and Wales, based on 2011 data and assumed that every individual with nAMD would contact NHS services. This estimation resulted in 33.7 million visits. If OCT was conducted at every monitoring visit, this would result in an undiscounted lifetime cost of above £1.7B [i.e. £51.27 (see *Table 2*) multiplied by 33.7 million people].

Alternative tests

Clinical evaluation (with slit-lamp biomicroscopy with or without use of diagnostic contact lens and evaluation of patients' symptoms)

The onset of exudative AMD is heralded by the appearance of central visual blurring and distortion. Most patients will complain that straight lines appear crooked or wavy. Sometimes patients do not notice visual symptoms when the first eye is affected. When nAMD occurs in the second eye, patients suddenly become limited in their daily activities, for example reading, driving and seeing fine detail such as facial expressions.

Examination of the macula usually reveals fluid and/or lipid (yellow deposition) and/or blood. Other features of AMD such as drusen and pigmentary irregularities are most often present. Sometimes these latter features are not observed once exudative AMD has supervened or in certain phenotypes such as IPCV.

TABLE 3 Neovascular age-related macular degeneration prevalence and lifetime total number of monitoring visits for England and Wales

Population by gender and age	Population for England and Wales, 2011 census-based estimates[15]	nAMD prevalence rates, %[6]	nAMD cases, *n*	Life expectancy (years)[16]	Total number of monthly monitoring visits (lifetime)
Men (age, years)					
65–69	1,096,335	0.38	4166	16.64	833,215
70–74	1,027,959	1.40	14,391	13.06	2,259,454
75–79	810,590	2.63	21,319	9.87	2,515,585
80–84	557,203	5.56	30,980	7.16	2,664,322
85–89	295,680	5.56	16,440	5.07	1,002,828
90–99	333,448	5.56	18,540	3.00	667,430
Total males					9,942,833
Women (age, years)					
65–69	1,154,292	0.92	10,619	19.15	2,442,482
70–74	1,140,959	1.42	16,202	15.20	2,948,694
75–79	976,657	2.17	21,193	11.59	2,945,891
80–84	788,087	10.50	82,749	8.46	8,440,412
85–89	532,677	10.50	55,931	5.95	3,971,107
90–99	717,989	10.50	75,389	3.36	3,015,554
Total females					23,764,139
Total overall population					33,706,973

However, the fellow eye would usually exhibit some or all of these AMD early clinical signs (drusen and RPE changes) and their presence is helpful in confirming that the neovascular lesion is due to AMD (again with the exception of IPCV where the fellow eye may also be normal). Following slit-lamp biomicroscopy (SLB) the presence or absence of the following signs should be noted:

- Subretinal or subRPE neovascularisation which may be visible as a dark grey lesion. Occasionally the lesion will have a dark pigmented edge which is thought to be due to proliferation of the RPE at the edge of the membrane.
- Serous detachment of the neurosensory retina.
- RPE detachment.
- Haemorrhages: subretinal pigment epithelial, subretinal, intraretinal or preretinal. Breakthrough bleeding into the vitreous may also occur, indicating most often the presence of IPCV.
- Hard exudates (lipids) within the macular area related to any of the above and not related to other retinal vascular disease.
- Epiretinal, intraretinal, subretinal or subpigment epithelial scar/glial tissue or fibrin-like deposits.
- RAPs: red, round, extra- or juxtafoveal lesions located within the retina.
- Polyps: red, round lesions located underneath the RPE or protruding through the RPE layer.

Visual acuity (for monitoring)

Visual acuity is a measure of the spatial resolution of the visual processing system. VA is tested by requiring the person whose vision is being tested to identify characters (like letters and numbers) on a chart from a set distance. Chart characters are typically represented as black symbols against a white background (for maximum contrast). The distance between the person's eyes and the testing chart is set at a sufficient distance to approximate infinity in the way the lens attempts to focus.

Amsler grid

The Amsler grid is a grid of horizontal and vertical lines used to monitor a person's central visual field. It is a diagnostic tool that aids in the detection of visual disturbances caused by changes in the retina, particularly the macula (e.g. macular degeneration). In the test, the person looks with each eye separately at the small dot in the centre of the grid. Patients with macular disease may see wavy lines or some lines may be missing. Amsler grids are supplied by ophthalmologists, optometrists or from websites, and may be used to test one's vision at home.

Colour fundus photographs

Colour fundus photography provides a record of the appearance of the macular retina. Stereoscopic images of the macula viewed appropriately can help localise pathology to the different tissue layers. For the purposes of recording macular pathology, stereoscopic pairs of images taken at 35 degrees centred on the macula are recommended. Red-free images (RFs) can help detect some features of the fundus associated with nAMD, such as haemorrhages.

Infrared reflectance

Confocal near-infrared fundus reflectance is a non-invasive en-face imaging technique using an 830-nm diode laser capable of visualising subretinal pathology. In contrast to visible wavelength illumination, fundus reflectance may be up to 10 times higher in the near-infrared wavelength and is then largely independent of melanin content, which advances the visibility of deep fundus structures.

Red-free images or blue reflectance

See *Colour fundus photographs*, above.

Fundus autofluorescence imaging or blue reflectance

This test can give an indication of the health of the RPE. The conventional FAF signal (obtained with 488 nm) originates, predominantly, from lipofuscin in RPE cells. The near-infrared autofluorescence (NIA) signal originates, predominantly, from melanin in the RPE, with some contribution from choroidal melanin. Increased FAF represents accumulation of lipofuscin and suggests that the RPE cells are beginning to fail. Absence of a FAF and NIA signal, which appears as black areas in FAF and NIA images, is due to loss of RPE cells. The finding of patches of absent autofluorescence may explain central scotoma patterns. Although different patterns have been described in early and late AMD, the exact diagnostic performance of autofluorescence is yet to be determined. The role of FAF may be more important in monitoring patients undergoing antiVEGF therapy to evaluate atrophy (e.g. for potential discontinuation of treatment).

Indocyanine green angiography, dynamic high speed or digital subtraction indocyanine green angiography

Indocyanine green (ICG) is an alternative dye to fluorescein which is used to visualise the choroidal circulation. This dye binds to plasma protein and hence does not egress easily through the fenestrae of the choroidal vessels, remaining within the vascular compartment. ICGA is obtained using longer wavelengths than FFA and, thus, can penetrate through areas of fluid/blood, permitting visualisation of pathology in circumstances where fluorescein may not. ICG also has some limitations and very thick blood or pigment can reduce or block transmission of the ICG infra-red wavelength and the emitted light is of lower intensity compared with that of fluorescein. The use of the SLO with video capture can, however, yield images of high resolution. Video ICGA also allows better imaging of RAP. As ICG dye does not leak into the subretinal and subpigment epithelial spaces to the same extent as fluorescein, the enhanced definition

of the vascularised tissue as a hotspot is possible and a combination of FFA and ICGA can produce complementary information. A dose of 25 mg of ICG in aqueous solution is usually injected intravenously and images acquired for up to 30 minutes.

Preferential hyperacuity perimetry

Preferential hyperacuity perimetry (PHP) is a psychophysical test of macular function that exploits the ability of the human visual system to perceive even minute differences in the relative localisation of two objects in space; a phenomenon termed hyperacuity. When there is separation of the retinal layers through breakdown of the blood–retinal barrier or blood–RPE barrier, distorted vision is the consequence. Through presentation of lines with artificial distortions of different intensities on the PHP, the presence of a real distortion in the patient's central visual field can be detected as the brain ignores the smaller deviation when a larger one is introduced.

In a PHP test, the macula is scanned with a succession of stimuli, each stimulus consisting of a series of dots arranged along a vertical or horizontal axis. In each stimulus, a small number of dots are misaligned, thereby creating an artificial distortion (bump or wave). The examinee's task is to perceive these artificial distortions and mark their locations on the visual field. When a stimulus is projected on a healthy portion of the retina, the examinee identifies the artificial distortion and is likely to mark a correct location. If the stimulus is projected on a damaged region of the retina, a pathological distortion may be perceived instead of the artificial distortion, especially if the pathological distortion is more prominent than the artificial distortion. The examinee may then mark a location that is distant from the artificial distortion, indicating that a pathological distortion may have been perceived. By manipulating the amplitude of artificial distortions, the amplitude of the pathology in the area of interest can be quantified. At the end of the test, comparison of the set of erroneous responses against a normative data base is used to determine if test results are within normal limits.

Microperimetry

One conventional measure of vision is subjective visibility thresholds of small, short-duration stimuli as performed by conventional automated static perimetry. In conventional perimetry, retinal localisation of a stimulus is implied indirectly from the assumed retinal location of fixation. This approach can work well when fixation is stable and foveal. However, loss of fixation stability or foveal vision, such as occurs commonly in nAMD, complicates the measurement of macular function with conventional perimetry. Accurate correspondence between retinal structures and visual function requires simultaneous imaging of the fundus. Microperimetry includes real-time automated tracking of the fundus and appropriate compensation of the location of stimulus presentation at predefined retinal loci.

Care pathway

See *Diagnosis of neovascular age-related macular degeneration and care pathway*, above.

Currently, patients with suspected nAMD seen by optometrists or other health professionals will be referred to secondary care where ophthalmologists with expertise on AMD will perform the following tests: VA measurement, SLB and, if the diagnosis of nAMD remains a possibility, FFA and OCT. The FFA and OCT imaging tests are used to confirm the diagnosis and they also provide a baseline reference for future comparisons during the follow-up of the patient. Alternative technologies are used at presentation in some units (e.g. FAF imaging), to evaluate the status of the RPE which may have prognostic implications.

Chapter 2 Definition of the decision problem

Decision problem

New treatments for nAMD have been approved by NICE for use in the NHS. These treatments often require repeated injections of antiVEGF over a period of years, with frequent monitoring greatly increasing the demand on secondary care AMD services.

Fundus fluorescein angiography, an invasive test, is the reference standard recommended for detecting nAMD at initial presentation and also for detecting recurrent activity at some monitoring visits (e.g. quarterly, or according to clinician criteria). OCT is a non-invasive test now widely used for detecting nAMD both at initial presentation and for detecting recurrent activity during monitoring visits. Two OCT systems are in use. The more recently introduced SD-OCT incorporates a number of improvements over the earlier TD-OCT. Depending on the performance of OCT, in some situations its use could possibly replace that of FFA. Also, as the interpretation of OCT images is more straightforward than that of FFA, it could potentially be interpreted by other health professionals (e.g. medical photographers, nurses).

However, the value of OCT has not been well-defined and given the burden of monthly lifelong monitoring by ophthalmologists, involving multiple tests, an assessment of the role of OCT in the diagnosis, monitoring and guiding of treatment for nAMD is needed.

Index test(s)

The index test considered was OCT, either alone or in combination with alternative tests as described below. Both TD-OCT and SD-OCT were considered.

Population

The population considered was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring.

The setting considered was secondary care.

Relevant comparators

The alternative tests considered included the following examinations:

- clinical evaluation (with SLB, with or without use of diagnostic contact lens and evaluation of patients' symptoms)
- VA (for monitoring)
- Amsler grid
- colour fundus photographs
- infrared reflectance (IR)
- RFs or blue reflectance
- FAF imaging
- ICGA, dynamic high-speed or digital subtraction indocyanine green angiography (DS-ICGA)
- PHP
- microperimetry.

Reference standard

The reference standard considered was ophthalmologist-interpreted FFA. FFA is generally acknowledged as being the recognised reference standard for detecting nAMD. The RCO states in its guidelines for management of AMD that FFA is currently the reference standard for diagnosing exudative disease.[1]

However, as few studies reported individual ophthalmologist-interpreted FFA (rather than reading centre-interpreted FFA), studies using FFA as the reference standard but with unclear information about which type of health-care professionals interpreted the images were also considered.

Outcomes

The following outcomes were considered for the use of OCT at presentation and during follow-up of patients with nAMD:

- diagnostic accuracy [e.g. sensitivity, specificity, likelihood ratios (LRs), diagnostic odds ratio (DOR)]
- clinical effectiveness (e.g. VA, anatomical control of the disease, patient-reported outcomes)
- interpretability of the test – to be defined as in included studies, considering the ability to acquire a quality image that can be interpreted or analysed
- acceptability of the test – to be defined as in included studies, considering users and health-care providers' perspective
- proportion of participants not able to receive the diagnostic test [due to an eye condition (e.g. lens or other media opacity), or personal circumstances (e.g. wheelchair bound)].

The evidence for the use of OCT was considered separately for the purposes of diagnosis and monitoring.

Key issues

The key issues to be addressed are:

- How good a test is OCT, when used either alone or in combination with alternative tests, in the diagnosis of people newly presenting with a suspicion of nAMD?
- How good a test is OCT, when used either alone or in combination with alternative tests, in detecting recurrent nAMD activity during surveillance monitoring of people previously diagnosed with the disease?
- Is SD-OCT a better test than TD-OCT?
- Could OCT images be interpreted by other health professionals in addition to ophthalmologists?
- Could OCT replace FFA in some situations in the diagnostic and/or monitoring pathways?
- How cost-effective are strategies involving OCT, both in the diagnostic and monitoring pathways?

Overall aims and objectives of assessment

The overall aim of the review was to determine the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected nAMD and (ii) monitoring those previously diagnosed with the disease.

Specific research objectives were:

- to determine the diagnostic performance of OCT, alone or in combination with alternative tests, in detecting nAMD, including accuracy, interpretability and acceptability
- to determine the performance of OCT and/or other alternative tests in the monitoring of the disease post diagnosis, specifically in detecting activity of the disease and the need for further treatment
- to determine the performance of other health professionals (e.g. medical photographers, nurses) compared with ophthalmologists in interpreting OCT findings
- to model the effects of using OCT and/or other alternative tests in the diagnosis and management of the disease and estimate the relative cost-effectiveness of alternative diagnostic and monitoring strategies, including determination of an optimal cut-off point for sensitivity and specificity for use in practice, and the alternative timing between tests during monitoring
- to identify future research needs.

Chapter 3 Methods for reviewing test performance

Methods were in accordance with the protocol.

Identification of studies

Published, unpublished and ongoing studies were identified from literature searches of electronic databases (from 1995 onwards) and appropriate websites. The search strategies were designed to be highly sensitive, including appropriate subject headings and text word terms that reflected both the clinical condition and diagnostic tests under review. There were no language restrictions. Databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Services and Science Citation Index for all reviews. The Cochrane Central Register of Controlled Trials was searched for additional reports of RCTs for the effectiveness review and PsycINFO and Applied Social Sciences Index and Abstracts for patient acceptability data. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion and Health Technology Assessment (HTA) database were searched for relevant systematic reviews and HTA reports. Abstracts and presentations from recent conferences (2009 onwards) of the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology (ARVO) and the European Association for Vision and Eye Research (EVER) were also searched. The World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov and European Union Clinical Trials Registry were searched for ongoing studies. Websites of professional organisations and manufacturers of OCT equipment were also consulted. Reference lists of all included studies were scanned and experts contacted for details of additional potentially relevant reports. The date of the final searches was March 2013. Full details of the search strategies used are provided in *Appendix 1*.

Inclusion and exclusion criteria

Types of studies

The following types of studies were considered.

i. Diagnostic studies:

- Direct (head-to head) comparisons in which the index test and comparator test(s) are evaluated in the same study population. These could be fully paired [all study participants receive the index test, comparator test(s) and the reference standard] or not fully paired (participants receive only a subset of the tests, e.g. a randomised direct comparison in which study participants are randomly allocated to receive the index test or the comparator and all receive the reference standard.
- Indirect comparisons in which estimates of the accuracy of the respective tests are obtained in different study groups, for example two-gate or 'case–control' type studies where different sets of criteria are used for those with and without the target condition. Indirect comparisons were to be considered if there was insufficient evidence from direct comparisons.

ii. Studies reporting clinical effectiveness:

- RCTs evaluating outcomes when treatment was based on OCT compared with FFA findings.

iii. Qualitative studies evaluating patients' and/or clinicians'/health-care professionals' acceptability and/or interpretability of the OCT tests.

Types of participants

The types of participants considered were people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring.

The setting considered was secondary care.

Index tests

The index test considered was OCT, either alone or in combination with alternative tests as described below. Both TD-OCT and SD-OCT were considered.

Comparator tests

The alternative tests considered included the following examinations:

- clinical evaluation (with SLB, with or without use of diagnostic contact lens and evaluation of patients' symptoms)
- VA (for monitoring)
- Amsler grid
- colour fundus photographs
- IR
- RFs or blue reflectance
- FAF imaging
- ICGA, dynamic high-speed or DS-ICGA
- PHP
- microperimetry.

Reference standard

The reference standard considered was ophthalmologist-interpreted FFA. FFA is generally acknowledged as being the recognised reference standard for detecting nAMD. The RCO states in its guidelines for management of AMD that FFA is currently the reference standard for diagnosing exudative (neovascular) AMD.[1] However, as few studies reported individual ophthalmologist-interpreted FFA (rather than reading centre interpreted FFA), studies using FFA as the reference standard but with unclear information about which type of health-care professionals interpreted the images were also considered.

Types of outcomes

The following outcomes were considered for the use of OCT at presentation and during follow-up of patients with nAMD:

- diagnostic accuracy (e.g. sensitivity, specificity, LRs, DOR)
- clinical effectiveness (e.g. VA, anatomical control of the disease, patient-reported outcomes)
- interpretability of the test – defined as in the included studies, considering the ability to acquire a quality image that can be interpreted or analysed
- acceptability of the test – defined as in the included studies, considering users and healthcare providers' perspective;
- proportion of participants not able to receive the diagnostic test [due to an eye condition (e.g. lens or other media opacity), or personal circumstances (e.g. wheelchair bound)].

The evidence for the use of OCT was considered separately for the purposes of diagnosis and monitoring.

Data extraction strategy

Two reviewers (MC plus GM or AAB) screened the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers (MC plus GM or AAB) independently assessed them for inclusion. Disagreements were resolved by consensus or arbitration by a third reviewer.

A data extraction form was developed and piloted. One reviewer (MC) extracted details of study design, participants, index, comparator and reference standard tests and outcome data, and a second reviewer (AAB or GM) checked the data extraction. Disagreements were resolved by consensus or arbitration by a third reviewer.

Critical appraisal strategy

Two reviewers (MC plus GM or AAB) independently assessed the risk of bias and applicability concerns of all included full-text diagnostic and monitoring studies using the updated quality assessment of diagnostic accuracy studies, version 2 (QUADAS-2) checklist.[17] Any disagreements were resolved by consensus or arbitration by a third party. The original QUADAS checklist was developed for use in systematic reviews of diagnostic studies through a formal consensus method and was based on empirical evidence. Following anecdotal reports and feedback which suggested problems with QUADAS, the QUADAS-2 tool was developed. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study, and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias. The first three domains are also assessed for concerns regarding their applicability in terms of whether (i) the participants and setting, (ii) the index test, its conduct or interpretation, and (iii) the target condition, as defined by the reference standard, match the question being addressed by the review. Within each domain signalling questions are included to assist in making a judgement about the risk of bias, with the standard tool containing 11 such questions across the four domains.

Both the original and updated checklists were designed to be adapted to be more applicable to a specific review topic. For this review, QUADAS-2 was modified by adding an additional signalling question to domain 1 (patient selection) to assess whether or not participant pre-selection had been avoided. Domains 2 (index test), 3 (reference standard) and 4 (flow and timing) were retained in their entirety. Therefore the modified tool contained 12 signalling questions, with each worded so that a rating of 'Yes' was always optimal in terms of methodological quality. If any signalling questions within a domain were rated 'No' then that domain was judged to be at high risk of bias. With regard to question 9 in the modified tool (appropriateness of the time interval between the index test and the reference standard), it was agreed that to be considered appropriate, the time interval between the index test and reference standard should be no longer than 1 week. An example of the QUADAS-2 checklist used in this review is shown at the end of the protocol (www.nets.nihr.ac.uk/__data/assets/pdf_file/0010/81685/PRO-10-57-22.pdf).

We planned to assess the methodological quality of any RCTs reporting effectiveness outcomes that met our inclusion criteria using the Cochrane risk of bias tool.[18] This tool addresses six specific domains relating to methodological quality (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). However, no RCTs reporting effectiveness outcomes were identified that met our inclusion criteria.

Methods of data synthesis

The results of the individual diagnostic studies were tabulated and, where data allowed, sensitivity, specificity, predictive values, LRs and DORs were calculated.

Summary receiver operating characteristic (SROC) curves were produced for each test where two or more diagnostic studies reported sufficient data. In the event of studies reporting 2 × 2 data [true positives (TPs), false positives (FPs), false negatives (FNs), true negatives (TNs)] for a number of different cut-off values we planned to select the most frequently used cut-off value across studies. However, this situation did not arise. Meta-analysis models were fitted using the hierarchical summary receiver operating characteristic (HSROC) model[19] in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). A symmetric SROC model was used, which takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects. The SROC curves from the HSROC models were produced on the corresponding SROC plots. Summary sensitivity, specificity, positive and negative LRs and DORs for each model were reported as point estimate and 95% confidence interval (CI).

If numerical difficulties were encountered with the HSROC model and there was no evidence of a threshold effect then we planned to pool sensitivity and specificity using the weighted average method.[20] Pooled LRs and DOR were to be calculated using the DerSimonian and Laird random-effects method.[21] These analyses were to be carried out using Metadisc software (version 1.4, Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid), with heterogeneity assessed using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.[22]

For relevant clinical outcomes reported based on use of the tests, where appropriate, we planned to use meta-analysis to estimate a summary measure of effect. Dichotomous outcome data were to be combined using the Mantel–Haenszel relative risk method and continuous outcomes were to be combined using the inverse-variance weighted mean difference method. For the estimates of relative risk and weighted mean difference, 95% CIs and *p*-values were to be calculated. Chi-squared tests and I^2 statistics were to be used to explore statistical heterogeneity across studies, with possible reasons for heterogeneity being investigated using sensitivity analysis. Heterogeneity is to be expected in diagnostic test accuracy studies, and random-effects models were to be used to describe the variability across studies. However, no studies reporting clinical outcomes based on use of the tests were identified that met our inclusion criteria.

Where a quantitative synthesis was considered inappropriate (e.g. studies reporting acceptability of tests), or not feasible, a narrative synthesis of results was provided.

Chapter 4 Assessment of diagnostic and monitoring studies

This chapter is structured as follows: *Quantity of research available* describes the quantity of research available for both diagnostic and monitoring studies together; *Assessment of diagnostic studies* and *Assessment of monitoring studies* report the results for the diagnostic and monitoring studies, respectively; and *Summary of the reviews of diagnostic and monitoring studies* provides a summary of the chapter. Within each of the sections on diagnostic and monitoring studies there are subsections on the characteristics of the included studies, their risk of bias, diagnostic accuracy results (single tests; studies directly comparing tests; studies reporting combinations of tests) and other outcomes of interest.

Quantity of research available

Number and type of studies included

Appendix 2 lists the 29 studies, published in 31 reports, that met the inclusion criteria for the review of diagnostic and monitoring studies.[23–53] There were two reports of the studies by Cachulo *et al.*[25,47] and Torron *et al.*[50,51] *Figure 3* shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

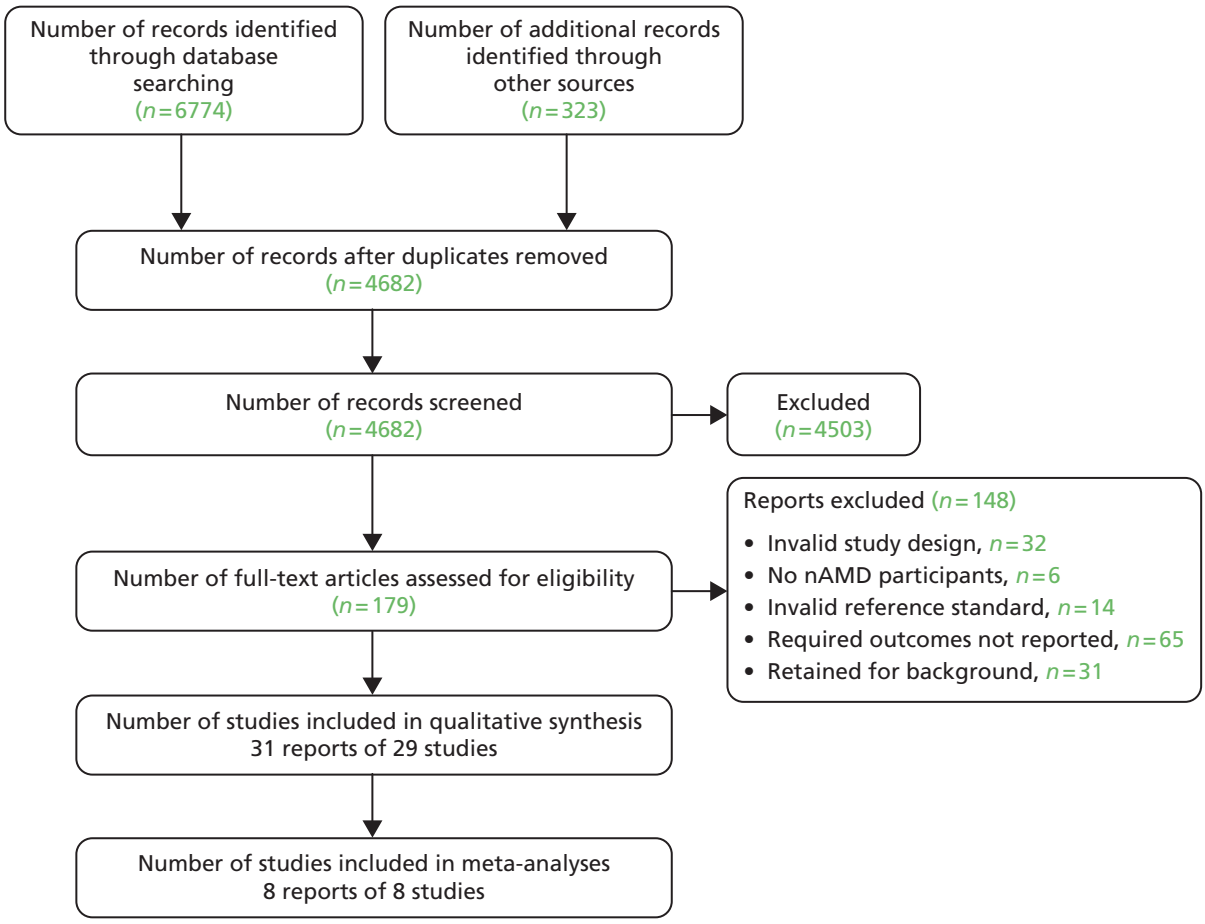


FIGURE 3 Flow diagram outlining the screening process.

Twenty-seven studies (29 reports in total as two studies each had two associated reports) were full-text papers and two studies were only available as abstracts.[34,42] Four studies (five reports) were non-English language, with one each in Japanese,[29] Chinese,[26] German[37] and Spanish.[50,51] Of the 29 included studies, 22 (24 reports)[24–27,29,31,33–42,44–51] were diagnostic studies involving people with suspected nAMD and eight[23,28,30,32,43,45,52,53] were monitoring studies involving people previously diagnosed with nAMD and under follow-up surveillance. One study, by Salinas-Alaman *et al.*,[45] reported results for both diagnosis and monitoring.

Number and type of studies excluded

A list of full-text papers that were excluded along with the reasons for their exclusion is given in *Appendix 3*. These reports were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test, reference standard or outcomes reported.

Assessment of diagnostic studies

Characteristics of the included diagnostic studies

Appendix 4 (see *Table 42*) provides details of the individual study characteristics for the 22 diagnostic studies. *Table 4* provides summary information for these studies. Of the 22 studies, nine were prospective[24,25,27,33,39–41,45,46] and seven were retrospective.[34–36,38,39,49,51] Seven studies did not provide this information.[26,29,31,37,42,44,48] (The study by Loewenstein *et al.*[39] reported both a prospective and retrospective component.) In 10 studies, participant recruitment was consecutive.[33,34,38,39,42,44–46,48,49] The studies enrolled more than 2000 participants. Twenty-one studies reported eye as the unit of analysis (1754 eyes), whereas one[42] reported patient as the unit of analysis (155 patients).

TABLE 4 Summary of the characteristics of the included diagnostic studies

Characteristic	Number	Number of studies
Participants enrolled[a]	2124	22
Analysed (eyes)	1754	21
Analysed (patients)	155	1
Age: median (range) of means/medians	76.0 (51.4–84.6)	15
Gender: male : female, *n* (%)	742 (45.4) : 891 (54.6)	14
Median (range) prevalence of nAMD[b]	80.0% (17.2–100.0%)	13
Tests reported (number enrolled)		
OCT	1335	13
TD-OCT	1316	12
SD-OCT	19	1
ICGA	458	8
PHP	491	3
Colour fundus photography	185	1
Amsler grid	98	1
FAF	62	1

a The study by Kozak *et al.*[36] enrolled 654 participants (1272 eyes analysed) with a diagnosis of suspected or confirmed macular oedema of various aetiologies, but did not specify how many were nAMD. Of these, 541 eyes with a diagnosis of suspected or confirmed nAMD were included in the analysis and this number has been included in the above table as an approximation of the number of nAMD participants enrolled by this study.

b The median (range) prevalence of nAMD was derived from 13 studies where this information was available at participant level. Studies reporting eye as the unit of analysis where it was not possible to ascertain the number of participants with nAMD, or studies reporting results only at phenotype level were not included in these calculations.

Seven studies were undertaken in the USA,[27,34,36,38,40,41,44] three in the UK,[33,46,49] two each in Japan,[29,31] Austria[37,48] and Spain,[45,51] and one each in Portugal,[25] Italy (involving eight centres),[42] the Republic of Korea[35] and China.[26] The remaining two studies were international, taking place in (a) seven centres in the USA, Germany, Israel, Austria and Portugal[24] and (b) 15 centres in Israel and the USA.[39] Of the three UK-based studies, two took place at the Royal Victoria Infirmary, Newcastle upon Tyne,[46,49] while the third took place at King's College Hospital, London.[33] One of the UK-based studies, by Talks *et al.*, involved a nurse-led, fast-track screening clinic.[49]

The largest study was by Kozak *et al.*,[36] which reported TD-OCT, was set in the USA and analysed 541 eyes, whereas the smallest was by Sulzbacher *et al.*,[48] reporting ICGA and included only 13 eyes.

Across 15 studies reporting the mean or median age of the participants,[24–27,29,31,35–37,39,40,45,46,49,51] the median (range) of these values was 76 years (51.4–84.6 years). Fourteen studies involving 1633 participants provided information on gender, in which 742 (45.4%) participants were men and 891 (54.6%) were women.[24,25,27,29,31,35,36,39–41,45,46,49,51] The median (range) prevalence of nAMD across 13 studies where this information was available at participant level was 80.0% (17.2–100.0%).[24,25,27,33,35,38–41,44,45,49,51]

In three studies, by Cachulo *et al.*,[25] Do *et al.*[27] and Padnick-Silver *et al.*,[40] the inclusion criteria specified that participants were required to have previously diagnosed nAMD in the non-study eye.

Thirteen studies reported OCT (12 TD-OCT;[25,27,33–38,40,45,46,49] one SD-OCT).[41] The study by Kozak *et al.*,[36] reporting TD-OCT, included a subset of patients who underwent additional examination with SD-OCT.[36]

Of the other tests reported, three studies reported PHP,[24,27,39] one reported colour fundus photography,[24] one Amsler grid,[27] one FAF imaging[25] and eight ICGA.[25,26,29,31,42,44,48,51] Of the studies reporting more than one test, Cachulo *et al.*[25] reported TD-OCT, ICGA and FAF, Do *et al.*[27] TD-OCT, Amsler grid and PHP, and Alster *et al.*[24] reported PHP and colour fundus photography. Two studies reported combinations of tests: Alster *et al.*[24] reported colour fundus photography plus VA, whereas Sandhu and Talks[46] reported TD-OCT plus colour fundus photography.

The 13 studies reporting OCT analysed 1262 eyes; in eight studies one eye per patient was analysed ($n = 479$ eyes) (all TD-OCT).[25,27,33–35,38,40,49] Eight studies reported detection of nAMD phenotypes (predominantly classic, minimally classic, occult CNV).[25,33,34,37,38,41,46,49] Four of these studies also reported detection of RAP.[25,34,37,38]

Of the eight studies reporting ICGA, seven used the eye as the unit of analysis (number of eyes analysed = 291).[25,26,29,31,44,48,51] In three of these studies, one eye per patient was analysed ($n = 109$ eyes).[25,31,44] Three studies only reported detection of nAMD phenotypes: IPCV;[31] occult CNV;[26] and type 2 CNV without an occult component.[48] The study by Parravano *et al.*,[42] with patient as the unit of analysis ($n = 155$ patients), also only reported detection of an nAMD phenotype – RAP.

The three studies reporting PHP analysed one eye per patient ($n = 302$ eyes),[24,27,39] as did the studies reporting colour fundus photography ($n = 120$ eyes),[24] Amsler grid ($n = 46$ eyes)[27] and FAF ($n = 50$ eyes).[25]

Risk of bias of the included diagnostic studies

All 20 full-text papers were assessed using a modified version of the QUADAS-2 tool containing 12 items. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias and the first three domains are also assessed for concerns regarding their applicability in terms of whether or not they match the question being addressed by the review. *Figure 4* presents a summary of the results for the QUADAS-2 risk of bias and applicability domains across the full-text diagnostic papers. *Appendix 5* (see *Table 44*) presents the results of the risk of bias and applicability concerns for the individual studies.

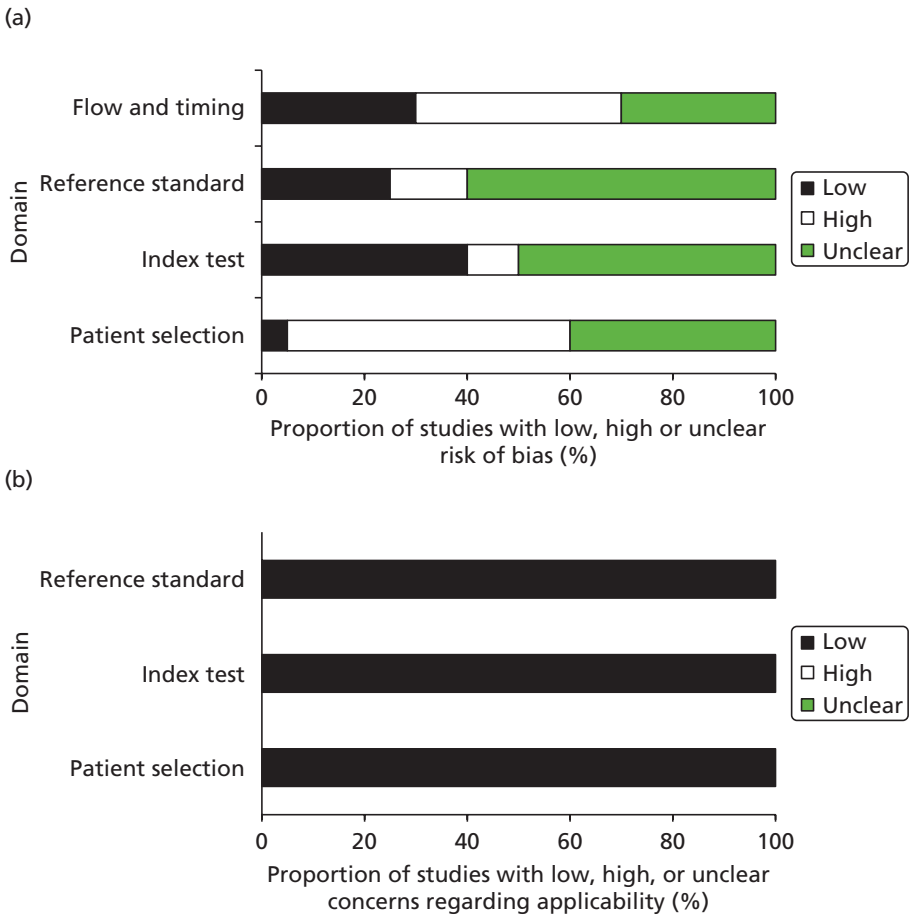


FIGURE 4 Summary of risk of bias and applicability domains (diagnostic studies).

No study was judged to have a low risk of bias across all domains; in three studies the risk of bias was judged to be unclear across all domains.[29,35,48] The domains in which the greatest number of studies were judged to be at high risk of bias were the patient selection domain ($n = 11$, 55%) and flow and timing domain ($n = 8$, 40%).

In the patient selection domain, only one study[36] was judged to be at low risk of bias, whereas the majority were considered to have either a high ($n = 11$, 55%)[24,27,31,37–41,44,45,49] or unclear ($n = 8$, 40%)[25,26,29,33,35,46,48,51] risk of bias. Reasons for studies being judged to be at high risk of bias included not enrolling a consecutive sample of participants,[27,37] not avoiding inappropriate exclusions[24,31,38–41,44] and not avoiding pre-selection of participants.[24,27,31,39,40,44,45,49]

In the index/comparator test domain, eight studies (40%) were judged to be at low risk of bias,[24,27,33,37,38,41,46,49] two (10%) were considered high risk of bias[44,51] and in half ($n = 10$, 50%) the risk of bias was considered to be unclear.[25,26,29,31,35,36,39,40,45,48] The reasons for the two studies being judged to be at high risk of bias were that the test (ICGA in both cases) was interpreted with knowledge of the results of the reference standard.

In the reference standard domain, five studies (25%) were judged to be at low risk of bias,[24,27,33,37,46] three (15%) were considered high risk of bias[44,49,51] and in the majority ($n = 12$, 60%) the risk of bias was considered to be unclear.[25,26,29,31,35,36,38–41,45,48] The reasons for the three studies being judged to be at high risk of bias were that the reference standard test was interpreted with knowledge of the results of the index test (TD-OCT)[49] or comparator test (ICGA).[44,51]

In the flow and timing domain, six studies (30%) were judged to be at low risk of bias,[26,31,37,38,41,44] and the majority were considered to have either a high ($n = 8$, 40%)[24,25,27,36,39,40,46,49] or unclear ($n = 6$, 30%)[29,33,35,45,48,51] risk of bias. Reasons for studies being judged to be at high risk of bias included an interval of more than 1 week between the index/comparator test and reference standard,[24,39] not all patients receiving the reference standard test,[39] or not all patients being included in the analysis.[24,25,27,36,37,40,46,49]

All 20 diagnostic studies were judged to have low concerns for applicability regarding the patient selection, index/comparator test and reference standard domains, in that the participants and setting, index/comparator test and target condition as defined by the reference standard were considered to match the question being addressed by the review.

Results: diagnostic accuracy

Individual study results are presented in *Appendix 6* (see *Table 46*).

Single tests

Optical coherence test

Thirteen studies, analysing 1262 eyes, reported the diagnostic accuracy of OCT in detecting nAMD (12 TD-OCT;[25,27,33–38,40,45,46,49] one SD-OCT[41]). In eight studies, one eye per patient was analysed ($n = 479$ eyes) (all TD-OCT).[25,27,33–35,38,40,49] Eight studies reported detection of nAMD phenotypes.[25,33,34,37,38,41,46,49]

The median (range) prevalence of nAMD across nine OCT studies where this information was available at participant level was 100.0% (17.2–100.0%).[25,27,33,35,38,40,41,45,49]

Figure 5 shows a forest plot of the sensitivity and specificity of the individual studies (excluding three where information was only available at phenotype level).[34,37,38] Across these 10 studies, the median (range) sensitivity and specificity values reported were 94.5% (36.0–100.0%) and 73.5% (66.0–94.0%) respectively. Only four studies (all TD-OCT) reported specificity. For TD-OCT, across the studies, the median (range) sensitivity values reported were 92.0% (36.0–100.0%) whereas the only SD-OCT study reported sensitivity of 100%.

The studies shown in *Figure 5* demonstrate heterogeneity across the sensitivities reported. The lowest sensitivity reported was by Hughes *et al.*[33] (36%) and Do *et al.*[27] (40%). In the study by Hughes *et al.*,[33] set in the UK, 22 individuals were classed as nAMD by FFA, seven with classic and 15 with occult CNV. TD-OCT detected six of the seven classic CNVs but only 2 of the 15 occult CNVs, hence the low overall sensitivity. The overall prevalence of nAMD in this study was 100%. Do *et al.*,[27] using TD-OCT in a study set in the USA, reported two separate sets of results, one for when the reference standard was FFA graded as positive by the reading centre irrespective of treatment decision (sensitivity 40.0%, specificity 70.8%), and one for when the reference standard was FFA graded as positive by the reading centre and the clinician recommended treatment (sensitivity 69.2%, specificity 66.2%) (see also *Appendix 6*, *Table 46*). The former reference standard was considered closer to the one used in this review and therefore it was these results that were taken to represent the study. Of 87 eyes analysed by Do *et al.*,[27] 15 were classed as

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cachulo 2011[25] (TD-OCT)	17	0	0	0	1.00 (0.80 to 1.00)	Not estimable
Do 2012[27] (TD)	6	21	9	51	0.40 (0.16 to 0.68)	0.71 (0.59 to 0.81)
Hughes 2005[33] (TD-OCT)	8	0	14	0	0.36 (0.17 to 0.59)	Not estimable
Kim 2003[35] (TD-OCT)	12	0	1	0	0.92 (0.64 to 1.00)	Not estimable
Kozak 2008[36] (TD-OCT)	514	0	14	0	0.97 (0.96 to 0.99)	Not estimable
Padnick-Silver 2011[40] (TD-OCT)	12	4	3	58	0.80 (0.52 to 0.96)	0.94 (0.84 to 0.98)
Park 2010[41] (SD-OCT)	21	0	0	0	1.00 (0.84 to 1.00)	Not estimable
Salinas-Alaman 2005[45] (TD-OCT)	60	0	2	0	0.97 (0.89 to 1.00)	Not estimable
Sandhu 2005[46] (TD-OCT)	63	12	18	38	0.78 (0.67 to 0.86)	0.76 (0.62 to 0.87)
Talks 2007[49] (TD-OCT)	73	13	0	25	1.00 (0.95 to 1.00)	0.66 (0.49 to 0.80)

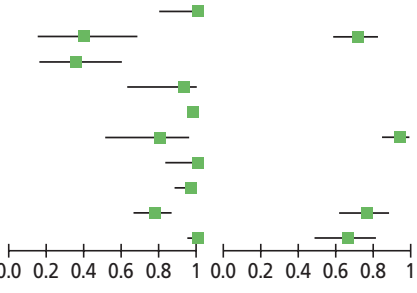


FIGURE 5 Individual study results for all OCT diagnostic studies reporting sensitivity and/or specificity.

nAMD by FFA, with 13 of the 15 CNVs described as occult with no classic. The overall prevalence of nAMD in this study was low at 17.2%. In theory, prevalence should not affect sensitivity, but if the low prevalence contained more people with phenotypes that were difficult to diagnose compared with studies with a higher prevalence of disease, then this might reduce the sensitivity of the test.

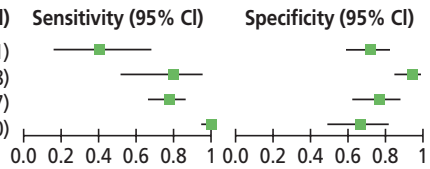
By far, the largest study was that by Kozak *et al.*[36] This retrospective study was set in the USA and involved the analysis of 1272 eyes of 654 participants with a diagnosis of confirmed or suspected macular oedema of various aetiologies; in 541 eyes (number of participants not reported) the aetiology was nAMD. In this study, no data were presented for TNs for the nAMD group and the total number of suspected nAMD classed by FFA as without disease was not reported; as such it was not possible to calculate specificity. The study stated that TD-OCT had detected nAMD in 13 eyes that had not been detected by FFA. As the reference standard of FFA, for the purposes of this review, was considered to have perfect sensitivity and specificity, these 13 cases were classed as TD-OCT FP (although not shown in *Figure 5* in order to prevent a spurious specificity value of 0% being calculated based on 13 FPs and zero TNs).

Pigment epithelial detachments can be classified as serous (non-specific) or vascularised. The latter are characteristic of nAMD. A serous PED can occur as a result of retinal conditions other than nAMD, such as central serous chorioretinopathy, angioid streaks or others. The study by Sandhu and Talks,[46] considered a serous PED to constitute presence of nAMD and on this basis reported sensitivity of 96.4% and specificity of 66.0%. However, as a serous PED did not fall within our definition of nAMD for diagnostic studies, cases with serous PED were classed as non-nAMD and the data from the study were recalculated accordingly, resulting in alternative values for sensitivity of 77.8% and specificity of 76.0% and it was these values that were taken to represent this study.

Four studies, all TD-OCT,[27,40,46,49] reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. One of the studies, by Talks *et al.*[49] was a retrospective audit on new patients referred with nAMD to a nurse-led, fast-track screening clinic. *Figure 6* shows a forest plot of the sensitivity

(a)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Do 2012[27] (TD-OCT)	6	21	9	51	0.40 (0.16 to 0.68)	0.71 (0.59 to 0.81)
Padnick-Silver 2011[40] (TD-OCT)	12	4	3	58	0.80 (0.52 to 0.96)	0.94 (0.84 to 0.98)
Sandhu 2005[46] (TD-OCT)	63	12	18	38	0.78 (0.67 to 0.86)	0.76 (0.62 to 0.87)
Talks 2004[49] (TD-OCT)	73	13	0	25	1.00 (0.95 to 1.00)	0.66 (0.49 to 0.80)



(b)

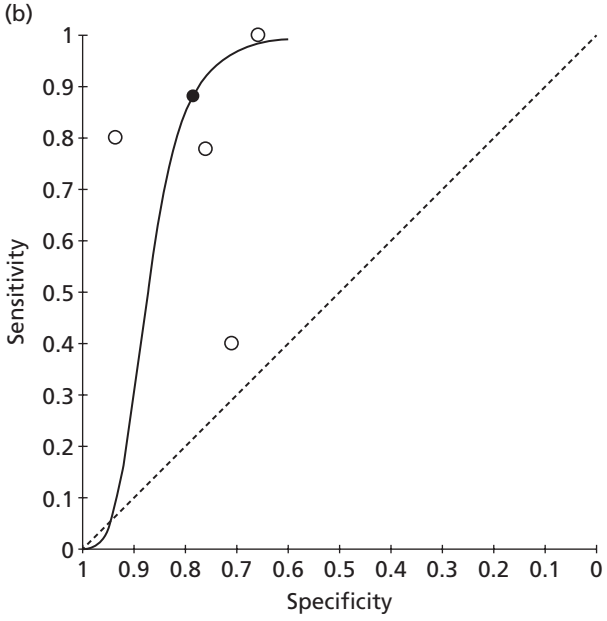


FIGURE 6 All OCT diagnostic studies reporting sensitivity and specificity. (a) Individual study results; and (b) SROC curve.

and specificity of the individual studies and a SROC curve for the four OCT studies. *Table 5* shows the pooled estimates for the OCT studies. For all OCT studies, the pooled sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%) respectively.

A LR describes how many times a person with disease is more likely to receive a positive (LR+) or negative (LR–) test result than a person without disease. It has been suggested that LR+s > 10 or LR–s < 0.1 can provide convincing diagnostic evidence, whereas those > 5 and < 0.2 demonstrate strong diagnostic evidence.[54] The LR+ did not exceed 5 for OCT.

The DOR is a single summary of diagnostic performance and describes the ratio of the odds of a positive test result in an individual with disease compared with someone without disease. It has been suggested that a DOR of 25 could provide strong diagnostic evidence and that a DOR of 100 could provide convincing diagnostic evidence.[20]

The risk of bias assessment of the four OCT studies included in the meta-analysis is shown in *Table 6*. The domains in which most studies were judged to be at high risk of bias were the patient selection domain, for reasons such as not enrolling a consecutive sample of participants,[27] not avoiding inappropriate exclusions[40] and not avoiding pre-selection of participants,[27,40,49] and the flow and timing domain, due to all patients not being included in the analysis (all four studies).

Eight studies[25,33,34,37,38,41,46,49] reported the sensitivity of OCT in the detection of nAMD phenotypes (*Table 7*). The studies by Cachulo *et al.*[25] and Khondkaryan *et al.*,[34] and Talks *et al.*,[49] using TD-OCT, and Park *et al.*[41] using SD-OCT showed equally high sensitivity for the detection of classic CNV compared with occult CNV. On the other hand, the studies by Hughes *et al.*[33] (TD-OCT), Krebs *et al.*[37] (TD-OCT), Liakopoulos *et al.*[38] (TD-OCT), and Sandhu and Talks[46] (TD-OCT) reported higher sensitivity for OCT in the detection of classic CNV compared with occult CNV.

TABLE 5 Pooled estimates for the OCT diagnostic studies

Test	Number of studies	Number of eyes analysed	Pooled estimates (95% CI)				
			Sensitivity, %	Specificity, %	LR+	LR–	DOR
All OCT	4	406	88 (46 to 98)	78 (64 to 88)	4.08 (2.37 to 7.04)	0.15 (0.02 to 0.98)	26.86 (3.36 to 214.81)

TABLE 6 Risk of bias of the four OCT studies included in the meta-analysis

Study	Risk of bias domain			
	Patient selection	Index/comparator test	Reference standard	Flow and timing
Do 2012[27]	High	Low	Low	High
Padnick-Silver 2012[40]	High	Unclear	Unclear	High
Sandhu 2005[46]	Unclear	Low	Low	High
Talks 2007[49]	High	Low	High	High

TABLE 7 Sensitivity of OCT in detecting nAMD phenotypes

Study ID	Test	Unit of analysis	nAMD phenotype	Number by FFA	OCT sensitivity, %
Cachulo 2011[25]	TD-OCT	Eye	Predominantly classic	2	100.0
			Minimally classic	4	100.0
			Occult	6	100.0
			RAP	5	100.0
Hughes 2005[33]	TD-OCT	Eye	Classic	7	85.7
			Occult	15	13.3
Khondkaryan 2009[34]	TD-OCT	Eye	Classic	Not reported	80.9
			Occult		81.1
			RAP		57.1
Krebs 2007[37]	TD-OCT	Eye	Primarily classic	5	100.0
			RAP	11	72.7
Liakopoulos 2008[38]	TD-OCT	Eye	Subretinal fluid		
			Predominantly classic	11	100.0
			Minimally classic	23	91.3
			Occult with no classic	24	79.2
			RAP stage III	8	50.0
			Cystoid oedema		
			Predominantly classic	11	81.8
			Minimally classic	23	73.9
			Occult with no classic	24	58.3
			RAP stage III	8	100.0
Park 2010[41]	SD-OCT	Eye	Classic	7	100.0
			Minimally classic	3	100.0
			Occult	11	100.0
Sandhu 2005[46]	TD-OCT	Eye	Classic	56	78.6
			Occult	25	20.0
	TD-OCT + fundus photo	Eye	Classic	56	82.1
			Occult	25	12.0
Talks 2007[49]	TD-OCT	Eye	Predominantly classic	22	100.0
			Minimally classic	6	100.0
			Occult	45	100.0

Amsler grid

One study, by Do *et al.*,[27] in an analysis of 46 eyes of 46 patients, reported sensitivity of 41.7% for the Amsler grid in detecting nAMD (specificity not reported and insufficient information to calculate prevalence of nAMD in this group). As this study also reported OCT, information on risk of bias is presented in that section.[27]

Fundus autofluorescence imaging

One study, by Cachulo *et al.*,[25] in an analysis of 50 eyes of 50 patients, reported sensitivity of 93.3% and specificity of 37.1% for FAF in detecting nAMD. The prevalence of nAMD in this group was 30.0%. As this study also reported ICGA, information on risk of bias is presented in that section.[25]

Colour fundus photography

One study, by Alster *et al.*,[24] in an analysis of 120 eyes of 120 patients, reported sensitivity of 70.0% and specificity of 95.0% for colour fundus photography in detecting nAMD. The prevalence of nAMD in this study was 53.3%. As this study also reported PHP, information on risk of bias is presented in that section.[24]

Preferential hyperacuity perimetry

Three studies analysing 302 eyes of 302 patients reported the diagnostic accuracy of the PHP test in detecting nAMD.[24,27,39] *Figure 7* shows a forest plot with the individual study results for sensitivity and specificity. The studies by Alster *et al.*[24] and Loewenstein *et al.*[39] reported similarly high sensitivity and specificity. However, it was not possible to calculate pooled estimates using HSROC methodology due to insufficient data. The study by Do *et al.*[27] reported lower sensitivity and did not report specificity. Across the studies the median (range) of sensitivity values reported was 82% (50–85%). The specificity values reported by Alster *et al.*[24] and Loewenstein *et al.*[39] were 88% and 85% respectively.

Across the three studies, the median (range) prevalence of nAMD was 50.4% (17.2–53.3%).

The risk of bias assessment of the three PHP studies is shown in *Table 8*. The domains in which most studies were judged to be at high risk of bias were the patient selection domain, for reasons such as inappropriate exclusions[24,39] and pre-selection of participants,[24,27,39] and the flow and timing domain, for reasons such as an interval of more than 1 week between the index test and reference standard,[24,39] not all patients receiving the reference standard test[39] and not all patients included in the analysis.[24,39]

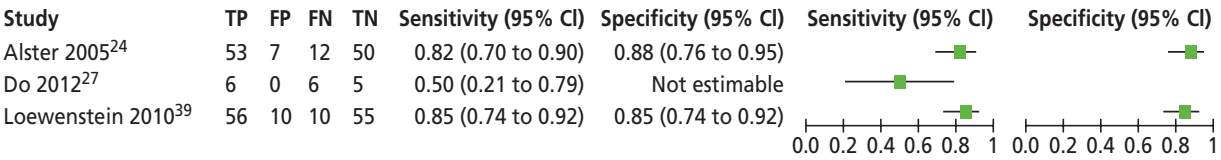


FIGURE 7 Preferential hyperacuity perimetry studies: individual study results for sensitivity and specificity.

TABLE 8 Risk of bias of the PHP studies

	Risk of bias domain			
Study	Patient selection	Index/comparator test	Reference standard	Flow and timing
Alster 2005[24]	High	Low	Low	High
Do 2012[27]	High	Low	Low	High
Loewenstein 2010[39]	High	Unclear	Unclear	High

Loewenstein *et al.*[39] also reported the ability of PHP in detecting nAMD phenotypes, with 90% (18/20) sensitivity for minimally or predominantly classic CNV and 82.6% (38/46) sensitivity for occult CNV.

Indocyanine green angiography

Eight studies reported the diagnostic accuracy of ICGA in detecting nAMD, of which seven[25,26,29,31,44,48,51] reported the eye as the unit of analysis and one[42] reported the patient as the unit of analysis. Four of these studies only reported detection of nAMD phenotypes: IPCV;[31] occult CNV;[26] type 2 CNV without an occult component;[48] and RAP.[42]

The median (range) prevalence of nAMD across three studies where this information was available at participant level (and excluding studies reporting results only at phenotype level) was 80.0% (32.7–100.0%).[25,44,51]

Figure 8 shows a forest plot of the sensitivity and specificity of the individual studies (excluding the four that only reported detection of phenotypes). Across the studies, the median (range) sensitivity reported was high at 93% (85–100%). Only the study by Fujii *et al.*[29] reported specificity, which was low at 37%.

In the study by Reichel *et al.*,[44] all participants were deemed to have nAMD (therefore there could be no TNs and it was not possible to calculate specificity). Only participants who were suspected to have a CNV obscured by haemorrhage were included in this study. The authors stated that ICGA had detected nAMD in four eyes that had not been detected by FFA. As the reference standard of FFA, for the purposes of this review, was considered to have perfect sensitivity and specificity, these four cases were classed as ICGA FPs (although not shown in *Figure 8* in order to prevent a spurious specificity value of 0% being calculated based on four FPs and zero TNs).

The risk of bias assessment of the four ICGA studies is shown in *Table 9*. The domains in which most studies were judged to be at high risk of bias were the index/comparator test domain, due to the ICGA test being interpreted with knowledge of the FFA results, and the reference standard domain, due to FFA being interpreted with knowledge of the ICGA results.[44,51]

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cachulo 2011[25]	16	0	1	0	0.94 (0.71 to 1.00)	Not estimable
Fujii 1996[29]	11	12	2	7	0.85 (0.55 to 0.98)	0.37 (0.16 to 0.62)
Reichel 1995[44]	16	0	0	0	1.00 (0.79 to 1.00)	Not estimable
Torron 2002[51]	94	0	8	0	0.92 (0.85 to 0.97)	Not estimable

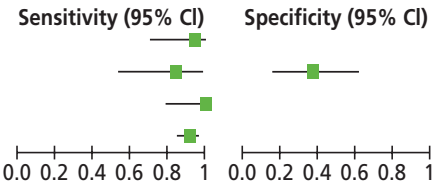


FIGURE 8 Indocyanine green angiography sensitivity and specificity: individual study results.

TABLE 9 Risk of bias of the four ICGA studies included in the forest plot

	Risk of bias domain			
Study	Patient selection	Index/comparator test	Reference standard	Flow and timing
Cachulo 2011[25]	Unclear	Unclear	Unclear	High
Fujii 1996[29]	Unclear	Unclear	Unclear	Unclear
Reichel 1995[44]	High	High	High	Low
Torron 2002[51]	Unclear	High	High	Unclear

Four studies[26,31,42,48] reported the sensitivity of ICGA in the detection of nAMD phenotypes, with each study reporting detection of a different phenotype (*Table 10*). Sensitivity was 100% for detection of IPCV[31] and type 2 CNV without an occult component,[48] high (85.1%) for detection of RAP[42] but lower (62.9%) for detection of occult CNV.[26]

Studies directly comparing tests

Preferential hyperacuity perimetry versus colour fundus photography versus colour fundus photography plus visual acuity

One study, by Alster *et al.*,[24] analysing one eye per patient, reported PHP ($n = 122$ eyes) compared with colour fundus photography ($n = 120$ eyes) and colour fundus photography plus VA ($n = 66$ eyes). Sensitivity was highest for PHP (81.5%), followed by colour fundus photography (70.0%) and lowest for colour fundus photography plus VA (53.0%). Specificity was similarly high for colour fundus photography (95.0%) and colour fundus photography plus VA (94.0%), followed by PHP (87.7%).

Time domain optical coherence tomography versus indocyanine green angiography versus fundus autofluorescence imaging

One study, by Cachulo *et al.*,[25] analysing one eye per patient, reported TD-OCT ($n = 52$ eyes) compared with ICGA ($n = 52$ eyes) and FAF ($n = 50$ eyes). Sensitivity was high for all three tests (TD-OCT 100.0%, ICGA 94.1%, FAF 93.3%). Specificity was only reported for FAF, which was low at 37.1%.

Time domain optical coherence tomography versus Amsler grid versus preferential hyperacuity perimetry

One study, by Do *et al.*,[27] analysing one eye per patient, reported TD-OCT ($n = 87$ eyes) compared with Amsler grid ($n = 46$ eyes) and PHP ($n = 49$ eyes). Based on the set of results for CNV defined as positive by FFA irrespective of the treatment decision, the sensitivity for all three tests was fairly low (PHP 50.0%, Amsler grid 41.7%, TD-OCT 40.0%). Specificity was only reported for TD-OCT, which was moderate at 70.8%. As previously stated, the overall prevalence of nAMD in this study was low at 17.2%, the majority of which were occult CNV, which might at least partly explain the low sensitivity reported by this study for TD-OCT.

Time domain optical coherence tomography versus time domain optical coherence tomography plus stereo colour fundus photography

One study, by Sandhu and Talks,[46] reported TD-OCT compared with TD-OCT plus stereo colour fundus photography (both $n = 131$ eyes of 118 participants). As previously stated, serous PED did not fall within this review's definition of nAMD for diagnostic studies and the study data were recalculated accordingly. Based on the recalculated data, sensitivity was similar and moderately high for both tests (TD-OCT 77.8%, TD-OCT plus stereo colour fundus photography 74.1%), whereas specificity was higher for the combination (92.0%) than for TD-OCT alone (76.0%).

TABLE 10 Sensitivity of ICGA in detecting nAMD phenotypes

Study	Test	Unit of analysis	nAMD phenotype	Number by FFA	ICGA sensitivity, %
Chen 2003[26]	ICGA	Eye	Occult CNV	35	62.9
Gomi 2007[31]	ICGA	Eye	IPCV	37	100.0
Sulzbacher 2011[48]	ICGA	Eye	Type 2 CNV without an occult component	13	100.0
Parravano 2012[42]	ICGA	Patient	RAP	155	85.1

Studies reporting combinations of tests

Two studies reported combinations of tests. Sandhu and Talks[46] reported TD-OCT combined with stereo colour fundus photography. Alster *et al.*[24] reported colour fundus photography combined with VA. As both studies also reported other tests, the results for the test combinations are included in the preceding section on studies directly comparing tests.

Assessment of other outcomes of interest

Clinical effectiveness

No studies were identified that met our inclusion criteria of providing information on clinical effectiveness outcomes (e.g. VA) when treatment was based on OCT compared with FFA findings.

Interpretability of the tests

Six diagnostic studies[24,25,27,36,39,46] provided information relating to the interpretability of the tests, in as much as they reported on the numbers excluded from analysis due to poor image quality (*Table 11*). In the TD-OCT study by Do *et al.*,[27] 166 individuals were screened and 98 were enrolled; in 6 of the 68 individuals screened but not enrolled, the reason given was poor image quality. However, it was unclear whether the excluded images related to OCT, colour fundus photography or FFA. In the TD-OCT study by Sandhu and Talks,[46] 10/128 individuals (7.8%) were excluded from the analysis due to poor image quality. It was also unclear in this study whether the excluded images related to OCT or FFA.

Acceptability of the tests

No studies were identified meeting our inclusion criteria that reported the acceptability of the tests, either to those providing the tests or to those receiving them.

TABLE 11 Studies reporting numbers excluded from analysis due to poor image quality

Study	Test	Excluded from analysis, *n* (%)	Reason
Alster 2005[24]	PHP	11/185 (5.9) individuals/eyes	Results judged to be unreliable
	Colour fundus photography	17/185 (9.2) individuals/eyes	Inadequate or poor-quality photographs
Cachulo 2011[25]	FAF	2/52 (3.8) individuals/eyes	Pattern of autofluorescence could not be determined
Do 2012[27]	TD-OCT, PHP, Amsler grid, colour fundus photography	6/104 (5.8) individuals/eyes[a]	Poor image quality that was insufficient to permit successful participation
Kozak 2008[36]	TD-OCT	35/1307 (2.7) eyes[b]	Poor quality or image decentration
Loewenstein 2010[39]	PHP, colour fundus photography	40/208 (19.2) individuals/eyes[c]	Geographic atrophy, early AMD, pattern dystrophy, no or poor-quality photographs
Sandhu 2005[46]	TD-OCT	10/128 (7.8) individuals	Poor quality of the images

a In the study by Do *et al.*,[27] 166 individuals were screened for study participation, of whom 98 were enrolled. Of the 68 individuals screened but not enrolled, the reason for this, in 6 of them, was poor image quality. Our calculation of 5.8% excluded from the analysis was based on 6 as a percentage of 104 (98 + 6), on the assumption that these six individuals would have been enrolled had their images been of sufficient quality.
b In the study by Kozak *et al.*,[36] of 1272 eyes analysed, 541 were nAMD with the remainder macular oedema due to other aetiologies. Thirty-five eyes were excluded prior to analysis due to poor quality or image decentration, but it was not reported how many of these specifically related to nAMD.
c In the study by Loewenstein *et al.*,[39] the specific number of individuals excluded solely due to poor-quality photographs was not reported.

Proportion of participants unable to receive the diagnostic test

Ten studies reported exclusion criteria relating to eye conditions (see *Appendix 7*, *Table 48*).[24,25,27,31,39–41,44,48,49] The studies detailed various eye-related exclusion criteria, for example evidence of macular disease other than AMD, previous surgical or laser treatment within the macular area, presence of any significant media opacity that precluded a clear view of the fundus, subretinal or subpigment epithelial haemorrhages that obscured lesions, and recent ocular surgery in the study eye.

A few non-ophthalmic exclusion criteria were reported, including current or past history of a medical condition that would preclude scheduled study visits or completion of the study,[25] allergy to fluorescein dye[27] and allergy to iodine-based dye.[44] In the PHP study by Loewenstein *et al.*,[39] individuals with no experience of using a computer mouse were taught how to use the mouse and participation in the study was conditional on passing an in-house computer mouse tutorial. The authors reported that 15 people did not pass the tutorial and were excluded from the study.

Other health professionals compared with ophthalmologists interpreting optical coherence tomography findings

No studies were identified meeting our inclusion criteria that reported the performance of other health professionals compared with ophthalmologists in interpreting OCT findings. The setting for the TD-OCT study by Talks *et al.*[49] was a nurse-led, fast-track screening clinic in the UK for new nAMD referrals, but did not involve a comparison with other health professionals in interpreting OCT findings. Trained nurses and an ophthalmic photographer, who consulted an ophthalmologist when in doubt, conducted the screening visit. If the VA was ≥ 6/60 an OCT was performed. If dry AMD or other retinal pathology was seen, the patient was referred for management appropriate to their condition but no further imaging was performed. The remaining patients underwent simultaneous FFA and ICGA. The images were taken, using standard protocols, by an ophthalmic photographer. The ophthalmologist reviewed the images the following day.[49]

Assessment of monitoring studies

Characteristics of the included monitoring studies

Appendix 4 (see *Table 43*) provides details of the individual study characteristics for the eight monitoring studies.[23,28,30,32,43,45,52,53] *Table 12* provides summary information for the studies. Of the eight monitoring studies, four were prospective,[32,43,45,53] three were retrospective,[23,28,30] and in the study by van de Moere *et al.*[52] this information was not reported. In five studies, the participants were a consecutive sample.[28,30,43,45,53] The eight studies enrolled 463 participants.

Five studies used the eye as the unit of analysis (363 eyes),[23,28,30,52,53] whereas three used test examination as the unit of analysis (61 pairs of OCT and FFA examinations,[32] 176 pairs of OCT and FFA examinations[45] and 54 pairs of ICGA and FFA examinations).[43]

Two studies were undertaken in the USA[23,43] and one each in Italy,[30] Germany,[32] the Netherlands,[53] Spain[45] and the UK (Royal Victoria Infirmary, Newcastle upon Tyne).[52] One study was international, taking place in two centres in the USA and Germany.[28]

The largest study was by van de Moere *et al.*,[52] which reported TD-OCT, was set in the UK and analysed 121 eyes, while the smallest was by van Velthoven *et al.*,[53] reporting TD-OCT and analysing 30 eyes.

Across seven studies[23,28,30,43,45,52,53] reporting the mean or median age of the participants, the median (range) of these values was 76.5 years (73.9–78.1 years). Six studies involving 378 participants provided information on gender,[28,30,43,45,52,53] in which 177 (46.8%) participants were men and 201 (53.2%) women. The median (range) prevalence of active nAMD across five studies where this information was available at participant level was 57.9% (49.2–83.3%).[23,28,30,52,53]

TABLE 12 Summary of the characteristics of the included monitoring studies

Characteristic	Number	Number of studies
Participants enrolled	463	8
Analysed (eyes)	363	5
Analysed (examinations, pairs)	291	3
Age: median (range) of means/medians	76.5 (73.9–78.1)	7
Gender: male : female, *n* (%)	177 (46.8) : 201 (53.2)	6
Median (range) prevalence of active nAMD[a]	57.9% (49.2–83.3%)	5
Tests reported (number enrolled)[b]		
OCT	442	7
TD-OCT	349	6
SD-OCT	152	2
ICGA	21	1
Type of treatment received		
AntiVEGF	149	2
PDT	293	5
Laser photocoagulation	21	1

PDT, photodynamic therapy

a The median (range) prevalence of active nAMD was derived from five studies where this information was available at participant level. Three studies reporting examination as the unit of analysis, where it was not possible to ascertain the number of participants with nAMD, were not included in these calculations.[32,43,45]

b One study reported both TD-OCT and SD-OCT.[23]

Seven studies reported OCT (six TD-OCT;[23,28,32,45,52,53] and two SD-OCT).[23,30] (The study by Khurana *et al.*[23] reported both TD-OCT and SD-OCT.) One study, by Regillo *et al.*,[43] reported ICGA.

Of the seven studies reporting OCT, five used the eye as the unit of analysis (number of eyes analysed = 363).[23,28,30,52,53] In four of these studies, one eye per patient was analysed ($n = 304$ eyes).[28,30,52,53] Two studies reported examination as the unit of analysis (both TD-OCT).[32,45] Two studies reported detection of nAMD phenotype activity: classic and occult CNV;[30] and PED and cystoid macular oedema.[52] The studies by Henschel *et al.*[32] and van de Moere *et al.*[52] also reported the performance of OCT in detecting intraretinal and subretinal fluid.

In two OCT monitoring studies,[23,30] the participants had received antiVEGF therapy and in five[28,32,45,52,53] the treatment was photodynamic therapy (PDT). In the study reporting ICGA,[43] the participants had received laser photocoagulation treatment.

Risk of bias of the included monitoring studies

Figure 9 presents a summary of the results for the QUADAS-2 risk of bias and applicability domains across the eight full-text monitoring papers. *Appendix 5* (see *Table 45*) presents the results of the risk of bias and applicability concerns for the individual studies.

No study was judged to have a low risk of bias across all domains. More studies in the patient selection domain ($n = 2$, 25%) and the flow and timing domain ($n = 2$, 25%) were judged to be at high risk of bias than in the index/comparator test domain ($n = 1$, 12.5%) and reference standard domain ($n = 1$, 12.5%).

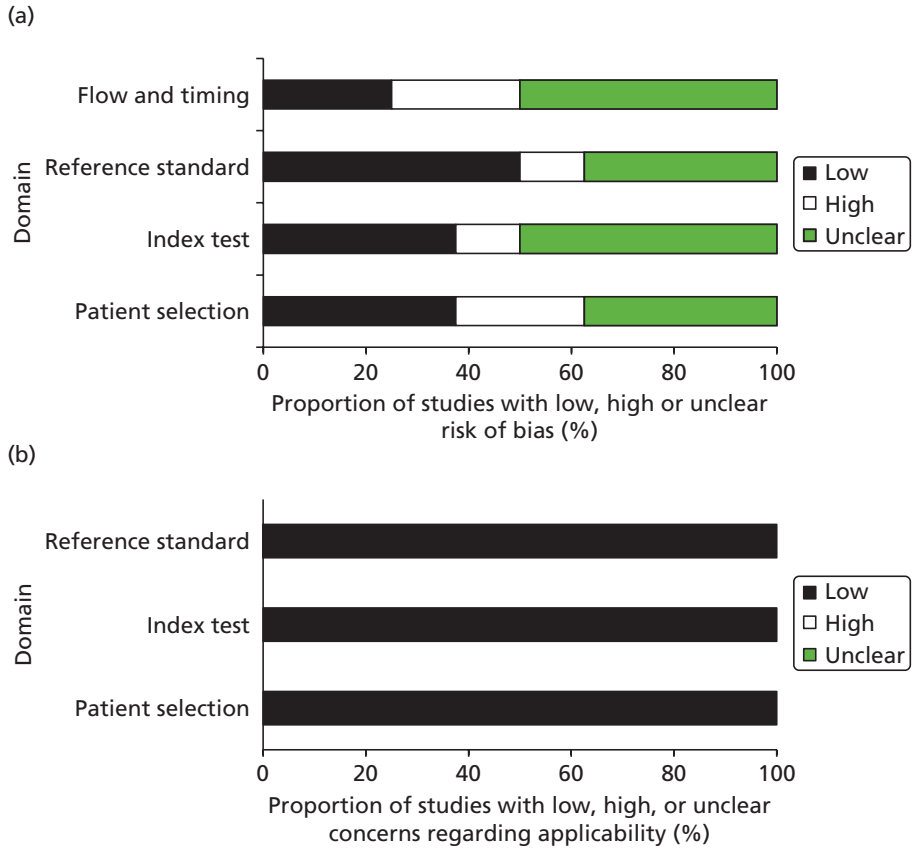


FIGURE 9 Summary of risk of bias and applicability domains (monitoring studies).

In the patient selection domain, three studies[43,52,53] (37.5%) were judged to be at low risk of bias, two[30,45] (25%) were considered to have a high risk of bias and in three[23,28,32] (37.5%) the risk of bias was unclear. The study by Giani *et al.*[30] was judged to be at high risk of bias due to not avoiding inappropriate exclusions and pre-selection of participants, whereas the study by Salinas-Alaman *et al.*[45] was judged to be at high risk of bias due to not avoiding pre-selection of participants.

In the index/comparator test domain, three studies (37.5%) were judged to be at low risk of bias,[28,30,32] one (12.5%) was considered high risk of bias[43] and in the remaining four (50%) the risk of bias was considered to be unclear.[23,45,52,53] The reasons for the study by Regillo *et al.*[43] being judged to be at high risk of bias was that the test (ICGA) was interpreted with knowledge of the results of the reference standard.

In the reference standard domain, four studies (50%) were judged to be at low risk of bias,[28,30,32,53] one (12.5%) was considered high risk of bias[43] and in the remaining three (37.5%) the risk of bias was considered to be unclear.[23,45,52] The Regillo *et al.*[43] study was judged to be at high risk of bias as the reference standard test was interpreted with knowledge of the results of the comparator test (ICGA).

In the flow and timing domain, two studies (25%) were judged to be at low risk of bias,[23,43] two[45,52] (25%) were considered to have a high risk of bias and in the remaining four[28,30,32,53] (50%) the risk of bias was considered to be unclear. The studies by Khurana *et al.*[23] and Regillo *et al.*[43] were judged to be at high risk of bias as not all patients were included in the analysis.

All eight studies were judged to have low concerns for applicability on the patient selection, index/comparator test and reference standard domains.

Results: detection of active neovascular age-related macular degeneration

Individual study results are presented in *Appendix 6* (see *Table 47*).

Single tests

Optical coherence tomography

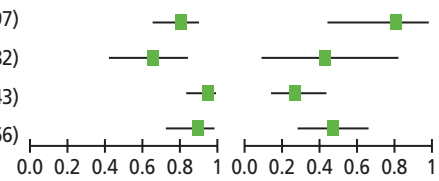
Seven studies reported the accuracy of OCT in detecting active nAMD, of which five reported TD-OCT,[28,32,45,52,53] one reported SD-OCT[30] and one reported both TD-OCT and SD-OCT.[23] In five studies the unit of analysis was the eye[23,28,30,52,53] and in two the unit of analysis was pairs of OCT and FFA examinations.[32,45]

The median (range) prevalence of active nAMD across five studies where this information was available at participant level was 57.9% (49.2–83.3%).[23,28,30,52,53]

Three TD-OCT studies[23,28,53] and two SD-OCT studies,[23,30] with eye as the unit of analysis, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. *Figure 10* shows forest plots of the sensitivity and specificity of the individual studies and SROC curves for (a) all of the OCT studies,

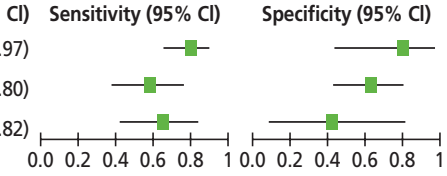
(a)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Eter 2005[28] (TD-OCT)	40	2	10	8	0.80 (0.66 to 0.90)	0.80 (0.44 to 0.97)
van Velthoven 2006[53] (TD-OCT)	15	4	8	3	0.65 (0.43 to 0.84)	0.43 (0.10 to 0.82)
Giani 2011[30] (SD-OCT)	49	30	3	11	0.94 (0.84 to 0.99)	0.27 (0.14 to 0.43)
Khurana 2010[23] (SD-OCT)	26	16	3	14	0.90 (0.73 to 0.98)	0.47 (0.28 to 0.66)



(b)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Eter 2005[28] (TD-OCT)	40	2	10	8	0.80 (0.66 to 0.90)	0.80 (0.44 to 0.97)
Khurana 2010[23] (TD-OCT)	17	11	12	19	0.59 (0.39 to 0.76)	0.63 (0.44 to 0.80)
van Velthoven 2006[53] (TD-OCT)	15	4	8	3	0.65 (0.43 to 0.84)	0.43 (0.10 to 0.82)



(c)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Giani 2011[30] (SD-OCT)	49	30	3	11	0.94 (0.84 to 0.99)	0.27 (0.14 to 0.43)
Khurana 2010[23] (SD-OCT)	26	16	3	14	0.90 (0.73 to 0.98)	0.47 (0.28 to 0.66)

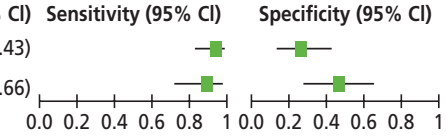


FIGURE 10 Optical coherence tomography monitoring studies reporting sensitivity and specificity for detection of nAMD activity: individual study results and SROC curves. (a) Sensitivity and specificity – individual study results – all OCT; (b) sensitivity and specificity – individual study results – TD-OCT; (c) sensitivity and specificity – individual study results – SD-OCT; (d) SROC curve – all OCT; (e) SROC curve – TD-OCT; and (f) SROC curve – SD-OCT. (*continued*)

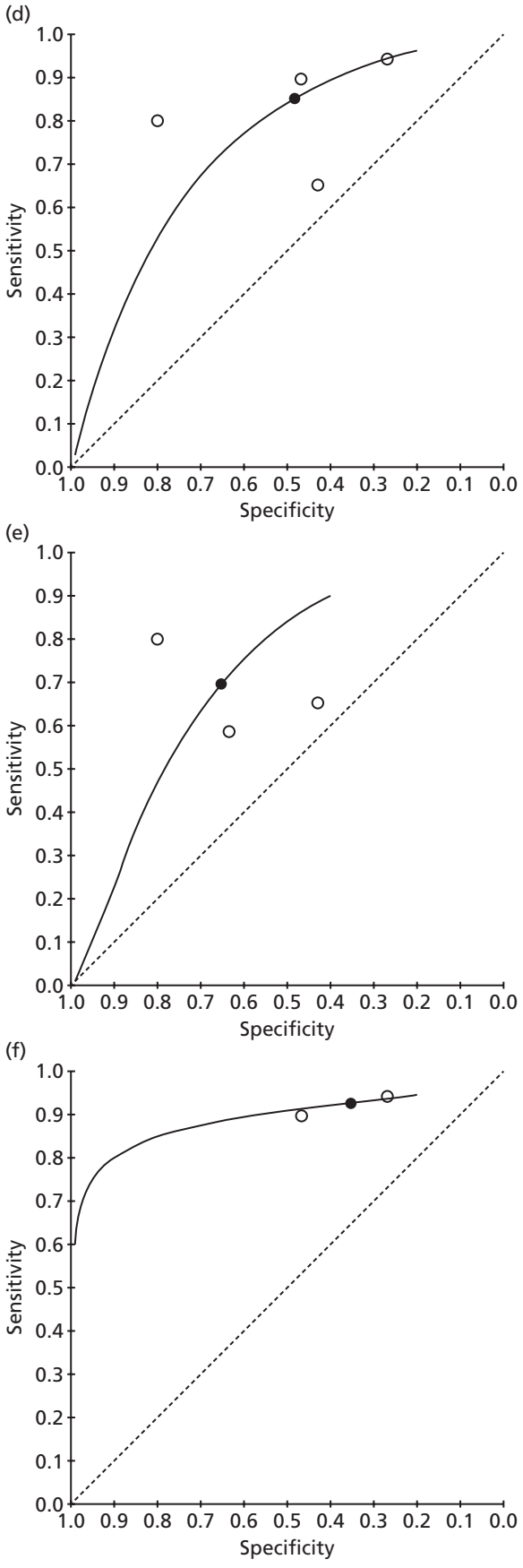


FIGURE 10 Optical coherence tomography monitoring studies reporting sensitivity and specificity for detection of nAMD activity: individual study results and SROC curves. (a) Sensitivity and specificity – individual study results – all OCT; (b) sensitivity and specificity – individual study results – TD-OCT; (c) sensitivity and specificity – individual study results – SD-OCT; (d) SROC curve – all OCT; (e) SROC curve – TD-OCT; and (f) SROC curve – SD-OCT.

(b) the three TD-OCT studies and (c) the two SD-OCT studies respectively. *Table 13* shows the pooled estimates for these studies. As the study by Khurana *et al.*[23] reported both TD-OCT and SD-OCT for the same 59 eyes, we chose to display only the data for SD-OCT from this study in the forest plot of all OCT studies and to include only the SD-OCT data from this study in the pooled estimates for all OCT studies, in order to avoid double counting and on the basis that the SD-OCT data were the more appropriate to include in the pooled estimates for all OCT. The TD-OCT data from Khurana *et al.*[23] are included in the forest plot and SROC curve for TD-OCT in *Figure 10* and were included in the pooled estimates for TD-OCT shown in *Table 13*. For all OCT studies, the pooled sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, the pooled sensitivity and specificity (95% CI) was 70% (56% to 80%) and 65% (48% to 79%) respectively. For both TD-OCT and the group of all four OCT studies, the LR and DOR values reported were below the level suggestive of strong diagnostic evidence.

It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT studies due to insufficient data. These studies reported sensitivities of 94%[30] and 90%[23] and specificities of 27%[30] and 47%,[23] which suggests that SD-OCT has higher sensitivity than TD-OCT but lower specificity.

The risk of bias assessment of the four OCT studies included in the meta-analysis is shown in *Table 14*. The only judgement of high risk of bias was for the study by Giani *et al.*[30] for the patient selection domain (inappropriate exclusions and pre-selection of participants).

TABLE 13 Pooled estimates for the OCT monitoring studies

Test	Number of studies	Number of eyes analysed	Pooled estimates (95% CI)				
			Sensitivity, %	Specificity, %	LR+	LR–	DOR
All OCT[a]	4	242	85 (72 to 93)	48 (30 to 67)	1.64 (1.19 to 2.26)	0.31 (0.18 to 0.54)	5.33 (2.57 to 11.06)
TD-OCT	3	149	70 (56 to 80)	65 (48 to 79)	2.00 (1.19 to 3.36)	0.47 (0.28 to 0.78)	4.27 (1.58 to 11.53)
SD-OCT	2	152	Not calculable using HSROC methodology				

a Khurana *et al.*[23] reported both TD-OCT and SD-OCT for the same 59 eyes of 56 patients analysed; only the SD-OCT data were included in the pooled estimates for 'All OCT' in order to avoid double counting.

TABLE 14 Risk of bias of the four OCT studies included in the meta-analysis

Study	Risk of bias domain			
	Patient selection	Index/comparator test	Reference standard	Flow and timing
Eter 2005[28]	Unclear	Low	Low	Unclear
Giani 2011[30]	High	Low	Low	Unclear
Khurana 2010[23]	Unclear	Unclear	Unclear	Low
van Velthoven 2006[53]	Low	Unclear	Low	Unclear

Two studies used examination as the unit of analysis. Henschel *et al.*,[32] in an analysis of 61 pairs of TD-OCT and FFA examinations from 14 patients, reported sensitivity of 96.8% and specificity of 36.7% for CNV based on detection of intraretinal and/or subretinal fluid. Salinas-Alaman *et al.*,[45] in an analysis of 176 pairs of TD-OCT and FFA examinations (number of patients not stated), reported sensitivity of 95.7% and specificity of 59.0% based on detection of intraretinal or subretinal fluid.

Four studies[23,30,32,52] reported the sensitivity of OCT in detecting active nAMD phenotypes or active nAMD based on detection of intraretinal/subretinal fluid (*Table 15*). The study by Giani *et al.*[30] reported high sensitivity for the detection by SD-OCT of both classic and occult CNV activity (90.9% and 100% respectively). In the studies by Henschel *et al.*[32] (unit of analysis: examination) and van de Moere *et al.*[52] (unit of analysis: eye) sensitivity was higher for nAMD activity based on detection of intraretinal fluid (90.3% and 82.9% respectively) compared with subretinal fluid (71.0% and 47.1% respectively). van de Moere *et al.*[52] also reported sensitivity of TD-OCT for detection of cystoid macular oedema and PED, both low at 22.9% and 5.7% respectively. In the study by Khurana *et al.*,[23] the sensitivity of SD-OCT was higher than that of TD-OCT for nAMD activity based on the detection of intraretinal fluid, retinal cystoid abnormalities or subretinal fluid.

Indocyanine green angiography

One study, by Regillo *et al.*,[43] in an analysis of 54 pairs of ICG angiograms compared with fluorescein angiograms, obtained from 24 eyes of 21 patients, reported sensitivity of 75.9% and specificity of 88.0% in detecting nAMD activity. It was not possible to ascertain (at participant-level) the prevalence of nAMD. This study was judged as high risk of bias for the index/comparator test and reference standard domains, due to the ICGA–FFA pairs being analysed directly from the computer monitor (ICGA test results interpreted with knowledge of the FFA results, and vice versa) and low risk of bias for the other domains.

TABLE 15 Sensitivity of OCT in detecting nAMD phenotype activity

Study	Unit of analysis	Detection of	Number by FFA	OCT sensitivity, %
Giani 2011[30] (SD-OCT)	Eye	Classic CNV	57	90.9
		Occult CNV	36	100.0
Khurana 2010[23] (TD-OCT)	Eye	Intraretinal fluid	29	37.9
		Retinal cystoid abnormalities	29	34.5
		Subretinal fluid	29	48.3
Khurana 2010[23] (SD-OCT)	Eye	Intraretinal fluid	29	65.5
		Retinal cystoid abnormalities	29	58.6
		Subretinal fluid	29	69.0
van de Moere 2006[52] (TD-OCT)	Eye	Intraretinal fluid	Not reported	82.9
		Subretinal fluid	Not reported	47.1
		CMO	Not reported	22.9
		PED	Not reported	5.7
Henschel 2009[32] (TD-OCT)	Exam	Intraretinal fluid	31	90.3
		Subretinal fluid	31	71.0

CMO, cystoid macular oedema.

Studies directly comparing tests

Time domain optical coherence tomography versus spectral domain optical coherence tomography

One study, by Khurana *et al.*,[23] compared TD-OCT with SD-OCT in an analysis of 59 eyes of 56 participants. Although sensitivity was considerably higher for SD-OCT than for TD-OCT (89.7% vs. 58.6%), specificity was lower (46.7% vs. 63.3%).

Assessment of other outcomes of interest

Clinical effectiveness

No studies were identified that met our inclusion criteria providing information on clinical effectiveness outcomes (e.g. VA) when treatment was based on OCT compared with FFA findings.

Interpretability of the tests

Only one monitoring study, by van de Moere *et al.*,[52] reported information relating to the interpretability of the tests. This TD-OCT study reported that, of 136 participants enrolled, 17 (12.5%) were excluded from the analysis due to the poor quality of the OCT or FFA images. The study did not specify how many of these poor quality images were OCT images and how many were FFA.

Acceptability of the tests

No studies were identified that met our inclusion criteria reporting the acceptability of the tests, either to those providing the tests or to those receiving them.

Proportion of participants unable to receive the monitoring test

Two studies reported exclusion criteria relating to eye conditions (see *Appendix 7*, see *Table 49*).[23,30] The study by Giani *et al.*[30] contained the following exclusion criteria: any previous laser treatment, PDT or vitreoretinal surgery on the study eye; significant macular haemorrhage that obscured the lesion; and a spherical refractive error > 6 diopters. The study by Khurana *et al.*[23] excluded patients with CNV resulting from causes other than AMD.

Other health professionals compared with ophthalmologists interpreting optical coherence tomography findings

No studies were identified meeting our inclusion criteria that reported the performance of other health professionals compared with ophthalmologists in interpreting OCT findings.

Summary of the reviews of diagnostic and monitoring studies

Diagnostic studies

Twenty-two diagnostic studies were included (20 full-text papers, two abstracts).[24–27,29,31,33–42,44–46,48,49,51] The full-text papers were assessed for risk of bias using the QUADAS-2 checklist. The domains in which the greatest number were judged to be at high risk of bias were the patient selection domain (55%, 11/20), for reasons such as inappropriate exclusions and pre-selection of participants, and flow and timing domain (40%, 8/20), for reasons such as the length of time between the index test and the reference standard, and not all participants being included in the analysis. The risk of bias in the index/comparator test and reference standard domains was judged to be unclear in 50% (10/20) and 60% (12/20) of studies respectively. All of the studies were judged to have low concerns in terms of their applicability to the question being addressed by the review.

A descriptive summary of the results of the diagnostic studies with eye as the unit of analysis is shown in *Table 16* (excluding studies that only reported detection at phenotype level). Across the studies the median (range) sensitivity was high for OCT (94.5%, range 36.0–100.0%; 10 studies[25,27,33,35,36,40,41,45,46,49]). Sensitivity was also high for ICGA (93.2%, range 84.6%–100.0%; four studies[25,29,44,51]) and FAF (93.3%; one study[25]), followed by PHP (81.5%, range 50.0–84.8%; three studies[24,27,29]), colour fundus photography (70.0%; one study[24]) and lowest for Amsler grid (41.7%; one study[27]). The median (range) specificity for OCT was moderate (73.5%, range 66.0–94.0%; four studies[27,40,46,49]). Specificity was highest for colour fundus photography (95%; one study[24]), followed by PHP (84.6% and 87.7%; two studies[24,39]), and was low for FAF (37.1%; one study[25]) and ICGA (36.8%; one study[29]).

Two studies reported the diagnostic accuracy of combinations of tests. Sensitivity and specificity for TD-OCT plus colour fundus photography[46] was 74.1% and 92.0%, respectively, whereas for colour fundus photography plus VA,[24] sensitivity was lower at 53.0% but with similarly high specificity at 94.0%.

Four OCT diagnostic studies (all TD-OCT) provided sufficient data for inclusion in a meta-analysis (*Table 17*).[27,40,46,49] The pooled sensitivity and specificity (95% CI) for all four OCT studies was 88% (46% to 98%) and 78% (64% to 88%) respectively.

Eight diagnostic studies reported the sensitivity of OCT in the detection of specific nAMD phenotypes.[25,33,34,37,38,41,46,49] Four showed equally high sensitivity for the detection of classic CNV compared with occult CNV.[25,34,41,49] In four others, sensitivity for OCT was higher in the detection of classic CNV (range 79–100%) compared with occult CNV (range 13–79%).[33,37,38,46] Four studies reported the sensitivity of ICGA in the detection of specific nAMD phenotypes.[25,29,44,51] Each study reported detection of a different phenotype, with 100% sensitivity for detection of IPCV and type 2 CNV without an occult component, high sensitivity (85.1%) for detection of RAP but lower sensitivity (62.9%) for detection of occult CNV.[25,29,44,51]

TABLE 16 Descriptive summary of sensitivity and specificity of diagnostic studies

Test	Number of studies	Number of eyes analysed	Median (range) sensitivity, %	Median (range) specificity, %
All OCT	10	1117	94.5 (36.0–100.0)	73.5 (66.0–94.0)
TD-OCT	9	1096	92.3 (36.0–100.0)	73.5 (66.0–94.0)
SD-OCT	1	21	100.0	Not reported
Amsler grid	1	46	41.7	Not reported
PHP	3	302	81.5 (50.0–84.8)	(84.6, 87.7)[a]
Colour fundus photography	1	120	70.0	95.0
FAF	1	50	93.3	37.1
ICGA	4	167	93.2 (84.6–100.0)	36.8
TD-OCT + colour fundus photography	1	131	74.1	92.0
Colour fundus photography + VA	1	66	53.0	94.0

a Only two studies reported specificity. Therefore no median is reported and values given are those reported in the two studies.

TABLE 17 Pooled estimates for the OCT diagnostic studies

			Pooled estimates (95% CI)	
Test	Number of studies	Number of eyes analysed	Sensitivity, %	Specificity, %
All OCT	4	406	88 (46 to 98)	78 (64 to 88)

Monitoring studies

Eight monitoring studies were included (all full-text papers).[23,28,30,32,43,45,52,53] Seven reported OCT,[23,28,30,32,45,52,53] five with eye as the unit of analysis[23,28,30,52,53] (one of which only reported detection at phenotype level[30]) and two with test examination as the unit of analysis.[32,45] One study reported ICGA.[43] As with the diagnostic studies, the QUADAS-2 domains in which the greatest number of monitoring studies were judged to be at high risk of bias were the patient selection domain (25%, 2/8),[30,45] for reasons such as inappropriate exclusions and pre-selection of participants, and flow and timing domain (25%, 2/8),[30,45] for reasons such as the length of time between the index test and the reference standard, and not all participants being included in the analysis. The risk of bias in the index/comparator test and reference standard domains was judged to be unclear in 50% (4/8)[23,45,52,53] and 37.5% (3/8)[23,45,52] of studies respectively. All of the monitoring studies were judged to have low concerns in terms of their applicability to the question being addressed by the review.

Four OCT monitoring studies, with eye as the unit of analysis, provided sufficient data for inclusion in a meta-analysis (*Table 18*). The pooled sensitivity and specificity (95% CI) for all four OCT studies was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, the pooled sensitivity and specificity was 70% (56% to 80%) and 65% (48% to 79%). It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT studies due to insufficient data. These two studies reported sensitivities of 94% and 90% and specificities of 27% and 47%, which suggests that SD-OCT has higher sensitivity than TD-OCT but lower specificity.

Two OCT monitoring studies used test examination as the unit of analysis. The first, in an analysis of 61 pairs of TD-OCT and FFA examinations from 14 patients, reported high sensitivity of 96.8% but low specificity of 36.7%, for CNV based on detection of intraretinal and/or subretinal fluid. The second, in an analysis of 176 pairs of TD-OCT and FFA examinations (number of patients not stated), reported similarly high sensitivity of 95.7% and moderate specificity of 59.0% based on detection of intraretinal or subretinal fluid.

One ICGA monitoring study used test examination as the unit of analysis. In an analysis of 54 pairs of ICGAs compared with fluorescein angiograms, obtained from 24 eyes of 21 patients, sensitivity of 75.9% and specificity of 88.0% was reported for detecting nAMD activity.

Three studies reported OCT sensitivity in detecting activity of specific nAMD phenotypes or nAMD activity based on detection of intraretinal/subretinal fluid. SD-OCT sensitivity was high for the detection of both classic and occult CNV activity (90.9% and 100% respectively) (one study).[30] Sensitivity of TD-OCT for detection of cystoid macular oedema and PED was low (22.9% and 5.7% respectively) (one study).[52] In two studies, sensitivity was higher for detection of nAMD activity based on intraretinal fluid (90.3% and 82.9% respectively) compared with subretinal fluid (71.0% and 47.1% respectively).[32,52]

TABLE 18 Pooled estimates for the OCT monitoring studies

Test	Number of studies	Number of eyes analysed	Pooled estimates (95% CI)	
			Sensitivity, %	Specificity, %
All OCT[a]	4	242	85 (72 to 93)	48 (30 to 67)
TD-OCT	3	149	70 (56 to 80)	65 (48 to 79)
SD-OCT	2	152	Not calculable using HSROC methods	

a Three studies reported TD-OCT and two studies reported SD-OCT, with one study reporting both TD-OCT and SD-OCT. Only the data for SD-OCT from this study were included in the pooled estimates for all OCT to avoid double counting.

Chapter 5 Assessment of cost-effectiveness

The health economic component of this study explored the evidence for the cost-effectiveness of using OCT for diagnosis and/or monitoring of individuals with nAMD. For this, a two-step approach was used, with (1) a systematic review of economic evaluations to retrieve any readily available evidence on cost-effectiveness, followed by (2) a de novo decision-analytic model to synthesise the available evidence on effectiveness, health-care resources used and costs. *Systematic review of economic evaluations* reports the systematic review of cost-effectiveness studies and *Economic evaluation modelling exercise* focuses on the economic model exercise.

Systematic review of economic evaluations

The aim of this review was to retrieve evidence, from the perspective of the UK NHS, on the cost-effectiveness of the use of OCT in the diagnosis and/or monitoring of individuals with nAMD. This was attempted by systematically identifying and quality assessing all economic evaluations comparing strategies that included OCT for diagnosing and/or monitoring of individuals with nAMD.

Inclusion and exclusion criteria

Inclusion criteria required the studies to be full economic evaluations,[55] that is, to consider cost and effects for more than one strategy, in order to be included in the review. No restrictions were imposed in the way cost and/or effects were calculated. In addition, at least one of the compared strategies for diagnosis or monitoring of nAMD had to include OCT. Finally, the studies were required to be performed in adults with nAMD.

Search strategy

Studies that reported both costs and outcomes in diagnosing nAMD using OCT were sought from a systematic review of the literature. No language restrictions or limitations to searches were imposed.

Databases searched were MEDLINE (1996–November Week 2 2012), EMBASE (1980–Week 45 2012), MEDLINE In-Process & Other Non-Indexed Citations (14 November 2012), NHS Economic Evaluation Database (inception to October 2012), HTA database (inception to October 2012), Health Management Information Consortium (1979–September 2012), Research Papers in Economics (September 2012) and ARVO meeting abstracts from April 2009. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in *Appendix 1*.

Results

From the database searches, 473 hits (titles and abstracts) were retrieved; from these 44 studies were selected for full-text assessment. No studies fulfilled the inclusion criteria as none of these were diagnosis or monitoring interventions for individuals with nAMD.

Economic evaluation modelling exercise

The aim of the economic model was to determine the relative efficiency of strategies for diagnosis and monitoring of individuals with nAMD. Care pathways were developed within the project management group and the project advisory group meetings. The groups initially considered all possible tests (see *Chapter 1*) and several combinations of these. After subsequent discussions, a number of these options were excluded. For instance, FFA only was originally considered as one of the (monthly) monitoring pathways. However, this option was deemed unfeasible (i.e. FFA is an invasive test) and consequently dropped. Three different strategies were finally selected for the nAMD diagnosis and monitoring stages, respectively, giving a total of nine diagnosis–monitoring combinations.

Diagnosis strategies

(a) (Stereoscopic) FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
(b) OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
(c) VA, OCT and SLB in all. If positive or unclear, then arrange for stereoscopic FFA. If negative, discharge. This is the strategy for diagnosis that best reflects standard practice.

Monitoring strategies

(a) OCT alone (interpreted by an ophthalmologist). If positive, treat; if negative or unclear, review in 1 month's time.
(b) VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in 1 month's time. If unclear, then the ophthalmologist will arrange for a stereoscopic FFA. This is the monitoring strategy that best reflects standard practice.
(c) VA and OCT interpreted by a technician or nurse. If negative, review in 1 month's time. If positive or unclear, refer for ophthalmologist assessment (e.g. SLB and ophthalmologist's own interpretation of VA and OCT test results). The ophthalmologist will make a decision: if positive, treat; if negative, review in 1 month's time; if unclear, arrange for stereoscopic FFA.

Monitoring strategy c has been included in the monitoring stage in order to explore the cost-effectiveness of the option, for example, of virtual clinics involving other health-care professionals (e.g. nurses, technicians). Virtual clinics are increasingly used in NHS services for monitoring patients with nAMD.[56]

Table 19 shows the final nine combined strategies incorporated into the decision model. All strategies considered monitoring on a monthly basis with a decision to treat when the disease was deemed active (i.e. retinal fluid on OCT). All monitoring strategies that relied on stereoscopic FFA as a final assessment step (e.g. monitoring strategies b and c) would treat if FFA positive, or review in a month's time if FFA negative. Treatment consisted of one injection only (i.e. 0.5 mg ranibizumab) with review in 1 month's time.

TABLE 19 Strategies for the economic evaluation model

Strategy	Strategy label	Diagnostic pathway	Monitoring pathway	Treatment
1	FFA & OCT	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month	One monthly injection if disease deemed active
2	FFA & Ophthalmologist	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	One monthly injection if disease deemed active
3	FFA & Nurse	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month time; if unclear, arrange for stereoscopic FFA	One monthly injection if disease deemed active

TABLE 19 Strategies for the economic evaluation model (*continued*)

Strategy	Strategy label	Diagnostic pathway	Monitoring pathway	Treatment
4	OCT & OCT	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologists). If positive, treat. If negative or unclear review in 1 month	One monthly injection if disease deemed active
5	OCT & Ophthalmologist	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	One monthly injection if disease deemed active
6	OCT & Nurse	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month's time; if unclear, arrange for stereoscopic FFA	One monthly injection if disease deemed active
7	Ophthalmologist & OCT	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month	One monthly injection if disease deemed active
8	Ophthalmologist & Ophthalmologist	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	One monthly injection if disease deemed active
9	Ophthalmologist & Nurse	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in 1 month; if unclear, arrange for stereoscopic FFA	One monthly injection if disease deemed active

The economic model

A Markov model approach was selected for the decision-analytic model exercise.[57–60] Markov models have Markov states where individuals spend a period of time, named a 'cycle'. At the end of each cycle the individuals can remain in their current Markov state or move to another state. The probabilities of moving to other Markov states or remaining in the current state are named 'transition probabilities'. Individuals in the model would accrue costs and benefits (e.g. 'life-years') depending on the time spent in each Markov state and the interventions and/or events modelled within each Markov state. Markov models are particularly suitable to model recurrent issues and chronic diseases. They allow incorporating health states to reflect the movement of the patients during diagnosis and monitoring. In the current study, model states reflect the underlying condition (e.g. nAMD active or inactive) together with the decision on treatment (e.g. treated or untreated nAMD) and VA states of the individuals (*Table 20*). In all these models, an absorbing state is included where all individuals would end up if the model was run for a sufficiently long period of time (e.g. death state).

The present model incorporates a first diagnosis stage combined with a recurrent (monthly) monitoring phase.

The Markov models

This section presents a stepwise introduction to the Markov models used to compare the alternative strategies. Individuals' VA status is set aside for the moment to focus on the other two issues and assumptions underpinning the movement of individuals throughout the model: (1) the underlying disease condition (e.g. if the disease is present or not and, if present, its active or inactive status) as well as (2) the diagnosis or monitoring test results on which the treatment decision will depend (i.e. a positive result will trigger a decision to treat and a negative results will trigger a decision not to treat). *Figure 11* shows the schematic diagram of the final model used for the economic evaluation for this study.

TABLE 20 Visual acuity states

Visual health states (Snellen fractions)		Visual health status
1	> 6/12	Normal VA
2	≤ 6/12 to > 6/24	Mild VA loss
3	≤ 6/24 to > 6/60	Moderate VA loss
4	≤ 6/60 to > 3/60	Severe VA loss
5	≤ 3/60	Profound visual loss/blindness

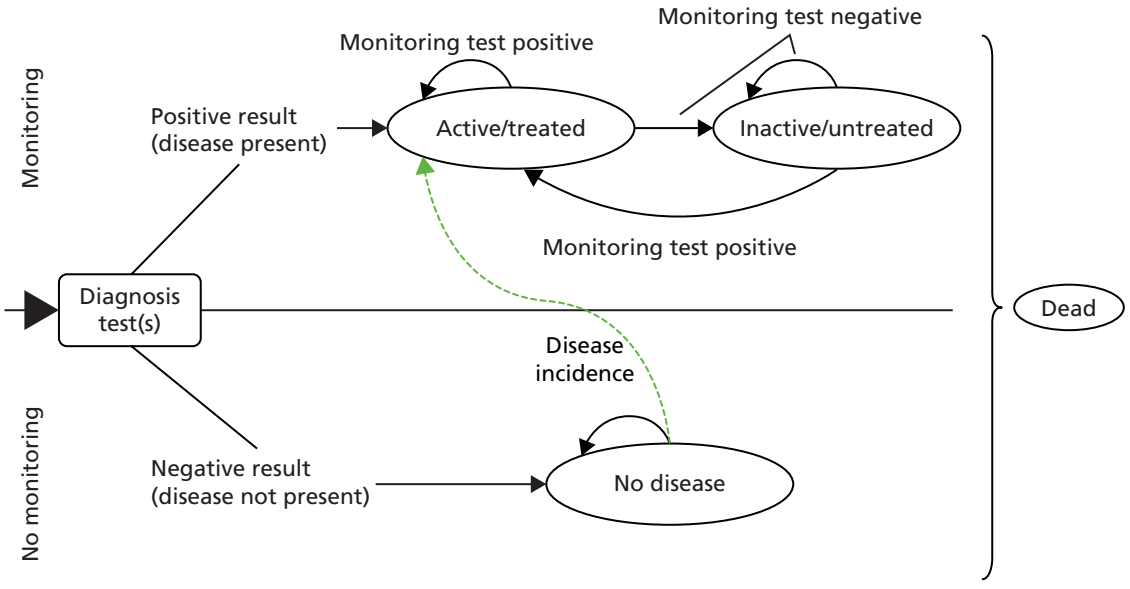


FIGURE 11 Markov model schematic diagram assuming imperfect information at diagnosis and monitoring stages. 'Inactive' = underlying condition regarded as inactive nAMD when the disease was actually not present.

This section presents three schematic diagrams for this model. The figures differ in the assumptions made with respect to the information retrieved from the diagnosis and/or monitoring test or assessments. Namely, if perfect information from the tests or assessments is assumed, then there would be no FP or FN results (i.e. equivalent to assuming that sensitivity and specificity are equal to 1). That is, the underlying condition is detected with certainty. When this assumption is relaxed, then the possibility of incorrect assessments appears.

Perfect information from diagnosis and monitoring tests

Figure 12 assumes perfect information at diagnosis and monitoring stages in the model. The whole modelled cohort starts at the black arrow on the left hand side of the figure (corresponding to an initial Markov model stage). The assumption of perfect information means that, at diagnosis stage, all individuals with the disease will have a positive result while all those without the disease will obtain a negative result. Individuals with a positive result will go to a monitoring scheme while those with a negative result will be discharged. Those individuals with the disease and positive results will start within a Markov model state with an 'active disease and under treatment' (e.g. 'active/treated' state). Note that 'active' refers to the underlying condition while 'treated' or not depends on the test or assessment result.

Assuming monthly monitoring visits and assessments, a positive result at a monitoring visit means the individual's disease is active (assuming, again, perfect information and no possibility of FP or FN results) and will therefore mean that the person remains in the 'active/treated' Markov state. If a negative result from the monitoring assessment is obtained, then it would mean that the individual's disease has become inactive and the decision not to administer treatment will follow. In this case, the individual will move to the 'inactive/untreated' Markov state. At each Markov cycle (monthly) individuals can become active or inactive; this status would be detected at the next monitoring visit with a positive or negative result, and the individual will either move from or stay in the corresponding Markov model state with a consistent treatment decision.

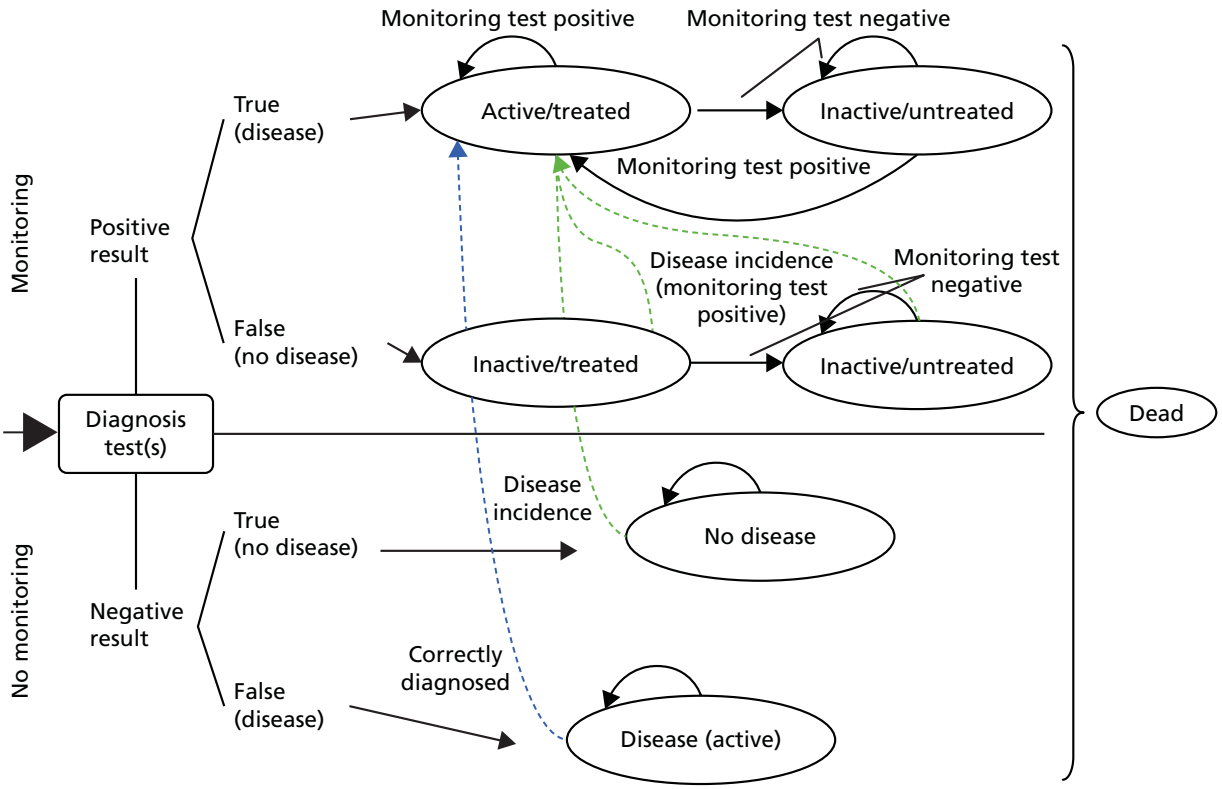


FIGURE 12 Markov model schematic diagram assuming perfect information at diagnosis and monitoring stages.

Individuals without the disease at the moment of first diagnosis could develop the disease in the future (i.e. incident cases among the population). In the model (see *Figures 11–13*), it was assumed that these individuals would be correctly diagnosed within a second visit and eventually moved to be monitored within the 'active/treated' state. Finally, the 'dead' state is the absorbing state in this model (i.e. a state that individuals cannot move out of); individuals can move from any other Markov state into the 'dead' absorbing state.

Imperfect information from diagnosis test combined with perfect information from monitoring tests

Figure 13 shows a similar schematic diagram but in this case there is imperfect information at the moment of first diagnosis. After this initial diagnostic intervention, further diagnosis and/or monitoring assessments will be done with certainty (e.g. assuming perfect information). This opens the possibility of obtaining TP,

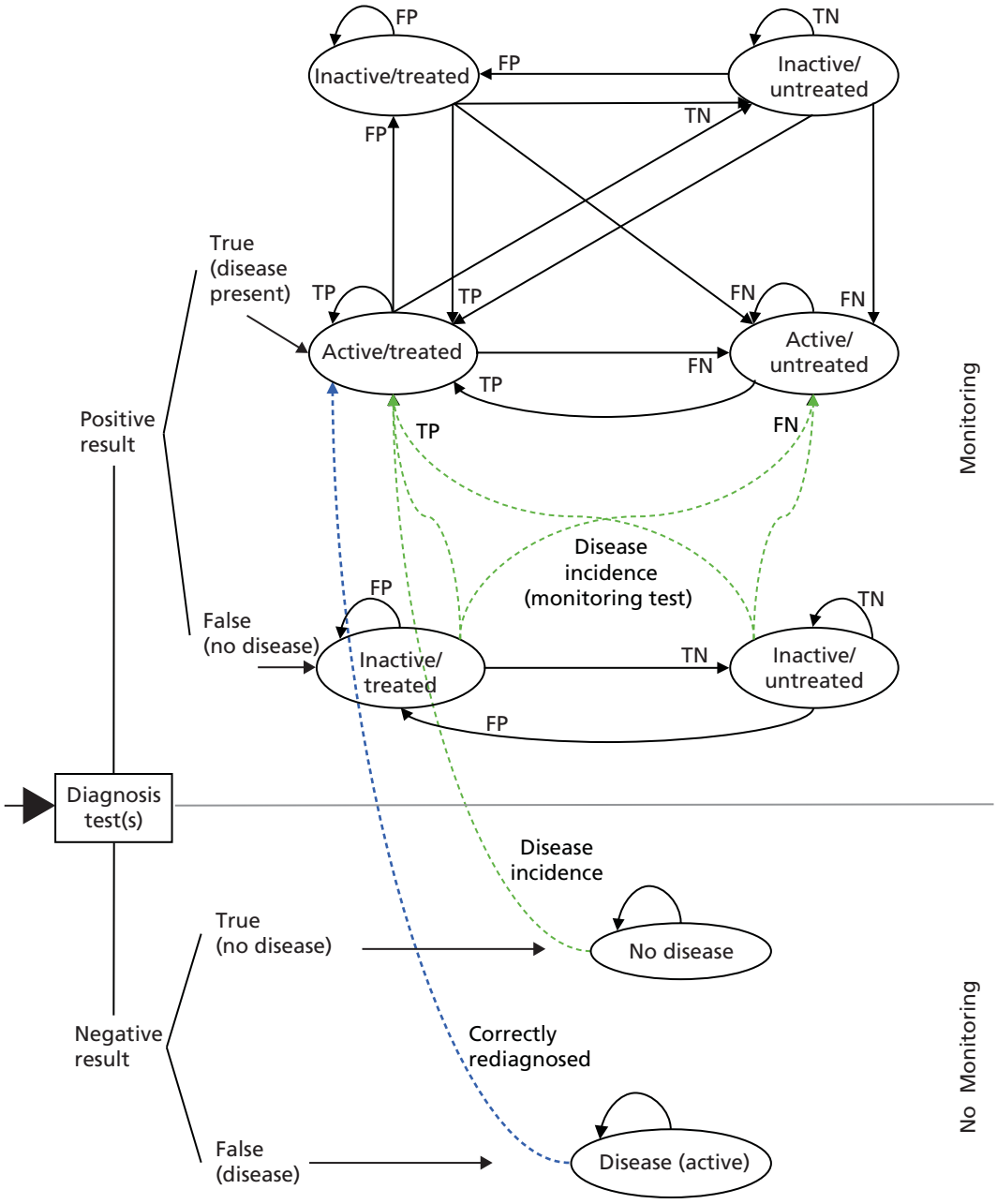


FIGURE 13 Markov model schematic diagram assuming imperfect information at diagnosis and perfect information at monitoring stage. 'Inactive' = underlying condition regarded as inactive nAMD when the disease was actually not present.

TN as well as FP and FN results from the initial diagnosis test/s. Individuals with positive results, therefore, might not have nAMD whereas individuals with negative diagnostic test results might actually have the disease. This situation will have an effect on the Markov states the individuals will start at after diagnosis. Those with a TP result will start with their active disease being treated and eventually move to an inactive state (e.g. 'inactive/untreated') depending on the treatment effect. Individuals with a FP result will not have nAMD but will be treated and monitored. However, this treatment cannot be effective as these people did not have the disease. As this schematic diagram assumes perfect information at the monitoring phase, these individuals would be correctly assessed in their subsequent monitoring visits, moving to the 'inactive/untreated' state.

In addition, if the person has a negative result at diagnosis, this could be a TN or a FN result. In either case the individual would be discharged under the belief that nAMD was not present. If TN, meaning that the disease was not present, the individual will start at the 'no disease' state and will remain at that stage unless they develop nAMD. If FN (patients with the disease and negative test), the person will start within the 'disease (active)' state.

Finally, an identical assumption of using FFA for diagnosis for those presenting for a second time (rediagnosis) is followed for those with FN results at first diagnosis. These people will start to be monitored and moved to the 'active/treated' state after second presentation for diagnosis. A further assumption is used for this subgroup: based on expert opinion, these nAMD individuals that have been missed at first diagnosis will present for rediagnosis within 3 months. The rationale behind this was the natural history of the disease and the belief that nAMD would advance with VA deterioration making the individual return for a further eye check.

Imperfect information from diagnosis and monitoring tests

Figure 11 shows the schematic diagram for the actual Markov model used. In this case, imperfect information at diagnosis as well as monitoring phases was assumed. The cases for those with first diagnosis negative results are identical to those in *Figure 13* (lower part of *Figure 11*). However, the diagram for those with positive results at first diagnosis will differ.

Individuals with TP results at first diagnosis will start as before within the 'active/treated' state. After this, depending on the underlying condition (e.g. active or inactive) and the monitoring assessment result (e.g. positive or negative, with a positive result reflecting the presence of disease activity), individuals will move to alternative Markov states (e.g. 'inactive/untreated'; 'inactive/treated'; 'active/untreated'). The arrows in the figure show the direction in which individuals can move due to their underlying condition and assessment while the arrow labels refer to the result of the assessment (e.g. TN, TP, FN, FP).

A further assumption in the model is that those individuals under monitoring who do not have nAMD (i.e. 'Inactive' states) that subsequently become nAMD would be detected by the monitoring strategy test/s. This monitoring strategy could include FFA (perfect information test) or other non-perfect information test (e.g. OCT alone). Therefore, these individuals that now have nAMD could move to 'active/treated' or 'active/untreated' depending on positive or negative monitoring assessment respectively.

Markov model states and health status valuation link

The former diagrams show how individuals can move in the model according to their underlying condition and the result of the test/s or assessments. However, it is not possible to attach utility weights to these Markov states. In essence, individuals can experience alternative active or inactive disease but no difference in their reported health status. The economic model attaches utility weights according to, mainly, VA. Therefore, the effect on health status will come through the deterioration in VA, whereas VA deterioration will result from the fact of individuals being misdiagnosed (e.g. no nAMD when actually the disease was present) or misclassified as inactive when their true condition was active nAMD.

In terms of the presented diagrams, the number of Markov states is multiplied by the number of VA ranges considered by the model. Therefore, there is a trade-off between the number of VA ranges in order to reflect differences in VA – and patient-reported health status – and the model complexity. Utility differences between the alternative model strategies result from the different periods of time individuals are misclassified within each strategy. It was considered that five VA states (see *Table 20*) would give sufficient refinement for utility differences to be reflected. This approach has been used in other models in this area of health care.[61] Therefore, each strategy (i.e. each Markov model) has 32 Markov model states [e.g. four VA states multiplied by six monitoring states, plus four VA states multiplied by one nAMD undiagnosed state, plus profound visual loss/blindness, a 'no disease' state (normal VA only), the absorbing state 'dead', and an initial state for first diagnosis].

Figure 14 shows a Markov model schematic diagram for the VA states considered in the model. Arrows in the figure show the possible movements in the model in one cycle (e.g. 1 month). Individuals' VA can remain the same, improve or deteriorate in one particular cycle. Individuals can have their VA improved and move one level up at the end of a cycle; however, their VA can deteriorate and move one or two levels down from their current VA state. Finally, the model considered that a VA deterioration of $\leq$ 3/60 (i.e. profound visual loss/blindness) was not reversible and the individual was referred to supportive care.

Parameter estimates used in the economic model

The parameter estimates required to populate the economic model were obtained from the systematic review of diagnostic and monitoring studies (see *Chapter 4*) as well as structured and focused literature searches. When no suitable data resulted from these searches, expert opinion was sought. The next section gives details of the probabilities, unit costs and utility weights used in the model. The section also provides details of the probability distributions used for the probabilistic sensitivity analysis.[62] Probabilistic sensitivity analysis involves attaching probability distributions to model parameters and conducting a number of Monte Carlo simulations (e.g. 1000). In each of these simulations a set of parameter values will be drawn from the attached distributions, the model is run and results calculated. It is possible then to obtain a distribution of the model cost-effectiveness results that reflects the overall parameter uncertainty in the economic evaluation model.[63,64]

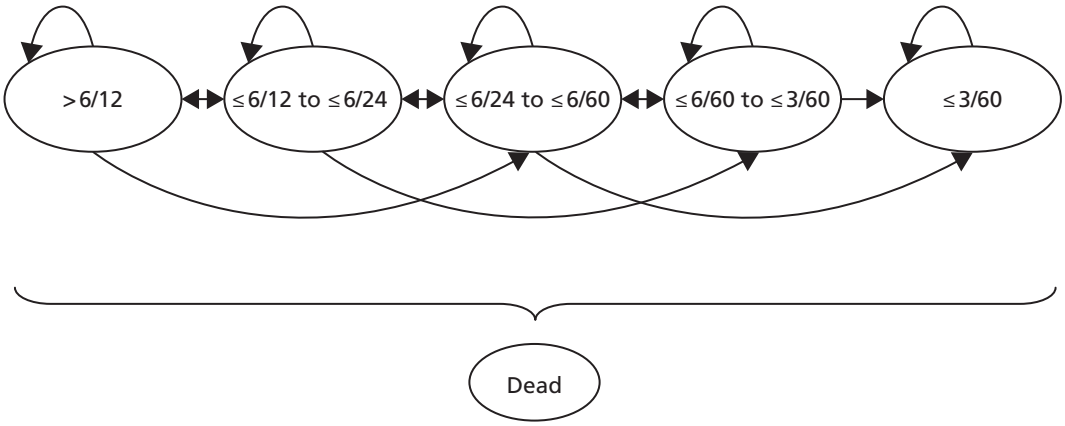


FIGURE 14 Markov model schematic diagram for VA states.

Probabilities

Table 21 shows data on nAMD prevalence, incidence and VA at the start of the model run. Colquitt *et al.*[61] reviewed studies assessing the prevalence and incidence of AMD and nAMD. The setting for this economic evaluation was secondary care; therefore, the prevalence rate to inform the model should be that corresponding to the group of individuals referred to hospital eye services with a suspected nAMD diagnosis. The prevalence rate used was obtained from the literature retrieved by the systematic review of test accuracy and agreed within the project management and advisory groups. An overall incidence of 1% per year was used based on Mitchell *et al.*[65] These incidence figures, presented for Australia, were similar to the results by van Leeuwen *et al.*[66] for the Rotterdam study but were reported in a form that could be readily incorporated into the economic model. Mortality data were obtained from Interim Life Tables for England and Wales (2009–11).[16] No difference in mortality rates were found when comparing age-specific mortality rates form the Interim Life Tables and those from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)[8] and the Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)[9] studies. Therefore, no excess mortality was included due to nAMD.[67,68] However, excess mortality risk was incorporated for the last disease VA stage (profound visual loss/blindness – VA ≤ 3/60).

Table 21 also shows probability distributions defined for the probabilistic sensitivity analysis. Uninformative uniform distributions were used for nAMD prevalence and profound visual loss/blindness excess mortality. Ranges for defining these were assumptions based on data from the literature if available (e.g. from the review of test accuracy). A gamma distribution was defined for nAMD incidence based on mean and standard deviation (e.g. 1/10 of the mean) using the tool provided by TreeAge (TreeAge Software, Inc., Williamstown, MA, 2013).

TABLE 21 Prevalence, incidence and VA at start

Variable	Value	Probability distribution		Source
Epidemiological data				
Prevalence for nAMD	70%	Uniform (0.6; 0.8)		Expert opinion and articles from SR test accuracy
Incidence rate of nAMD (monthly)	0.084%	Gamma (1; 1190)		Mitchell *et al.*[65]
Mortality	Various			Interim Life Tables, England and Wales (2009–11)[16]
Profound visual loss/blindness excess mortality	17%	Uniform (0.1; 0.5)		Assumption
Cohort details at start				
Age (years)	65	n/a	n/a	Assumption based on expert opinion
Mean VA				
Individuals with nAMD				
≤ 6/12 to > 6/24 state	100%	n/a	n/a	Assumption based on expert opinion and CATT and IVAN RCTs mean VA at start
Individuals without nAMD				
> 6/12	100%	n/a	n/a	Assumption based on expert opinion

n/a, not applicable.

The cohort start age was set at 65 years as this is the age where particular changes are observed in the retina and macula (Dr Noemi Lois and Project Advisory Group, NHS Grampian, 2012, personal communication). In addition, mean VA at the start was set at between ≤ 6/12 to > 6/24 for those individuals with nAMD. This was agreed to be the most common VA at presentation by experts and also the mean VA at baseline in the CATT and IVAN studies.[8,9]

Table 22 presents diagnostic test performance data. As mentioned above, three strategies were defined for diagnosis within the economic model. For each of these strategies, sensitivity and specificity data were needed, specifically for FFA, OCT, and ophthalmologist assessment (i.e. with VA test, SLB, and the results from the OCT). FFA interpreted by an ophthalmologist was stated as the reference standard for the diagnosis of nAMD; therefore, perfect information was assumed from this test, with sensitivity and specificity equal to 1. OCT sensitivity and specificity were obtained from the systematic review of diagnostic studies. These data correspond to OCT pooled estimates (four studies, number of eyes 406).[27,40,46,49] No studies were identified on the ophthalmologist assessment diagnostic performance. Hence, sensitivity and specificity estimates were derived from expert opinion.

Sensitivity and specificity data are bounded between 0 and 1. Therefore, beta distributions were defined for probabilistic sensitivity analysis. For OCT, these were obtained using mean values and standard deviation in order to obtain values within the 95% CI provided by the systematic review of diagnostic studies (see *Chapter 4*, *Table 17*). Probability distributions for ophthalmologist diagnosis assessment were obtained using the approximation tool provided by TreeAge, based on mean and standard deviation (e.g. 1/10 of mean).

TABLE 22 Test performance parameters: diagnosis of nAMD

Variable	Value	Range	Probability distribution	Source
FFA				
Sensitivity	1	n/a	n/a	Assumption
Specificity	1	n/a	n/a	Assumption
OCT				
Sensitivity	0.88	0.46–0.98	Beta(36.3; 4.9)	Systematic review of diagnostic studies
Specificity	0.78	0.64–0.88	Beta(82.9; 23.4)	Systematic review of diagnostic studies
Ophthalmologist assessment (with VA, OCT and SLB)				
Sensitivity	0.99		Beta(0.22; 0.002)	Assumption based on expert opinion, using the systematic review results as a starting point
Specificity	0.9		Beta(9.1; 1)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1	0.0–0.5	Beta(89.9; 809.1)	Assumption based on expert opinion

n/a, not applicable.

Table 23 shows similar data to *Table 22* but for monitoring of individuals with nAMD. FFA was also stated as the reference standard to detect disease activity; therefore, perfect information was assumed, with sensitivity and specificity defined as equal to 1. OCT monitoring sensitivity and specificity data were obtained from the systematic review of test performance (see *Chapter 4*). Pooled estimates (e.g. four studies, $n = 242$), were used.[23,28,30,53] No studies were identified reporting the diagnostic performance of nurse or technician assessment, or for ophthalmologist assessment. Therefore, estimates for the sensitivity and specificity of these strategies were derived from expert opinion.

A similar approach to the one used for the sensitivity and specificity of diagnostic tests was used for this information for monitoring tests. Beta probability distributions were approximated and defined using mean and standard deviation (e.g. 1/10 of the mean) values. The range of values of OCT used in the model did not exceed the 95% CI values obtained from the systematic review of monitoring studies (i.e. OCT range data in *Table 23*).

Disease progression in the model was defined in terms of VA changes. Gaining or losing three lines in the Snellen chart (approximately 15 letters in the ETDRS chart) was assumed to make individuals move from their current Markov model state to the next level (see *Table 20* and *Figure 14*). Data for this were obtained from Rosenfeld *et al.*[69] [i.e. the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study]. This study was based in the USA, involved 716 participants and compared monthly treatment with ranibizumab (0.3 mg, $n = 238$ or 0.5 mg, $n = 240$) against sham injection ($n = 238$). Data from treatment (0.5 mg) and control groups were used to calculate monthly progression probabilities for active treated and non-treated individuals respectively. No VA progression was assumed for nAMD inactive individuals as well as non-AMD individuals.

TABLE 23 Test performance data: monitoring of nAMD

Variable	Value	Range	Probability distribution	Source
FFA				
Sensitivity	1	n/a	n/a	Assumption
Specificity	1	n/a	n/a	Assumption
OCT				
Sensitivity	0.85	0.72–0.93	Beta(105; 18.5)	Systematic review of monitoring studies
Specificity	0.48	0.30–0.67	Beta(32.8; 35.5)	Systematic review of monitoring studies
Technician/nurse assessment (VA and OCT)				
Sensitivity	0.9		Beta(108.9; 12.1)	Assumption based on expert opinion, using the systematic review results as a starting point
Specificity	0.6		Beta(72.6; 48.4)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1		Beta(89.9; 809.1)	Assumption based on expert opinion
Ophthalmologist assessment (VA, OCT and SLB)				
Sensitivity	0.97		Beta(2.51; 0.08)	Assumption based on expert opinion, using the systematic review results as a starting point
Specificity	0.8		Beta(19.2; 4.8)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1		Beta(89.9; 809.1)	Assumption based on expert opinion

n/a, not applicable.

Beta distributions were attached to VA progression data for probabilistic sensitivity analysis (*Table 24*). Unfortunately, there were no data available to construct CIs around mean values used in the model. As such, probability distributions parameter values were developed using mean values and assuming 1/10 of mean values for standard errors.

Additional data were required on disease status, namely the probability of becoming active when the individual's disease was inactive and under no treatment, as well as the probability of becoming inactive when the individual's disease was active and under treatment. First year data for these were developed using data from the IVAN study (Dr Chris Rogers, University of Bristol, 12 June 2013, personal communication). The IVAN study was a 2 × 2 factorial design and adults with untreated nAMD were randomised into four groups: ranibizumab or bevacizumab, given either every month (continuous) or as needed (discontinuous). All individuals were reviewed on a monthly basis. Survival data for participants' first treatment failure (e.g. subretinal fluid, increasing intraretinal fluid, or fresh blood) for the discontinuous arm ($n = 302$) were used to develop mean probability values. All individuals were active at baseline and 95% of these did not fail the retreatment criteria (i.e. did not need to be treated) at 3 months. This rate was used to obtain the monthly probability of becoming inactive when active and under treatment.[62] At month 6, 54% of individuals were still inactive. The difference between the proportion of inactive individuals at months 3 and 6 was used to develop the probability of becoming active when inactive and under no treatment (*Table 25*). Probability distributions were developed using the 95% CI from the IVAN study survivor function using Crystal Ball software (release 11.1.2.0.00, 2010, Oracle Corporation, Redwood Shores, CA, USA) (see *Table 25*).

TABLE 24 Disease progression data: VA

	Year 1		Year 2 onwards	
Variable	Value	Probability distribution	Value	Probability distribution
Treatment				
Gain at least three lines	0.0338	Beta(96.6; 2761.9)	0.0167	Beta(98.3; 5777)
Gain or lose less than three lines	Default		Default	
Lose between three and six lines	0.0036	Beta(99.6; 27817)	0.0032	Beta(99.7; 30634)
Lose six lines or more	0.0010	Beta(99.9; 99252)	0.0011	Beta(99.9; 94640)
No treatment				
Gain at least three lines	0.0043	Beta(99.6; 23244)	0.0016	Beta(99.8; 61799)
Gain or lose less than three lines	Default		Default	
Lose between three and six lines	0.0221	Beta(97.8; 4331)	0.0116	Beta(98.8; 8431)
Lose six lines or more	0.0128	Beta(98.7; 7627)	0.0107	Beta(98.9; 9171)

TABLE 25 Disease progression data: active and inactive nAMD

Variable	Value	Probability distribution	Source
Probability of becoming			
Inactive when active and under treatment			
Year 1	0.616	Beta(176.6; 110)	Based on data from IVAN study[9]
Year 2 onwards	0.365	Beta(63.1; 110)	Based on data from CATT study[8]
Active when inactive and under no treatment			
Year 1	0.306	Beta(148; 335)	Based on data from IVAN study[9]
Year 2 onwards	0.097	Gamma(100; 1029)	Based on Horster *et al.*[70]
Active when inactive and under treatment	0.5 × active when inactive and under no treatment		

Second year data for the probability of becoming inactive were developed using data from the CATT study. The inclusion criteria and the treatment group for the CATT study were similar to that of the IVAN study. However, within the IVAN study three monthly injections were administered when participants failed the disease inactive criteria. The CATT study administered one injection only and reviewed participants in 1 month's time before making a further treatment decision. A monthly probability was sought in order to obtain the CATT study mean number of injections within the as needed arm at 2 years. A beta distribution was attached based on mean value and 1/10 of the mean value as standard error (TreeAge software).

Second year data for the probability of becoming active when participants were inactive and under no treatment was developed using data reported by Horster *et al.*[70] The authors reviewed data on all patients receiving intravitreal ranibizumab injections for nAMD at the University of Cologne, Germany. Eyes with at least two recurrences (i.e. reappearance of intraretinal or subretinal fluid on OCT, and/or leakage on angiography) were selected. The mean follow-up time (months) and number of recurrences were 28.8 and 2.8 respectively.

A number of individuals that were inactive at 3 months within the monthly treatment group in the IVAN study[9] failed the no retreatment criteria (e.g. subretinal fluid, increasing intraretinal fluid, or fresh blood) in subsequent months. This means that, even under monthly treatment, inactive individuals could become active again. Based on this, half the probability of becoming active when inactive and under no treatment was assumed for the probability of becoming active when inactive and under treatment.

Diagnosis or monitoring strategies could result in over- or undertreatment; therefore, it was believed important to include adverse events as a result of treatment. Two recent studies[8,9] report systemic and ocular adverse event rates. It was not clear from inspection of these data that systemic adverse events could be due to treatment of nAMD. Therefore, only ocular adverse events were included in the model. *Table 26* shows monthly estimates for the proportion of individuals that were under treatment that experienced cataract, endophthalmitis, glaucoma, retinal detachment and uveitis.

Costs

Table 27 shows cost estimates used in the model. Prices are expressed in 2011–12 pounds sterling (£). Strategy assessment costs were a combination of the cost of a visit (e.g. ophthalmologist, nurse or technician) and the cost of a particular test used for the assessment (e.g. FFA or OCT). For instance, the diagnosis cost for strategies where diagnosis was conducted using FFA only was calculated adding up the cost of an ophthalmologist visit and the cost for an FFA (e.g. £79.74 + £117.26 = £197.00). NHS reference costs were used for all but the ranibizumab unit costs in *Table 27*, for which *British National Formulary* (BNF) data were used (£742.17).[12] The unit cost for face-to-face consultant-led follow-up attendance that resulted in non-admission for the ophthalmology service was used for the cost of a diagnosis or monitoring visit to the ophthalmologist (£79.74). Likewise, non-consultant led was used for the cost of a nurse or technician monitoring visit (£58.53). Minor vitreous retinal procedures cost category [Healthcare Resource Group (HRG) BZ23Z code] was used to cost FFA (£117.26). Finally, after consultation with clinical

TABLE 26 Adverse events

Variable	Value (monthly %)	Source
Cataract	0.34	The CATT research group[8]
Endophthalmitis	0.40	The CATT research group[8]
Glaucoma	0.05	The CATT research group[8]
Retinal detachment	0.03	The CATT research group[8]
Uveitis	0.03	The CATT research group[8]

TABLE 27 Unit costs

Variable	£ (2011–12)	Range	Probability distribution	Source
Ophthalmologist visit	79.74	68–86	Gamma(309.9; 3.9)	*NHS Reference Costs* 2011–12 (consultant led: follow-up attendance non-admitted face to face. 130: ophthalmology)[11]
Nurse/technician visit	58.53	42–71	Gamma(34.3; 0.59)	*NHS Reference Costs* 2011–12 (non-consultant led: follow-up attendance non-admitted face to face. 130: ophthalmology)[11]
FFA	117.26		Gamma(25; 0.21)	*NHS Reference Costs* 2011–12 (HRG BZ23Z minor vitreous retinal procedures)[11]
OCT	51.27	32–62	Gamma(48.8; 0.95)	*NHS Reference Costs* 2011–12 (HRG RA23Z Ultrasound scan, less than 20 minutes)[11]
Treatment				
Medication ranibizumab	742.17		Gamma(4; 0.01)	BNF[12]

experts, an ultrasound scan (HRG RA23Z Ultrasound scan, less than 20 minutes) was deemed more likely to reflect the cost of an OCT test (£51.27).

Gamma probability distributions were defined for unit cost data for probabilistic sensitivity analysis as these are defined non-negative and provide a possibility of a right tail that could account for few very high unit cost cases. Ranges for reference cost based data are also reported in *Table 27*; these are lower and upper quartiles. These were used to tailor cost probability distributions.

The cost of profound visual loss/blindness from the NHS and Personal Social Services perspective was calculated following Colquitt *et al.*[61] The authors used proportion for service utilisation developed by Meads and Hyde[71] (*Table 28*). The unit costs reported by Colquitt *et al.*[61] were updated using Hospital and Community Health Service specific price inflation index (base 2005 = 100) for March 2012 (e.g. £121.85). Using an alternative weekly cost figure of £497 for residential care (the item in the list with higher unit cost) reported by Curtis,[72] results in an annual cost of £556 and £537 for the first and subsequent years, respectively, and these were used as the basis for deterministic sensitivity analysis.

TABLE 28 Cost of profound visual loss/blindness

Variable	Requiring (%)	Cost (£, 2005)	Cost (£, 2012)	Annual cost (£)	Monthly cost (£)
Severe sight impairment registration	95	115	140	133	11.09
Low-vision aids	33	150	183	60	5.03
Low-vision rehabilitation	11	259	316	35	2.89
Community care	6	6552	7984	479	39.92
Residential care	30	13,577	16,544	4963	413.59
Depression	39	431	525	205	17.07
Hip replacement	5	5379	6554	328	27.31
Total year 1				6203	517.00
Total year 2+				5975	498.00

Utility weights

Guidelines for economic evaluation of health-care technologies in the UK advocate the use of a preference-based measure of utility.[73] We conducted a focused search for these data for AMD individuals. It was confirmed that one group had the majority of studies in this area[74,75] and data from Brown *et al.*[74] were included in the economic model. The study by Brown *et al.*[75] used the time trade-off approach on 72 consecutive patients seen at the Retina Vascular Unit at Wills Eye Hospital, Philadelphia, USA, to obtain utility weights for alternative VA scores. *Table 29* presents utility weights used in the economic model according to the Markov model health state. CIs were also obtained from Brown *et al.*[74] Mean utility weights and CIs were used to define beta distributions (see *Table 29*) for probabilistic sensitivity analysis.

Utility decrements due to adverse events were retrieved from Brown *et al.*[75] The authors derived utility values from 233 patients with AMD and decrement values were obtained from individuals who experienced alternative adverse events. *Table 29* shows the (monthly) utility decrements used within the model. These were applied to the proportion of individuals who experienced an adverse event from within those that were under treatment (see *Table 26*). Searches were conducted to retrieve information on the effect of treatment injections on the quality of life of patients with nAMD; however, no evidence was found. Moreover, from discussions within the project advisory group and clinical experts, anxiety seemed to be associated with the uncertainty of the disease condition (i.e. active or inactive) rather than the treatment itself. Adding a utility decrement for each monthly monitoring visit for all strategies would have had no effect on the final results. As such, no utility adjustments were conducted due to treatment injections.

Base-case and sensitivity analyses

The UK NICE guidelines of methods for technology appraisals were followed.[73] The model base-case analysis was run for a cohort of 65-year-old men for a time horizon of 35 years (lifetime). A 1-month cycle length was defined. The analysis was conducted from the NHS and Personal Social Services perspective. Costs were expressed in 2011–12 pounds sterling and effectiveness in quality-adjusted life-years (QALYs). Costs and QALYs were discounted at 3.5%.[73] Cost-effectiveness analysis results are reported using incremental cost-effectiveness ratios (ICERs).[55] ICERs are calculated as the ratio between the difference in average cost between two alternative strategies and the difference in average QALYs. This ratio measures the additional cost that would have to be paid in order to obtain an extra unit of effectiveness (i.e. an extra QALY). Probabilistic analysis results are reported using cost-effectiveness acceptability curves (CEACs).[76,77] CEACs show the probability of a particular strategy to be cost-effective at alternative values of willingness to pay for an extra QALY.

TABLE 29 Utility weights

Health state	Mean	95% CI	Probability distribution	Source
> 6/12	0.89	0.82 to 0.96	Beta(12.7; 1.6)	Colquitt *et al.*[61] based on Brown *et al.*[74]
≤ 6/12 to > 6/24	0.81	0.73 to 0.89	Beta(18.7; 4.4)	
≤ 6/24 to > 6/60	0.57	0.47 to 0.67	Beta(42.4; 32)	
≤ 6/60 to > 3/60	0.52	0.38 to 0.66	Beta(51.4; 47.4)	
≤ 3/60	0.4	0.29 to 0.50	Beta(59.6; 89.4)	
Utility decrements (monthly) due to adverse events				
Cataract	0.012			Brown *et al.*[75]
Endophthalmitis	0.025			
Retinal detachment	0.023			
Uveitis	0.025			Assumed equal to endophthalmitis

Sensitivity analysis

Uncertainty in the economic model was explored conducting one-way sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. As mentioned above, the base-case analysis was run for a male cohort. Gender-specific data were not available and the only different data for men and women were mortality rates. Female mortality data show longer life expectancy. These could result in longer time for benefits, but also costs. A further analysis was conducted using mortality data for women to observe the effect of longer life expectancy in the model results.

One-way sensitivity analyses were conducted on test diagnosis sensitivity and specificity, the probability of ophthalmologist diagnosis or monitoring results being unclear, tests and assessment monitoring sensitivity and specificity, probability of the nurse or technician assessment being unclear, and unit costs for OCT, FFA and ranibizumab.

Further deterministic sensitivity analyses were conducted using alternative discount rates for costs and QALYs, as well as prevalence rates for nAMD. In addition, population utility weights were retrieved from Czoski-Murray *et al.*[78] The authors elicited time trade-off-based utility values from 108 healthy individuals for AMD states simulated using contact lenses.

Given base-case and sensitivity analyses results, three scenario analyses were tested. All of these incorporated data that favoured OCT (*Table 30*). Scenario 1 used the upper limit for the 95% CI for OCT sensitivity and specificity for diagnosis and monitoring obtained from the systematic review of diagnostic and monitoring studies, together with £20.90 and £139 unit costs for OCT and FFA respectively. Scenario 2 used the same data as for scenario 1 but assuming a cost per treatment injection of £50 instead of £742. Finally, scenario 3 assumed the same input data as for scenario 1 but monitoring pathways that based their decisions on OCT only considered the unit cost of the OCT test for the monitoring visit as that of the OCT test for an optometry community service (£20.90).[80] The cost of an ophthalmologist visit was not considered in every monitoring visit but added only if the patient needed to be treated. This scenario explored the effect of monitoring patients within the community and only referred them to secondary care for treatment.

Base-case and selected sensitivity analyses are presented in the next section. Full sensitivity analysis results are reported in *Appendix 8*.

TABLE 30 Input data for scenario analyses

Variable	Diagnosis	Monitoring	Source
FFA			
Sensitivity	0.99	0.99	Assumption
Specificity	0.99	0.99	Assumption
OCT			
Sensitivity	0.98	0.93	Systematic review of diagnostic and monitoring studies
Specificity	0.88	0.67	Systematic review of diagnostic and monitoring studies
Unit costs (£, 2011–12)			
FFA	139		*NHS Reference Costs 2011–12* (HRG BZ23Z minor vitreous retinal procedures)[11]
OCT	20.9		*General Ophthalmic Services: Increases to NHS Sight Test Fee*[79]

Results

Table 31 reports base-case analysis results for men for the nine compared strategies. Model strategies are ordered in terms of average cost in an ascending order. Diagnosis with FFA combined with the nurse or technician-led monitoring strategy (e.g. nurse or technician as first monitoring contact conducting a VA examination and interpreting OCT test results; if negative, discharge, if positive or unclear, refer to an ophthalmologist for further assessment) was the strategy with the lowest average total cost. The next non-dominated strategy (i.e. dominated strategy meaning a strategy with higher expected costs and lower expected QALYs) is diagnosis based on FFA only, followed by ophthalmologist-led monitoring. This strategy has higher total expected cost but also produces higher total expected QALYs. However, the incremental cost for an extra QALY (i.e. ICER) to adopt this strategy is above the often accepted cost-effectiveness threshold (i.e. £30,000).[73] All other strategies are dominated by either of the strategies that based diagnosis in FFA only followed by nurse-led or ophthalmologist-led monitoring. Diagnosis based only on OCT appears in third place combined with nurse-led monitoring. In terms of costs, the strategies' order is driven mainly by the monitoring pathway, with the lowest average total costs coming from the nurse-led monitoring pathway (first to third places), then the ophthalmologist-led (fourth to sixth) and OCT only-based (seventh to ninth) monitoring pathways respectively. It should be noted, then, that the three model strategies that used OCT only as the basis for monitoring criteria were the strategies with higher average costs (see *Table 31*). This is due to the cost of treatment, that represents 76% of the total average cost within these strategies, the highest proportion for all compared strategies (e.g. average 65% and minimum 55%).

Figure 15 shows the cost-effectiveness plane for the base-case analysis and the nine diagnosis–monitoring combination strategies. For easier interpretation, data marker shapes relate to the diagnosis strategy and marker filling/colour relates to the monitoring strategy. Namely, square, circle and triangle shapes are used for FFA only, OCT only, and ophthalmologist stepwise diagnosis respectively. In addition, blue, green and none marker fillings correspond to ophthalmologist-led, nurse- or technician-led and OCT only-based monitoring respectively.

Three clusters can be seen in *Figure 15* according to the monitoring strategy. As such, the ophthalmologist-led monitoring strategy cluster seems to produce higher expected QALYs and slightly higher expected costs than the nurse- or technician-led monitoring strategy. The OCT only monitoring strategy cluster results in a higher expected cost and lower expected QALYs than the other two monitoring strategies.

TABLE 31 Base-case cost-effectiveness results: men

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)[a]
(3) FFA & Nurse	39,769	–	10.473	0.000	0
(9) Ophthalmologist & Nurse	39,790	21	10.472	–0.001	–33,237
(6) OCT & Nurse	41,607	1838	10.465	–0.008	–224,403
(2) FFA & Ophthalmologist	44,649	4880	10.575	0.102	47,768
(8) Ophthalmologist & Ophthalmologist	44,669	20	10.574	–0.001	–31,094
(5) OCT & Ophthalmologist	47,131	2482	10.567	–0.008	–293,938
(1) FFA & OCT	62,759	18,110	10.449	–0.126	–144,229
(7) Ophthalmologist & OCT	62,778	18,129	10.449	–0.126	–143,662
(4) OCT & OCT	67,421	22,772	10.442	–0.133	–170,859

a The ICERs are calculated against the next cheapest non-dominated strategy.

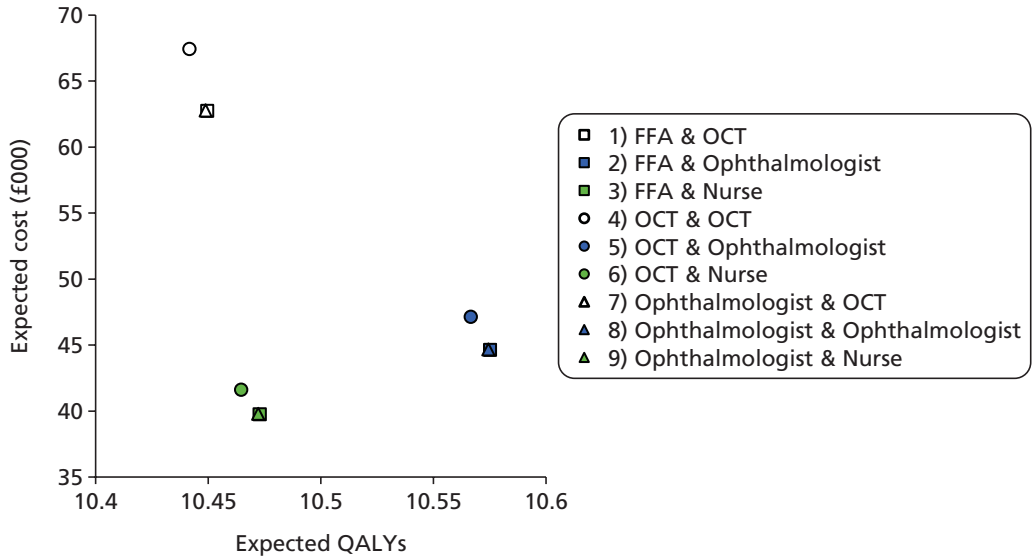


FIGURE 15 Base-case cost-effectiveness results: men.

Within each of these clusters, the FFA diagnosis strategy dominates OCT only as well as the ophthalmologist stepwise diagnosis strategy (e.g. VA, OCT and SLB in all, followed by FFA if positive or unclear results). Also, to note is that the ophthalmologist diagnostic and FFA diagnostic pathways have very similar expected cost and QALYs within each cluster and, as such, data markers seem to overlap. This is due to the close values assumed for diagnosis sensitivity and specificity in these two diagnostic pathways.

Table 32 and *Figure 16* show probabilistic sensitivity analysis for the base case. Diagnosing with FFA only followed by nurse- or technician-led monitoring has the highest probability of being cost-effective for up to £40,000 willingness to pay for an extra QALY. At higher threshold values (e.g. £50,000) diagnosing with FFA only followed by ophthalmologist-based monitoring has a higher probability of being cost-effective. Overall, diagnosis with FFA with either nurse- or ophthalmologist-led monitoring has more than a 70% chance of being cost-effective at willingness-to-pay values for an extra QALY of between £10,000 and £50,000. These strategies lose some ground against ophthalmologist-based diagnosis (e.g. 'Ophthalmologist & Ophthalmologist' and 'Ophthalmologist & Nurse') at high levels of willingness to pay for extra QALY threshold values (see *Table 32* and *Figure 16*). At £30,000 willingness to pay for a

TABLE 32 Probabilistic sensitivity analysis: base case – men

	Probability of strategy being cost-effective at alternative threshold values for society's willingness to pay for a QALY (%)				
Strategy	£10,000	£20,000	£30,000	£40,000	£50,000
(1) FFA & OCT	0.6	0.9	1.2	1.2	1.7
(2) FFA & Ophthalmologist	12.2	21.8	31.3	36.7	42.6
(3) FFA & Nurse	67.7	57.4	46.4	39.0	29.9
(4) OCT & OCT	0.0	0.0	0.0	0.0	0.0
(5) OCT & Ophthalmologist	0.0	0.0	0.0	0.0	0.0
(6) OCT & Nurse	0.0	0.0	0.0	0.0	0.0
(7) Ophthalmologist & OCT	0.0	0.1	0.1	0.3	0.5
(8) Ophthalmologist & Ophthalmologist	1.5	3.3	7.2	10.3	13.8
(9) Ophthalmologist & Nurse	18.0	16.5	13.8	12.5	11.5

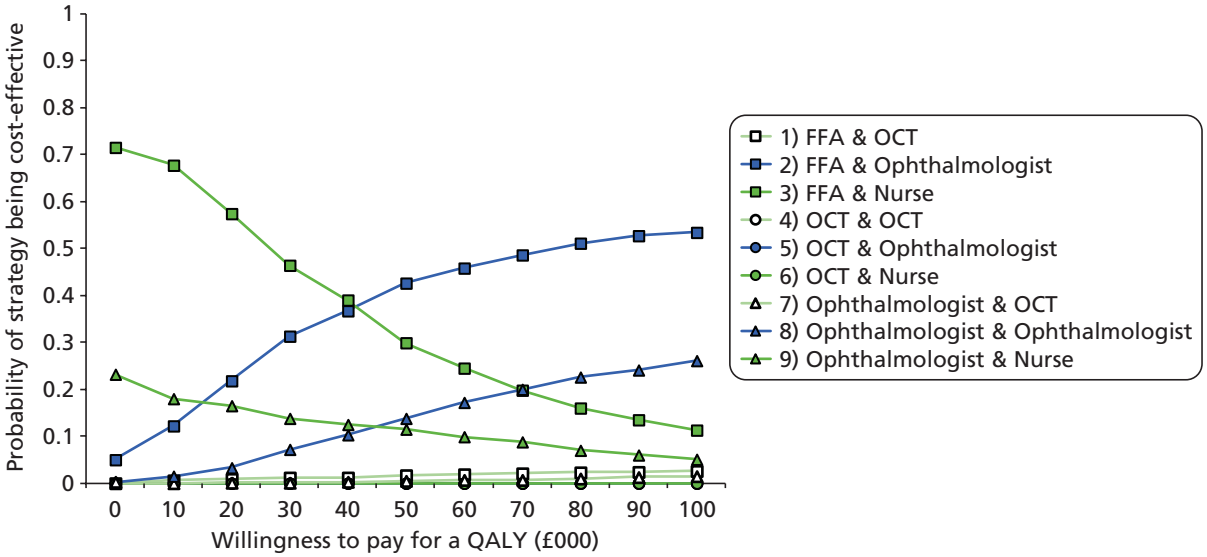


FIGURE 16 Base case cost-effectiveness acceptability curves: men.

QALY threshold value and regardless of the diagnosis pathways (e.g. FFA only, OCT only or ophthalmologist), nurse- or technician-led monitoring has a 61% probability of being cost-effective.

Figure 16 shows that when expanding this range up to £100,000, diagnosing with FFA only followed by the ophthalmologist-based monitoring strategy will have more than a 50% chance of being cost-effective. In addition, FFA only-based diagnosis strategies lose some ground against ophthalmologist-based diagnosis strategies (i.e. 'Ophthalmologist & Ophthalmologist' and 'Ophthalmologist & Nurse') at high levels of willingness to pay threshold values (see *Table 32* and *Figure 16*).

Sensitivity analysis

Using mortality rate data for women

Table 33 and *Figure 17* present cost-effectiveness results for women. As expected, all strategies produce more QALYs, incurring higher average costs. This is because of the longer life expectancy for women. This affects all of the model strategies in a similar manner. As such, there are no differences in the (average cost) order of the strategies or the general results compared with those for the base-case analysis for men (see *Table 31*). Diagnosing with FFA followed by nurse- or technician-led monitoring is still the strategy with the lowest average cost and dominates all other compared strategies, apart from diagnosis

TABLE 33 Cost-effectiveness results: women

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)
(3) FFA & Nurse	44,099	0	11.604	0.000	0
(9) Ophthalmologist & Nurse	44,119	21	11.603	–0.001	–30,521
(6) OCT & Nurse	46,125	2026	11.595	–0.009	–226,433
(2) FFA & Ophthalmologist	49,527	5428	11.725	0.121	44,959
(8) Ophthalmologist & Ophthalmologist	49,547	20	11.724	–0.001	–28,491
(5) OCT & Ophthalmologist	52,262	2735	11.715	–0.009	–296,276
(1) FFA & OCT	69,712	20,185	11.576	–0.148	–136,016
(7) Ophthalmologist & OCT	69,731	20,204	11.576	–0.149	–135,517
(4) OCT & OCT	74,847	25,321	11.568	–0.157	–161,433

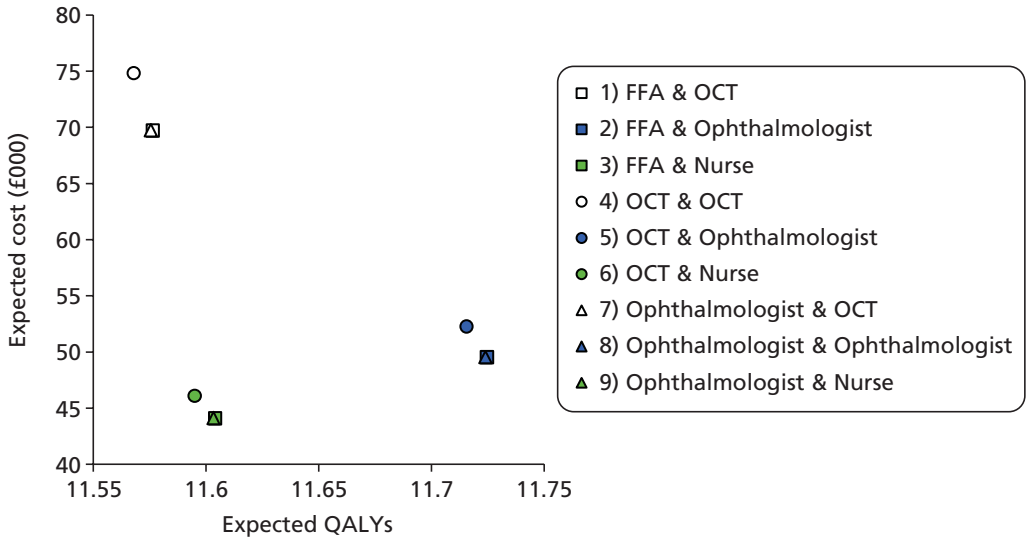


FIGURE 17 Cost-effectiveness results: women.

with FFA followed by ophthalmologist-led monitoring. However, the ICER for moving to the latter strategy is above the usually accepted cost-effectiveness threshold (i.e. £30,000).[73]

Similar clusters can be observed in the cost-effectiveness results for men (see *Figure 15*) and women (see *Figure 17*), with the three clusters depending on the monitoring care pathway (i.e. OCT only, nurse-, technician-, or ophthalmologist-led monitoring). As was the case with *Figure 15*, the ophthalmologist diagnostic and FFA diagnostic pathways have very similar expected cost and QALYs within each cluster and, as such, data markers seem to overlap. The *Table 33* and *Figure 17* results indicate that no dramatic differences can be expected for the women and men model run results. Therefore, further sensitivity analyses were conducted only for the male cohort.

One-way sensitivity analyses

Extensive one-way sensitivity analyses were undertaken. This section reports a selected number of these, with full results presented in *Appendix 8*. All one-way sensitivity analyses show results moving in the expected direction (i.e. lower sensitivity or specificity for OCT would result in OCT-based strategies being less cost-effective). *Tables 34–38* show one-way sensitivity analysis for OCT diagnostic sensitivity and specificity, OCT monitoring sensitivity and specificity and OCT unit cost respectively. The base-case analysis results seem robust. In all reported sensitivity analyses, diagnosis with FFA combined with nurse- or technician-led monitoring (based on VA and OCT with a referral to the ophthalmologist if positive or unclear) has the lowest total expected costs and dominates all others, apart from FFA for diagnosis with ophthalmologist-led monitoring. In a limited number of model runs, alternative strategies stop being dominated by diagnosis with FFA followed by nurse- or technician-led monitoring. However, in many of these cases the variable values used to run the analysis were extreme (see *Tables 34* and *36* for OCT diagnostic and monitoring sensitivities equal to 1 respectively). Results are sensitive to the value of monitoring specificity for OCT. *Table 37* suggests that OCT monitoring specificity above 80% could make diagnosis with FFA combined with monitoring with OCT only, a cost-effective strategy. However, this is to almost double the specificity values reported for monitoring in *Chapter 4*.

Scenario analysis

Scenario analysis favouring the OCT test was conducted to explore conditions under which OCT only-based strategies could become cost-effective. The scenarios are described in *Base-case and sensitivity analyses* and the input data used reported in *Table 30*. Best possible OCT test sensitivity and specificity were incorporated into the model. In addition, the lowest possible unit cost for OCT and a higher assumed unit cost value for FFA were used. Scenario 2 differs in the unit cost assumed for each treatment injection (£50) and scenario 3 explores community monitoring (e.g. unit cost for OCT as for community optometrist and an

TABLE 34 One-way sensitivity analysis: OCT diagnostic sensitivity

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
0.8	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,594	10.459	1824	–0.014	–133,258
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,114	10.561	2465	–0.014	–173,407
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	67,394	10.436	22,745	–0.139	–163,795
0.9	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,611	10.466	1841	–0.007	–270,172
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,135	10.568	2486	–0.007	–355,119
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	67,428	10.443	22,779	–0.132	–172,719
1.0	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,628	10.473	1859	0.000	31,635,704
	(2) FFA & Ophthalmologist	44,649	10.575	3021	0.102	29,593
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,157	10.575	2507	0.000	11,797,675
	(1) FFA & OCT	62,759	10.449	15,602	–0.126	–124,050
	(7) Ophthalmologist & OCT	62,778	10.449	15,621	–0.126	–123,584
	(4) OCT & OCT	67,462	10.450	20,306	–0.125	–162,290

TABLE 35 One-way sensitivity analysis: OCT diagnostic specificity

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
0.55	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	43,619	10.465	3850	–0.008	–473,564
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	49,821	10.567	5172	–0.008	–629,095
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	72,407	10.442	27,758	–0.133	–209,343
0.60	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	43,182	10.465	3412	–0.008	–419,079
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	49,236	10.567	4587	–0.008	–554,702
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	71,324	10.442	26,674	–0.133	–200,943
0.65	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	42,744	10.465	2975	–0.008	–364,772
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	48,651	10.567	4002	–0.008	–481,174
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	70,240	10.442	25,590	–0.133	–192,562
0.70	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	42,307	10.465	2538	–0.008	–310,643
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	48,067	10.567	3418	–0.008	–408,495

TABLE 35 One-way sensitivity analysis: OCT diagnostic specificity (*continued*)

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	69,156	10.442	24,507	–0.133	–184,200
0.75	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,870	10.465	2100	–0.008	–256,690
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,482	10.567	2833	–0.008	–336,651
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	68,072	10.442	23,423	–0.133	–175,856
0.80	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,432	10.465	1663	–0.008	–202,914
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	46,897	10.567	2248	–0.008	–265,626
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	66,988	10.442	22,339	–0.133	–167,531
0.85	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	40,995	10.465	1226	–0.008	–149,312
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	46,312	10.567	1663	–0.009	–195,408
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	65,904	10.442	21,255	–0.133	–159,225

continued

TABLE 35 One-way sensitivity analysis: OCT diagnostic specificity (*continued*)

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
0.90	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	40,558	10.465	788	–0.008	–95,884
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	45,727	10.566	1078	–0.009	–125,982
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	64,820	10.441	20,171	–0.134	–150,937
0.95	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	40,120	10.465	351	–0.008	–42,629
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	45,143	10.566	494	–0.009	–57,335
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662
	(4) OCT & OCT	63,736	10.441	19,087	–0.134	–142,667
1.0	(6) OCT & Nurse	39,683	10.465			
	(3) FFA & Nurse	39,769	10.473	86	0.008	10,453
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(5) OCT & Ophthalmologist	44,558	10.566	4789	0.094	51,214
	(2) FFA & Ophthalmologist	44,649	10.575	91	0.009	10,545
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	4) OCT & OCT	62,652	10.441	18,003	–0.134	–134,416
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662

TABLE 36 One-way sensitivity analysis: OCT monitoring sensitivity

Monitoring sensitivity OCT	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
0.9	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	63,312	10.503	18,663	–0.072	–260,619
	(7) Ophthalmologist & OCT	63,331	10.503	18,682	–0.072	–258,561
	(4) OCT & OCT	67,974	10.495	23,325	–0.080	–293,337
1.0	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	64,277	10.600	19,628	0.025	788,482
	(7) Ophthalmologist & OCT	64,296	10.599	19	–0.001	–28,229
	(4) OCT & OCT	68,939	10.592	4662	–0.008	–565,643

TABLE 37 One-way sensitivity analysis: OCT monitoring specificity

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental cost	Incremental effectiveness	ICER
0.3	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	74,212	10.459	29,563	–0.116	–255,643
	(7) Ophthalmologist & OCT	74,230	10.459	29,581	–0.116	–254,397
	(4) OCT & OCT	80,083	10.452	35,434	–0.123	–287,514

continued

TABLE 37 One-way sensitivity analysis: OCT monitoring specificity (*continued*)

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental cost	Incremental effectiveness	ICER
0.4	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	67,780	10.454	23,130	–0.121	–190,790
	(7) Ophthalmologist & OCT	67,798	10.453	23,149	–0.122	–189,953
	(4) OCT & OCT	72,979	10.446	28,330	–0.129	–219,784
0.5	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	61,521	10.448	16,872	–0.127	–133,240
	(7) Ophthalmologist & OCT	61,540	10.448	16,891	–0.127	–132,734
	(4) OCT & OCT	66,049	10.441	21,400	–0.134	–159,275
0.6	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	55,429	10.443	10,780	–0.132	–81,774
	(7) Ophthalmologist & OCT	55,449	10.443	10,800	–0.132	–81,537
	(4) OCT & OCT	59,286	10.435	14,636	–0.140	–104,824
0.7	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
	(1) FFA & OCT	49,498	10.438	4849	–0.137	–35,432
	(7) Ophthalmologist & OCT	49,518	10.438	4869	–0.137	–35,418
	(4) OCT & OCT	52,683	10.430	8033	–0.145	–55,508

TABLE 37 One-way sensitivity analysis: OCT monitoring specificity (*continued*)

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental cost	Incremental effectiveness	ICER
0.8	(3) FFA & Nurse	39,769	10.473			
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(1) FFA & OCT	43,721	10.433	3952	–0.040	–99,944
	(7) Ophthalmologist & OCT	43,742	10.433	3973	–0.040	–98,928
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(4) OCT & OCT	46,234	10.425	1585	–0.150	–10,589
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
0.9	(1) FFA & OCT	38,093	10.429			
	(7) Ophthalmologist & OCT	38,114	10.428	21	–0.001	–34,221
	(3) FFA & Nurse	39,769	10.473	1676	0.044	37,884
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(4) OCT & OCT	39,934	10.421	164	–0.052	–3,146
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938
1.0	(1) FFA & OCT	32,608	10.424			
	(7) Ophthalmologist & OCT	32,629	10.423	21	–0.001	–35,125
	(4) OCT & OCT	33,776	10.416	1168	–0.008	–144,031
	(3) FFA & Nurse	39,769	10.473	7161	0.049	146,783
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938

TABLE 38 One-way sensitivity analysis: OCT unit cost

Unit Cost OCT	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
30	(9) Ophthalmologist & Nurse	37,446	10.472			
	(3) FFA & Nurse	37,446	10.473	1	0.001	835
	(6) OCT & Nurse	39,071	10.465	1625	–0.008	–198,353
	(8) Ophthalmologist & Ophthalmologist	42,317	10.574	4870	0.102	47,980
	(2) FFA & Ophthalmologist	42,318	10.575	1	0.001	1398
	(5) OCT & Ophthalmologist	44,586	10.567	2268	–0.008	–268,648
	(7) Ophthalmologist & OCT	60,434	10.449	18,116	–0.126	–143,560
	(1) FFA & OCT	60,436	10.449	18,118	–0.126	–144,295
	(4) OCT & OCT	64,885	10.442	22,567	–0.133	–169,320
40	(3) FFA & Nurse	38,538	10.473			
	(9) Ophthalmologist & Nurse	38,548	10.472	9	–0.001	–15,184
	(6) OCT & Nurse	40,263	10.465	1725	–0.008	–210,601
	(2) FFA & Ophthalmologist	43,414	10.575	4875	0.102	47,723
	(8) Ophthalmologist & Ophthalmologist	43,423	10.574	9	–0.001	–13,878
	(5) OCT & Ophthalmologist	45,783	10.567	2369	–0.008	–280,538
	(1) FFA & OCT	61,528	10.449	18,114	–0.126	–144,264
	(7) Ophthalmologist & OCT	61,536	10.449	18,122	–0.126	–143,608
	(4) OCT & OCT	66,078	10.442	22,664	–0.133	–170,044
50	(3) FFA & Nurse	39,630	10.473			
	(9) Ophthalmologist & Nurse	39,650	10.472	19	–0.001	–31,202
	(6) OCT & Nurse	41,456	10.465	1825	–0.008	–222,848
	(2) FFA & Ophthalmologist	44,510	10.575	4879	0.102	47,763
	(8) Ophthalmologist & Ophthalmologist	44,529	10.574	19	–0.001	–29,154
	(5) OCT & Ophthalmologist	46,979	10.567	2469	–0.008	–292,428
	(1) FFA & OCT	62,620	10.449	18,110	–0.126	–144,233
	(7) Ophthalmologist & OCT	62,638	10.449	18,128	–0.126	–143,656
	(4) OCT & OCT	67,270	10.442	22,760	–0.133	–170,767
60	(3) FFA & Nurse	40,722	10.473			
	(9) Ophthalmologist & Nurse	40,752	10.472	29	–0.001	–47,221
	(6) OCT & Nurse	42,648	10.465	1926	–0.008	–235,095
	(2) FFA & Ophthalmologist	45,606	10.575	4884	0.102	47,803
	(8) Ophthalmologist & Ophthalmologist	45,635	10.574	29	–0.001	–44,429
	(5) OCT & Ophthalmologist	48,176	10.567	2569	–0.008	–304,319
	(1) FFA & OCT	63,712	10.449	18,106	–0.126	–144,201
	(7) Ophthalmologist & OCT	63,740	10.449	18,134	–0.126	–143,703
	(4) OCT & OCT	68,462	10.442	22,856	–0.133	–171,491

TABLE 38 One-way sensitivity analysis: OCT unit cost (*continued*)

Unit Cost OCT	Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
70	(3) FFA & Nurse	41,814	10.473			
	(9) Ophthalmologist & Nurse	41,854	10.472	39	–0.001	–63,240
	(6) OCT & Nurse	43,840	10.465	2026	–0.008	–247,342
	(2) FFA & Ophthalmologist	46,702	10.575	4888	0.102	47,842
	(8) Ophthalmologist & Ophthalmologist	46,741	10.574	39	–0.001	–59,705
	(5) OCT & Ophthalmologist	49,372	10.567	2670	–0.008	–316,209
	(1) FFA & OCT	64,805	10.449	18,102	–0.126	–144,170
	(7) Ophthalmologist & OCT	64,842	10.449	18,140	–0.126	–143,751
	(4) OCT & OCT	69,655	10.442	22,953	–0.133	–172,214

ophthalmologist visit cost added only when treatment was needed). *Tables 39–41* show the scenario analysis results. For scenario 1 (see *Table 39*) and scenario 3 (see *Table 41*) strategies that based their diagnosis or monitoring decisions on OCT test results only are dominated (i.e. have higher expected costs and lower expected QALYs). It should be noted that, due to the lower unit cost for the OCT test, the strategy with the lower expected cost is diagnosis by an ophthalmologist combined with nurse- or technician-led monitoring.

Table 40 shows results for scenario 2 (i.e. the same input data as for scenario 1 but assuming cost of treatment of £50 per injection). The pathway strategy with the lowest cost is the ophthalmologist stepwise diagnosis followed by monitoring decisions based on OCT only. The next costly strategy is the one that based the diagnosis decision on FFA only and the monitoring treatment decision on OCT test results only. However, this strategy is dominated by the former. The next non-dominated strategy was diagnosis by an ophthalmologist followed by ophthalmologist-led monitoring (e.g. 'Ophthalmologist & Ophthalmologist') with an ICERs of £19,917. This is within the usual £30,000[73] threshold and potentially worthwhile to adopt. The results in *Table 40* indicate that OCT strategies could become cost-effective if the cost of treatment was lower. In terms of the economic model, this would be a lower penalisation for those strategies that treat individuals who do not need to be treated (i.e. those tests or strategies that result in lower specificity and therefore a higher number of FP results).

TABLE 39 Scenario analysis 1

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)
(9) Ophthalmologist & Nurse	36,320	–	10.478		
(3) FFA & Nurse	36,707	387	10.471	–0.007	–54,280
(6) OCT & Nurse	37,417	1097	10.470	–0.008	–140,873
(8) Ophthalmologist & Ophthalmologist	41,284	4964	10.579	0.101	49,012
(2) FFA & Ophthalmologist	41,740	456	10.573	–0.006	–73,232
(5) OCT & Ophthalmologist	42,781	1497	10.573	–0.007	–218,869
(7) Ophthalmologist & OCT	48,24	6957	10.536	–0.043	–161,687
(1) FFA & OCT	48,791	7507	10.530	–0.050	–151,253
(4) OCT & OCT	50,273	8989	10.529	–0.050	–179,277

–, there is no incremental cost on this option.

TABLE 40 Scenario analysis 2

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)
(7) Ophthalmologist & OCT	13,983	–	10.536		
(1) FFA & OCT	14,158	175	10.530	–0.007	–26,423
(4) OCT & OCT	14,583	600	10.529	–0.007	–84,256
(8) Ophthalmologist & Ophthalmologist	14,840	857	10.579	0.043	19,917
(2) FFA & Ophthalmologist	15,024	184	10.573	–0.006	–29,567
(5) OCT & Ophthalmologist	15,477	636	10.573	–0.007	–93,000
(9) Ophthalmologist & Nurse	15,601	761	10.478	–0.101	–7,511
(3) FFA & Nurse	15,790	949	10.471	–0.108	–8,757
(6) OCT & Nurse	16,218	1377	10.470	–0.109	–12,627

–, there is no incremental cost in this option.

TABLE 41 Scenario analysis 3

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)
(9) Ophthalmologist & Nurse	36,320	–	10.478	0.000	0
(3) FFA & Nurse	36,707	387	10.471	–0.007	–54,280
(6) OCT & Nurse	37,417	1097	10.470	–0.008	–140,873
(8) Ophthalmologist & Ophthalmologist	41,284	4964	10.579	0.101	49,012
(2) FFA & Ophthalmologist	41,740	456	10.573	–0.006	–73,232
(5) OCT & Ophthalmologist	42,781	1497	10.573	–0.007	–218,869
(7) Ophthalmologist & OCT	43,527	2243	10.536	–0.043	–52,132
(1) FFA & OCT	44,018	2734	10.530	–0.050	–55,084
(4) OCT & OCT	45,257	3974	10.529	–0.050	–79,247

–, there is no incremental cost in this option.

Summary and discussion

This chapter reported on a systematic review of economic evaluations and a model-based economic evaluation of alternative strategies for the diagnosis and monitoring of individuals with nAMD. No studies identified in the literature met the inclusion criteria for the systematic review.

Nine strategies (combinations of three different diagnostic and monitoring pathways) were considered within the economic model. The strategies used OCT for diagnosis and/or monitoring of nAMD individuals to a different extent. Extensive deterministic and probabilistic sensitivity analyses were conducted. The strategy that based its diagnosis decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as the first monitoring step, with a referral to an ophthalmologist if the first monitoring assessment was positive or unclear ('FFA & Nurse'), had the lowest expected total cost. This strategy dominated (i.e. lower expected costs and higher expected QALYs) all others apart from one: diagnosis with FFA only, combined with monitoring by an ophthalmologist ('FFA & Ophthalmologist'). The 'FFA & Nurse' and 'FFA & Ophthalmologist' strategies had, respectively, a 46.5% and 29.8% probability of being cost-effective at the £30,000 threshold value of willingness to pay for an extra QALY. In addition, the 'FFA & Nurse' strategy dominated all others in the great majority of sensitivity analyses.

The strategies that used OCT only for their monitoring decisions were in almost every model run ordered last in terms of total expected cost and were often dominated by others. The strategy that used OCT only for both diagnosis and monitoring decisions was in almost every model run, the most costly strategy.

Scenario analysis was conducted in order to explore the conditions under which an OCT only strategy would become cost-effective. Three scenarios were developed using the best test performance data for OCT combined with a lower cost for OCT (£20.90) and a higher cost for FFA (£137). Scenario 2 added to this a lower unit cost for treatment (e.g. equivalent to the cost of bevacizumab, £50, instead of the £742 cost of ranibizumab considered for the base-case analysis). This scenario showed the ophthalmologist stepwise pathway for diagnosis combined with OCT only for monitoring, to be, on average, the least costly strategy. Alternative strategies were either dominated (i.e. more costly and produced fewer QALYs) or the resulted ICER was well above the usual threshold accepted for policy decisions.[73] This was an expected result. The low OCT specificity for monitoring in these scenarios and in the base case (0.61 and 0.44, respectively) meant that a high number of positive results would actually be FPs. The lower cost of treating individuals who do not need to be treated reduced the model penalisation for the OCT only-based strategies and therefore improved their cost-effectiveness.

Best practice guidelines were followed for this model-based economic evaluation exercise.[73,81] In spite of this, these results should be interpreted with caution. A considerable effort was made to retrieve the best available test or assessment performance data by conducting a systematic review of the literature. Other data were obtained from focused but reproducible searches. Nevertheless, there is an inherent problem with model-based economic evaluations that incorporate evidence from several sources, even when these data have been obtained systematically. The limitations of the SD-OCT performance data incorporated into the economic model have been mentioned in *Chapter 4*, with no SD-OCT studies contributing to the diagnosis performance data and only two SD-OCT studies[23,30] contributing to the monitoring performance data. Moreover, although OCT diagnosis and monitoring performance data were retrieved from a systematic review of the literature, no such data were available for the strategies involving diagnosis or monitoring assessment by an ophthalmologist or monitoring assessment by a nurse or technician. Therefore, these data for the model were obtained from expert opinion. This constitutes a major caveat of the analysis and further research in this area is needed.

This economic model needed to consider individuals' disease status (i.e. active or inactive nAMD) as well as test results on a monthly basis. In addition, these had to be combined with alternative VA states in order to incorporate utility weights into the model. It was felt that considering the effect of a fellow eye status (VA and nAMD status) would add major complexity to the model without a great deal of benefit from such incorporation. This is the most common approach used among economic models in this health area but constitutes a limitation of the current study. Utility weights used were obtained from nAMD individuals and grouped according to VA in the better-seeing eye. It is believed that this would better reflect individuals' health status. However, the clear limitation of 'one eye models' is the underestimation of resources used. A proportion of monitored nAMD individuals will have this condition in both eyes instead of one, and, had the disease been active, would be receiving treatment injections in each eye. Intuitively, this would increase the treatment cost for those strategies with a higher number of TP and FP results (i.e. higher sensitivity and lower specificity) and hence would be unlikely to modify the overall conclusions of this economic evaluation.

The model did not consider effects on utility due to treatment injections. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to the uncertainty of the underlying condition (i.e. whether or not nAMD was active) and not the effects of the treatment injections. No evidence was obtained on this issue in spite of focused searches. Further research in this area is needed. Utility weight decrements from treatment adverse effects were included and this might partially overcome the above-mentioned potential limitation.

Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Data were retrieved from the literature and also from a UK-based RCT.[9] Survival data were received from the IVAN study (Dr Chris Rogers, personal communication) on first retreatment failure criteria (i.e. inactive individuals who needed to be retreated). These were used to develop model parameter values for the first year of the model run. There were no such data available for further failures and we had to rely on the available limited data from the literature[70] or on expert opinion for year 2 onwards. In addition, progression data on VA were based on the 2-year follow-up MARINA study.[69] All of these were relatively short-term follow-up studies (around 2 years) but used to inform model parameters for a lifetime time horizon. These are clear limitations of the model and therefore its results should be interpreted with caution. Further research investigating individuals' nAMD active/inactive status (e.g. probability of disease changing from inactive to active) would be desirable.

Conclusions

A strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step, with a referral to an ophthalmologist if this first monitoring assessment was positive or unclear, had the lowest expected total cost. This strategy had a 46.5% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. In addition, this strategy dominated all others apart from one (i.e. diagnosis with FFA combined with ophthalmologist-led monitoring) in the great majority of sensitivity analyses. Strategies that used OCT test results alone to make diagnosis or monitoring treatment decisions were unlikely to be a cost-effective use of resources. This result seemed to be driven by the OCT low specificity that resulted in a high number of FP results. The present analysis indicated that a further refinement of monitoring (i.e. a further monitoring step other than OCT alone) seemed desirable.

These results should be interpreted with caution. The economic model would benefit from further research to better inform a number of model parameter values. Studies that investigate the likelihood of nAMD individuals becoming active or inactive after subsequent treatments are desirable. In addition, a preference-based health status and process of care valuation study to explore the effects of treatment injections on individuals' utility weights is needed. Finally, a comparative study to establish the performance of the ophthalmologist-based strategy compared with the nurse- or technician-based strategy for monitoring individuals with nAMD is required to inform future economic models in this area.

Chapter 6 Assessment of factors relevant to the NHS and other parties

The introduction of OCT and other diagnostic technologies for the diagnosis and monitoring of patients with nAMD has a range of implications for the NHS, patients and other parties. There has already been a shift in the diagnostic pathway for this group of patients caused by the adoption of OCT, rather than the previously used FFA, as a method of establishing the diagnosis and of evaluating disease activity. There are consequential effects not only on patient outcomes but also on service delivery, health-care professionals and wider society of this change in preferred diagnostic technologies used.

Factors relevant to the NHS

Estimating the numbers of patients with neovascular age-related macular degeneration

A summary of the epidemiology of nAMD has been described in this study. In brief, the prevalence and incidence of nAMD and the consequent burden to the NHS will increase over the next few decades because of the ageing population. By 2060, mean life expectancy will grow by 8.5 years for men (to 84.5 years) and 6.9 years for women (to 89.0 years).[82]

Implications for service provision

The clinical workload associated with the frequent follow-up required for patients with nAMD is substantial. As more new patients are diagnosed and the population continues to age, the patient population will continue to increase. It is thus vital that clinical services continue to adapt so that they can provide a fast and efficient service for patients with nAMD.

There are still challenges and questions about whether or not ophthalmology departments have sufficient capacity and the means to offer relevant testing and treatments within adequate time scales. Local diagnostic pathways require updating and assessment to ensure compliance with national guidelines (e.g. to detect recurrence of active disease in these subjects). Occasional local disruptions may occur if OCT equipment suffers technical failures.

In 2012, Amoaku *et al.*[56] published a document entitled 'Action on AMD' that was developed by eye health-care professionals and patient representatives with the intention of highlighting the urgent and continuing need for change within nAMD services. This document also provided examples of good practice and service development, including the possibility of involving other health professionals and using OCT in the community.

Considerations regarding the performance of optical coherence tomography for diagnosis and monitoring

At the diagnostic stage, OCT is currently used in addition to FFA to provide a baseline that will be used for comparisons during the monitoring stage.

For monitoring, OCT has virtually replaced FFA in most NHS units.[83] During follow-up, monitoring also includes VA testing. There is larger variability in the adoption of other tests and perceived need for FFA during follow-up. The replacement of FFA is probably due to the convenience of OCT (e.g. non-invasive, user friendly, quick, efficient). However, expert clinicians recognise the difficulty of interpreting FFA and OCT in patients with previously treated nAMD who often develop atrophic changes. The low specificity of OCT observed in this study would suggest that OCT alone should not be used for monitoring.

Another consideration is the evolving technology. For example, theoretically an increased sensitivity and specificity of new versions or novel technologies (SD-OCT) would lead to more patients being correctly diagnosed with active nAMD, and fewer wrongly diagnosed as having no active disease. This review did not find sufficient evidence on the performance of SD-OCT and it is unclear if it is superior to TD-OCT.

Regarding cost implications, there will be little cost implications for procuring and maintaining OCT equipment because most centres already use this technology. Although many units will already have access to the new SD-OCT equipment, other centres may have to upgrade the current TD-OCT (e.g. purchase or lease new SD-OCT equipment).

There may be a need for training ophthalmology staff to ensure adequate technical skills to interpret the OCT scans. There is a learning curve to interpreting OCT images, especially in relation to those patients who are being monitored after treatment. Adequate quality control and quality assurance programmes would be needed in order to maintain high standards of interpretation.

Factors relevant to patients and other parties

A highly specific test may reduce the number of patients undergoing unnecessarily treatment with antiVEGF injections, avoiding the associated discomfort, side effects and possible complications. Using OCT alone for diagnosis or monitoring would be associated with a number of FPs and unnecessary treatments. From the efficiency point of view, a specificity of at least 80% would be required for a monitoring strategy using OCT alone to be cost-effective.

From a patient preference point of view, if the diagnostic performance were adequate, it is likely that patients would prefer OCT when compared with FFA because of the unpleasantness of the latter procedure.

Monitoring in the community would be a positive development for patients and carers, who would have less distance to travel to access OCT testing. This may be possible as OCT is becoming increasingly used by community optometrists but would need to be associated with another test (e.g. VA). Local arrangements and financial support would need to be put in place as community optometrists would need to be trained and reimbursed for their services. Community optometrists should also be able to communicate their findings in a timely and efficient way to clinicians in secondary care. However, inequalities in access may arise as people from disadvantaged socioeconomic backgrounds may be reluctant to attend private community optometrists.

Chapter 7 Discussion

Diagnostic accuracy

Statement of principal findings

Diagnostic studies

Twenty-two diagnostic studies were included (20 full-text papers,[24–27,29,31,33,35–41,44–51] two abstracts[34,42]) involving over 2000 participants. The studies reported the performance of OCT (13 studies[25,27,33–38,40,41,45,46,49]), ICGA (eight studies[25,26,29,31,42,44,48,51]), PHP (three studies[24,27,39]), colour fundus photography, Amsler grid[27] and FAF[25] (one study each) in the detection of nAMD. Studies that reported true and false positive and true and false negative or provided information that allowed these data to be calculated were considered for inclusion in pooled estimates (meta-analyses), which were performed with eye as the unit of analysis.

Full-text papers were assessed for risk of bias using the QUADAS-2 tool. The domains with the greatest number of studies judged to be at high risk of bias were the patient selection domain (55%, 11/20), for reasons such as inappropriate exclusions and pre-selection of participants, and the flow and timing domain (40%, 8/20), for reasons such as the length of time between the index test and the reference standard being longer than 1 week, and not all participants being included in the analysis. In the index/comparator test domain and reference standard domain, the risk of bias was judged to be unclear in around half of the studies [50% (10/20) and 60% (12/20) respectively]. However, all of the studies were judged to be of low concern in terms of their applicability to the review question.

Only four OCT diagnostic studies (all TD-OCT)[27,40,46,49] provided sufficient data for inclusion in a meta-analysis. The pooled sensitivity and specificity (95% CI) for all OCT was moderately high at 88% (46% to 98%) and 78% (64% to 88%) respectively.

Of the other tests of interest, median sensitivity (range) was similarly high for ICGA [93.2% (84.6–100%); four studies[25,29,44,51]] and FAF (93.3%; one study[25]), followed by PHP [81.5% (50.0–84.8%); three studies[24,27,39]] and colour fundus photography (70.0%; one study[24]) and was lowest for Amsler grid (41.7%; one study[27]). Specificity was highest for colour fundus photography (95%; one study[24]), followed by PHP (84.6% and 87.7%; two studies[24,39]), and was similarly low for FAF (37.1%; one study[25]) and ICGA (36.8%; one study[29]).

Two studies reported test combinations. For OCT plus colour fundus photography,[46] sensitivity was moderate at 74.1%, with specificity high at 92.0%. For colour fundus photography plus VA,[24] sensitivity was low at 53.0% but again specificity was high at 94.0%.

Monitoring studies

Eight monitoring studies[23,28,30,32,43,45,52,53] were included (all full-text) involving over 400 participants. Seven reported the performance of OCT (five TD-OCT,[28,32,45,52,53] one SD-OCT,[30] one both types[23]) and one the performance of ICGA in the detection of nAMD activity.[43] As with the diagnostic studies, the QUADAS-2 domains with the greatest number of monitoring studies judged to be at high risk of bias were the patient selection domain (25%, 2/8)[30,45] and flow and timing domain (25%, 2/8),[45,52] for similar reasons to those reported above. In the index/comparator test domain and reference standard domain the risk of bias was judged to be unclear in 50% (4/8)[23,45,52,53] and 37.5% (3/8)[23,45,52] of studies respectively. Similar to the diagnostic studies, all of the monitoring studies were judged to be of low concern in terms of their applicability to the review question.

Four of the OCT studies provided sufficient data for inclusion in a meta-analysis.[23,28,30,53] The pooled sensitivity (95% CI) for all OCT was moderately high at 85% (72% to 93%) but with low specificity at 48% (30% to 67%). For TD-OCT,[23,28,53] the pooled sensitivity and specificity was moderate at 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates for the two SD-OCT studies[23,30] using HSROC methodology due to insufficient data. These studies reported sensitivities of 94%[30] and 90%[23] and specificities of 27%[30] and 47%.[23] These results suggest that SD-OCT has higher sensitivity but lower specificity than TD-OCT. In particular, the specificity of the SD-OCT monitoring studies was quite low.

Other than OCT, one study reported ICGA,[43] with sensitivity of 75.9% and specificity of 88.0% for the detection of active nAMD.

Strengths and limitations of the assessment

In terms of strengths, a comprehensive literature search was undertaken and non-English-language studies were included. Risk of bias was assessed using a modified QUADAS-2 questionnaire, tailored to the needs of this review. A HSROC model was used for the analysis, which takes account of the trade-off between TPs/FPs and models between-study heterogeneity.[84] The evidence for diagnosis and monitoring was considered separately. In addition to the pooled estimates for all OCT, separate pooled estimates were undertaken for TD-OCT (monitoring studies). It was not possible to undertake separate pooled estimates for SD-OCT as no SD-OCT studies were included in the diagnosis meta-analysis, and, in the monitoring meta-analysis, there were insufficient data from the two SD-OCT studies to use HSROC methods.

There was a very limited amount of evidence available for evaluating the performance of SD-OCT, both for diagnosis (one study) and for surveillance monitoring of those previous diagnosed with nAMD. There was also limited evidence for the performance of TD-OCT for surveillance monitoring. Although this review considered a number of alternative tests, only a few of these were reported by studies that met our inclusion criteria. There was insufficient information to address the questions of (1) the clinical effectiveness of OCT compared with FFA; (2) the acceptability of the tests; and (3) the performance of other health professionals compared with ophthalmologists in interpreting OCT findings.

Uncertainties

Reference standard

Fundus fluorescein angiography interpreted by an ophthalmologist was our reference standard test and as such was assumed to have perfect sensitivity and specificity for the detection of active nAMD. Therefore, it was not possible to address the question of whether or not OCT might actually have better sensitivity or specificity than FFA; the optimal judgement that could have been made about OCT was that it had equally high sensitivity and specificity as FFA. In fact, although OCT did have very high sensitivity, the specificity for diagnosis and monitoring was suboptimal.

Glasziou *et al.*[85] considered the question of when a new test should replace the existing reference standard. They suggested that this might be determined by a 'fair umpire' test applied to the cases where the new test and reference standard differed. This third test, although potentially less accurate than either the new test or reference standard, could be considered a fair umpire, if its errors were considered to be independent of the other tests, although it was acknowledged that this would usually be difficult to demonstrate. Possible umpires suggested included causal exposures, concurrent testing, prognosis, or response to treatment. Glasziou *et al.*[85] argued that using this approach, the umpire test might be able to distinguish which test was the better reference standard. An example given was that of a new test for tuberculosis, with the tuberculin skin test as the reference standard, interferon-γ enzyme-linked immunospot (ELISpot) assays as the new test and tuberculosis exposure as the fair umpire.[85] However, none of the studies included in our review provided a sufficient level of information to allow such a 'fair umpire' approach to be applied.

False positives

Excluding studies where information was only available for detection of phenotypes,[34,37,38,52] specificity for OCT was reported by six[23,28,30,32,45,53] of seven monitoring studies, but only 4[27,40,46,49] of 10 diagnostic studies.

As already reported, specificity for OCT for diagnosis was only moderate and for monitoring was lower, with a large number of FP results. A few studies provided some additional information on their FP results, with suggested reasons for these including the presence of a disciform scar with persistent cystic cavities,[45] an increase in the central subfield measurement,[27] drusen/atrophy,[46,49] cystoid abnormalities,[23] subretinal fluid being detected before FFA leakage was observed,[40] and the detection of remnants of intraretinal fluid that had not yet been resorbed even though the underlying CNV was no longer actively leaking fluid.[32] Do *et al.*[27] suggested that SD-OCT may have lower specificity for the detection of CNV than TD-OCT because it is more likely to detect structural changes in the retina, which may be a normal anatomic variant and not necessarily representative of secondary changes in the retina owing to CNV.

Sandhu and Talks[46] noted that the OCT FP rate was reduced with the addition of stereo colour images (separate test). In current practice OCT is typically associated with VA data which may improve the specificity of the test.

In two of the monitoring studies,[23,30] participants had been treated with antiVEGF therapy and in five[28,32,45,52,53] they were treated with PDT. For all OCT, median sensitivity was similar across the antiVEGF (90%) and PDT (88%) groups of studies, whereas median specificity was slightly higher across the PDT studies (51%) compared with the antiVEGF studies (43%). It is possible that following treatment with PDT there is less likelihood of having fluid in the retina than following therapy with antiVEGF, as fluid is a common feature in eyes treated with antiVEGF, even after many sessions of treatment. Currently PDT is rarely used for nAMD, but the reviewed literature reflects this older modality of treatment. OCT (especially the newer version with the highest resolution, SD-OCT) may detect fluid, even when only a small amount is present and it does not necessarily relate to CNV activity (e.g. fluid may be present if there is RPE dysfunction/damage as a result of the disease or its treatment, as in normal circumstances RPE pumps fluid out of the retina). Therefore, it is possible that there might be more OCT FPs resulting in lower specificity for detecting active nAMD following antiVEGF compared with PDT treatment.

In two diagnostic studies, by Kozak *et al.*[36] and Reichel *et al.*,[44] some patients were classed as having nAMD who were negative on FFA but positive on one of the other tests being assessed (13/541 eyes by TD-OCT in the Kozak *et al.* study[36] and 4/20 participants by ICGA in the Reichel *et al.*[44] study). For the purposes of this review, these cases were considered to be test FPs (as the reference standard of FFA was considered to have perfect sensitivity and specificity). However, in some cases (e.g. with retinal haemorrhage), it is possible that ICGA may be better than FFA in detecting nAMD.

Heterogeneity across the studies

Other than the fact that one group of studies was concerned with initial diagnosis of nAMD and another with monitoring of those previously diagnosed, there were a number of other differences across the studies. In terms of differences across the participant groups, the prevalence of nAMD in the diagnostic studies ranged from 17.2% to 100% (median 80.0%) and of active nAMD in the monitoring studies from 49.2% to 83.3% (median 57.9%). The proportion of participants classed as having specific nAMD phenotpyes (e.g. classic CNV, occult CNV) varied across the studies. In eight diagnostic studies[24,27,31,39,40,44,45,49] and one monitoring study[30] participants were judged to have been pre-selected.

Detection of phenotypes

Twelve studies (eight diagnostic,[25,33,34,37,38,41,46,49] four monitoring[23,30,32,52]) reported the sensitivity of OCT in the detection of nAMD phenotypes (predominantly classic, minimally classic, occult or RAP). None of the studies reported detection of IPCV. Results were mixed and overall there was insufficient evidence to understand whether or not the performance of OCT differs among the different phenotypes.

The monitoring study by Giani *et al.*[30] (SD-OCT) reported high sensitivity for the detection of both classic and occult CNV activity (90.9% and 100% respectively).

Across four (TD-OCT) diagnostic studies[25,34,37,38] reporting detection of RAP the median (range) sensitivity was 65% (50–100%). Of the monitoring studies, Khurana *et al.*[23] reported higher sensitivity for SD-OCT (59%) compared with TD-OCT (35%) for detecting retinal cystoid abnormalities, whereas van de Moere *et al.*[52] reported poor sensitivity for TD-OCT for detecting cystoid macular oedema (23%) and PED (6%).

Unit of analysis issues

Twelve OCT studies used one eye per patient in the analysis.[25,27,28,30,33–35,38,40,49,52,53] In three of these studies[25,27,40] the inclusion criteria stipulation for the fellow eye meant that only one (study) eye per subject was eligible for analysis. In the remaining studies, the inclusion criteria were such that both eyes of some subjects might have been potentially eligible.[23,36,37,41,45,46] Of these, however, only the study by van de Moere *et al.*[52] reported the method used for selecting the study eye in the event of such a situation, stating that if both eyes were eligible one eye was randomly chosen for analysis. It was unclear from the other studies whether only one eye per subject had met the inclusion criteria or whether for some subjects both eyes were eligible but only one was selected.

In six OCT studies, both eyes of some participants met the inclusion criteria and were included in the analysis;[23,36,37,41,45,46] however, none of these studies mentioned the issue of the possible influence that the non-independence of the fellow eye might have on the analysis.

All studies included in the meta-analyses used one eye per subject, apart from the study by Sandhu and Talks[46] (meta-analysis of diagnostic studies) and the study by Khurana *et al.*[23] (meta-analysis of monitoring studies). In the study by Sandhu and Talks,[46] 131 eyes of 118 patients were included in the analysis, as 13 patients had bilateral activity. In the study by Khurana *et al.*,[23] 59 eyes of 56 patients were included in the analysis, as three patients had received antiVEGF treatment for nAMD in both eyes. These studies did not report whether or not any adjustment had been made to take account of the non-independence of the fellow eye and contained an insufficient level of detail to allow for an exploration of this issue. However, the potential impact of fellow eye non-independence would probably be minor, at most, given the small number of subjects in the two studies for whom both eyes were included in the analysis.

Other relevant factors

Ongoing studies

No ongoing studies were identified of OCT or alternative tests of interest compared with a reference standard of FFA for the diagnosis, monitoring and guiding of treatment for nAMD.

Comparison of our results with other systematic reviews/health technology assessments

Our searches identified four HTA reports that included an assessment of OCT in the detection of nAMD.[14,86–88] The German HTA report by Stürzlinger *et al.*[87] (report summary in English, full text in German), published in 2007, considered head-to-head comparisons between OCT and FFA for newly presenting patients. Eight studies were included, of which three were included in our review.[33,35,46] The other five studies did not meet our inclusion criteria (assessment of RPE tear,[89] retinal PED,[90] drusen,[91] geographic atrophy,[92] and no diagnostic outcomes reported).[93] The report's conclusions were that although OCT yielded diagnostic findings in addition to FFA results, OCT could not replace FFA during the primary diagnostic procedure.

The Belgian Health Care Knowledge Centre report by Van den Bruel *et al.*,[88] published in 2008, considered five ophthalmic tests in clinical practice, including OCT. The assessment identified the German HTA report and included an additional three studies,[28,37,45] all three of which were included in our review.

The review considered FFA as the reference standard for neovascular AMD, and, similar to our review, reported high sensitivity (96–97%) and moderate specificity (66%) of OCT in detecting CNV.

In the Australian Medical Services Advisory Committee (MSAC) report,[86] published in 2009, OCT was compared (a) with FFA or clinical observation in the diagnosis of macular diseases; (b) in addition to FFA and clinical examination in the monitoring of patients with macular diseases; (c) in addition to computerised perimetry and clinical examination in the diagnosis of glaucoma; and (d) in addition to computerised perimetry and clinical examination in the monitoring of patients with glaucoma. Regarding the diagnostic accuracy of OCT for AMD, the MSAC report concluded that due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of macular abnormalities could not be assessed. This approach contradicted our study, the German and Belgian HTA reports and also current practice in the UK where FFA is considered the reference standard for the diagnosis of nAMD.

In the evidence-based analysis by the Medical Advisory Secretariat, Ontario, Canada,[14] published in 2009, OCT was compared with the reference standard of FFA for AMD and diabetic macular oedema. The evaluation summarised the German HTA report and the study by Sandhu and Talks[46] that was also included in our review. This report also questioned the validity of FFA as a reference standard and presented conclusions that were based on expert consultations.

Aflibercept

In May 2013, NICE published final draft guidance recommending aflibercept solution for injection as an option for treating nAMD (www.nice.org.uk/guidance/ta294). Full guidance was published in July 2013 (www.nice.org.uk/guidance/ta294/resources/guidance-aflibercept-solution-for-injection-for-treating-wet-agerelated-macular-degeneration-pdf). The treatment and monitoring schedule for this drug differs from that of ranibizumab. According to the summary of product characteristics for aflibercept, treatment should be given monthly for three consecutive 2-mg doses, followed by one injection every 2 months, with no need for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes, with the schedule for monitoring determined by the treating doctor. In terms of the economic model, extending the length of time between monitoring visits would reduce the cost associated with monitoring as well as the number of treatment courses needed. However, this would be expected to affect all model strategies in a similar manner and therefore would be unlikely to modify the general conclusions from the economic analysis. This might nevertheless reduce the cost associated with treatment and monitoring of nAMD patients for the NHS.

Future technological developments

It is likely that future technological developments in OCT will be introduced. Most OCT devices create cross-sectional images of the retina. En-face OCT technology is an emerging imaging technique derived from SD-OCT that creates images of frontal sections of retinal layers that are compatible with conventional fundus images.

Another emerging technique is OCT angiography, which uses high-speed Fourier-domain OCT for non-invasive three-dimensional imaging of the vasculature and blood flow at the posterior part of the eye.

Cost-effectiveness

Statement of principal findings

No studies met the inclusion criteria for the systematic review of economic evaluations as none compared diagnostic or monitoring strategies for individuals with nAMD.

Nine strategies that used to a different extent OCT for diagnosis and/or monitoring of nAMD individuals were considered within the Markov cohort economic evaluation model. The strategy that based its diagnosis decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse

or technician as the first monitoring step, with a referral to an ophthalmologist if the first monitoring assessment was positive or unclear ('FFA & Nurse'), had the lowest expected total cost. This strategy dominated (i.e. lower expected costs and higher expected QALYs) all others apart from one: diagnosis with FFA only, combined with monitoring by an ophthalmologist ('FFA & Ophthalmologist'). The 'FFA & Nurse' and 'FFA & Ophthalmologist' strategies had, respectively, a 46.5% and 29.8% probability of being cost-effective at the £30,000 threshold value of willingness to pay for an extra QALY. In addition, the 'FFA & Nurse' strategy dominated all others in the great majority of sensitivity analyses.

The strategies that used OCT only for their monitoring decisions were, in almost every model run, ordered last in terms of ascending total expected cost and were often dominated by others. The strategy that used OCT as its only criteria for diagnosis and monitoring decisions was in almost every model run the most costly strategy.

Results were sensitive to the unit cost of treatment injections. A scenario with a lower unit cost for treatment (e.g. £50, equivalent to the cost of bevacizumab, instead of £742 considered for the base-case analysis) resulted in the FFA only for diagnosis combined with OCT only for monitoring strategy having the lowest total expected cost. Alternative strategies were either dominated or had an ICER well above the usual threshold stated for cost-effectiveness (i.e. £30,000).

Strengths and limitations of the economic assessment

The major strength of the economic evaluation is that it attempted to use the best available evidence with the compared strategies developed from extensive discussions within the project team and advisory group. Best practice guidelines were followed for this economic evaluation exercise.[73] For instance, test performance data were obtained from the systematic review of the literature with other data retrieved from focused but reproducible searches. There is, however, an inherent problem with model-based economic evaluations that incorporate evidence from several sources, even when these data have been retrieved systematically.

The economic model needed to consider individuals' disease status (i.e. active or inactive nAMD) as well as test results on a monthly basis. In addition, these had to be combined with alternative VA states in order to incorporate utility weights into the model. It was felt that considering the effect of fellow eye status (VA and nAMD status) would add major complexity to the model without much benefit from this incorporation. A clear limitation of the so-called 'one eye models' is the underestimation of resources used. A proportion of nAMD individuals will have this condition in both eyes instead of one eye and would need treatment injections in each eye should the disease be active. In the current model this would increase the cost for those strategies with higher numbers of FPs (i.e. lower specificity) and therefore would be unlikely to modify the general conclusions of this study. A 'one eye model' has also been adopted by other teams involved in economic evaluations in this health area.[61]

The model did not consider effects on utility due to treatment injections. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to the uncertainty of the underlying condition (i.e. active or inactive nAMD) and not the effects of the treatment injections. No evidence was obtained on this from the utility weight searches. However, utility weight decrements from adverse effects as a result of the treatment were included and this might partially overcome the above-mentioned potential limitation. The model did not consider factors relating to patient experience of alternative monitoring schemes. As such, there was no consideration of the process of care on patient preferences and only the effect of VA and the adverse effects of treatment on individual utility were incorporated into the model.

Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Data were retrieved from the literature, from a UK-based RCT (Dr Chris Rogers, personal communication) and expert opinion. In addition, progression data on VA were based on the 2-year follow-up MARINA study.[69] All these data were based on short follow-up but in a number of cases extrapolated to a lifetime time horizon. These clear limitations

of the analysis indicate that its results should be interpreted with caution. Further research looking at the individual's nAMD active/inactive status is desirable. A conditional or a retrospective analysis of existing data sets would be helpful in order to obtain data to inform future economic models.

The analysis was conducted from the NHS and Personal Social Services perspective, incorporating cost of visual impairment that considered, for instance, cost for community care and residential care. The model, however, did not take into account the cost for patients or their carers. For instance, as this is likely to be an elderly population, someone might accompany the patient for their monitoring visits. These costs have not been considered in the model.

Uncertainties of the economic analysis

Undoubtedly, the limitations of the data together with the assembly of key data of varied quality are of most concern. No SD-OCT studies contributed to the diagnosis performance data and only two SD-OCT studies[23,30] contributed to the monitoring performance data in the economic model. Moreover, although OCT diagnosis and monitoring sensitivity and specificity data were retrieved from a systematic review of the literature, no such data were available for other tests proposed in alternative diagnosis or monitoring pathways (e.g. examination by the ophthalmologist or the monitoring assessment by a nurse or technician). Therefore, data for the model were obtained from expert opinion. These constitute major limitations of the analysis and further research in these areas is needed.

Chapter 8 Conclusions

Implications for service provision

In terms of OCT test performance, the evidence, which was limited in quantity, especially for monitoring studies, and variable in quality, suggests that:

- For diagnosis of newly suspected nAMD, OCT has high sensitivity (88%) and moderate specificity (78%) (meta-analysis)
- For monitoring of those previously diagnosed with nAMD, OCT has relatively high sensitivity (85%) but low specificity (48%) (meta-analysis)
- SD-OCT had higher sensitivity than TD-OCT but lower specificity (monitoring studies).

The strategy that based its diagnostic decision on the results of FFA only, combined with a nurse- or technician-led stepwise approach for monitoring, had the lowest expected total cost and a 47% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. In addition, this strategy dominated all others apart from one (i.e. diagnosis with FFA combined with stepwise ophthalmologist-led monitoring) in the great majority of sensitivity analyses. The economic evaluation results suggest that strategies that used OCT test results alone to make diagnosis or monitoring treatment decisions were unlikely to be a cost-effective use of resources. This seems to be driven by the OCT low specificity inducing a high number of individuals with FP test results being treated.

There has already been a shift in the diagnostic and monitoring pathways for nAMD caused by the adoption of OCT. At the diagnostic stage, OCT is currently used in addition to FFA (reference standard), whereas for monitoring it has largely replaced FFA, which is only used in selected circumstances. The evidence suggests that using OCT as the only test for monitoring patients with nAMD and detecting activity would, potentially, result in a substantial proportion of patients receiving treatment unnecessarily with intraocular injections of antiVEGF.

The continuing rise in the ageing population, with increasing numbers of people being diagnosed with nAMD and moving on to monitoring for renewed disease activity, will continue to present challenges for ophthalmology departments to have sufficient capacity to provide timely testing, and treatment.

Suggested research priorities

- Regarding monitoring of nAMD, in current practice OCT is routinely used and FFA is used only in particular scenarios. There is a substantial disagreement between OCT and FFA. There is a need to research if OCT (without FFA) is an acceptable way of detecting active nAMD and guiding treatment. As there is the theoretical possibility of OCT being better in some cases than the current reference standard, such studies might be designed to include a 'fair umpire' test, if available, to examine differences between OCT and FFA, or should be designed to incorporate a period of follow-up to assess the consequences of the tests in terms of clinical effectiveness outcomes (e.g. VA). Currently used SD-OCT models should be evaluated, rather than TD-OCT.
- Regarding diagnosis of nAMD, current practice consists of FFA (as reference standard) associated with OCT. Further research should be considered to establish the added value of OCT, and whether or not OCT (associated with SLB and VA) can fully replace FFA. As above, such studies might be designed to include a 'fair umpire' test, or the evaluation of the consequences of the diagnostic intervention. Currently used SD-OCT models should be evaluated, rather than TD-OCT.

- Regarding the different phenotypes of nAMD, further evidence on the natural history, efficacy of treatment and diagnostic performance of OCT according to phenotype of nAMD is required.
- For both diagnosis and monitoring of nAMD, prospective studies are required to assess the diagnostic accuracy and clinical effectiveness of strategies involving possible different combinations and sequences of tests (e.g. VA, SLB, FAF imaging, OCT), including a comparison of their interpretation by ophthalmologists compared with other health professionals.
- To strengthen the evidence base used to develop the economic model, it would be important to explore the likelihood of active and inactive nAMD individuals becoming inactive or active respectively. In addition, a preference-based study to assess utility weights (e.g. decrements) associated with treatment and frequent monitoring is needed.
- Further research is needed to evaluate health status (utilities) in patients with nAMD, taking into consideration the visual function and spectrum of disease in both eyes and exploring the value added by inclusion of fellow eye information.

Acknowledgements

We thank David Findlay Clark (service user with the condition), Graham Findlay (Chief Executive, North East Sensory Services) and Helen Jackman (Chief Executive, Macular Society) for providing valuable consumer insight and advice, and for commenting on the *Plain English summary*, and Malcolm McPherson (Community Optometrist) for providing a community optometrist perspective, through their participation as members of the study's project advisory group; Usha Chakravarthy, Chris Rogers and colleagues for providing data from the IVAN trial; Mari Imamura and Xueli Jia for translating non-English language papers; and Lara Kemp for secretarial support.

The economic model developed for the analysis was informed by an existing economic model developed by the Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, UK. The intellectual property rights associated with the SHTAC economic model are owned by the University of Southampton (UK) – all rights reserved. We thank Andrew Clegg and Jeremy Jones for providing access to the SHTAC AMD economic evaluation model (see www.southampton.ac.uk/shtac/research/published/eyediseases.page?).

This report was commissioned by the National Institute for Health Research (NIHR) HTA Programme as project number 10/57/22. The Health Services Research Unit and Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, are core-funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The views and opinions expressed are those of the authors and do not necessarily reflect those of the funders.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Contributions of authors

Graham Mowatt (coprincipal investigator, Senior Research Fellow) co-ordinated the study and wrote the decision problem, methods and assessment of diagnostic and monitoring studies chapters and sections of the scientific summary, discussion and conclusions chapters.

Rodolfo Hernández (Research Fellow) conducted the economic evaluation and wrote the cost-effectiveness chapter and sections of the scientific summary, discussion and conclusions chapters.

Mayret Castillo (Research Assistant) led the day-to-day running of the study and reviewed the evidence on test performance with assistance from **Graham Mowatt** and **Augusto Azuara-Blanco**.

Noemi Lois (Professor of Ophthalmology) wrote sections of the background and factors relevant to the NHS and other parties chapters.

Andrew Elders (Statistician) provided statistical support.

Cynthia Fraser (Information Specialist) developed and ran the search strategies, managed the reference database and formatted references.

Olatunde Aremu (Research Fellow) was involved with the initial development of the economic model (model conceptualisation), with supervision from **Rodolfo Hernández**.

Noemi Lois, **Augusto-Azuara-Blanco**, **Winfried Amoaku** (Clinical Associate Professor and Reader in Ophthalmology and Visual Sciences), **Jennifer Burr** (Reader) and **Andrew Lotery** (Professor of Ophthalmology) provided expert advice on clinical aspects of the study.

Craig Ramsay (Health Care Assessment Programme Director) and **Jennifer Burr** provided advice on methodological aspects of the study.

Augusto Azuara-Blanco (coprincipal investigator, Professor of Ophthalmology) jointly co-ordinated the study with Graham Mowatt, wrote the background and factors relevant to the NHS and other parties chapters, sections of the scientific summary, discussion and conclusions chapters, and was responsible for the final editing.

All authors commented on drafts of the report.

References

1. Royal College of Ophtalmologists. *Age-Related Macular Degeneration – Guidelines for Management*. London: Royal College of Ophthalmologists; 2013. URL: www.rcophth.ac.uk/page.asp?section=451 (accessed August 2014).
2. Imamura Y, Engelbert M, Iida T, Freund KB, Yannuzzi LA. Polypoidal choroidal vasculopathy: a review. *Surv Ophthalmol* 2010;**55**:501–15. http://dx.doi.org/10.1016/j.survophthal.2010.03.004
3. Obata R, Yanagi Y, Kami J, Takahashi H, Inoue Y, Tamaki Y. Polypoidal choroidal vasculopathy and retinochoroidal anastomosis in Japanese patients eligible for photodynamic therapy for exudative age-related macular degeneration. *Jpn J Ophthalmol* 2006;**50**:354–60. http://dx.doi.org/10.1007/s10384-005-0337-2
4. Minassian DC, Reidy A, Lightstone A, Desai P. Modelling the prevalence of age-related macular degeneration (2010–2020) in the UK: expected impact of anti-vascular endothelial growth factor (VEGF) therapy. *Br J Ophthalmol* 2011;**95**:1433–6. http://dx.doi.org/10.1136/bjo.2010.195370
5. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* 2012;**96**:752–6. http://dx.doi.org/10.1136/bjophthalmol-2011-301109
6. Augood CA, Vingerling JR, de Jong PT, Chakravarthy U, Seland J, Soubrane G, *et al.* Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). *Arch Ophthalmol* 2006;**124**:529–35. http://dx.doi.org/10.1001/archopht.124.4.529
7. National Insititute for Health and Care Excellence (NICE). *Pegaptanib and Ranibizumab for the Treatment of Age-Related Macular Degeneration. NICE Technology Appraisal Guidance TA155*. London: NICE; 2008. URL: http://guidance.nice.org.uk/TA155/Guidance/pdf/English (accessed June 2013).
8. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, *et al.* Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;**119**:1388–98. http://dx.doi.org/10.1016/j.ophtha.2012.03.053
9. Ivan SI, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, *et al.* Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;**119**:1399–411. http://dx.doi.org/10.1016/j.ophtha.2012.04.015
10. Holz FG, Korobelnik JF, Lanzetta P, Mitchell P, Schmidt-Erfurth U, Wolf S, *et al.* The effects of a flexible visual acuity-driven ranibizumab treatment regimen in age-related macular degeneration: outcomes of a drug and disease model. *Invest Ophthalmol Vis Sci* 2010;**51**:405–12. http://dx.doi.org/10.1167/iovs.09-3813
11. Department of Health. *NHS Reference Costs 2011–12*. London: Department of Health; 2012. URL: www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 (accessed May 2013).
12. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No. 65, 2013. London: BMA and RPS; 2013.
13. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;**117**:2134–40. http://dx.doi.org/10.1016/j.ophtha.2010.02.032

14. Medical Advisory Secretariat. *Optical Coherence Tomography for Age-Related Macular Degeneration and Diabetic Macular Edema: An Evidence-Based Analysis. Ont Health Technol Assess Ser* 2009;**9**(13). URL: www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_oct_20090925.pdf (accessed June 2013).
15. Office for National Statistics. *Statistical Bulletin: 2011 Census – Population and Household Estimates for England and Wales, March 2011*. 2011. URL: www.ons.gov.uk/ons/rel/census/2011-census/population-and-household-estimates-for-england-and-wales/stb-e-w.html (accessed June 2013).
16. Office for National Statistics. *Interim Life Tables.* London: UK Government Actuary's Department; 2013. URL: www.gad.gov.uk/Demography%20Data/Life%20Tables/index.html (accessed May 2013).
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36. http://dx.doi.org/10.7326/0003-4819-155-8-201110180-00009
18. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration; 2011. URL: www.cochrane-handbook.org/ (accessed April 2013).
19. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;**20**:2865–84. http://dx.doi.org/10.1002/sim.942
20. Deeks J. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001;**323**:157–62. http://dx.doi.org/10.1136/bmj.323.7305.157
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88. http://dx.doi.org/10.1016/0197-2456(86)90046-2
22. The Cochrane Collaboration. *Glossary of Cochrane Terms.* Oxford: The Cochrane Collaboration; 2013. URL: www.cochrane.org/glossary (accessed June 2013).
23. Khurana RN, Dupas B, Bressler NM. Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. *Ophthalmology* 2010;**117**:1376–80. http://dx.doi.org/10.1016/j.ophtha.2009.11.039
24. Alster Y, Bressler NM, Bressler SB, Brimacombe JA, Crompton RM, Duh YJ, *et al.* Preferential hyperacuity perimeter (PreView PHP) for detecting choroidal neovascularization study. *Ophthalmology* 2005;**112**:1758–65. http://dx.doi.org/10.1016/j.ophtha.2005.06.008
25. Cachulo L, Silva R, Fonseca P, Pires I, Carvajal-Gonzalez S, Bernardes R, *et al.* Early markers of choroidal neovascularization in the fellow eye of patients with unilateral exudative age-related macular degeneration. *Ophthalmologica* 2011;**225**:144–9. http://dx.doi.org/10.1159/000321064
26. Chen S, Han M, Wang L. Indocyanine green angiography of exudative age-related macular degeneration. *Chin Ophthalmic Res* 2003;**21**:428–30.
27. Do DV, Gower EW, Cassard SD, Boyer D, Bressler NM, Bressler SB, *et al.* Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study. *Ophthalmology* 2012;**119**:771–8. http://dx.doi.org/10.1016/j.ophtha.2011.10.019
28. Eter N, Spaide RF. Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. *Retina* 2005;**25**:691–6. http://dx.doi.org/10.1097/00006982-200509000-00002
29. Fujii C, Inobe K, Sugimoto Y, Sugimoto A, Takahashi Y, Akagi Y. Indocyanine green angiographic findings in eyes with age-related macular degeneration. *Folia Ophthalmol Japonica* 1996;**47**:300–5.

30. Giani A, Luiselli C, Esmaili DD, Salvetti P, Cigada M, Miller JW, *et al.* Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. *Invest Ophthalmol Vis Sci* 2011;**52**:5579–86. http://dx.doi.org/10.1167/iovs.10-6617

31. Gomi F, Sawa M, Mitarai K, Tsujikawa M, Tano Y. Angiographic lesion of polypoidal choroidal vasculopathy on indocyanine green and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1421–7. http://dx.doi.org/10.1007/s00417-007-0564-y

32. Henschel A, Spital G, Lommatzsch A, Pauleikhoff D. Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. *Eur J Ophthalmol* 2009;**19**:831–5.

33. Hughes EH, Khan J, Patel N, Kashani S, Chong NV. In vivo demonstration of the anatomic differences between classic and occult choroidal neovascularization using optical coherence tomography. *Am J Ophthalmol* 2005;**139**:344–6. http://dx.doi.org/10.1016/j.ajo.2004.07.058

34. Khondkaryan A, Keane PA, Liakopoulos S, Walsh AC, Sadda SR. Comparison of optical coherence tomography and fluorescein angiography for the classification of neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2009;**50**:E-abstract 5259.

35. Kim SG, Lee SC, Seong YS, Kim SW, Kwon OW. Choroidal neovascularization characteristics and its size in optical coherence tomography. *Yonsei Med J* 2003;**44**:821–7.

36. Kozak I, Morrison VL, Clark TM, Bartsch DU, Lee BR, Falkenstein I, *et al.* Discrepancy between fluorescein angiography and optical coherence tomography in detection of macular disease. *Retina* 2008;**28**:538–44. http://dx.doi.org/10.1097/IAE.0b013e318167270b

37. Krebs I, Binder S, Stolba U, Krepler K, Zeiler F, Glittenberg C. The value of optical coherence tomography in diagnosis and therapy of age-related macular degeneration. *Spektrum der Augenheilkunde* 2007;**21**:33–8. http://dx.doi.org/10.1007/s00717-006-0169-6

38. Liakopoulos S, Ongchin S, Bansal A, Msutta S, Walsh AC, Updike PG, *et al.* Quantitative optical coherence tomography findings in various subtypes of neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2008;**49**:5048–54. http://dx.doi.org/10.1167/iovs.08-1877

39. Loewenstein A, Ferencz JR, Lang Y, Yeshurun I, Pollack A, Siegal R, *et al.* Toward earlier detection of choroidal neovascularization secondary to age-related macular degeneration: multicenter evaluation of a preferential hyperacuity perimeter designed as a home device. *Retina* 2010;**30**:1058–64. http://dx.doi.org/10.1097/IAE.0b013e3181d1a75e

40. Padnick-Silver L, Weinberg AB, Lafranco FP, MacSai MS. Pilot study for the detection of early exudative age-related macular degeneration with optical coherence tomography. *Retina* 2012;**32**:1045–56. http://dx.doi.org/10.1097/IAE.0b03e31823fb82b

41. Park SS, Truong SN, Zawadzki RJ, Alam S, Choi SS, Telander DG, *et al.* High-resolution Fourier-domain optical coherence tomography of choroidal neovascular membranes associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2010;**51**:4200–6. http://dx.doi.org/10.1167/iovs.09-4256

42. Parravano M, Varano M, Virgili G. Integrated imaging approach in RAP diagnosis. *Acta Ophthalmol (Copenh)* 2012;**90**:abstract no. 4426.

43. Regillo CD, Blade KA, Custis PH, O'Connell SR. Evaluating persistent and recurrent choroidal neovascularization. The role of indocyanine green angiography. *Ophthalmology* 1998;**105**:1821–6. http://dx.doi.org/10.1016/S0161-6420(98)91022-3

44. Reichel E, Duker JS, Puliafito CA. Indocyanine green angiography and choroidal neovascularization obscured by hemorrhage. *Ophthalmology* 1995;**102**:1871–6. http://dx.doi.org/10.1016/S0161-6420(95)30781-6

45. Salinas-Alaman A, Garcia-Layana A, Maldonado MJ, Sainz-Gomez C, Alvarez-Vidal A. Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. *Am J Ophthalmol* 2005;**140**:23–8. http://dx.doi.org/10.1016/j.ajo.2005.01.044

46. Sandhu SS, Talks SJ. Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. *Br J Ophthalmol* 2005;**89**:967–70. http://dx.doi.org/10.1136/bjo.2004.060863

47. Silva R, Cachulo ML, Fonseca P, Bernardes R, Nunes S, Vilhena N, *et al.* Age-related macular degeneration and risk factors for the development of choroidal neovascularisation in the fellow eye: a 3-year follow-up study. *Ophthalmologica* 2011;**226**:110–18. http://dx.doi.org/10.1159/000329473

48. Sulzbacher F, Kiss C, Munk M, Deak G, Sacu S, Schmidt-Erfurth U. Diagnostic evaluation of type 2 (classic) choroidal neovascularization: optical coherence tomography, indocyanine green angiography, and fluorescein angiography. *Am J Ophthalmol* 2011;**152**:799–806e1. http://dx.doi.org/10.1016/j.ajo.2011.04.011

49. Talks J, Koshy Z, Chatzinikolas K. Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration. *Br J Ophthalmol* 2007;**91**:600–1. http://dx.doi.org/10.1136/bjo.2006.108043

50. Torron FB, Melcon SF, Ferrer N, Ruiz M, Honrubia L. Indocyanine green angiography and subretinal neovascularization. Patterns in age related macular degeneration. *Arch Soc Esp Oftalmol* 2001;**76**:221–8.

51. Torron FB, Perez O, Melcon SF, Ferrer N, Ruiz-Moreno O, Honrubia L. Dynamic angiography in age related macular degeneration. *Arch Soc Esp Oftalmol* 2002;**77**:353–9.

52. van de Moere A, Sandhu SS, Talks SJ. Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. *Br J Ophthalmol* 2006;**90**:304–6. http://dx.doi.org/10.1136/bjo.2005.079947

53. van Velthoven ME, de Smet MD, Schlingemann RO, Magnani M, Verbraak FD. Added value of OCT in evaluating the presence of leakage in patients with age-related macular degeneration treated with PDT. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:1119–23. http://dx.doi.org/10.1007/s00417-005-0209-y

54. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1994;**271**:389–91. http://dx.doi.org/10.1001/jama.1994.03510290071040

55. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes.* 3rd edn. Oxford: Oxford University Press; 2005.

56. Amoaku W, Blakeney S, Freeman M, Gale R, Johnston R, Kelly SP, *et al.* Action on AMD. Optimising patient management: act now to ensure current and continual delivery of best possible patient care. *Eye* 2012;**26**:S2–21. http://dx.doi.org/10.1038/eye.2011.343

57. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004;**9**:110–18. http://dx.doi.org/10.1258/135581904322987535

58. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ* 2006;**15**:1295–310. http://dx.doi.org/10.1002/hec.1148

59. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, *et al.* State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Value Health* 2012;**15**:812–20. http://dx.doi.org/10.1016/j.jval.2012.06.014

60. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;**13**:322–38. http://dx.doi.org/10.1177/0272989X9301300409

61. Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(16).

62. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation.* Oxford: Oxford University Press; 2006.

63. Briggs A. Handling Uncertainty in Economic Evaluation and Presenting the Results. In Drummond M, McGuire A, editors. *Economic Evaluation in Health Care: Merging Theory with Practice.* Oxford: Oxford University Press; 2001. pp. 172–214.

64. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, *et al.* Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value Health* 2012;**15**:835–42. http://dx.doi.org/10.1016/j.jval.2012.04.014

65. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology* 2002;**109**:1092–7. http://dx.doi.org/10.1016/S0161-6420(02)01055-2

66. van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT. The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study. *Arch Ophthalmol* 2003;**121**:519–26. http://dx.doi.org/10.1001/archopht.121.4.519

67. Thiagarajan M, Evans JR, Smeeth L, Wormald RP, Fletcher AE. Cause-specific visual impairment and mortality: results from a population-based study of older people in the United Kingdom. *Arch Ophthalmol* 2005;**123**:1397–403. http://dx.doi.org/10.1001/archopht.123.10.1397

68. Xu L, Wang YX, Wang J, Jonas JJ. Mortality and ocular diseases: the Beijing Eye Study. *Ophthalmology* 2009;**116**:732–8. http://dx.doi.org/10.1016/j.ophtha.2008.11.003

69. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al.* Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31. http://dx.doi.org/10.1056/NEJMoa054481

70. Horster R, Ristau T, Sadda SR, Liakopoulos S. Individual recurrence intervals after anti-VEGF therapy for age-related macular degeneration. *Graefes Arch Clin Exp Ophthal* 2011;**249**:645–52. http://dx.doi.org/10.1007/s00417-010-1588-2

71. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**:1201–4. http://dx.doi.org/10.1136/bjo.87.10.1201

72. Curtis L. *Unit Costs of Health and Social Care 2012*. Canterbury: Personal Social Services Research Unit; 2012. URL: www.pssru.ac.uk/project-pages/unit-costs/2012/ (accessed May 2013).

73. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal*. London: NICE; 2013. URL: www.nice.org.uk/article/PMG9/chapterhttp://www.nice.org.uk/article/PMG9/ (accessed June 2013).

74. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:47–51. http://dx.doi.org/10.1001/archopht.118.1.47

75. Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. *Ophthalmology* 2007;**114**:1170–8. http://dx.doi.org/10.1016/j.ophtha.2006.09.019

76. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–15. http://dx.doi.org/10.1002/hec.903

77. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19. http://dx.doi.org/10.1002/hec.4730030505

78. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. *Value Health* 2009;**12**:793–9. http://dx.doi.org/10.1111/j.1524-4733.2009.00527.x

79. NHS England. *General Ophthalmic Services: Increases to NHS Sight Test Fee*. Redditch: NHS England; 2013. URL: www.england.nhs.uk/wp-content/uploads/2013/04/sight-test-fee.pdf (accessed June 2013).

80. *The General Ophthalmic Services Contracts (Payments) Directions 2013*. Redditch: NHS, England; 2013. URL: www.england.nhs.uk/wp-content/uploads/2013/04/gos-pay-dir.pdf (accessed June 2013).

81. Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. *BMJ* 2011;**342**:d1766. http://dx.doi.org/10.1136/bmj.d1766

82. Rechel B, Grundy E, Robine JM, Cylus J, Mackenbach JP, Knai C, *et al.* Ageing in the European Union. *Lancet* 2013;**381**:1312–22. http://dx.doi.org/10.1016/S0140-6736(12)62087-X

83. Chakravarthy U, Evans J, Rosenfeld PJ. Age related macular degeneration. *BMJ* 2010;**340**:526–30.

84. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;**149**:889–97. http://dx.doi.org/10.7326/0003-4819-149-12-200812160-00008

85. Glasziou P, Irwig L, Deeks JJ. When should a new test become the current reference standard? *Ann Intern Med* 2008;**149**:816–22. http://dx.doi.org/10.7326/0003-4819-149-11-200812020-00009

86. *Optical Coherence Tomography MSAC Application 1116*. Canberra: Medical Services Advisory Committee (MSAC); 2009. URL: www.msac.gov.au/internet/msac/publishing.nsf/Content/app1116-1 (accessed June 2013).

87. Stürzlinger H, Fröschl B, Genser D. *Evaluation of Optical Coherence Tomography in the Diagnosis of Age Related Macular Degeneration Compared with Fluorescence Angiography*. Cologne: The German Agency for Health Technology Assessment (DAHTA); 2007. URL: http://portal.dimdi.de/de/hta/hta_berichte/hta149_bericht_de.pdf (accessed June 2013).

88. Van den Bruel A, Gailly J, Vijens F, Devriese S. *Guidance for the Use of Five Ophthalmic Tests in Clinical Practice KCE reports 71C.* Brussels: The Belgian Health Care Knowledge Centre (KCE); 2008. URL: https://kce.fgov.be/publication/report/guidance-for-the-use-of-five-ophthalmic-tests-in-clinical-practice (accessed June 2013).

89. Giovannini A, Amato G, Mariotti C, Scassellati-Sforzolini B. Optical coherence tomography in the assessment of retinae pigment epithelial tear. *Retina* 2000;**20**:37–40. http://dx.doi.org/10.1097/00006982-200001000-00007

90. Sato T, Iida T, Hagimura N, Kishi S. Correlation of optical coherence tomography with angiography in retinal pigment epithelial detachment associated with age-related macular degeneration. *Retina* 2004;**24**:910–14. http://dx.doi.org/10.1097/00006982-200412000-00011

91. Hassenstein A, Ruhl R, Richard G. OCT in age related macular degeneration and differential diagnosis. *Spektrum der Augenheilkunde* 2000;**14**:209–13. http://dx.doi.org/10.1007/BF03162805

92. Hassenstein A, Ruhl R, Richard G. [Optical coherence tomography in geographic atrophy – a clinicopathologic correlation.] *Klin Monatsbl Augenheilkd* 2001;**218**:503–9. http://dx.doi.org/10.1055/s-2001-16293

93. Ting TD, Oh M, Cox TA, Meyer CH, Toth CA. Decreased visual acuity associated with cystoid macular edema in neovascular age-related macular degeneration. *Arch Ophthalmol* 2002;**120**:731–7. http://dx.doi.org/10.1001/archopht.120.6.731

Appendix 1 Search strategies

Clinical effectiveness and diagnostic accuracy of optical coherence tomography for age-related macular degeneration

EMBASE, Ovid MEDLINE(R) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Searched: 1988 to 2013 Week 12 (EMBASE), 1946 to March Week 2 2013 [Ovid MEDLINE(R)] and 25 March 2013 [Ovid MEDLINE(R)] (In-Process & Other Non-Indexed Citations).

Ovid multifile search. URL: https://shibboleth.ovid.com/.

Date of search: 25 March 2013.

Search strategy

1. (*macular degeneration/ or wet macular degeneration/) use mesz
2. macular edema/ not (diabetic or diabetes).hw.
3. (*retina macula age related degeneration/ or exudative macular degeneration/) use emed
4. retinal hemorrhage/ use mesz or choroid hemorrhage/ use mesz
5. retina haemorrhage/ use emed or choroid haemorrhage/ use emed
6. choroidal neovascularization/ use mesz
7. subretinal neovascularization/ use emed
8. retinal neovascularization/ use mesz not (diabetes or diabetic).hw.
9. retina neovascularization/ use emed not (diabetes or diabetic).hw.
10. ((exudative or wet or neovascular) and amd).tw.
11. ((exudative or wet or neovascular) adj3 age related).tw.
12. ((exudative or wet or neovascular) adj3 degenerat$).tw.
13. ((exudative or wet or neovascular) adj3 macula$).tw.
14. or/1-13
15. Tomography, Optical Coherence/ use mesz
16. optical coherence tomography/ use emed
17. oct.tw.
18. (stratus or cirrus or spectralis or rtvue or soct).tw.
19. or/15-18
20. autofluorescence.tw.
21. autofluorescence/ use emed
22. (fund$ adj3 (photograph$ or imag$)).tw.
23. photography/ use mesz
24. eye photography/ use emed
25. (microperimetry or micro perimetry).tw.
26. (visual acuity adj3 (test$ or assess$ or measure$ or value$ or exam$)).tw.
27. (dva or nva or bcva).tw
28. icga.tw.
29. indocyanine green angiograph$.tw
30. (dynamic adj3 angiograph$).tw
31. digital subtraction angiograph$.tw
32. preferential hyperacuity perimet$.tw
33. amsler$.tw.
34. clinical exam$.tw.
35. (ophthalmol$ adj1 (exam$ or assess$ or evaluat$)).tw.

36. or/20-35
37. 14 and (19 or 36)
38. nonhuman/ not human/
39. animals/ not humans/
40. 37 not (38 or 39)
41. 40 not (letter or editorial or comment).pt.
42. 41 not case report/
43. ("2008" or "2007").yr. and conference abstract.pt.
44. 42 not 43 (4803)
45. remove duplicates from 44
46. limit 45 to yr="1995 –Current"

Science Citation Index and Bioscience Information Services

Searched: 1995–22 March 2013 (Science Citation Index) and 1995–22 March 2013 (Bioscience Information Services).

ISI Web of Knowledge. URL: http://wok.mimas.ac.uk/.

Date of search: 22 March 2013.

Search strategy

#1 ((TS=(AMD and (exudative or wet or neovascular*))))

#2 ((TS=((exudative or wet or neovascular) NEAR/3 "age related")))

#3 (((TS=((exudative or wet or neovascular) NEAR/3 degenerat*))

#4 (((TS=((exudative or wet or neovascular) NEAR/3 macula*))))

#5 ((TS=(choroid* NEAR/1 neovascular*)))

#6 (TS= (macular NEAR/1 (edema or oedema))

#7 (((TS=(retina* NEAR/1 neovascular*))))

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 (((TS=optical coherence tomography)))

#10 (((TS=(stratus or cirrus or spectralis or rtvue or soct))))

#11 ((TS=autofluorescence)))

#12 (((TS=(fundus NEAR/3 (photograph* or imag*)))))

#13 (((TS=(microperimetry or "micro perimetry"))))

#14 TS=(dva or nva or bcva)

#15 TS=icga

#16 TS= indocyanine green angiograph*

#17 TS=(dynamic NEAR/3 angiograph*)

#18 TS= digital subtraction angiograph*

#19 TS= preferential hyperacuity perimet*

#20 TS=amsler*

#21 TS=clinical exam*

#22 TS=(ophthalmol* NEAR/1 (exam* or assess* or evaluat*))

#23 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 #8 and #23

The Cochrane Library

Searched: Cochrane Database of Systematic Reviews Issue 2 2013; Cochrane Central Register of Controlled Trials Issue 1 2013.

URL: www3.interscience.wiley.com/.

Date of search: 22 March 2013.

Search strategy

#1 MeSH descriptor Macular Degeneration, this term only

#2 MeSH descriptor Macular Edema, this term only

#3 MeSH descriptor Wet Macular Degeneration explode all trees

#4 MeSH descriptor Retinal Hemorrhage, this term only

#5 MeSH descriptor Choroid Hemorrhage, this term only

#6 MeSH descriptor Choroidal Neovascularization, this term only

#7 MeSH descriptor Retinal Neovascularization, this term only

#8 (exudative or wet or neovascular) and amd:ti,ab,kw or (exudative or wet or neovascular) NEAR/3 age related:ti,ab,kw and (exudative or wet or neovascular) NEAR/3 degenerat*:ti,ab,kw and (exudative or wet or neovascular) NEAR/3 macula*:ti,ab,kw

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

#10 MeSH descriptor Tomography, Optical Coherence, this term only

#11 (stratus or cirrus or spectralis or rtvue or soct or oct):ti,ab,kw

#12 (#10 OR #11)

#13 (autofluorescence):ti,ab,kw or (fund* NEAR/3 (photograph* or imag*)):ti,ab,kw or (microperimetry or micro perimetry):ti,ab,kw or (visual acuity NEAR/3 (test* or assess* or measure* or value* or exam*)):ti,ab,kw or (dva or nva or bcva):ti,ab,kw

#14 (clinical exam*):ti,ab,kw or (ophthalmol* NEAR/1 (exam* or assess* or evaluat*)).:ti,ab,kw

#15 (#13 OR #14)

#16 (#9 AND #12)

#17 (#9 AND #15)

#18 (#16 OR #17)

#19 (diabetes):ti,ab,kw or (diabetic):ti,ab,kw

#20 (#18 AND NOT #19)

#21 (#20), from 1995 to 2012

Health Technology Assessment database/Database of Abstracts of Reviews of Effects

Searched: inception until March 2013.

Centre for Reviews and Dissemination. URL: www.york.ac.uk/inst/crd/index.htm.

Date of search: March 2013.

Search strategy

#1 MeSH macular degeneration EXPLODE 1

#2 Amd or macular degeneration

#3 MeSH Tomography, Optical Coherence EXPLODE 1

#4 # 1 or #2 or #3

Medion

Searched: inception until March 2013.

URL: www.mediondatabase.nl/.

Date of search: March 2013.

Search strategy

Textword=Macular degeneration

ClinicalTrials.gov
Searched: inception until March 2013.

URL: http://clinicaltrials.gov/ct/gui/c/r.

Date of search: October 2014.

Search strategy
Condition=macular degeneration AND tomograph*

International Clinical Trials Registry Platform
Searched: inception until March 2013.

World Health Organization. URL: www.who.int/ictrp/en/.

Date of search: October 2012.

Search strategy
Condition=macular degeneration AND Intervention=tomography

Conference proceedings

Association for Research In Vision and Ophthalmology
Searched: 2009–12.

URL: www.iovs.org/search?arvomtgsearch=true.

Date of search: March 2013.

Search strategy
macular degeneration (as phrase) in title and wet exudative neovascular (any words) in title or abstract, from January 2009 through January 2012.

American Association of Ophthalmology
Searched: 2009–12.

URL: http://aao.scientificposters.com/.

Date of search: October 2012.

Search strategy
Macular degeneration and tomography

European Association for Vision and Eye Research
Searched: 2009–12.

URL: www.ever.be/.

Date of search: October 2012.

EVER 2009, September 30–3 October 2009 Portoroz, Slovenia.

EVER 2010, October 6–9, Crete, Greece.

EVER 2011, October 5–8, Crete, Greece.

EVER 2012, October 10–13, Nice, France.

Search strategy

Manufacturers' websites

Date of search: March 2013

Carl Zeiss Meditec: www.meditec.zeiss.com/.

Optovue: www.optovue.com/.

Heidelberg Engineering: http://www.heidelbergengineering.co.uk/.

Topcon: www.topconmedical.com/categories/imaging.htm.

Patient acceptability of optical coherence tomography

EMBASE Ovid MEDLINE(R), Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations

Searched: 1988 to 2013 Week 12 [EMBASED Ovid MEDLINE(R)], 1946 to March Week 2 2013 [Ovid MEDLINE(R)] and 25 March 2013 (In-Process & Other Non-Indexed Citations).

Ovid multifile search. URL: https://shibboleth.ovid.com/.

Date of search: 25 March 2013.

Search strategy

1. *macular degeneration/ or wet macular degeneration/ use mesz
2. macular edema/
3. *retina macula age related degeneration/ or exudative macular degeneration/ use emed
4. retinal hemorrhage/ use mesz or choroid hemorrhage/ use mesz
5. retina haemorrhage/ use emed or choroid haemorrhage/ use emed
6. choroidal neovascularization/ use mesz
7. subretinal neovascularization/ use emed
8. retinal neovascularization/ use mesz
9. retina neovascularization/ use emed
10. ((exudative or wet or neovascular) and amd).tw.
11. ((exudative or wet or neovascular) adj3 age related).tw.
12. ((exudative or wet or neovascular) adj3 degenerat$).tw.
13. ((exudative or wet or neovascular) adj3 macula$).tw.
14. or/1-13
15. Tomography, Optical Coherence/ use mesz
16. optical coherence tomography/ use emed
17. oct.tw.
18. (stratus or cirrus or spectralis or rtvue or soct).tw.

19. or/15-18
20. 14 and 19
21. exp patient acceptance of health care/ use mesz
22. exp patient attitude/ use emed
23. consumer satisfaction/ use mesz
24. patient dropouts/ use mesz
25. attitude of health personnel/ use mesz
26. health personnel attitude/ use emed
27. (patient? adj3 (compliance or participat$ or accept$ or refus$)).tw.
28. ((patient? or ophthalmolog$ or optometr$ or clinician?) adj3 (attitide? or prefer$ or perception? or satisfaction)).tw.
29. qualitative research/
30. questionnaires/
31. (qualitative or interview$ or focus group? or questionnaire$ or survey$).tw.
32. (ethno$ or grounded or thematic or interpretive or narrative).tw.
33. or/21-32
34. 20 and 33
35. exp eye diseases/
36. *Tomography, Optical Coherence/ use mesz
37. *optical coherence tomography/ use emed
38. oct.ti.
39. (stratus or cirrus or spectralis or rtvue or soct).ti.
40. 35 and (36 or 37 or 38 or 39)
41. 33 and 40 (124)
42. 34 or 41 (212)
43. remove duplicates from 42
44. limit 43 to yr="1995 -Current"

Applied Social Science Index and Abstracts (1995–23 March 2013)

Searched: 1995–23 March 2013.

ProQuest. URL: http://search.proquest.com/assia/.

Date of search: 23 March 2013.

Search strategy

KW=(OCT or optical coherence tomograph*)

PsycINFO

Searched: 1995–26 March 2013.

EBSCO*host*. URL: http://web.ebscohost.com/ehost/.

Date of search: 26 March 2013.

Search strategy

Optical coherence tomograph* AND macular degeneration (ALL TEXT)

Cost-effectiveness for coherence tomography for age-related macular degeneration

EMBASE, Ovid MEDLINE(R) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Searched: 1980–2012 week 45 (EMBASE), 1996–November week 2 2012 [Ovid MEDLINE(R)] and 14 November 2012 (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations)

Ovid Multifile Search URL: https://shibboleth.ovid.com/

Date searched: November 2012.

Search strategy

1. *macular degeneration/ or wet macular degeneration/ use mesz
2. macular edema/
3. *retina macula age related degeneration/ or exudative macular degeneration/ use emez
4. retinal hemorrhage/ use mesz or choroid hemorrhage/ use mesz
5. retina haemorrhage/ use emez or choroid haemorrhage/ use emez
6. choroidal neovascularization/ use mesz
7. subretinal neovascularization/ use emez
8. retinal neovascularization/ use mesz
9. [retina neovascularization/ use emez
10. ((exudative or wet or neovascular) and amd).tw.
11. ((exudative or wet or neovascular) adj3 age related).tw.
12. ((exudative or wet or neovascular) adj3 degenerat$).tw.
13. ((exudative or wet or neovascular) adj3 macula$).tw.
14. or/1-13
15. Tomography, Optical Coherence/ use mesz
16. optical coherence tomography/ use emed
17. (stratus or cirrus or spectralis or rtvue or soct).tw.
18. or/14-18
19. exp "costs and cost analysis"/ use mesz
20. exp economic evaluation/ use emez
21. economics/
22. health economics/ use emez
23. exp economics,hospital/ use mesz
24. exp economics,medical/ use mesz
25. economics,pharmaceutical/ use mesz
26. exp budgets/
27. exp models, economic/ use mesz
28. exp decision theory/
29. monte carlo method/
30. markov chains/
31. exp technology assessment, biomedical/
32. cost$.ti.
33. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
34. economics model$.tw
35. (economic$ or pharmacoeconomic$).tw.
36. (price or prices or pricing).tw.
37. (value adj1 money).tw.
38. markov$.tw
39. monte carlo.tw.

40. (decision$ adj2 (tree? or analy$ or model$)).tw.
41. or/15-36
42. 14 and 37
43. remove duplicates from 38
44. 39 not (letter or editorial or comment).pt.

Health Technology Assessment/NHS Economic Evaluation Databases

Searched: inception until October 2012.

Centre for Reviews & Dissemination. URL: http://nhscrd.york.ac.uk/welcome.htm

Date searched: October 2012.

Search strategy

#1 MeSH macular degeneration EXPLODE 1

#2 Amd or macular degeneration

#3 MeSH Tomography, Optical Coherence EXPLODE 1

#4 # 1 or #2 or #3

Health Management Information Consortium

Searched: 1979 September 2012.

Ovid URL: https://shibboleth.ovid.com/

Date of search: November 2012.

Search strategy

1. macular degeneration/
2. retinal diseases/
3. ((exudative or wet or neovascular) and amd).tw.
4. ((exudative or wet or neovascular) adj3 age related).tw.
5. ((exudative or wet or neovascular) adj3 degenerat$).tw.
6. ((exudative or wet or neovascular) adj3 macula$).tw.
7. or/1-6

Research Papers in Economics

Searched: inception until September 2012.

URL: http://repec.org/

Date of search: September 2012.

Search strategy

macula or macular

Association for Research In Vision and Ophthalmology

Searched: January 2009 to January 2012.

URL: www.iovs.org/search?arvomtgsearch=true.

Date searched: January 2012.

Search strategy

macular degeneration (as phrase) in title and wet exudative neovascular (any words) in title or abstract.

Quality of life and neovascular age-related macular degeneration

EMBASE, Ovid MEDLINE(R) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Searched: 1980–2012 week 45 (Embase), 1946–November week 2 2012 [Ovid MEDLINE(R)], 14 November 2012 [Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations].

Ovid Multifile Search URL: https://shibboleth.ovid.com/

Date searched: November 2012.

Search strategy

1. *macular degeneration/ or wet macular degeneration/
2. macular edema/ not (diabetic or diabetes).hw
3. *retina macula age related degeneration/ or exudative macular degeneration/
4. retinal hemorrhage/ use mesz or choroid hemorrhage/
5. retina haemorrhage/ use emez or choroid haemorrhage/
6. choroidal neovascularization/
7. subretinal neovascularization/
8. retinal neovascularization/ use mesz not (diabetes or diabetic).hw.
9. retina neovascularization/ use emed not (diabetes or diabetic).hw.
10. ((exudative or wet or neovascular) and amd).tw.
11. ((exudative or wet or neovascular) adj3 age related).tw.
12. ((exudative or wet or neovascular) adj3 degenerat$).tw.
13. ((exudative or wet or neovascular) adj3 macula$).tw.
14. or/1-13
15. quality of life/
16. quality adjusted life year/
17. "Value of Life"/ use mesz
18. health status indicators/ use mesz
19. health status/ use emez
20. sickness impact profile/ use mesz
21. disability evaluation/ use mesz
22. disability/ use emez
23. activities of daily living/ use mesz
24. exp daily life activity/ use emez
25. cost utility analysis/ use emez
26. rating scale/
27. questionnaires
28. (quality adj1 life).tw.

29. quality adjusted life.tw.
30. disability adjusted life.tw.
31. (qaly? or qald? or qale? or qtime? or daly?).tw
32. (euroqol or euro qol or eq5d or eq 5d).tw.
33. (hql or hqol or h qol or hrqol or hr qol).tw.
34. (hye or hyes).tw.
35. health$ year$ equivalent$.tw.
36. (hui or hui1 or hui2 or hui3).tw
37. (health adj3 (utilit$ or disutili$)).tw.
38. (health adj3 (state or status)).tw.
39. (sf36 or sf 36 or short form 36 or shortform 36).tw.
40. (sf6 or sf 6 or short form 6 or shortform 6).tw.
41. (sf12 or sf 12 or short form 12 or shortform 12).tw.
42. (sf16 or sf 16 or short form 16 or shortform 16).tw.
43. (sf20 or sf 20 or short form 20 or shortform 20).tw.
44. willingness to pay.tw.
45. standard gamble.tw
46. trade off.tw.
47. conjoint analys?s.tw.
48. discrete choice.tw.
49. (case report or editorial or letter).pt.
50. case report/
51. (VQOL or NEI-VFQ-25 or MACDQOL or ADVS or VF-14 or SIPV).tw.
52. or/15-48,51
53. 14 and 52
54. 53 not (49 or 50)
55. remove duplicates from 54

Appendix 2 List of included studies

Diagnostic studies

Alster 2005

Alster Y, Bressler NM, Bressler SB, Brimacombe JA, Crompton RM, Duh YJ, *et al.* Preferential hyperacuity perimeter (PreView PHP) for detecting choroidal neovascularization study. *Ophthalmology* 2005;**112**:1758–65.

Cachulo 2011

Cachulo L, Silva R, Fonseca P, Pires I, Carvajal-Gonzalez S, Bernardes R, *et al.* Early markers of choroidal neovascularization in the fellow eye of patients with unilateral exudative age-related macular degeneration. *Ophthalmologica* 2011;**225**:144–9.

Silva R, Cachulo ML, Fonseca P, Bernardes R, Nunes S, Vilhena N, *et al.* Age-related macular degeneration and risk factors for the development of choroidal neovascularisation in the fellow eye: a 3-year follow-up study. *Ophthalmologica* 2011;**226**:110–18. (Secondary to Cachulo 2011.)

Chen 2003

Chen S, Han M, Wang L. Indocyanine green angiography of exudative age-related macular degeneration. *Chin Ophthalmol Res* 2003;**21**:428–30.

Do 2012

Do DV, Gower EW, Cassard SD, Boyer D, Bressler NM, Bressler SB, *et al.* Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study. *Ophthalmology* 2012;**119**:771–8.

Fujii 1996

Fujii C, Inobe K, Sugimoto Y, Sugimoto A, Takahashi Y, Akagi Y. Indocyanine green angiographic findings in eyes with age-related macular degeneration. *Folia Ophthalmol Jpn* 1996;**47**:300–5.

Gomi 2007

Gomi F, Sawa M, Mitarai K, Tsujikawa M, Tano Y. Angiographic lesion of polypoidal choroidal vasculopathy on indocyanine green and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1421–7.

Hughes 2005

Hughes EH, Khan J, Patel N, Kashani S, Chong NV. In vivo demonstration of the anatomic differences between classic and occult choroidal neovascularization using optical coherence tomography. *Am J Ophthalmol* 2005;**139**:344–6.

Khondkaryan 2009

Khondkaryan A, Keane PA, Liakopoulos S, Walsh AC, Sadda SR. Comparison of optical coherence tomography and fluorescein angiography for the classification of neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2009;**50**:E-abstract 5259.

Kim 2003

Kim SG, Lee SC, Seong YS, Kim SW, Kwon OW. Choroidal neovascularization characteristics and its size in optical coherence tomography. *Yonsei Med J* 2003;**44**:821–7.

Kozak 2008
Kozak I, Morrison VL, Clark TM, Bartsch DU, Lee BR, Falkenstein I, *et al.* Discrepancy between fluorescein angiography and optical coherence tomography in detection of macular disease. *Retina* 2008;**28**:538–44.

Krebs 2007
Krebs I, Binder S, Stolba U, Krepler K, Zeiler F, Glittenberg C. The value of optical coherence tomography in diagnosis and therapy of age-related macular degeneration. *Spektrum der Augenheilkunde* 2007;**21**:33–8.

Liakopoulos 2008
Liakopoulos S, Ongchin S, Bansal A, Msutta S, Walsh AC, Updike PG, *et al.* Quantitative optical coherence tomography findings in various subtypes of neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2008;**49**:5048–54.

Loewenstein 2010
Loewenstein A, Ferencz JR, Lang Y, Yeshurun I, Pollack A, Siegal R, *et al.* Toward earlier detection of choroidal neovascularization secondary to age-related macular degeneration: multicenter evaluation of a preferential hyperacuity perimeter designed as a home device. *Retina* 2010;**30**:1058–64.

Padnick-Silver 2012
Padnick-Silver L, Weinberg AB, Lafranco FP, MacSai MS. Pilot study for the detection of early exudative age-related macular degeneration with optical coherence tomography. *Retina* 2012;**32**:1045–56.

Park 2010
Park SS, Truong SN, Zawadzki RJ, Alam S, Choi SS, Telander DG, *et al.* High-resolution Fourier-domain optical coherence tomography of choroidal neovascular membranes associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2010;**51**:4200–6.

Parravano 2012
Parravano M, Varano M, Virgili G. Integrated imaging approach in RAP diagnosis. *Acta Ophthalmol* 2012;**90**:abstract 4426.

Reichel 1995
Reichel E, Duker JS, Puliafito CA. Indocyanine green angiography and choroidal neovascularization obscured by hemorrhage. *Ophthalmology* 1995;**102**:1871–6.

Salinas-Alaman 2005
Salinas-Alaman A, Garcia-Layana A, Maldonado MJ, Sainz-Gomez C, Alvarez-Vidal A. Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. *Am J Ophthalmol* 2005;**140**:23–8.

Sandhu 2005
Sandhu SS, Talks SJ. Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. *Br J Ophthalmol* 2005;**89**:967–70.

Sulzbacher 2011
Sulzbacher F, Kiss C, Munk M, Deak G, Sacu S, Schmidt-Erfurth U. Diagnostic evaluation of type 2 (classic) choroidal neovascularization: optical coherence tomography, indocyanine green angiography, and fluorescein angiography. *Am J Ophthalmol* 2011;**152**:799–806e1.

Talks 2007
Talks J, Koshy Z, Chatzinikolas K. Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration. *Br J Ophthalmol* 2007;**91**:600–1.

Torron 2002
Torron FB, Perez O, Melcon SF, Ferrer N, Ruiz-Moreno O, Honrubia L. Dynamic angiography in age related macular degeneration. *Arch Soc Esp Oftalmol* 2002;**77**:353–9.

Torron FB, Melcon SF, Ferrer N, Ruiz M, Honrubia L. Indocyanine green angiography and subretinal neovascularization. Patterns in age related macular degeneration. *Archiv Soc Esp Oftalmol* 2001;**76**:221–8. (Secondary to Torron 2002.)

Monitoring studies

Eter 2005
Eter N, Spaide RF. Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. *Retina* 2005;**25**:691–6.

Giani 2011
Giani A, Luiselli C, Esmaili DD, Salvetti P, Cigada M, Miller JW, *et al.* Spectral-domain optical coherence tomography as an indicator of fluorescein angiography leakage from choroidal neovascularization. *Invest Ophthalmol Vis Sci* 2011;**52**:5579–86.

Henschel 2009
Henschel A, Spital G, Lommatzsch A, Pauleikhoff D. Optical coherence tomography in neovascular age related macular degeneration compared to fluorescein angiography and visual acuity. *Eur J Ophthalmol* 2009;**19**:831–5.

Khurana 2010
Khurana RN, Dupas B, Bressler NM. Agreement of time-domain and spectral-domain optical coherence tomography with fluorescein leakage from choroidal neovascularization. *Ophthalmology* 2010;**117**:1376–80.

Regillo 1998
Regillo CD, Blade KA, Custis PH, O'Connell SR. Evaluating persistent and recurrent choroidal neovascularization. The role of indocyanine green angiography. *Ophthalmology* 1998;**105**:1821–6.

Salinas-Alaman 2005
Salinas-Alaman A, Garcia-Layana A, Maldonado MJ, Sainz-Gomez C, Alvarez-Vidal A. Using optical coherence tomography to monitor photodynamic therapy in age related macular degeneration. *Am J Ophthalmol* 2005;**140**:23–8.

van de Moere 2006
van de Moere A, Sandhu SS, Talks SJ. Correlation of optical coherence tomography and fundus fluorescein angiography following photodynamic therapy for choroidal neovascular membranes. *Br J Ophthalmol* 2006;**90**:304–6.

van Velthoven 2006
van Velthoven ME, de Smet MD, Schlingemann RO, Magnani M, Verbraak FD. Added value of OCT in evaluating the presence of leakage in patients with age-related macular degeneration treated with PDT. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:1119–23.

Appendix 3 List of excluded studies

Study design (*n* = 30)

Arias L, Garcia-Arumi J, Ramon JM, Badia M, Rubio M, Pujol O. Optical coherence tomography analysis of a randomized study combining photodynamic therapy with intravitreal triamcinolone. *Graefes Arch Clin Exp Ophthalmol* 2008;**246**:245–54.

Baranano AE, Keane PA, Ruiz-Garcia H, Walsh AC, Sadda SR. Impact of scanning density on spectral domain optical coherence tomography assessments in neovascular age-related macular degeneration. *Acta Opthalmol* 2012;**90**:e274–80.

Bojke L, Claxton K, Sculpher MJ, Palmer S. Identifying research priorities: the value of information associated with repeat screening for age-related macular degeneration. *Med Decis Making* 2008;**28**:33–43.

Cruess AF, Zlateva G, Pleil AM, Wirostko B. Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties. *Acta Ophthalmol* 2009;**87**:118–32.

Dunavoelgyi R, Sacu S, Simader C, Pruente C, Schmidt-Erfurth U. Changes in macular sensitivity after reduced fluence photodynamic therapy combined with intravitreal triamcinolone. *Acta Opthalmol* 2011;**89**:166–71.

Elsner H, Barbazetto I, Schmidt-Erfurth U. Natural course of events in subfoveal choroidal neovascularisation by age-linked macular degeneration. *Ophthalmologe* 2001;**98**:665–70.

Freund KB, Ho IV, Barbazetto IA, Koizumi H, Laud K, Ferrara D, *et al.* Type 3 neovascularization – the expanded spectrum of retinal angiomatous proliferation. *Retina* 2008;**28**:201–11.

Gupta B, Adewoyin T, Patel SK, Sivaprasad S. Comparison of two intravitreal ranibizumab treatment schedules for neovascular age-related macular degeneration. *Br J Ophthalmol* 2011;**95**:386–90.

Heimes B, Lommatzsch A, Zeimer M, Gutfleisch M, Spital G, Dietzel M, *et al.* Long-term visual course after anti-VEGF therapy for exudative AMD in clinical practice evaluation of the German reinjection scheme. *Graefes Arch Clin Exp Ophthalmol* 2011;**249**:639–44.

Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Cost-effectiveness of ranibizumab compared with pegaptanib in neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2010;**248**:467–76.

Holz FG, Jorzik J, Schutt F, Flach U, Unnebrink K. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-Study). *Ophthalmology* 2003;**110**:400–5.

Horster R, Ristau T, Sadda SR, Liakopoulos S. Individual recurrence intervals after anti-VEGF therapy for age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2011;**249**:645–52.

Javier Hernandez-Pastor Lle, Ortega A, Garcia-Layana A, Giraldez J. Cost-effectiveness of ranibizumab compared with photodynamic treatment of neovascular age-related macular degeneration. *Clin Ther* 2008;**30**:2436–51.

Kaiser RS, Berger JW, Williams GA, Tolentino MJ, Maguire AM, Alexander J, *et al.* Variability in fluorescein angiography interpretation for photodynamic therapy in age-related macular degeneration. *Retina* 2002;**22**:683–90.

Katz G, Giavedoni L, Muni R, Evans T, Pezda M, Wong D, *et al.* Effectiveness at 1 year of monthly versus variable-dosing intravitreal ranibizumab in the treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2012;**32**:293–8.

Kubicka-Trzaska A. The differential diagnosis of exudative age-related macular degeneration with posterior pole choroidal tumours. *Klinika Oczna* 2005;**107**:147–55.

Loewenstein A. Use of home device for early detection of neovascular age-related macular degeneration. *Ophthalmic Res* 2012;**48**(Suppl. 1):11–15.

Maier MM, Feucht N, Fegert C, Fiore B, Winkler V, Lohmann C. [Intravitreal Ranibizumab Injection for the Treatment of Occult and Classic CNV in Exsudative AMD.] *Klin Monatsbl Augenheilkd* 2011;**228**:161–7.

Mekjavic PJ, Kraut A, Urbancic M, Lenassi E, Hawlina M. Efficacy of 12-month treatment of neovascular age-related macular degeneration with intravitreal bevacizumab based on individually determined injection strategies after three consecutive monthly injections. *Acta Opthalmol* 2011;**89**:647–53.

Mookhtiar M, Downey L. Combined OCT and colour fundus photography in virtual clinic assessments of wet AMD patients. *Eye* 2012;**26**:619.

Neubauer AS, Holz FG, Sauer S, Wasmuth T, Hirneiss C, Kampik A, *et al.* Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: model analysis from the perspective of Germany's statutory health insurance system. *Clin Ther* 2010;**32**:1343–56.

Nischler C, Oberkofler H, Ortner C, Paikl D, Riha W, Lang N, *et al.* Complement factor H Y402H gene polymorphism and response to intravitreal bevacizumab in exudative age-related macular degeneration. *Acta Opthalmol* 2011;**89**:e344–9.

Patel PJ, Browning AC, Chen FK, Da C, Tufail A. Interobserver agreement for the detection of optical coherence tomography features of neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2009;**50**:5405–10.

Pieniazek M, Sobaszek A, Nowak W, Hachol A, Misiuk-Hojlo M. Pupil reactivity in infrared pupillometry in patients with varied stages of age related macular degeneration. 10th European Neuro-Ophthalmology Society, EUNOS Meeting Barcelona, Spain, 2011.

Pumariega NM, Smith RT, Sohrab MA, Letien V, Souied EH. A prospective study of reticular macular disease. *Ophthalmology* 2011;**118**:1619–25.

Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J, Blodi B, *et al.* Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. *Ophthalmology* 2011;**118**:523–30.

Scholl HP, Peto T, Dandekar S, Bunce C, Xing W, Jenkins S, *et al.* Inter- and intra-observer variability in grading lesions of age-related maculopathy and macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2003;**241**:39–47.

Smiddy WE. Economic implications of current age-related macular degeneration treatments. *Ophthalmology* 2009;**116**:481–7.

Trikha R, Morse LS, Zawadzki RJ, Werner JS, Park SS. Ten-year follow-up of eyes treated with stereotactic fractionated external beam radiation for neovascular age-related macular degeneration. *Retina* 2011;**31**:1303–15.

van Zeeburg EJ, Cereda MG, van der Schoot J, Pertile G, van Meurs JC. Early perfusion of a free RPE-choroid graft in patients with exudative macular degeneration can be imaged with spectral domain-OCT. *Invest Ophthalmol Vi Sci* 2011;**52**:5881–6.

Not age-related macular degeneration (*n* = 6)

Helb HM, Charbel I, Fleckenstein M, Schmitz-Valckenberg S, Scholl HP, Meyer CH, *et al.* Clinical evaluation of simultaneous confocal scanning laser ophthalmoscopy imaging combined with high-resolution, spectral-domain optical coherence tomography. *Acta Opthalmol* 2010;**88**:842–9.

Krebs I, Binder S, Stolba U. Value of the optical coherence tomography (OCT) for follow up examinations after photodynamic therapy (PDT). *Spek Augenheilkd* 2003;**17**:164–9.

Kuerzinger GR, Lang GK, Lang GE. [Retinal angiomatous proliferation in age-related macular degeneration.] *Klin Monatsbl Augenheilkd* 2006;**223**:691–5.

Sikorski BL, Bukowska D, Kaluzny JJ, Szkulmowski M, Kowalczyk A, Wojtkowski M. Drusen with accompanying fluid underneath the sensory retina. *Ophthalmol* 2011;**118**:82–92.

Spraul CW, Lang GE, Lang GK. Optical coherence tomography of age-related macular degeneration. Correlation of diagnostic techniques of fluorescence angiography and OCT. *Klin Monatsbl Augenheilkd* 1998;**212**:141–8.

Toju R, Iida T, Sekiryu T, Saito M, Maruko I, Kano M. Near-infrared autofluorescence in patients with idiopathic submacular choroidal neovascularization. *Am J Ophthalmol* 2012;**153**:314–19.

Reference standard (*n* = 13)

Brancato R, Introini U, Pierro L, Setaccioli M, Forti M, Bolognesi G, *et al.* Optical coherence tomography (OCT) in retinal angiomatous proliferation (RAP). *Eur J Ophthalmol* 2002;**12**:467–72.

Coscas G, De Benedetto U, Coscas F, Li Calzi CI, Vismara S, Roudot-Thoraval F, *et al.* Hyperreflective dots: a new spectral-domain optical coherence tomography entity for follow-up and prognosis in exudative age-related macular degeneration. *Ophthalmologica* 2013:**229**:32–7.

El-Mollayess GM, Mahfoud Z, Schakal AR, Salti HI, Jaafar D, Bashshur ZF. Fixed-interval versus OCT-guided variable dosing of intravitreal bevacizumab in the management of neovascular age-related macular degeneration: a 12-month randomized prospective study. *Am J Ophthalmol* 2012;**153**:481–9.

Giacomelli G, Volpe R, Scrivanti M, Mencucci R, Salvi G. Fluorangiography and indocyanine green angiography by SLO in detecting choroidal neovessels in age related macular degeneration. *Anna Ottalmol Clin Oculist* 1996;**122**:97–106.

Hoerster R, Muether PS, Hermann MM, Koch K, Kirchhof B, Fauser S. Subjective and functional deterioration in recurrences of neovascular AMD are often preceded by morphologic changes in optic coherence tomography. *Br J Ophthalmol* 2011;**95**:1424–6.

Jain S, Hamada S, Membrey WL, Chong V. Screening for age-related macular degeneration using nonstereo digital fundus photographs. *Eye* 2006;**20**:471–5.

Khan S, Engelbert M, Imamura Y, Freund KB. Polypoidal choroidal vasculopathy: simultaneous indocyanine green angiography and eye-tracked spectral domain optical coherence tomography findings. *Retina* 2012;**32**:1057–68.

Mantel I, Deli A, Iglesias K, Ambresin A. Prospective study evaluating the predictability of need for retreatment with intravitreal ranibizumab for age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2013;**251**:697–704.

Pece A, Sannace C, Menchini U, Virgili G, Galli L, Isola V, *et al.* Fluorescein angiography and indocyanine green angiography for identifying occult choroidal neovascularization in age-related macular degeneration. *Eur J Ophthalmol* 2005;**15**:759–63.

Pirbhai A, Sheidow T, Hooper P. Prospective evaluation of digital non-stereo color fundus photography as a screening tool in age-related macular degeneration. *Am J Ophthalmol* 2005;**139**:455–61.

Querques G, Querques L, Rafaeli O, Canoui-Poitrine F, Bandello F, Souied EH. Preferential hyperacuity perimeter as a functional tool for monitoring exudative age-related macular degeneration in patients treated by intravitreal ranibizumab. *Invest Ophthalmol Vis Sci* 2011;**52**:7012–18.

Vujosevic S, Vaclavik V, Bird AC, Leung I, Dandekar S, Peto T. Combined grading for choroidal neovascularisation: colour, fluorescein angiography and autofluorescence images. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1453–60.

Yannuzzi LA, Negrao S, Iida T, Carvalho C, Rodriguez-Coleman H, Slakter J, *et al.* Retinal angiomatous proliferation in age-related macular degeneration. *Retina* 2001;**21**(Suppl. 1):416–34.

Outcomes ($n = 63$)

Ahlers C, Michels S, Elsner H, Birngruber R, Pruente C, Schmidt-Erfurth U. Topographic angiography and optical coherence tomography: a correlation of imaging characteristics. *Eur J Ophthalmol* 2005;**15**:774–81.

Almony A, Mansouri A, Shah GK, Blinder KJ. Efficacy of intravitreal bevacizumab after unresponsive treatment with intravitreal ranibizumab. *Can J Ophthalmol* 2011;**46**:182–5.

Amaro MH, Amaro FAH, Roller AB, Motta CT, Motta MMD. Treatment of nonsubfoveal choroidal neovascularization in age-related macular degeneration. Analysis of a cases series and revision paper. *Rev Bras Oftalmol* 2011;**70**:261–7.

Ampornpruet A, Ruamviboonsuk P, Kokekhuntod S. The fundoscopic features for differentiation between polypoidal choroidal vasculopathy and choroidal neovascularization from age-related macular degeneration. *J Med Assoc Thai* 2005;**88**:S51–6.

Atmaca L, Batioglu F, Atmaca P. Detection of subretinal neovascular membranes with idiocynanine green videoangiography. *J Fr Ophtalmol* 1997;**20**:189–94.

Bearelly S, Espinosa-Heidmann DG, Cousins SW. The role of dynamic indocyanine green angiography in the diagnosis and treatment of retinal angiomatous proliferation. *Br J Ophthalmol* 2008;**92**:191–6.

Bermig J, Tylla H, Jochmann C, Nestler A, Wolf S. Angiographic findings in patients with exudative age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2002;**240**:169–75.

Bernardes R, Santos T, Serranho P, Lobo C, Cunha-Vaz J. Noninvasive evaluation of retinal leakage using optical coherence tomography. *Ophthalmologica* 2011;**226**:29–36.

Bidot ML, Malvitte L, Bidot S, Bron A, Creuzot-Garcher C. [Efficacy of three intravitreal injections of bevacizumab in the treatment of exudative age-related macular degeneration.] *J Fr Opthalmol* 2011;**34**:376–81.

Byun YJ, Lee SJ, Koh HJ. Predictors of response after intravitreal bevacizumab injection for neovascular age-related macular degeneration. *Jpn J Ophthalmol* 2010;**54**:571–7.

Campa C, Hagan R, Sahni JN, Brown MC, Beare NA, Heimann H, *et al.* Early multifocal electroretinogram findings during intravitreal ranibizumab treatment for neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011;**52**:3446–51.

Campa C, Harding SP, Pearce IA, Beare NA, Briggs MC, Heimann H. Incidence of neovascularization in the fellow eye of patients with unilateral retinal angiomatous proliferation. *Eye* 2010;**24**:1585–9.

Coscas G, Coscas F, Vismara S, Souied E, Soubrane G. [Spectral Domain OCT in age-related macular degeneration: preliminary results with Spectralis HRA-OCT.] *J Fr Opthalmol* 2008;**31**:353–61.

Coscas F, Querques G, Forte R, Terrada C, Coscas G, Souied EH. Combined fluorescein angiography and spectral-domain optical coherence tomography imaging of classic choroidal neovascularization secondary to age-related macular degeneration before and after intravitreal ranibizumab injections. *Retina* 2012;**32**:1069–76.

Coscas F, Coscas G, Querques G, Massamba N, Querques L, Bandello F, *et al.* En face enhanced depth imaging optical coherence tomography of fibrovascular pigment epithelium detachment. *Invest Ophthalmol Vis Sci* 2012;**53**:4147–51.

Dandekar SS, Jenkins SA, Peto T, Scholl HP, Sehmi KS, Fitzke FW, *et al.* Autofluorescence imaging of choroidal neovascularization due to age-related macular degeneration. *Arch Ophthalmol* 2005;**123**:1507–13.

de Bruin DM, Burnes DL, Loewenstein J, Chen YL, Chang S, Chen TC, *et al.* In vivo three-dimensional imaging of neovascular age-related macular degeneration using optical frequency domain imaging at 1050 nm. *Invest Ophthalmol Vis Sci* 2008;**49**:4545–52.

Giani A, Esmaili DD, Luiselli C, Cigada M, Salvetti P, Miller JW, *et al.* Displayed reflectivity of choroidal neovascular membranes by optical coherence tomography correlates with presence of leakage by fluorescein angiography. *Retina* 2011;**31**:942–8.

Grunwald JE, Daniel E, Ying GS, Pistilli M, Maguire MG, Alexander J, *et al.* Photographic assessment of baseline fundus morphologic features in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology* 2012;**119**:1634–41.

Gutfleisch M, Heimes B, Schumacher M, Dietzel M, Lommatzsch A, Bird A, *et al.* Long-term visual outcome of pigment epithelial tears in association with anti-VEGF therapy of pigment epithelial detachment in AMD. *Eye* 2011;**25**:1181–6.

Haddad WM, Coscas G, Soubrane G. Eligibility for treatment and angiographic features at the early stage of exudative age related macular degeneration. *Br J Ophthalmol* 2002;**86**:663–9.

He S, Wang W, Li X, Tang R. [Characteristics of optical coherence tomography for exudative age-related macular degeneration.] *Chin J Ophthalmol* 2002;**38**:543–5.

Hee MR, Baumal CR, Puliafito CA, Duker JS, Reichel E, Wilkins JR, *et al.* Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology* 1996;**103**:1260–70.

Helbig H, Niederberger H, Valmaggia C, Bischoff P. Simultaneous fluorescein and indocyanine green angiography for exudative macular degeneration. *Klin Monatsbl Augenheilkd* 2005;**222**:202–5.

Kang SW, Chung SE, Shin WJ, Lee JH. Polypoidal choroidal vasculopathy and late geographic hyperfluorescence on indocyanine green angiography. *Br J Ophthalmol* 2009;**93**:759–64.

Krebs I, Ansari-Shahrezaei S, Goll A, Binder S. Activity of neovascular lesions treated with bevacizumab: comparison between optical coherence tomography and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol* 2008;**246**:811–15.

Krebs I, Binder S, Stolba U, Schmid K, Glittenberg C, Brannath W, *et al.* Optical coherence tomography guided retreatment of photodynamic therapy. *Br J Ophthalmol* 2005;**89**:1184–7.

Li X, Tang Y. The application of fundus angiography and OCT in the classification of choroidal neovascularization complicated in central exudative choretinopathy. *Chin Ophthalmic Res* 2009;**27**:490–3.

Malamos P, Sacu S, Georgopoulos M, Kiss C, Pruente C, Schmidt-Erfurth U. Correlation of high-definition optical coherence tomography and fluorescein angiography imaging in neovascular macular degeneration. *Invest Ophthalmol Vis Sci* 2009;**50**:4926–33.

Maruko I, Iida T, Saito M, Nagayama D. Combined cases of polypoidal choroidal vasculopathy and typical age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2010;**248**:361–8.

McBain VA, Townend J, Lois N. Fundus autofluorescence in exudative age-related macular degeneration. *Br J Ophthalmol* 2007;**91**:491–6.

Mendrinos E, Petropoulos IK, Pournaras CJ. Retinal angiomatous proliferations: when should we suspect them and how should we detect them? *Klin Monatsbl Augenheilkd* 2009;**226**:284–8.

Miura M, Elsner AE, Beausencourt E, Kunze C, Hartnett ME, Lashkari K, *et al.* Grading of infrared confocal scanning laser tomography and video displays of digitized color slides in exudative age-related macular degeneration. *Retina* 2002;**22**:300–8.

Moutray T, Alarbi M, Mahon G, Stevenson M, Chakravarthy U. Relationships between clinical measures of visual function, fluorescein angiographic and optical coherence tomography features in patients with subfoveal choroidal neovascularisation. *Br J Ophthalmol* 2008;**92**:361–4.

Nazemi PP, Fink W, Lim JI, Sadun AA. Scotomas of age-related macular degeneration detected and characterized by means of a novel three-dimensional computer-automated visual field test. *Retina* 2005;**25**:446–53.

Okubo A, Hirakawa M, Ito M, Sameshima M, Sakamoto T. Clinical features of early and late stage polypoidal choroidal vasculopathy characterized by lesion size and disease duration. *Graefes Arch Clin Exp Ophthalmol* 2008;**246**:491–9.

Otsuji Tokaj, Tsumura A, Takahashi K, Sho K, Nagai Y, Fukuchi T, *et al.* Evaluation of cases of polypoidal choroidal vasculopathy showing classic choroidal neovascularization in their natural course. *Nippon Ganka Gakkai Zasshi* 2006;**110**:454–61.

Parravano M, Pilotto E, Musicco I, Varano M, Introini U, Staurenghi G, *et al.* Reproducibility of fluorescein and indocyanine green angiographic assessment for RAP diagnosis: a multicenter study. *Eur J Ophthalmol* 2012;**22**:598–606.

Pauleikhoff D, Kirchhof B. Retreatment criteria in anti-VEGF therapy of exudative AMD: critical analysis of present regimes and new morphological definition of 'lesion activity'. *Graefes Arch Clin Exp Ophthalmol* 2011;**249**:631–2.

Petropoulos IK, Matter MA, Katsimpris JM, Desmangles PM. The role of spectral-domain optical coherence tomography in the diagnosis of retinal angiomatous proliferation. *Klin Monatsbl Augenheilkd* 2010;**227**:309–11.

Reichel E, Pollock DA, Duker JS, Puliafito CA. Indocyanine green angiography for recurrent choroidal neovascularization in age-related macular degeneration. *Ophthalmic Surg Lasers* 1995;**26**:513–18.

Rouvas AA, Papakostas TD, Ntouraki A, Douvali M, Vergados I, Ladas ID. Angiographic and OCT features of retinal angiomatous proliferation. *Eye* 2010;**24**:1633–42.

Rouvas AA, Ladas ID, Georgalas I, Vergados I, Papakonstantinou D, Kotsolis AI. Ranibizumab for the treatment of exudative age-related macular degeneration associated with retinal pigment epithelial tear. *Retina* 2011;**31**:1083–8.

Sadda SR, Liakopoulos S, Keane PA, Ongchin SC, Msutta S, Chang KT, *et al.* Relationship between angiographic and optical coherence tomographic (OCT) parameters for quantifying choroidal neovascular lesions. *Graefes Arch Clin Exp Ophthalmol* 2010;**248**:175–84.

Sahni J, Stanga P, Wong D, Harding S. Optical coherence tomography in photodynamic therapy for subfoveal choroidal neovascularisation secondary to age related macular degeneration: a cross sectional study. *Br J Ophthalmol* 2005;**89**:316–20.

Sarks J, Arnold J, Ho IV, Sarks S, Killingsworth M. Evolution of reticular pseudodrusen. *Br J Ophthalmol* 2011;**95**:979–85.

Sato T, Iida T, Hagimura N, Kishi S. Correlation of optical coherence tomography with angiography in retinal pigment epithelial detachment associated with age-related macular degeneration. *Retina* 2004;**24**:910–14.

Semoun O, Guigui B, Tick S, Coscas G, Soubrane G, Souied EH. Infrared features of classic choroidal neovascularisation in exudative age-related macular degeneration. *Br J Ophthalmol* 2009;**93**:182–5.

Spaide RF. Enhanced depth imaging optical coherence tomography of retinal pigment epithelial detachment in age-related macular degeneration. *Am J Ophthalmol* 2009;**147**:644–52.

Squirrell DM, Bacon JF, Brand CS. To investigate the prevalence of polypoidal choroidal vasculopathy in presumed age-related peripapillary subretinal neovascular membranes. *Clin Exp Ophthalmol* 2009;**37**:368–72.

Strauss RW, Rombold F, Kampik A, Neubauer AS. Fluorescein angiography compared to three-dimensional measurements by the retinal thickness analyzer in classic choroidal neovascularization. *Ophthalmic Res* 2007;**39**:98–102.

Suren E, Batioglu F, Ozmert E. Autofluorescence characteristics of choroidal neovascular membranes in age related macular degeneration before and after treatment. *Retina Vitreus* 2009;**17**:120–4.

Tamura H, Tsujikawa A, Otani A, Gotoh N, Sasahara M, Kameda T, *et al.* Polypoidal choroidal vasculopathy appearing as classic choroidal neovascularisation on fluorescein angiography. *Br J Ophthalmol* 2007;**91**:1152–9.

Tang KC, Liu HA. Scanning laser ophthalmoscopy of choroidal neovascularisation using indocyanine green. *Aust NZ J Ophthalmol* 1995;**23**:195–202.

Theelen T, Berendschot TTJM, Hoyng CB, Boon CJF, Klevering BJ. Near-infrared reflectance imaging of neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2009;**247**:1625–33.

Vaclavik V, Vujosevic S, Dandekar SS, Bunce C, Peto T, Bird AC. Autofluorescence imaging in age-related macular degeneration complicated by choroidal neovascularization: a prospective study. *Ophthalmology* 2008;**115**:342–6.

Vandelli G, Giacomotti E, Nozza F. Fluorescein and indocyanine green angiography in the diagnosis of coroideal neovascolarization. *Ann Ottalmol Clin Oculist* 2000;**126**:201–15.

Watzke RC, Klein ML, Hiner CJ, Chan BK, Kraemer DF. A comparison of stereoscopic fluorescein angiography with indocyanine green videoangiography in age-related macular degeneration. *Ophthalmology* 2000;**107**:1601–6.

Windisch R, Windisch BK, Cruess AF. Use of fluorescein and indocyanine green angiography in polypoidal choroidal vasculopathy patients following photodynamic therapy. *Can J Ophthalmol* 2008;**43**:678–82.

Xiao M. Analysis on fundus fluorescein angiography in patients with age related macular degeneration. *Int J Ophthalmol* 2010;**10**:962–3.

Yaylali SA, Akcakaya AA, Erbil HH, Candemir B, Mesci C, Acar H. The relationship between optical coherence tomography patterns, angiographic parameters and visual acuity in age-related macular degeneration. *Int Ophthalmol* 2012;**32**:25–30.

Zahlava J, Karel I, Dubska Z, Lestak J. [Optical coherence tomography in age-related macular degeneration.] *Ceska Slov Oftalmol* 2002;**58**:98–104.

Zuo CG, Wen F, Huang SZ, Luo GW, Yan H, Wu WJ, *et al.* Angiographic leakage of polypoidal choroidal vasculopathy on indocyanine angiography. *Chin Med J* 2010;**123**:1548–52.

Appendix 4 Characteristics of the included studies

TABLE 42 Diagnostic studies

Study	Participants	Tests	Outcomes reported
Alster 2005[24] *Full text:* Yes *Study type*: Comparative, concurrent, non-randomised *Prospective:* Yes *Multicentre:* Yes (seven centres) *Country:* USA *Study start/end dates:* 15 October 2003/ 23 August 2004 *Duration of study:* 10 months, 1 week	*Enrolled:* 185 *Analysed:* 122 patients (65 CNV; 57 intermediate AMD) *Consecutive:* Yes *Age (years) median:* 77 *Gender M : F:* 26 : 39 *Baseline BCVA:* 20/63 (Snellen equivalent) *Inclusion criteria:* Age ≥ 50 years, BCVA 220/160 or better, newly diagnosed (≤ 60 days) non-treated neovascular lesion from AMD, mental and physical ability to perform PHP test, ability to tolerate intravenous fluorescein angiography, subject able and willing to sign consent form and participate in study *Exclusion criteria:* Evidence of macular disease other than AMD, previous surgical or laser treatment within the macular area, presence of any significant media opacity that precludes a clear view of the macular area as identified by biomicroscopy, fundus photography, or fluorescein angiography, any non-macular-related ocular surgery performed within 3 months before the study	*Index test(s):* N/R *Definition of positive test result:* n/a *Interpreted by:* N/R *Comparator test(s):* PHP *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Experienced photograph reading centre	*Unit of analysis* (n): Patient (one eye per patient) If both eyes per subject eligible, how was study eye selected: The enrolling ophthalmologist and the participant made a joint decision regarding which eye would be the study eye *Diagnostic accuracy:* Yes *Sensitivity:* PHP 82% (95% CI 70% to 90%) Colour fundus photography 70% Colour fundus photography + VA 53% (95% CI 30% to 76%) *Specificity:* PHP 88% (95% CI 76% to 95%) Colour fundus photography 95% Colour fundus photography + VA 94% (95% CI 83% to 99%) *Clinical effectiveness:* N/R *Interpretability of the test:* 11 patients (5.9%) were excluded from analysis as PHP results were judged to be unreliable *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Cachulo 2011[25] (Silva 2011 – 3 years secondary report to Cachulo 2011)[47] *Full text:* Yes *Study type:* Observational, longitudinal 2 years plus 1-year extension study *Prospective:* Yes *Multicentre:* No *Country:* Portugal *Study start/end dates:* N/R *Duration of study:* 3 years	*Enrolled:* 62 patients *Analysed:* 52 patients *Consecutive:* Unclear *Age (years) mean (range/SD):* 76 (56–92/6) *Gender M : F:* 26 : 26 *Baseline BCVA:* N/R *Inclusion criteria:* Patients aged ≥ 50 years, any race and either sex, early age-related maculopathy in the study eye (at least ≥ 5 intermediate drusen, ≥ 1 large soft drusen or confluent drusen within 3000 µm of the foveal centre; with or without pigmentary changes), nAMD in the fellow eye, signed inform consent, able to returned to the required visits *Exclusion criteria:* Other fundus disease (e.g. vascular retinopathy, central serous chorioretinopathy, inflammation or non-AMD CNV), current or past history of intraocular surgery within 60 days prior to enrolling in the study, evidence of past or present CNV in the study eye	*Index test:* TD-OCT (Stratus OCT™, Carl Zeiss Meditec, Dublin, CA) *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA, FAF *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Non-stereoscopic FFA *Interpreted by:* N/R (assumed interpreted by ophthalmologist)	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* n/a *Diagnostic accuracy:* Yes *Sensitivity – Cachulo 2011:*[25] TD-OCT 100% ICGA 94.1% FAF 93.3% *Sensitivity – Silva 2011:*[47] 100% *Specificity – Cachulo 2011:*[25] TD-OCT N/R ICGA N/R FAF 37% *Specificity – Silva 2011*[47] N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Chen 2003[26] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective/ retrospective:* N/R *Multicentre:* Unclear *Country:* China *Study start/end dates:* November 1999/ December 2000 *Duration of study:* 1 year	*Enrolled:* 52 patients *Analysed:* 52 patients *Consecutive:* Unclear *Age (years) mean (range/SD):* 64.12 (51–80/8.59) *Gender M : F:* N/R *Baseline BCVA:* ≈0.7 (index/30 cm) *Inclusion criteria:* Patients with diagnosis of exudative AMD following the diagnostic criteria in Chinese ophthalmology diagnosing guidance *Exclusion criteria:* N/R	*Index test:* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test:* ICGA *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (unclear if stereoscopic or not)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient, except in 13 patients with both eyes assessed) *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 62.90% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Do 2012[27] *Full text:* Yes *Study type:* Direct head-to-head observational *Prospective:* Yes *Multicentre:* Yes (four centres) *Country:* USA *Study start/end dates:* N/R *Duration of study:* 2 years	*Enrolled:* 98 patients *Analysed:* 87 patients *Consecutive:* No *Age (years) median (range):* 79 (58–91) *Gender M : F:* 31 : 56 *Baseline BCVA:* Median 20/25 (Snellen equivalent), range (66–95) *Inclusion criteria:* Minimum age 50 years, nAMD in the non-study eye, BCVA (ETDRS) of $\geq$ 65 (Snellen of approximately 20/50), no evidence of CNV or foveal geographic atrophy in the fellow eye (candidate study eye), $\geq$ 1 large druse (> 125 μm) and focal RPE hyperpigmentation within 3600 μm of the macula centre, visible on colour or red-free fundus photographs or FFA *Exclusion criteria:* Allergy to fluorescein dye, advanced AMD with CNV in both eyes confirmed on FFA, geographic atrophy extending through the centre of the macula in the candidate study eye, positive OCT for the candidate eye, evidence of macular disease other than AMD in the candidate study eye, prior surgical or laser treatment to the macula in the study eye	*Index test:* TD-OCT (Stratus OCT™) *Definition of positive test result:* 10% increase in the central subfield thickness measurement relative to baseline, subretinal fluid questioned or graded as definitely present, intraretinal cystoid abnormalities questioned or graded as definitely present *Interpreted by:* trained masked graders at the reading centre *Comparator test(s):* Amsler grid (supervised) PHP *Definition of positive test result:* Any defect perceived by the subject *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* two trained masked graders at the reading centre	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* n/a *Diagnostic accuracy:* Yes *Sensitivity:* CNV defined by the reading centre only Irrespective of treatment decision TD-OCT 40% (95% CI 16% to 68%) Amsler grid 41.7% (95% CI 15% to 72%) PHP 50% *Specificity:* TD-OCT 70.8% Amsler grid N/R PHP N/R *Clinical effectiveness:* N/R *Interpretability of the test:* 6/68 (8.8%) screened but not enrolled as ineligible and excluded cases due to poor image quality that was insufficient to permit successful study participation *Acceptability of the test:* n/a *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Fujii 1996[29] Full *text:* Yes *Study type:* Direct head-to-head [all participants receive index and comparator test(s) and reference standard] *Prospective/ retrospective:* Unclear *Multicentre:* No *Country*: Japan *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 24 patients (32 eyes) *Analysed:* 24 patients (32 eyes) *Consecutive:* Unclear *Age (years) mean (range):* 68.6 (61–86) *Gender M : F:* 17 : 7 *Baseline BCVA:* N/R *Inclusion criteria:* Patients with diagnosis of AMD with CNV not detected by FFA, or unlikely to be the subject of photocoagulation (e.g. CNV located in the fovea) *Exclusion criteria:* N/R	*Index test:* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test:* ICGA *Definition of positive test result:* Four stages: stage I neovascularisation of RPE without injury of palisade tissue; stage II bleeding (leakage) – subretinal haemorrhage injury of RPE, exudates subretinal space; stage III subretinal fibrosis and membranes proliferation plus stage II; and stage IV scar tissue *Interpreted by:* N/R *Reference standard:* Non-stereoscopic FFA interpreted by ophthalmologist *Interpreted by:* N/R	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 84.61% *Specificity:* 36.84% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Gomi 2007[31] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective/ retrospective:* Unclear *Multicentre:* No *Country:* Japan *Study start/end dates:* July 2005/January 2006 *Duration of study:* 6 months	*Enrolled:* 37 patients *Analysed:* 37 patients *Consecutive:* Unclear *Age (years) mean (range):* 71.6 (54–83) *Gender M : F:* 27 : 10 *Baseline BCVA:* N/R *Inclusion criteria:* Patients diagnosed with PCV in the macular region; informed consent provided *Exclusion criteria:* Eyes with subretinal or subpigment epithelial haemorrhages that obscured lesions; eyes with a history of any previous treatment and any other macular pathologies such as CNV or central serous chorioretinopathy	*Index test:* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test:* ICGA *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Non-stereoscopic FFA *Interpreted by:* Images were traced by two readers. When no agreement was reached by the readers on the location of the lesion borders, another author arbitrated	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 100% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test*: N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Hughes 2005[33] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective:* Yes *Multicentre:* No *Country:* UK *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 22 patients *Analysed:* 22 patients *Consecutive:* Yes *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R Baseline BCVA: N/R *Inclusion criteria:* Patients with acute CNV *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (OCT 3000™, Carl Zeiss Ophthalmic Systems Inc., Dublin, CA) *Definition of positive test result:* Presence of a discreet subretinal lesion indicating a CNV membrane *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (unclear if stereoscopic or not)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 36.36% *Specificity:* n/a *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Khondkaryan 2009[34] *Abstract:* Yes *Study type:* Direct head-to-head [all participants receive index and comparator test(s) and reference standard] *Retrospective:* Yes *Multicentre:* N/R *Country:* USA *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 51 patients (51 eyes) *Analysed:* 51 patients (51 eyes) *Consecutive:* Yes *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* Newly diagnosed patients with nAMD who underwent stratus OCT imaging and FFA at the time of diagnosis *Exclusion criteria:* N/R	*Index test:* TD-OCT (Stratus OCT™) *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether stereoscopic or not)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* Classic CNV 80.90% RAP 57.10% Occult CNV 81.10% *Specificity:* Classic CNV 56.70% RAP 81.80% Occult CNV 42.90% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Kim 2003[35] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* the Republic of Korea *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 32 patients (32 eyes) *Analysed:* 13 eyes *Consecutive:* Unclear *Age (years) mean (SD):* 51.38 (20.68) *Gender M : F:* 16 : 16 *Baseline BCVA:* N/R *Inclusion criteria:* Patients with diagnosis of CNV *Exclusion criteria:* N/R	*Index test:* TD-OCT (manufacturer N/R) *Definition of positive test result:* Lesion classed as well defined, poorly defined, fibrovascular PED, haemorrhagic PED and serous PED (not considered as this is a diagnostic study) *Interpreted by:* N/R *Comparator test:* ICGA *Definition of positive test result:* Hyperfluorescent lesion by ICGA was confined as the leaking on late phase, and measured relative to the diameter of the optic disc *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic) *Interpreted by:* N/R	*Unit of analysis* (n): Eye *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 92.30% *Specificity:* N/R *Clinical effectiveness:* No *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Kozak 2008[36] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* USA *Study start/end dates:* 1 October 2005/ 1 October 2006 *Duration of study:* 12 months	*Enrolled:* Unclear (541 eyes) *Analysed:* 541 eyes *Consecutive:* Yes *Age (years) mean/median (range/SD):* 54 ± 12.1 years *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* Patients with diagnosis of macular oedema (confirmed or suspected) *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (Stratus OCT™) although a subset of patients received SD-OCT (SLO, OTI Ophthalmic Technologies, Inc., Toronto, ON, Canada) *Definition of positive test result:* Macular oedema defined as loss of central contour, intraretinal cysts, subretinal fluid, retinal thickening > 250 μm (foveal and perifoveal) *Interpreted by:* Ophthalmologists *Comparator test(s):* Colour fundus photograph (TRC-50 VT, Topcon, Tokyo, Japan) *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Ophthalmologists (retina specialists)	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 97.3% *Specificity:* n/a *Clinical effectiveness:* N/R *Interpretability of the test:* 35 eyes (6.5%) were excluded from the analysis due to poor quality or image decentration *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Krebs 2007[37] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* Austria *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 50 patients *Analysed:* 50 patients *Consecutive:* No *Age (years) mean/median (range/SD):* 77.8 ± 6.4 years *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* N/R *Exclusion criteria:* N/R	Index test(s): TD-OCT (OCT 3000™) *Definition of positive test result:* Increase retinal thickness compared with healthy retina of the study eye or fellow eye, neurosensory detachment, PED *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* CNV primarily classic 100% RAP 72.7% *Specificity:* 100% for dry AMD (as negative diagnosis) *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Liakopoulos 2008[38] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* USA *Studystart/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 66 patients (eyes) *Analysed:* 66 patients (eyes) *Consecutive:* Y/N *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* Previously untreated, active subfoveal CNV due to AMD, stratus OCT and FFA imaging performed on the same date, the entire CNV lesion had to fall within a 6 mm-diameter circle centred on the fovea *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (Stratus OCT™) *Definition of positive test result:* Active CNV defined as the presence of haemorrhage or evidence of lesion growth within the prior 3 months *Interpreted by:* Certified graders *Comparator test(s):* Colour fundus photographs (TOPCON 50 I X, Topcon, Tokyo, Japan) *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Ophthalmologists (certified graders)	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity based on subretinal fluid:* Occult with no classic 79.2% Minimally classic 91.3% Predominantly classic 100% RAP stage III 50% All subtypes 83.3% *Specificity:* n/a *Sensitivity based on cystoid oedema:* Occult with no classic 79.2% Minimally classic 91.3% Predominantly classic 81.8% RAP stage III 100% All subtypes 72.7% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Loewenstein 2010[39] *Full text:* Yes *Study type:* Prospective and retrospective *Prospective/ retrospective:* Yes *Multicentre:* Yes *Country:* Israel, USA (for the prospective part only) *Study start/end dates:* Retrospective part: January–September 2007 Prospective part: April–September 2008 *Duration of study:* Retrospective part: 8 months Prospective part: 5 months	*Enrolled:* Retrospective: 109 patients Prospective: 99 patients *Analysed:* Retrospective part: 77 patients Prospective part: 54 patients *Consecutive:* Retrospective part: Unclear Prospective part: Yes *Age (years) mean/median (range/SD):* Retrospective part: 76 years Prospective part: 78 years *Gender M : F:* Retrospective part: 41 : 35 (one unknown) Prospective part: 17 : 34 (three unknown) *Baseline BCVA:* Retrospective part: 20/33 (iAMD group); 20/63 (CNV group) Prospective part: 20/30 (iAMD group); 20/63 (CNV group) *Inclusion criteria:* Retrospective part: Passing an in-house tutorial Prospective part: Mouse experience, willingness and ability to sign a written informed consent, intermediate AMD (using the definition from Age-Related Eye Disease study), recent onset CNV within 3000 µm of the fovea in the study eye, aged > 50 years, CVA > 20/200 on Snellen charts	*Index test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* PHP *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* N/R	*Unit of analysis (n):* Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* Retrospective part: 85.3% Prospective part: 84.4% All: 84.8% *Specificity:* Prospective part: 83.7% Retrospective part: 86.4% All: 84.6% *Clinical effectiveness:* N/R *Interpretability of the test:* 40 patients (19.2%) were excluded from the analysis due to geographic atrophy, early AMD, pattern dystrophy, no or poor-quality photographs Acceptability of the test: N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
	Exclusion criteria: Macular disease other than AMD, geographic atrophy, media opacity precluding a clear view of the fundus, no or poor-quality photographs that prevented unambiguous grading, ocular surgery in the study eye within the previous 3 months		
Padnick-Silver 2012[40] *Full text:* Yes *Study type:* Observational, non-randomised *Prospective:* Yes *Multicentre:* No *Country:* USA *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 79 patients *Analysed:* 77 patients *Consecutive:* Unclear *Age (years) mean/median (range/SD):* 79.7 ± 6.3 years *Gender M : F:* 24 : 55 *Baseline BCVA:* 0.27 ± 0.21 (≈20/40) in the study eye, 1.42 ± 0.74 (< 20/400) in the fellow eye *Inclusion criteria:* Patients with bilateral AMD who had developed unilateral exudative changes *Exclusion criteria:* Presence of other retinal disease in the eye with non-exudative AMD, for example, significant diabetic retinopathy, glaucomatous retinal atrophy, retinal detachment	*Index test(s):* TD-OCT (Stratus OCT™) *Definition of positive test result:* Subretinal pigment epithelial or subretinal fluid *Interpreted by:* Retinal physician *Comparator test(s):* N/R *Definition of positive test result:* n/a *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* n/a *Diagnostic accuracy:* Yes *Sensitivity:* 80% *Specificity:* 93.5% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Park 2010[41] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective:* Yes *Multicentre:* No *Country:* USA *Study start/end dates:* September 2005/June 2006 *Duration of study:* 9 months	*Enrolled:* 19 patients (21 eyes) *Analysed:* 21 eyes *Consecutive:* Unclear *Age (years) Mean/median (range/SD):* 78 (48–92) years *Gender M : F:* 8 : 11 *Baseline BCVA:* N/R *Inclusion criteria:* Patients newly diagnosed with exudative AMD *Exclusion criteria:* Eyes diagnosed with RAP or concurrent macular haemorrhage that may obscure part of the CNM on FFA	*Index test(s):* SD-OCT (Fourier domain) (constructed at the University of California, Davis Medical Centre) *Definition of positive test result:* CNVM images as a highly reflective lesion in the subretinal space, subretinal pigment epithelial space or both *Interpreted by:* Ophthalmologists (retinal specialists) *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* Ophthalmologists (retinal specialists)	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 100% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Parravano 2012[42] *Abstract:* Yes *Study type:* Diagnostic cross-sectional *Prospective:* Yes *Multicentre:* Yes (eight centres) *Country:* Italy *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 155 patients (201 eyes) *Analysed:* 155 patients *Consecutive:* Yes *Age (years) mean/median (range/SD):* 76 ± 8 years *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* Patients with newly diagnosed neovascular AMD *Exclusion criteria:* N/R	*Index test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA *Definition of positive test result:* N/R *Interpreted by:* All images were graded by two observers from different institutions *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* All images were graded by two observers from different institutions	*Unit of analysis* (n): Patient *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 85.1% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Reichel 1995[44] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective/ retrospective:* N/R *Multicentre:* No *Country:* USA *Study start/end dates:* September 1991/ January 1993 *Duration of study:* 16 months	*Enrolled:* 200 patients *Analysed:* 20 patients *Consecutive:* Yes *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* Patients with central visual symptoms with clinical suspicious for CNV due to the presence of a retinal PED, exudates, subretinal fluid, macular oedema and/or subretinal or intraretinal haemorrhage, patients suspected to have a CNV obscured by haemorrhage *Exclusion criteria:* Patients with small amounts of intraretinal or subretinal haemorrhage (no significant thickening on slit lamp biomicroscopy), known allergy to iodine-base dye, previous laser photocoagulation in the study eye	*Index test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 100% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Salinas-Alaman 2005[45] *Full text:* Yes *Study type:* Direct head-to-head comparison, observational *Prospective:* Yes *Multicentre:* No *Country:* Spain *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 53 patients *Analysed:* 62 eyes (53 patients) *Consecutive:* Yes *Age (years) mean/median (range/SD):* 76.50 ± 7.5 years *Gender M : F:* 26 : 27 *Baseline BCVA:* 20/80 *Inclusion criteria:* Patients presenting with signs of exudative AMD with predominantly classic CNV *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (OCT 2000™, Humphrey Instruments, San Leonardo, CA) *Definition of positive test result:* Presence of subretinal or intraretinal fluid *Interpreted by:* Unclear (independent observers) *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* Unclear (independent observers)	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 96.8% *Specificity:* n/a *Clinical effectiveness:* N/R *Interpretability of the test:* 20 cases (9.6%) were excluded from the analysis as OCT tests were performed by a less experienced technician *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Sandhu 2005[46] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective:* Yes *Multicentre:* No *Country:* UK *Study start/end dates:* N/R *Duration of study:* 6 months	*Enrolled:* 128 patients *Analysed:* 118 patients (131 eyes) *Consecutive:* Yes *Age (years) mean/median (range/SD):* 73.2 ± 13.7 (30–97) years *Gender M : F:* 42.4% : 57.6% *Baseline BCVA:* N/R *Inclusion criteria:* First time presentation of suspected CNV with potentially treatable lesion; predominantly classic CNV with no PED *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (OCT 3™, Zeiss, Dublin, CA) *Definition of positive test result:* (a) classic CNV – subretinal band (RPE) with choriocapilaris thickened and disrupted-fusiform shape with/without intraretinal or subretinal fluid; (b) occult CNV – less well-defined band than '(a)' but more subRPE with more disorganisation of the retina and intraretinal fluid (cystoid)/subretinal fluid; (c) serous PED – dome shape elevation of the reflective band (RPE) with area of low reflectivity underneath *Interpreted by:* Ophthalmologists *Comparator test(s):* SD-OCT + stereo colour fundus photography *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Ophthalmologists	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* SD-OCT: 77.8% SD-OCT + stereo colour fundus photograph: 74.1% *Specificity:* SD-OCT: 76% SD-OCT + stereo colour fundus photograph): 92.0% *Clinical effectiveness:* N/R *Interpretability of the test:* 10 patients (7.8%) were excluded from the analysis due to poor quality of images *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Sulzbacher 2011[48] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective/ retrospective:* Unclear *Multicentre:* No *Country:* Austria (Vienna) *Study start/end dates:* July 2008/August 2009 *Duration of study:* 12 months	*Enrolled:* 13 eyes *Analysed:* 13 eyes *Consecutive:* Yes *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R *Baseline BCVA:* N/R *Inclusion criteria:* CNV type 2 treatment-naive eyes without an occult component *Exclusion criteria:* Occult component (CNV), neovascular maculopathy from pathologic myopia, angioid streaks, infectious inflammatory chorioretinal disease, tumours, hereditary disorders or trauma	*Index test(s):* SD-OCT (Spectralis™, Heidelberg Engineering, Heidelberg, Germany) *Definition of positive test result:* N/R *Interpreted by:* Certified reader at the Vienna reading centre (non-ophthalmologist technician, optometrist, nurse, or other) *Comparator test(s):* ICGA *Definition of positive test result:* Detection of type 2 CNV (without an occult component): area of choroidal hyperfluorescence with well-demarcated boundaries, with progressive leakage beyond the initial boundaries of the CNV and an area of hypercyanescence without marked leakage activity on ICGA (early phase – neovascular complex; late phase – retinal leakage) *Interpreted by:* Certified reader at the Vienna reading centre (non-ophthalmologist technician, optometrist, nurse, or other) *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* Ophthalmologists (experienced readers)	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 100% *Specificity:* N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 42 Diagnostic studies (*continued*)

Study	Participants	Tests	Outcomes reported
Talks 2007[49] *Full text:* Yes *Study type:* Retrospective audit *Retrospective:* Yes *Multicentre:* No *Country:* UK *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 134 patients *Analysed:* 111 patients *Consecutive:* Yes *Age (years) mean/median (range/SD):* 84.6 (58–97) years *Gender M : F:* 53:81 *Baseline BCVA:* N/R *Inclusion criteria*: Patients referred with suspected wet AMD *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (OCT 3™, Zeiss) *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA *Definition of positive test result:* N/R *Interpreted by:* Ophthalmologists *Reference standard:* Stereoscopic FFA *Interpreted by:* Ophthalmologists	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 100% *Specificity:* 65.8% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Torron 2002[51] (and 2-year interim study – Torron 2001)[50] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* Spain *Study start/end dates:* April 1998/April 2001 *Duration of study:* 3 years	*Enrolled:* Torron 2002[51] – 95 patients (102 eyes) Torron 2001[50] – 55 patients (56 eyes) *Analysed:* Torron 2002[51] – 102 eyes Torron 2001[50] – 56 eyes *Consecutive:* Unclear *Age (years) mean/median (range/SD):* 75.3 (60–85) years *Gender M : F:* 44 : 51 *Baseline BCVA:* ≤ 0.1 (42 eyes), 0.1–0.3 (28 eyes), > 0.3 (30 eyes) *Inclusion criteria:* N/R *Exclusion criteria:* N/R	*Index test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA (SLO 101, Rodenstock, Germany) *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* N/R	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* Torron 2002:[51] 92.2% Torron 2001:[50] 89.3% *Specificity:* Torron 2002[51]/2001:[50] N/R *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

BCVA, best corrected visual acuity; CNM, choroidal neovascular membrane; F, female; iAMD, intermediate age-related macular degeneration; M, male; n/a, not applicable; N/R, not reported; PCV, polpoidal choroidal vasculopathy; SD, standard deviation.

a Agreement by the research group on studies with no information on FFA. It was assumed that in these studies, non-stereoscopic FFA-interpreted by ophthalmologists has been performed.

TABLE 43 Monitoring studies

Study	Participants	Tests	Outcomes reported
Eter 2005[28] *Full text:* Yes *Study type*: Direct head-to head comparison *Retrospective:* Yes *Multicentre:* Yes (two centres) *Country:* Germany *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 60 patients (60 eyes) *Analysed:* 60 patients (60 eyes) *Consecutive:* Yes *Age (years) median:* 78 years *Gender M : F:* 31 : 29 *Baseline BCVA:* 20/100 *Inclusion criteria:* Patients with predominantly classic CNV secondary to AMD treated with PDT with verteporfin *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (Zeiss, Humphrey Instruments) *Definition of positive test result:* Subretinal fluid or cystoid spaces within the retina. Subretinal fluid defined as hyporeflective, black zone between retinal pigment epithelial layer and outer neuro-sensory retinal surface. Cystoid spaces defined as hyporeflective black area of at least 2 × 2 pixels within the neuro-retina *Interpreted by:* Ophthalmologists *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (unclear if stereoscopic or not)[a] *Interpreted by:* N/R	*Unit of analysis (n): Eye (one eye per patient)* *If both eyes per subject eligible, how was study eye selected: N/R* *Diagnostic accuracy: Yes* *Sensitivity: 80%* *Specificity: 80%* *Clinical effectiveness: N/R* *Interpretability of the test: N/R* *Acceptability of the test: N/R* *Proportion of participants not able to receive the test due to an eye condition/personal circumstances: N/R*
Giani 2011[30] *Full text:* Yes *Study type:* Direct head-to-head comparison, cross-sectional *Retrospective:* Yes *Multicentre:* No *Country:* Italy (Milan) *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 93 patients (93 eyes) *Analysed:* 93 patients (93 eyes) *Consecutive:* Yes *Age (years) mean (range/SD):* 77 years *Gender M : F:* 41 : 52 *BCVA:* Mean 0.40 (SD 0.25) *Inclusion criteria:* Clinical history of AMD, FFA diagnosis of subfoveal CNV, previous treatment with antiVEGF agents for CNV *Exclusion criteria:* Any previous laser treatment, PDT, vitreo-retinal surgery, macular haemorrhage (significant) that obscured the lesion, spherical refractive error > 6 diopters	*Index test(s):* SD-OCT (HRA + OCT Spectralis™) *Definition of positive test result:* At least one of the following parameters: intraretinal cystic spaces, without differentiation in retinal layer localisation, content, or number/density; RPE detachment (PED), defined as a localised elevation of RPE due to fluid or fibrovascular tissue; and neurosensory retinal detachment, defined as a fluid detachment of the retinal layers from the RPE *Interpreted by:* N/R (two different examiners) *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Dynamic video FFA (unclear if stereoscopic or not)[a] *Interpreted by:* N/R	Unit of analysis (*n*): Eye (1 eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* Overall: 94.2% Classic: 90.9% Occult: 100% *Specificity:* Overall: 26.8% Classic: 37.5% Occult: 11.8% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 43 Monitoring studies (*continued*)

Study	Participants	Tests	Outcomes reported
Henschel 2009[32] *Full text:* Yes *Study type*: Direct head-to-head comparison *Prospective:* Yes *Multicentre:* No *Country:* Germany *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* 14 patients (61 examinations) *Analysed:* 61 pair of examinations (OCT and FFA) *Consecutive:* Unclear *Age (years) mean/median (range/SD):* N/R *Gender M : F:* N/R *BCVA:* 20/32 – 20/200 (range) *Inclusion criteria:* Patients with CNV for AMD (different types as predominantly classic and occult) *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (Stratus OCT™) *Definition of positive test result:* Presence of intraretinal or subretinal fluid present when loculated hyporeflective cystoid spaces were visible in one of the acquired scans; subretinal fluid was rated as present if a hyporeflective space was definable between the outer retinal surface and the hyporeflective RPE/choriocapilary complex in one of the OCT scans *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (unclear if stereoscopic or not)[a] *Interpreted by:* Ophthalmologists	*Unit of analysis* (n): Examination *Diagnostic accuracy:* Yes *Sensitivity:* CNV based in detection of intraretinal fluid: 90.3% CNV based on detection of subretinal fluid: 71% CNV based on detection of intraretinal and/or subretinal fluid: 96.8% *Specificity:* CNV based in detection of intraretinal fluid: 40% CNV based on detection of subretinal fluid: 73.3% CNV based on detection of intraretinal and/or subretinal fluid: 36.7% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 43 Monitoring studies (*continued*)

Study	Participants	Tests	Outcomes reported
Khurana 2010[23] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country*: USA *Study start/end dates:* November 2007/ June 2008 *Duration of study:* 8 months	*Enrolled:* 56 patients (59 eyes) *Analysed:* 59 eyes *Consecutive:* Yes *Age (years) mean/median (range/SD):* 78.1 (7.8) *Gender M : F:* N/R *BCVA:* 0.64 ± 0.35 (mean, log-MAR); Snellen equivalent 20/80 (median) *Inclusion criteria:* Age ≥ 50 years, CNV secondary to AMD, FFA, TD-OCT and SD-OCT performed at the same visit *Exclusion criteria:* Patients with CNV resulting from other causes	*Index test(s):* TD-OCT (Stratus OCT™) and SD-OCT (Cirrus™, Carl Zeiss Meditec, Dublin, CA) *Definition of positive test result:* Presence of interstitial retinal fluid, retinal cystoid abnormalities, and subretinal fluid (subretinal pigment epithelial abnormalities were not evaluated) *Interpreted by:* Trained grader (non-ophthalmologist technician, optometrist, nurse, or other) *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Trained grader (non-ophthalmologist technician, optometrist, nurse, or other)	*Unit of analysis* (n): Eye *Was adjustment made for non-independence of fellow eyes for cases where both eyes per subject included:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* TD-OCT: 58.6% SD-OCT: 89.7% *Specificity:* TD-OCT: 63.3% SD-OCT: 46.7% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R
Regillo 1998[43] *Full text:* Yes *Study type:* Direct head-to-head comparison *Prospective:* Yes *Multicentre:* No *Country:* USA *Study start/end dates:* April 1995/ December 1996 *Duration of study:* 20 months	*Enrolled:* 21 patients (24 eyes) *Analysed:* 54 examinations *Consecutive:* Yes Age (years) mean/median (range/SD): 75 (59–91) years *Gender M : F:* 11 : 10 *BCVA:* N/R *Inclusion criteria:* patients with eAMD that had conventional laser treatment for CNV, first post-treatment visit and all subsequent follow-up *Exclusion criteria:* N/R	*Index test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Comparator test(s):* ICGA (H1024, Topcon, Tokyo, Japan) *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Unclear if FFA stereoscopic or not [as macular stereoscopic colour fundus photographs were taken at the beginning of all angiogram (or FFA) pairs] *Interpreted by:* Ophthalmologists	*Unit of analysis* (n): Examination *Diagnostic accuracy:* Yes *Sensitivity:* 75.9% *Specificity:* 88% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 43 Monitoring studies (*continued*)

Study	Participants	Tests	Outcomes reported
Salinas-Alaman 2005[45] *Full text:* Yes *Study type:* Direct head-to-head comparison, observational *Prospective:* Yes *Multicentre:* No *Country:* Spain *Study start/end dates:* N/R *Duration of study:* N/R	*Enrolled:* N/R *Analysed:* Follow-up at 6 months 62 eyes Follow-up at 12 months 42 eyes *Consecutive:* Yes *Age (years) mean/median (range/SD):* 76.5 ± 7.5 years at 6 months (N/R at 12 months) *Gender M : F:* 26 : 27 at 6 months (N/R at 12 months) *BCVA: N*/R *Improvement of BCVA reported:* At 6 months: 40 eyes same VA; 7 eyes improved VA; 15 eyes with worse VA At 12 months: 25 eyes same VA; 5 eyes improved VA; 12 eyes with worse VA *Inclusion criteria:* Patients presenting with signs of exudative AMD with predominantly classic CNV *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (OCT 2000™, Humphrey Instruments) *Definition of positive test result:* Presence of subretinal or intraretinal fluid *Interpreted by:* Unclear (independent observers) *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* FFA (not specified whether or not stereoscopic)[a] *Interpreted by:* Unclear (independent observers)	*Unit of analysis* (n): Remarks (= examination) *Diagnostic accuracy:* Yes (CNV activity after PDT treatment) *Sensitivity:* 95.7% *Specificity:* 59% *Clinical effectiveness:* N/R *Interpretability of the test:* 20 cases (9.6%) were excluded from the analysis as OCT tests were performed by a less experienced technician *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

continued

TABLE 43 Monitoring studies (*continued*)

Study	Participants	Tests	Outcomes reported
van de Moere 2006[52] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* UK *Study start/end dates:* July 2001/October 2004 *Duration of study:* 3 years, 3 months	*Enrolled:* 136 patients *Analysed:* 121 eyes (121 patients) *Consecutive*: Yes *Age (years) mean/median (range/SD):* 73.9 (30–94) years *Gender M : F:* 55 : 66 *BCVA:* N/R *Inclusion criteria:* Patients who had all received initial PDT with verteporfin (Visudyne®, Novartis AG) for a classic or predominantly classic subfoveal CNV secondary to AMD *Exclusion criteria:* Poor quality of the OCT or FFA images	*Index test(s):* TD-OCT (OCT 3™, Zeiss) *Definition of positive test result:* PED (not specified if vascular component present or not), subretinal fluid, intraretinal fluid (solitary foveal cyst, sponge-like retinal thickening, intraretinal cysts or cystoid macular oedema), vitreomacular tractions *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* Ophthalmologists	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected*: If both eyes were eligible, one eye was randomly chosen for analysis *Diagnostic accuracy:* Yes *Sensitivity:* PED: 5.7% Subretinal fluid: 47.1% Intraretinal fluid: 82.9% Cystoid macular oedema: 98% *Specificity:* PED: 100% Subretinal fluid: 84.3% Intraretinal fluid: 52.9% Cystoid macular oedema: 22.9% *Clinical effectiveness:* N/R *Interpretability of the test:* 17 cases (12.5%) were excluded from analysis due to poor quality of OCT or FFA *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

TABLE 43 Monitoring studies (*continued*)

Study	Participants	Tests	Outcomes reported
van Velthoven 2006[53] *Full text:* Yes *Study type:* Direct head-to-head comparison *Retrospective:* Yes *Multicentre:* No *Country:* Netherlands *Study start/end dates:* July 2003/October 2003 *Duration of study:* 3 months	*Enrolled:* 30 patients (30 eyes) *Analysed:* 30 patients (30 eyes) *Consecutive:* Yes *Age (years) mean/median (range/SD):* 75.5 ± 9.0 years *Gender M : F:* 13 : 17 *BCVA:* Mean 45 ± 14 (SD) *Inclusion criteria:* Patients with AMD and subfoveal CNV who had received at least one prior PDT treatment *Exclusion criteria:* N/R	*Index test(s):* TD-OCT (Stratus OCT™) *Definition of positive test result:* OCT activity score – positive if any sign of leakage, that is cystoid macular oedema and/or subretinal fluid and/or retinal thickening *Interpreted by:* N/R *Comparator test(s):* N/R *Definition of positive test result:* N/R *Interpreted by:* N/R *Reference standard:* Stereoscopic FFA *Interpreted by:* N/R	*Unit of analysis* (n): Eye (one eye per patient) *If both eyes per subject eligible, how was study eye selected:* N/R *Diagnostic accuracy:* Yes *Sensitivity:* 65.2% *Specificity:* 42.9% *Clinical effectiveness:* N/R *Interpretability of the test:* N/R *Acceptability of the test:* N/R *Proportion of participants not able to receive the test due to an eye condition/personal circumstances:* N/R

eAMD, exudative age-related macular degeneration; N/R, not reported; SD, standard deviation.
a Agreement by the research group on studies with no information on FFA. It was assumed that in these studies, non-stereoscopic FFA-interpreted by ophthalmologists has been performed.

Appendix 5 Results of the risk of bias and applicability concerns for the individual full-text studies

TABLE 44 Diagnostic studies ($n = 20$ studies, 22 reports)

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Alster 2005[24]	–	+	+	–	+	+	+
Cachulo 2011[25]	?	?	?	–	+	+	+
Chen 2003[26]	?	?	?	+	+	+	+
Do 2012[27]	–	+	+	–	+	+	+
Fujii 1996[29]	?	?	?	?	+	+	+
Gomi 2007[31]	–	?	?	+	+	+	+
Hughes 2005[33]	?	+	+	?	+	+	+
Kim 2003[35]	?	?	?	?	+	+	+
Kozak 2008[36]	+	?	?	–	+	+	+
Krebs 2007[37]	–	+	+	+	+	+	+
Liakopoulos 2008[38]	–	+	?	+	+	+	+
Loewenstein 2010[39]	–	?	?	–	+	+	+
Padnick-Silver 2011[40]	–	?	?	–	+	+	+
Park 2010[41]	–	+	?	+	+	+	+
Reichel 1995[44]	–	–	–	+	+	+	+
Salinas-Alaman 2005[45]	–	?	?	?	+	+	+
Sandhu 2005[46]	?	+	+	–	+	+	+
Silva 2011[47]	?	?	?	–	+	+	+
Sulzbacher 2011[48]	?	?	?	?	+	+	+
Talks 2007[49]	–	+	–	–	+	+	+
Torron 2001[50]	?	–	–	+	+	+	+
Torron 2002[51]	?	–	–	?	+	+	+

–, high risk; +, low risk; ?, unclear.

TABLE 45 Monitoring studies ($n = 8$ studies, 8 reports)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Eter 2005[28]	?	+	+	?	+	+	+
Giani 2011[30]	–	+	+	?	–	+	+
Henschel 2009[32]	?	+	+	?	+	+	+
Khurana 2010[23]	?	?	?	+	+	+	+
Regillo 1998[43]	+	–	–	+	+	+	+
Salinas-Alaman 2005[45]	–	?	?	–	+	+	+
van de Moere 2006[52]	+	?	?	–	+	+	+
van Velthoven 2006[53]	+	?	+	?	+	+	+

–, high risk; +, low risk; ?, unclear.

Appendix 6 Individual study results

TABLE 46 Diagnostic studies ($n = 24$ reports of 22 studies)

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Alster 2005[24]	PHP	Eye/patient	122	53	7	12	50	81.5	87.7
	Colour fundus photography	Eye/patient	120	45	3	19	53	70.0	95.0
	Colour fundus photography plus VA	Eye/patient	66	10	3	9	44	53.0	94.0
Cachulo 2011[25]	TD-OCT	Eye/patient	52	17		0		100.0	NC
	ICGA	Eye/patient	52	16		1		94.1	NC
	FAF (but not clear whether before conversion or at time of conversion so may not be usable)	Eye/patient	50	14	22	1	13	93.3	37.1
Silva 2011[47] (secondary report to Cachulo 2011[25])	TD-OCT	Eye/patient	52	24		0		100.0	NC
Chen 2003[26]	ICGA	Eye							
		Occult CNV detection	35	22		13		62.9	NC
Do 2012[27]	CNV defined as FFA positive by the Reading Centre irrespective of treatment decision ($n = 15$)								
	TD-OCT	Eye/patient	87	6	21	9	51	40.0	70.8
	Amsler grid	Eye/patient	46	5	NC	7	34	41.7	N/R
	PHP	Eye/patient	49	6	NC	6	37	50.0	N/R
	CNV defined as FFA positive by the Reading Centre and the clinician recommended treatment ($n = 13$)								
	TD-OCT	Eye/patient	87	9	25	4	49	69.2	66.2
	Amsler grid	Eye/patient	47	5	NC	5	37	50.0	N/R
	PHP	Eye/patient	45	7	NC	3	35	70.0	N/R

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Fujii 1996[29]	ICGA/DH/DS	Eye	32	11	12	2	7	84.6	36.8
Gomi 2007[31]	ICGA/DH/DS	Eye/patient							
		PCV detection	37	37	NC	0	NC	100.0	NC
Hughes 2005[33]	TD-OCT	Eye/patient	22	8		14		36.4	NC
Khondkaryan 2009[34]	TD-OCT	Eye/patient							
		Detection of occult	51	30	8	7	6	81.1	42.9
		Detection of classic	51	17	13	4	17	80.9	56.7
		Detection of RAP	51	4	8	3	36	57.1	81.8
Kim 2003[35]	TD-OCT	Eye/patient	13	12		1		92.3	NC
Kozak 2008[36]	TD-OCT (although subset of patients received SD-OCT)	Eye	541	514	13	14	NC	97.3	NC
Krebs 2007[37]	TD-OCT	Eye							
		Primarily classic	5	5		0		100.0	
		RAP	11	8		3		72.7	
		Dry AMD as negative diagnosis	12		0		12		100.0

continued

TABLE 46 Diagnostic studies ($n = 24$ reports of 22 studies) (*continued*)

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Liakopoulos 2008[38]	TD-OCT	Eye/patient ($n = 66$ for both)							
		Subretinal fluid							
		Occult with no classic	24	19		5		79.2	NC
		Minimally classic	23	21		2		91.3	NC
		Predominantly classic	11	11		0		100.0	NC
		RAP stage III	8	4		4		50.0	NC
		All	66	55		11		83.3	NC
		Cystoid oedema							
		Occult with no classic	24	14		10		58.3	NC
		Minimally classic	23	17		6		73.9	NC
		Predominantly classic	11	9		2		81.8	NC
		RAP stage III	8	8		0		100.0	NC
		All	66	48		18		72.7	NC
Loewenstein 2010[39]	PHP	Eye/patient							
		Retrospective part	77	29	7	5	36	85.3	83.7
		Prospective part	54	27	3	5	19	84.4	86.4
		All	131	56	10	10	55	84.8	84.6

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Padnick-Silver 2012[40]	TD-OCT	Eye/patient	77	12	4	3	58	80.0	93.5
Park 2010[41]	SD-OCT	Eye	21	21		0		100.0	NC
Parravano 2012[42]	ICGA	Patient							
		Detection of RAP	155	40		7		85.1	NC
Reichel 1995[44]	ICGA	Eye/patient	20	16	4	0	NC	100.0	NC
Salinas-Alaman 2005[45]	TD-OCT	Eye	62	60		2		96.8	NC
Sandhu 2005[46]	TD-OCT	Eye	131	63	12	18	38	77.8[a]	76.0[a]
	SD-OCT + stereo colour fundus photography	Eye	131	60	4	21	46	74.1[a]	92.0[a]
Sulzbacher 2011[48]	ICGA	Eye							
		Detection of type 2 CNV without an occult component	13	13		0		100.0	NC
Talks 2007[49]	TD-OCT	Eye/patient	111	73	13	0	25	100.0	65.8
Torron 2002[51]	ICGA	Eye	102	94		8		92.2	NC
Torron 2001[50] (secondary report to Torron 2002[51])	ICGA	Eye	56	50		6		89.3	NC

DH, direct head-to-head comparison; DS, diagnostic study; NC, not calculable; N/R, not reported; PCV, polpoidal choroidal vasculopathy.

a The values given for TP, FP, FN, TN and sensitivity and specificity are our calculations, not those of Sandhu and Talks.[46] Sandhu and Talks[46] reported sensitivity and specificity including serous PED as presence of nAMD. However, as a serous PED did not fall within our definition of nAMD for diagnostic studies, data presented in the paper were recalculated accordingly. The values reported by Sandhu and Talks[46] were SD-OCT, sensitivity 96.4%, specificity 66.0%; SD-OCT plus stereo colour fundus photographs, sensitivity 94.0%, specificity 89.4%.

TABLE 47 Monitoring studies ($n = 8$ reports of 8 studies)

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Eter 2005[28]	TD-OCT	Eye/patient	60	40	2	10	8	80.0	80.0
Giani 2011[30]	SD-OCT	Eye/patient							
		Classic CNV	57	30	15	3	9	90.9	37.5
		Occult CNV	36	19	15	0	2	100.0	11.8
		Overall CNV	93	49	30	3	11	94.2	26.8
Henschel 2009[32] (14 patients; 61 pairs of OCT and FFA examinations)	TD-OCT	Examination							
		CNV based on detection of intraretinal fluid	61	28	18	3	12	90.3	40.0
		CNV based on detection of subretinal fluid	61	22	8	9	22	71.0	73.3
		CNV based on detection of intraretinal and/or subretinal fluid	61	30	19	1	11	96.8	36.7
Khurana 2010[23]	TD-OCT	Eye	59	17	11	12	19	58.6	63.3
	SD-OCT	Eye	59	26	16	3	14	89.7	46.7
Regillo 1998[43] (54 angiogram pairs obtained from 24 eyes of 21 patients)	ICGA/DH/DS	Examination	54	22	3	7	22	75.9	88.0
Salinas-Alaman 2005[45]	TD-OCT	Remark (= examination)	176	110	25	5	36	95.7	59.0

Study ID	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
van de Moere 2006[52]	TD-OCT	Eye/patient							
		Detection of PED as criteria for positive test result	121	4	0	66	51	5.7	100.0
		Detection of subretinal fluid as positive test result	121	33	8	37	43	47.1	84.3
		Detection of intraretinal fluid as positive test result	121	58	24	12	27	82.9	52.9
		Detection of CMO as a positive test result	121	16	1	54	50	22.9	98.0
van Velthoven 2006[53]	TD-OCT	Eye/patient	30	15	4	8	3	65.2	42.9

CMO, cystoid macular oedema; DH, direct head-to-head comparison; DS, diagnostic study.

Appendix 7 Studies reporting eye-related exclusion criteria

TABLE 48 Diagnostic studies

Study	Eye-related exclusion criteria
Alster 2005[24]	• Presence of any significant media opacity that precludes a clear view of the fundus on fundus photography and FFA • Any non-macular-related ocular surgery performed within 3 months before the study
Cachulo 2011[25]	• Current or past history of an ophthalmic disease in the study eye (other than AMD) that would likely compromise the VA of the study eye • Clinical signs of myopic retinopathy or refractive power > 8 diopters or fundoscopic evidence of degenerative myopia • Past history of intraocular surgery within 60 days prior to enrolling in the study • Evidence of past or present CNV in the study eye
Do 2012[27]	• Evidence of CNV or foveal geographic atrophy in the fellow (candidate study) eye
Gomi 2007[31]	• Subretinal or subpigment epithelial haemorrhages that obscured lesions • History of any previous treatment and any other macular pathologies such as CNV or central serous chorioretinopathy
Loewenstein 2010[39]	• Macular disease other than AMD • Geographic atrophy • Media opacity precluding a clear view of the fundus • Ocular surgery in the study eye with in the previous 3 months
Padnick-Silver 2012[40]	• Presence of other retinal disease in the eye with non-nAMD (e.g. significant diabetic retinopathy, glaucomatous retinal atrophy, retinal detachment)
Park 2010[41]	• RAP or concurrent macular haemorrhage that might obscure part of the CNVM on FFA
Reichel 1995[44]	• Previous laser photocoagulation in the study eye
Sulzbacher 2011[48]	• Neovascular maculopathy from pathologic myopia, angioid streaks, infectious inflammatory chorioretinal disease, tumours, hereditary disorders, or trauma
Talks 2007[49]	• Macular holes • Central serous retinopathy • Disciform scar

TABLE 49 Monitoring studies

Study	Eye-related exclusion criteria
Giani 2011[30]	• Any previous laser treatment, PDT, or vitreoretinal surgery on the study eye • Significant macular haemorrhage that obscured the lesion • Spherical refractive error > 6 diopters
Khurana 2010[23]	• CNV resulting from other causes

Appendix 8 Sensitivity analysis results

One-way sensitivity analysis

All analyses show results moving in the expected direction (e.g. lower sensitivity or specificity for OCT would result in OCT-based strategies being less cost-effective). Briefly, base-case analysis results seem robust. In a limited number of model runs, alternative OCT-based strategies stopped being dominated or became cost-effective. However, in these cases the variable values used to run the analysis were extreme. For instance, diagnosing with OCT combined with nurse-/technician-led monitoring seemed worthwhile when OCT diagnosis sensitivity and specificity was equal to 1. It should be noted that it is unlikely that the other strategies' diagnostic assessment that were also based on OCT and other tests would result in a lower sensitivity and specificity than using OCT only (interpreted by the same ophthalmologist) (*Tables 50–74*).

TABLE 50 One-way sensitivity analysis: OCT diagnosis sensitivity

Diagnosis sensitivity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,474	10.411	1705	–0.062	–27,580	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	46,965	10.510	2316	–0.065	–35,789	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,155	10.387	22,506	–0.188	–119,903	Dominated
0.2	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,491	10.418	1722	–0.055	–31,342	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	46,986	10.518	2337	–0.057	–40,649	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,189	10.394	22,540	–0.181	–124,721	Dominated
0.3	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,508	10.425	1739	–0.048	–36,180	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,008	10.525	2358	–0.050	–46,904	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,223	10.401	22,574	–0.174	–129,926	Dominated
0.4	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,525	10.432	1756	–0.041	–42,633	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated

TABLE 50 One-way sensitivity analysis: OCT diagnosis sensitivity (*continued*)

Diagnosis sensitivity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
	(5) OCT & Ophthalmologist	47,029	10.532	2380	–0.043	–55,254	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,257	10.408	22,608	–0.167	–135,566	Dominated
0.5	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,542	10.439	1773	–0.034	–51,673	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,050	10.539	2401	–0.036	–66,965	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,292	10.415	22,642	–0.160	–141,699	Dominated
0.6	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,559	10.445	1790	–0.027	–65,241	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,071	10.546	2422	–0.029	–84,573	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,326	10.422	22,677	–0.153	–148,392	Dominated
0.7	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,576	10.452	1807	–0.021	–87,881	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,093	10.554	2444	–0.021	–114,038	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,360	10.429	22,711	–0.146	–155,725	Dominated

continued

TABLE 50 One-way sensitivity analysis: OCT diagnosis sensitivity (*continued*)

Diagnosis sensitivity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.8	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,594	10.459	1824	–0.014	–133,258	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,114	10.561	2465	–0.014	–173,407	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,394	10.436	22,745	–0.139	–163,795	Dominated
0.9	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,611	10.466	1841	–0.007	–270,172	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,135	10.568	2486	–0.007	–355,119	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,428	10.443	22,779	–0.132	–172,719	Dominated
1.0	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,628	10.473	1859	0.000	31,635,704	
	(2) FFA & Ophthalmologist	44,649	10.575	3021	0.102	29,593	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,157	10.575	2507	0.000	11,797,675	
	(1) FFA & OCT	62,759	10.449	15,602	–0.126	–124,050	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	15,621	–0.126	–123,584	Dominated
	(4) OCT & OCT	67,462	10.450	20,306	–0.125	–162,290	Dominated

TABLE 51 One-way sensitivity analysis: OCT diagnosis specificity

Diagnosis specificity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.55	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	43,619	10.465	3850	–0.008	–473,564	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	49,821	10.567	5172	–0.008	–629,095	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	72,407	10.442	27,758	–0.133	–209,343	Dominated
0.60	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	43,182	10.465	3412	–0.008	–419,079	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	49,236	10.567	4587	–0.008	–554,702	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	71,324	10.442	26,674	–0.133	–200,943	Dominated
0.65	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	42,744	10.465	2975	–0.008	–364,772	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	48,651	10.567	4002	–0.008	–481,174	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	70,240	10.442	25,590	–0.133	–192,562	Dominated
0.70	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	42,307	10.465	2538	–0.008	–310,643	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	

continued

TABLE 51 One-way sensitivity analysis: OCT diagnosis specificity (*continued*)

Diagnosis specificity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	48,067	10.567	3418	–0.008	–408,495	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	69,156	10.442	24,507	–0.133	–184,200	Dominated
0.75	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,870	10.465	2100	–0.008	–256,690	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,482	10.567	2833	–0.008	–336,651	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	68,072	10.442	23,423	–0.133	–175,856	Dominated
0.80	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,432	10.465	1663	–0.008	–202,914	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	46,897	10.567	2248	–0.008	–265,626	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	66,988	10.442	22,339	–0.133	–167,531	Dominated
0.85	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	40,995	10.465	1226	–0.008	–149,312	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	46,312	10.567	1663	–0.009	–195,408	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	65,904	10.442	21,255	–0.133	–159,225	Dominated

TABLE 51 One-way sensitivity analysis: OCT diagnosis specificity (*continued*)

Diagnosis specificity OCT	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.90	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	40,558	10.465	788	–0.008	–95,884	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	45,727	10.566	1078	–0.009	–125,982	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	64,820	10.441	20,171	–0.134	–150,937	Dominated
0.95	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	40,120	10.465	351	–0.008	–42,629	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	45,143	10.566	494	–0.009	–57,335	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	63,736	10.441	19,087	–0.134	–142,667	Dominated
1.00	(6) OCT & Nurse	39,683	10.465				
	(3) FFA & Nurse	39,769	10.473	86	0.008	10,453	
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(5) OCT & Ophthalmologist	44,558	10.566	4789	0.094	51,214	
	(2) FFA & Ophthalmologist	44,649	10.575	91	0.009	10,545	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(4) OCT & OCT	62,652	10.441	18,003	–0.134	–134,416	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.60	0.55	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,312	10.4229	240,374	
		(5) OCT & Ophthalmologist	49,761	10.5466	266,636	
		(6) OCT & Nurse	43,571	10.4455	269,793	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.60	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	71,228	10.4227	241,454	
		(5) OCT & Ophthalmologist	49,177	10.5465	267,220	
		(6) OCT & Nurse	43,134	10.4455	270,230	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.65	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	70,144	10.4226	242,533	
		(5) OCT & Ophthalmologist	48,592	10.5465	267,803	
		(6) OCT & Nurse	42,696	10.4454	270,667	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.60	0.70	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	69,060	10.4224	243,613	
		(5) OCT & Ophthalmologist	48,007	10.5464	268,386	
		(6) OCT & Nurse	42,259	10.4454	271,104	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.75	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	67,976	10.4223	244,692	
		(5) OCT & Ophthalmologist	47,422	10.5464	268,970	
		(6) OCT & Nurse	41,822	10.4454	271,541	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.80	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	66,892	10.4221	245,772	
		(5) OCT & Ophthalmologist	46,837	10.5463	269,553	
		(6) OCT & Nurse	41,384	10.4454	271,978	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.60	0.85	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,808	10.4220	246,851	
		(5) OCT & Ophthalmologist	46,253	10.5463	270,136	
		(6) OCT & Nurse	40,947	10.4454	272,415	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.90	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	64,724	10.4218	247,931	
		(5) OCT & Ophthalmologist	45,668	10.5462	270,720	
		(6) OCT & Nurse	40,510	10.4454	272,851	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	0.95	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	63,641	10.4217	249,010	
		(5) OCT & Ophthalmologist	45,083	10.5462	271,303	
		(6) OCT & Nurse	40,072	10.4454	273,288	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.60	1.00	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	62,557	10.4215	250,089	
		(5) OCT & Ophthalmologist	44,498	10.5462	271,886	
		(6) OCT & Nurse	39,635	10.4453	273,725	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.70	0.55	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,346	10.4299	240,550	
		(5) OCT & Ophthalmologist	49,783	10.5538	266,831	
		(6) OCT & Nurse	43,588	10.4523	269,982	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.60	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	71,262	10.4297	241,629	
		(5) OCT & Ophthalmologist	49,198	10.5538	267,415	
		(6) OCT & Nurse	43,151	10.4523	270,419	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.65	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	70,178	10.4296	242,708	
		(5) OCT & Ophthalmologist	48,613	10.5537	267,998	
		(6) OCT & Nurse	42,714	10.4523	270,856	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.70	0.70	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	69,094	10.4294	243,788	
		(5) OCT & Ophthalmologist	48,028	10.5537	268,581	
		(6) OCT & Nurse	42,276	10.4523	271,293	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.75	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	68,010	10.4293	244,867	
		(5) OCT & Ophthalmologist	47,444	10.5536	269,165	
		(6) OCT & Nurse	41,839	10.4523	271,730	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.80	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	66,926	10.4291	245,947	
		(5) OCT & Ophthalmologist	46,859	10.5536	269,748	
		(6) OCT & Nurse	41,402	10.4523	272,167	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.70	0.85	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,842	10.4290	247,026	
		(5) OCT & Ophthalmologist	46,274	10.5535	270,331	
		(6) OCT & Nurse	40,964	10.4523	272,604	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.90	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	64,759	10.4288	248,106	
		(5) OCT & Ophthalmologist	45,689	10.5535	270,915	
		(6) OCT & Nurse	40,527	10.4522	273,041	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.70	0.95	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	63,675	10.4287	249,185	
		(5) OCT & Ophthalmologist	45,104	10.5534	271,498	
		(6) OCT & Nurse	40,090	10.4522	273,478	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.70	1.00	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	62,591	10.4285	250,265	
		(5) OCT & Ophthalmologist	44,520	10.5534	272,081	
		(6) OCT & Nurse	39,652	10.4522	273,914	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.55	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,380	10.4368	240,725	
		(5) OCT & Ophthalmologist	49,804	10.5610	267,026	
		(6) OCT & Nurse	43,605	10.4592	270,171	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.60	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	71,296	10.4367	241,804	
		(5) OCT & Ophthalmologist	49,219	10.5610	267,610	
		(6) OCT & Nurse	43,168	10.4592	270,608	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.80	0.65	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	70,212	10.4365	242,884	
		(5) OCT & Ophthalmologist	48,634	10.5609	268,193	
		(6) OCT & Nurse	42,731	10.4592	271,045	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.70	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	69,128	10.4364	243,963	
		(5) OCT & Ophthalmologist	48,050	10.5609	268,776	
		(6) OCT & Nurse	42,293	10.4592	271,482	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.75	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	68,044	10.4362	245,043	
		(5) OCT & Ophthalmologist	47,465	10.5608	269,360	
		(6) OCT & Nurse	41,856	10.4592	271,919	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.80	0.80	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	66,961	10.4361	246,122	
		(5) OCT & Ophthalmologist	46,880	10.5608	269,943	
		(6) OCT & Nurse	41,419	10.4592	272,356	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.85	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,877	10.4359	247,201	
		(5) OCT & Ophthalmologist	46,295	10.5607	270,526	
		(6) OCT & Nurse	40,981	10.4591	272,793	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	0.90	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	64,793	10.4358	248,281	
		(5) OCT & Ophthalmologist	45,710	10.5607	271,110	
		(6) OCT & Nurse	40,544	10.4591	273,230	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.80	0.95	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	63,709	10.4356	249,360	
		(5) OCT & Ophthalmologist	45,126	10.5606	271,693	
		(6) OCT & Nurse	40,107	10.4591	273,667	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.80	1.00	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	62,625	10.4355	250,440	
		(5) OCT & Ophthalmologist	44,541	10.5606	272,277	
		(6) OCT & Nurse	39,669	10.4591	274,104	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.55	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,414	10.4438	240,900	
		(5) OCT & Ophthalmologist	49,825	10.5682	267,222	
		(6) OCT & Nurse	43,622	10.4661	270,360	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.90	0.60	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	71,330	10.4437	241,979	
		(5) OCT & Ophthalmologist	49,241	10.5682	267,805	
		(6) OCT & Nurse	43,185	10.4661	270,797	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.65	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	70,246	10.4435	243,059	
		(5) OCT & Ophthalmologist	48,656	10.5681	268,388	
		(6) OCT & Nurse	42,748	10.4661	271,234	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.70	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	69,163	10.4434	244,138	
		(5) OCT & Ophthalmologist	48,071	10.5681	268,972	
		(6) OCT & Nurse	42,310	10.4661	271,671	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.90	0.75	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	68,079	10.4432	245,218	
		(5) OCT & Ophthalmologist	47,486	10.5680	269,555	
		(6) OCT & Nurse	41,873	10.4660	272,108	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.80	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	66,995	10.4431	246,297	
		(5) OCT & Ophthalmologist	46,901	10.5680	270,138	
		(6) OCT & Nurse	41,436	10.4660	272,545	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.85	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,911	10.4429	247,377	
		(5) OCT & Ophthalmologist	46,317	10.5679	270,722	
		(6) OCT & Nurse	40,998	10.4660	272,982	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.90	0.90	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	64,827	10.4428	248,456	
		(5) OCT & Ophthalmologist	45,732	10.5679	271,305	
		(6) OCT & Nurse	40,561	10.4660	273,419	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	0.95	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	63,743	10.4426	249,535	
		(5) OCT & Ophthalmologist	45,147	10.5678	271,888	
		(6) OCT & Nurse	40,124	10.4660	273,856	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.90	1.00	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	62,659	10.4425	250,615	
		(5) OCT & Ophthalmologist	44,562	10.5678	272,472	
		(6) OCT & Nurse	39,686	10.4660	274,293	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
1.00	0.55	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,448	10.4508	241,075	
		(5) OCT & Ophthalmologist	49,847	10.5754	267,417	
		(6) OCT & Nurse	43,639	10.4730	270,550	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.60	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	71,365	10.4506	242,154	
		(5) OCT & Ophthalmologist	49,262	10.5754	268,000	
		(6) OCT & Nurse	43,202	10.4730	270,986	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.65	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	70,281	10.4505	243,234	
		(5) OCT & Ophthalmologist	48,677	10.5753	268,583	
		(6) OCT & Nurse	42,765	10.4729	271,423	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
1.00	0.70	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	69,197	10.4503	244,313	
		(5) OCT & Ophthalmologist	48,092	10.5753	269,167	
		(6) OCT & Nurse	42,327	10.4729	271,860	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.75	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	68,113	10.4502	245,393	
		(5) OCT & Ophthalmologist	47,507	10.5752	269,750	
		(6) OCT & Nurse	41,890	10.4729	272,297	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.80	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	67,029	10.4500	246,472	
		(5) OCT & Ophthalmologist	46,923	10.5752	270,333	
		(6) OCT & Nurse	41,453	10.4729	272,734	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.85	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,945	10.4499	247,552	
		(5) OCT & Ophthalmologist	46,338	10.5752	270,917	
		(6) OCT & Nurse	41,015	10.4729	273,171	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 52 Two-way sensitivity analysis: OCT diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

OCT diagnosis		Strategy	Expected Cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
1.00	0.90	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	64,861	10.4497	248,631	
		(5) OCT & Ophthalmologist	45,753	10.5751	271,500	
		(6) OCT & Nurse	40,578	10.4729	273,608	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	0.95	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	63,777	10.4496	249,711	
		(5) OCT & Ophthalmologist	45,168	10.5751	272,083	
		(6) OCT & Nurse	40,141	10.4729	274,045	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.00	1.00	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	
		(4) OCT & OCT	62,693	10.4494	250,790	
		(5) OCT & Ophthalmologist	44,583	10.5750	272,667	
		(6) OCT & Nurse	39,703	10.4728	274,482	✓
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

NMB, net monetary benefit.

TABLE 53 One-way sensitivity analysis: ophthalmologist diagnosis sensitivity

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(9) Ophthalmologist & Nurse	39,587	10.417				
	(3) FFA & Nurse	39,769	10.473	182	0.056	3267	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,433	10.517	4664	0.044	106,648	
	(2) FFA & Ophthalmologist	44,649	10.575	216	0.058	3696	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,439	10.393	17,790	–0.182	–97,705	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(9) Ophthalmologist & Nurse	39,610	10.423				
	(3) FFA & Nurse	39,769	10.473	159	0.050	3215	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,460	10.523	4691	0.050	93,392	
	(2) FFA & Ophthalmologist	44,649	10.575	189	0.052	3647	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,477	10.399	17,828	–0.176	–101,411	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.3	(9) Ophthalmologist & Nurse	39,633	10.430				
	(3) FFA & Nurse	39,769	10.473	136	0.043	3149	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,486	10.530	4717	0.057	83,170	
	(2) FFA & Ophthalmologist	44,649	10.575	163	0.045	3584	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,515	10.405	17,866	–0.170	–105,393	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 53 One-way sensitivity analysis: ophthalmologist diagnosis sensitivity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(9) Ophthalmologist & Nurse	39,656	10.436				
	(3) FFA & Nurse	39,769	10.473	114	0.037	3061	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,513	10.536	4744	0.063	75,047	
	(2) FFA & Ophthalmologist	44,649	10.575	136	0.039	3501	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,553	10.412	17,904	–0.163	–109,680	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(9) Ophthalmologist & Nurse	39,678	10.442				
	(3) FFA & Nurse	39,769	10.473	91	0.031	2938	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,539	10.543	4770	0.070	68,438	
	(2) FFA & Ophthalmologist	44,649	10.575	110	0.032	3383	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,591	10.418	17,942	–0.157	–114,311	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.6	(9) Ophthalmologist & Nurse	39,701	10.448				
	(3) FFA & Nurse	39,769	10.473	68	0.025	2754	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,566	10.549	4797	0.076	62,955	
	(2) FFA & Ophthalmologist	44,649	10.575	83	0.026	3207	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,629	10.424	17,980	–0.151	–119,327	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 53 One-way sensitivity analysis: ophthalmologist diagnosis sensitivity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(9) Ophthalmologist & Nurse	39,724	10.454				
	(3) FFA & Nurse	39,769	10.473	45	0.019	2446	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,592	10.556	4823	0.083	58,333	
	(2) FFA & Ophthalmologist	44,649	10.575	57	0.019	2914	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,667	10.431	18,018	–0.144	–124,780	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.8	(9) Ophthalmologist & Nurse	39,746	10.460				
	(3) FFA & Nurse	39,769	10.473	23	0.012	1831	
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,619	10.562	4850	0.089	54,384	
	(2) FFA & Ophthalmologist	44,649	10.575	30	0.013	2328	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,706	10.437	18,056	–0.138	–130,729	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.9	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,769	10.467	0	–0.006	–15	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(8) Ophthalmologist & Ophthalmologist	44,645	10.569	4876	0.096	50,971	
	(2) FFA & Ophthalmologist	44,649	10.575	4	0.006	569	
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(7) Ophthalmologist & OCT	62,744	10.443	18,095	–0.132	–137,244	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 53 One-way sensitivity analysis: ophthalmologist diagnosis sensitivity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,792	10.473	23	0.000	0	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,672	10.575	23	0.000	0	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,782	10.449	18,133	–0.126	–144,410	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 54 One-way sensitivity analysis: ophthalmologist diagnosis specificity

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,815	10.472	46	–0.001	–74,082	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,695	10.574	45	–0.001	–70,022	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,803	10.449	18,154	–0.126	–143,862	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,812	10.472	43	–0.001	–68,977	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,691	10.574	42	–0.001	–65,156	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,800	10.449	18,151	–0.126	–143,837	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.3	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,809	10.472	40	–0.001	–63,871	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,688	10.574	39	–0.001	–60,290	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,797	10.449	18,148	–0.126	–143,812	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 54 One-way sensitivity analysis: ophthalmologist diagnosis specificity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,806	10.472	36	–0.001	–58,765	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,685	10.574	36	–0.001	–55,424	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,794	10.449	18,145	–0.126	–143,787	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,802	10.472	33	–0.001	–53,659	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,682	10.574	33	–0.001	–50,558	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,791	10.449	18,141	–0.126	–143,762	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.6	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,799	10.472	30	–0.001	–48,554	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,679	10.574	30	–0.001	–45,692	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2,482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,787	10.449	18,138	–0.126	–143,737	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 54 One-way sensitivity analysis: ophthalmologist diagnosis specificity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,796	10.472	27	–0.001	–43,448	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,676	10.574	27	–0.001	–40,826	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,784	10.449	18,135	–0.126	–143,712	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.8	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,793	10.472	24	–0.001	–38,342	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,673	10.574	23	–0.001	–35,960	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,781	10.449	18,132	–0.126	–143,687	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.9	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 54 One-way sensitivity analysis: ophthalmologist diagnosis specificity (*continued*)

Diagnosis sensitivity ophthalmologist assessment	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,787	10.472	17	–0.001	–28,131	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,666	10.574	17	–0.001	–26,228	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,775	10.449	18,126	–0.126	–143,637	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 55 Two-way sensitivity analysis: ophthalmologist diagnosis sensitivity and specificity (NMB at £30,000)

Ophthalmologist diagnosis		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.8	0.5	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,204	10.531	249,730	
		(8) Ophthalmologist & Ophthalmologist	44,632	10.562	272,229	
		(9) Ophthalmologist & Nurse	39,759	10.460	274,055	
0.8	0.6	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,201	10.531	249,733	
		(8) Ophthalmologist & Ophthalmologist	44,628	10.562	272,232	
		(9) Ophthalmologist & Nurse	39,756	10.460	274,058	
0.8	0.7	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,197	10.531	249,736	
		(8) Ophthalmologist & Ophthalmologist	44,625	10.562	272,235	
		(9) Ophthalmologist & Nurse	39,753	10.460	274,061	
0.8	0.8	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	

TABLE 55 Two-way sensitivity analysis: ophthalmologist diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist diagnosis		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	66,194	10.531	249,739	
		(8) Ophthalmologist & Ophthalmologist	44,622	10.562	272,239	
		(9) Ophthalmologist & Nurse	39,750	10.460	274,064	
0.8	0.9	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,191	10.531	249,743	
		(8) Ophthalmologist & Ophthalmologist	44,619	10.562	272,242	
		(9) Ophthalmologist & Nurse	39,746	10.460	274,068	
0.8	1.0	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,188	10.531	249,746	
		(8) Ophthalmologist & Ophthalmologist	44,616	10.562	272,245	
		(9) Ophthalmologist & Nurse	39,743	10.460	274,071	
0.9	0.5	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,244	10.538	249,886	
		(8) Ophthalmologist & Ophthalmologist	44,658	10.569	272,397	
		(9) Ophthalmologist & Nurse	39,782	10.467	274,218	
0.9	0.6	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓

continued

TABLE 55 Two-way sensitivity analysis: ophthalmologist diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist diagnosis		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,241	10.538	249,890	
		(8) Ophthalmologist & Ophthalmologist	44,655	10.569	272,400	
		(9) Ophthalmologist & Nurse	39,779	10.467	274,221	
0.9	0.7	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,238	10.538	249,893	
		(8) Ophthalmologist & Ophthalmologist	44,652	10.569	272,404	
		(9) Ophthalmologist & Nurse	39,776	10.467	274,224	
0.9	0.8	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,235	10.538	249,896	
		(8) Ophthalmologist & Ophthalmologist	44,649	10.569	272,407	
		(9) Ophthalmologist & Nurse	39,772	10.467	274,227	
0.9	0.9	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,232	10.538	249,899	
		(8) Ophthalmologist & Ophthalmologist	44,645	10.569	272,410	
		(9) Ophthalmologist & Nurse	39,769	10.467	274,231	

TABLE 55 Two-way sensitivity analysis: ophthalmologist diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist diagnosis		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.9	1.0	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,228	10.538	249,902	
		(8) Ophthalmologist & Ophthalmologist	44,642	10.569	272,413	
		(9) Ophthalmologist & Nurse	39,766	10.467	274,234	
1.0	0.5	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,285	10.544	250,043	
		(8) Ophthalmologist & Ophthalmologist	44,685	10.575	272,566	
		(9) Ophthalmologist & Nurse	39,805	10.473	274,381	
1.0	0.6	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,281	10.544	250,046	
		(8) Ophthalmologist & Ophthalmologist	44,681	10.575	272,569	
		(9) Ophthalmologist & Nurse	39,801	10.473	274,384	
1.0	0.7	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	

continued

TABLE 55 Two-way sensitivity analysis: ophthalmologist diagnosis sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist diagnosis		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	66,278	10.544	250,049	
		(8) Ophthalmologist & Ophthalmologist	44,678	10.575	272,572	
		(9) Ophthalmologist & Nurse	39,798	10.473	274,387	
1.0	0.8	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
1.0	0.8	(7) Ophthalmologist & OCT	66,275	10.544	250,053	
		(8) Ophthalmologist & Ophthalmologist	44,675	10.575	272,575	
		(9) Ophthalmologist & Nurse	39,795	10.473	274,390	
1.0	0.9	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,272	10.544	250,056	
		(8) Ophthalmologist & Ophthalmologist	44,672	10.575	272,578	
		(9) Ophthalmologist & Nurse	39,792	10.473	274,393	
1.0	1.0	(1) FFA & OCT	66,249	10.544	250,079	
		(2) FFA & Ophthalmologist	44,649	10.575	272,601	
		(3) FFA & Nurse	39,769	10.473	274,416	✓
		(4) OCT & OCT	72,821	10.544	243,493	
		(5) OCT & Ophthalmologist	47,971	10.574	269,244	
		(6) OCT & Nurse	42,237	10.472	271,910	
		(7) Ophthalmologist & OCT	66,269	10.544	250,059	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.575	272,581	
		(9) Ophthalmologist & Nurse	39,789	10.473	274,397	

NMB, net monetary benefit.

TABLE 56 One-way sensitivity analysis: probability of ophthalmologist diagnosis unclear results

Ophthalmologist diagnoses unclear results (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,786	10.472	17	–0.001	–24,950	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,666	10.574	17	–0.001	–23,196	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,774	10.449	18,125	–0.126	–143,554	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.1	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,793	10.472	24	–0.001	–43,595	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,673	10.574	24	–0.001	–40,966	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,782	10.449	18,132	–0.126	–143,770	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 56 One-way sensitivity analysis: probability of ophthalmologist diagnosis unclear results (*continued*)

Ophthalmologist diagnoses unclear results (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.3	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,797	10.472	27	0.000	–56,912	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,676	10.575	27	–0.001	–53,658	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,785	10.449	18,136	–0.126	–143,878	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.4	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,800	10.472	31	0.000	–74,669	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,680	10.575	31	0.000	–70,581	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,789	10.449	18,140	–0.126	–143,986	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,803	10.473	34	0.000	–99,528	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,683	10.575	34	0.000	–94,274	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,792	10.449	18,143	–0.126	–144,094	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 57 One-way sensitivity analysis: OCT monitoring sensitivity

OCT monitoring sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	54,070	9.686	9421	–0.889	–10,596	Dominated
	(7) Ophthalmologist & OCT	54,090	9.686	9441	–0.890	–10,614	Dominated
	(4) OCT & OCT	58,742	9.681	14,093	–0.894	–15,761	Dominated
0.5	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	56,826	9.915	12,177	–0.661	–18,436	Dominated
	(7) Ophthalmologist & OCT	56,846	9.914	12,197	–0.661	–18,453	Dominated
	(4) OCT & OCT	61,495	9.909	16,845	–0.666	–25,281	Dominated
0.6	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	59,000	10.103	14,351	–0.472	–30,377	Dominated
	(7) Ophthalmologist & OCT	59,019	10.102	14,370	–0.473	–30,384	Dominated
	(4) OCT & OCT	63,666	10.096	19,017	–0.479	–39,707	Dominated

continued

TABLE 57 One-way sensitivity analysis: OCT monitoring sensitivity (*continued*)

OCT monitoring sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	60,740	10.259	16,090	–0.316	–50,949	Dominated
	(7) Ophthalmologist & OCT	60,759	10.259	16,110	–0.316	–50,918	Dominated
	(4) OCT & OCT	65,404	10.252	20,754	–0.323	–64,283	Dominated
0.8	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,151	10.391	17,502	–0.184	–95,174	Dominated
	(7) Ophthalmologist & OCT	62,170	10.391	17,521	–0.185	–94,962	Dominated
	(4) OCT & OCT	66,814	10.384	22,165	–0.191	–115,799	Dominated
0.9	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	63,312	10.503	18,663	–0.072	–260,619	Dominated
	(7) Ophthalmologist & OCT	63,331	10.503	18,682	–0.072	–258,561	Dominated
	(4) OCT & OCT	67,974	10.495	23,325	–0.080	–293,337	Dominated

TABLE 57 One-way sensitivity analysis: OCT monitoring sensitivity (*continued*)

OCT monitoring sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2,482	–0.008	–293,938	Dominated
	(1) FFA & OCT	64,277	10.600	19,628	0.025	788,482	
	(7) Ophthalmologist & OCT	64,296	10.599	19	–0.001	–28,229	Dominated
	(4) OCT & OCT	68,939	10.592	4662	–0.008	–565,643	Dominated

TABLE 58 One-way sensitivity analysis: OCT monitoring specificity

OCT monitoring specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.3	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	74,212	10.459	29,563	–0.116	–255,643	Dominated
	(7) Ophthalmologist & OCT	74,230	10.459	29,581	–0.116	–254,397	Dominated
	(4) OCT & OCT	80,083	10.452	35,434	–0.123	–287,514	Dominated
0.4	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	67,780	10.454	23,130	–0.121	–190,790	Dominated
	(7) Ophthalmologist & OCT	67,798	10.453	23,149	–0.122	–189,953	Dominated
	(4) OCT & OCT	72,979	10.446	28,330	–0.129	–219,784	Dominated
0.5	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	61,521	10.448	16,872	–0.127	–133,240	Dominated
	(7) Ophthalmologist & OCT	61,540	10.448	16,891	–0.127	–132,734	Dominated
	(4) OCT & OCT	66,049	10.441	21,400	–0.134	–159,275	Dominated

TABLE 58 One-way sensitivity analysis: OCT monitoring specificity (*continued*)

OCT monitoring specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.6	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	55,429	10.443	10,780	–0.132	–81,774	Dominated
	(7) Ophthalmologist & OCT	55,449	10.443	10,800	–0.132	–81,537	Dominated
	(4) OCT & OCT	59,286	10.435	14,636	–0.140	–104,824	Dominated
0.7	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	49,498	10.438	4849	–0.137	–35,432	Dominated
	(7) Ophthalmologist & OCT	49,518	10.438	4869	–0.137	–35,418	Dominated
	(4) OCT & OCT	52,683	10.430	8033	–0.145	–55,508	Dominated
0.8	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(1) FFA & OCT	43,721	10.433	3952	–0.040	–99,944	Dominated
	(7) Ophthalmologist & OCT	43,742	10.433	3973	–0.040	–98,928	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(4) OCT & OCT	46,234	10.425	1585	–0.150	–10,589	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated

continued

TABLE 58 One-way sensitivity analysis: OCT monitoring specificity (*continued*)

OCT monitoring specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.9	(1) FFA & OCT	38,093	10.429				
	(7) Ophthalmologist & OCT	38,114	10.428	21	–0.001	–34,221	Dominated
	(3) FFA & Nurse	39,769	10.473	1676	0.044	37,884	
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(4) OCT & OCT	39,934	10.421	164	–0.052	–3,146	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
1.0	(1) FFA & OCT	32,608	10.424				
	(7) Ophthalmologist & OCT	32,629	10.423	21	–0.001	–35,125	Dominated
	(4) OCT & OCT	33,776	10.416	1168	–0.008	–144,031	Dominated
	(3) FFA & Nurse	39,769	10.473	7161	0.049	146,783	
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.8	0.3	(1) FFA & OCT	73,512	10.4055	238,652	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	79,384	10.3981	232,558	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	73,531	10.4048	238,615	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.4	(1) FFA & OCT	67,127	10.3974	244,794	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	72,327	10.3899	239,370	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	67,146	10.3967	244,757	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.5	(1) FFA & OCT	60,925	10.3896	250,762	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	65,454	10.3821	246,008	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	60,944	10.3890	250,725	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.6	(1) FFA & OCT	54,899	10.3821	256,564	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	58,756	10.3745	252,480	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	54,918	10.3815	256,527	

continued

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.7	(1) FFA & OCT	49,041	10.3749	262,206	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	52,226	10.3672	258,791	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	49,061	10.3743	262,168	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.8	(1) FFA & OCT	43,344	10.3680	267,695	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	45,858	10.3602	264,949	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	43,365	10.3674	267,656	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	0.9	(1) FFA & OCT	37,803	10.3613	273,035	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	39,645	10.3535	270,960	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	37,824	10.3607	272,997	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.8	1.0	(1) FFA & OCT	32,411	10.3548	278,234	✓
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	
		(4) OCT & OCT	33,581	10.3469	276,828	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	32,432	10.3542	278,195	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.3	(1) FFA & OCT	74,844	10.5091	240,429	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	80,715	10.5013	234,324	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	74,862	10.5084	240,391	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.4	(1) FFA & OCT	68,371	10.5059	246,806	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	73,570	10.4980	241,371	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	68,389	10.5052	246,768	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.5	(1) FFA & OCT	62,063	10.5028	253,020	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	66,591	10.4949	248,255	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	62,082	10.5021	252,982	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.6	(1) FFA & OCT	55,915	10.4998	259,078	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	59,770	10.4918	254,982	

continued

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	55,934	10.4991	259,040	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.7	(1) FFA & OCT	49,920	10.4968	264,985	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	53,103	10.4887	261,559	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	49,939	10.4962	264,946	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.8	(1) FFA & OCT	44,072	10.4940	270,747	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	46,584	10.4858	267,990	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	44,093	10.4933	270,707	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.9	(1) FFA & OCT	38,367	10.4912	276,368	✓
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	
		(4) OCT & OCT	40,207	10.4829	274,282	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	38,388	10.4906	276,329	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	1.0	(1) FFA & OCT	32,800	10.4885	281,854	✓
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(4) OCT & OCT	33,967	10.4801	280,438	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	32,821	10.4878	281,815	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.3	(1) FFA & OCT	75,937	10.5978	241,996	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	81,809	10.5897	235,882	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	75,955	10.5971	241,958	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.4	(1) FFA & OCT	69,399	10.5990	248,571	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	74,598	10.5908	243,126	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	69,417	10.5983	248,532	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.5	(1) FFA & OCT	63,011	10.6001	254,992	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	67,539	10.5919	250,217	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	63,030	10.5994	254,953	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

continued

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
1.0	0.6	(1) FFA & OCT	56,770	10.6011	261,265	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	60,625	10.5928	257,159	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	56,789	10.6005	261,225	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.7	(1) FFA & OCT	50,669	10.6021	267,394	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	53,852	10.5937	263,958	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	50,689	10.6014	267,354	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.8	(1) FFA & OCT	44,705	10.6030	273,384	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	47,215	10.5945	270,619	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	44,725	10.6023	273,344	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
1.0	0.9	(1) FFA & OCT	38,872	10.6038	279,241	✓
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	
		(4) OCT & OCT	40,710	10.5952	277,145	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	38,893	10.6031	279,201	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

TABLE 59 Two-way sensitivity analysis: OCT monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

OCT monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
1.0	1.0	(1) FFA & OCT	33,167	10.6045	284,968	✓
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	
		(4) OCT & OCT	34,331	10.5958	283,543	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	33,188	10.6038	284,928	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	

NMB, net monetary benefit.

TABLE 60 One-way sensitivity analysis: ophthalmologist monitoring sensitivity

Ophthalmologist monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(3) FFA & Nurse	35,469	8.830				
	(9) Ophthalmologist & Nurse	35,491	8.830	22	0.000	–121,961	Dominated
	(2) FFA & Ophthalmologist	35,931	8.920	462	0.089	5167	
	(8) Ophthalmologist & Ophthalmologist	35,953	8.920	22	0.000	–108,940	Dominated
	(6) OCT & Nurse	37,324	8.828	1392	–0.092	–15,092	Dominated
	(5) OCT & Ophthalmologist	38,432	8.917	2501	–0.003	–810,442	Dominated
	(1) FFA & OCT	62,759	10.449	26,828	1.530	17,539	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.2	(3) FFA & Nurse	36,017	9.133				
	(9) Ophthalmologist & Nurse	36,039	9.133	22	0.000	–84,837	Dominated
	(2) FFA & Ophthalmologist	37,512	9.243	1495	0.109	13,708	
	(8) Ophthalmologist & Ophthalmologist	37,534	9.242	22	0.000	–76,050	Dominated
	(6) OCT & Nurse	37,869	9.130	358	–0.113	–3,169	Dominated
	(5) OCT & Ophthalmologist	40,010	9.238	2498	–0.004	–609,285	Dominated
	(1) FFA & OCT	62,759	10.449	25,247	1.207	20,919	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.3	(3) FFA & Nurse	36,593	9.397				
	(9) Ophthalmologist & Nurse	36,615	9.397	22	0.000	–66,222	Dominated
	(6) OCT & Nurse	38,444	9.392	1851	–0.005	–402,106	Dominated
	(2) FFA & Ophthalmologist	38,913	9.517	2320	0.120	19,394	
	(8) Ophthalmologist & Ophthalmologist	38,934	9.516	21	0.000	–59,673	Dominated
	(5) OCT & Ophthalmologist	41,408	9.512	2495	–0.005	–499,702	Dominated
	(1) FFA & OCT	62,759	10.449	23,846	0.933	25,560	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated

TABLE 60 One-way sensitivity analysis: ophthalmologist monitoring sensitivity (*continued*)

Ophthalmologist monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	37,161	9.625				
	(9) Ophthalmologist & Nurse	37,183	9.625	21	0.000	–55,221	Dominated
	(6) OCT & Nurse	39,010	9.620	1849	–0.005	–345,207	Dominated
	(2) FFA & Ophthalmologist	40,137	9.749	2976	0.124	24,018	
	(8) Ophthalmologist & Ophthalmologist	40,159	9.749	21	0.000	–50,052	Dominated
	(5) OCT & Ophthalmologist	42,630	9.744	2492	–0.006	–432,284	Dominated
	(1) FFA & OCT	62,759	10.449	22,621	0.700	32,314	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.5	(3) FFA & Nurse	37,703	9.824				
	(9) Ophthalmologist & Nurse	37,725	9.824	21	0.000	–48,047	Dominated
	(6) OCT & Nurse	39,550	9.818	1847	–0.006	–306,735	Dominated
	(2) FFA & Ophthalmologist	41,202	9.948	3499	0.124	28,209	
	(8) Ophthalmologist & Ophthalmologist	41,223	9.948	21	0.000	–43,812	Dominated
	(5) OCT & Ophthalmologist	43,692	9.942	2490	–0.006	–387,406	Dominated
	(1) FFA & OCT	62,759	10.449	21,557	0.501	43,001	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.6	(3) FFA & Nurse	38,211	9.997				
	(9) Ophthalmologist & Nurse	38,232	9.997	21	0.000	–43,049	Dominated
	(6) OCT & Nurse	40,055	9.991	1845	–0.007	–279,334	Dominated
	(2) FFA & Ophthalmologist	42,128	10.119	3917	0.121	32,250	
	(8) Ophthalmologist & Ophthalmologist	42,148	10.118	21	–0.001	–39,488	Dominated
	(5) OCT & Ophthalmologist	44,615	10.112	2488	–0.007	–355,836	Dominated
	(1) FFA & OCT	62,759	10.449	20,631	0.331	62,364	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated

continued

TABLE 60 One-way sensitivity analysis: ophthalmologist monitoring sensitivity (*continued*)

Ophthalmologist monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	38,680	10.149				
	(9) Ophthalmologist & Nurse	38,701	10.148	21	–0.001	–39,397	Dominated
	(6) OCT & Nurse	40,523	10.141	1843	–0.007	–259,036	Dominated
	(2) FFA & Ophthalmologist	42,934	10.266	4254	0.117	36,287	
	(8) Ophthalmologist & Ophthalmologist	42,955	10.265	21	–0.001	–36,346	Dominated
	(5) OCT & Ophthalmologist	45,420	10.258	2486	–0.007	–332,704	Dominated
	(1) FFA & OCT	62,759	10.449	19,825	0.184	107,925	
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.8	(3) FFA & Nurse	39,113	10.281				
	(9) Ophthalmologist & Nurse	39,134	10.281	21	–0.001	–36,631	Dominated
	(6) OCT & Nurse	40,954	10.274	1841	–0.008	–243,534	Dominated
	(2) FFA & Ophthalmologist	43,639	10.394	4526	0.112	40,409	
	(1) FFA & OCT	62,759	10.449	19,119	0.056	341,760	
	(8) Ophthalmologist & Ophthalmologist	43,660	10.393	20	–0.001	–33,978	Dominated
	(5) OCT & Ophthalmologist	46,124	10.386	2484	–0.008	–315,219	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	19	–0.001	–30,303	Dominated
	(4) OCT & OCT	67,421	10.442	4662	–0.008	–604,118	Dominated
0.9	(3) FFA & Nurse	39,511	10.399				
	(9) Ophthalmologist & Nurse	39,531	10.398	21	–0.001	–34,477	Dominated
	(6) OCT & Nurse	41,350	10.391	1839	–0.008	–231,400	Dominated
	(2) FFA & Ophthalmologist	44,259	10.505	4749	0.106	44,674	
	(8) Ophthalmologist & Ophthalmologist	44,280	10.504	20	–0.001	–32,144	Dominated
	(5) OCT & Ophthalmologist	46,742	10.497	2483	–0.008	–301,676	Dominated
	(1) FFA & OCT	62,759	10.449	18,500	–0.056	–332,463	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,519	–0.056	–329,091	Dominated
	(4) OCT & OCT	67,421	10.442	23,162	–0.063	–365,551	Dominated

TABLE 60 One-way sensitivity analysis: ophthalmologist monitoring sensitivity (*continued*)

Ophthalmologist monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	39,875	10.503				
	(9) Ophthalmologist & Nurse	39,896	10.502	21	–0.001	–32,760	Dominated
	(6) OCT & Nurse	41,713	10.494	1838	–0.008	–221,712	Dominated
	(2) FFA & Ophthalmologist	44,806	10.603	4931	0.100	49,125	
	(8) Ophthalmologist & Ophthalmologist	44,827	10.602	20	–0.001	–30,691	Dominated
	(5) OCT & Ophthalmologist	47,288	10.595	2481	–0.009	–290,979	Dominated
	(1) FFA & OCT	62,759	10.449	17,953	–0.154	–116,811	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	17,972	–0.154	–116,459	Dominated
	(4) OCT & OCT	67,421	10.442	22,615	–0.161	–140,112	Dominated

TABLE 61 One-way sensitivity analysis: ophthalmologist monitoring specificity

Ophthalmologist monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(3) FFA & Nurse	56,447	10.483				
	(9) Ophthalmologist & Nurse	56,467	10.482	19	–0.001	–30,720	Dominated
	(6) OCT & Nurse	60,233	10.475	3786	–0.008	–475,573	Dominated
	(1) FFA & OCT	62,759	10.449	6312	–0.033	–189,611	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	6331	–0.034	–186,661	Dominated
	(4) OCT & OCT	67,421	10.442	10,974	–0.041	–267,627	Dominated
	(2) FFA & Ophthalmologist	84,302	10.575	27,854	0.092	301,922	
	(8) Ophthalmologist & Ophthalmologist	84,319	10.574	18	–0.001	–26,020	Dominated
	(5) OCT & Ophthalmologist	91,018	10.567	6716	–0.008	–845,509	Dominated
0.2	(3) FFA & Nurse	53,989	10.481				
	(9) Ophthalmologist & Nurse	54,009	10.481	20	–0.001	–31,085	Dominated
	(6) OCT & Nurse	57,497	10.473	3508	–0.008	–438,888	Dominated
	(1) FFA & OCT	62,759	10.449	8770	–0.032	–275,574	Dominated
0.2	(7) Ophthalmologist & OCT	62,778	10.449	8789	–0.032	–270,828	Dominated
	(4) OCT & OCT	67,421	10.442	13,432	–0.040	–339,701	Dominated
	(2) FFA & Ophthalmologist	78,264	10.575	24,275	0.094	258,685	
	(8) Ophthalmologist & Ophthalmologist	78,282	10.574	18	–0.001	–26,767	Dominated
	(5) OCT & Ophthalmologist	84,376	10.567	6112	–0.008	–763,048	Dominated
0.3	(3) FFA & Nurse	51,557	10.480				
	(9) Ophthalmologist & Nurse	51,577	10.479	20	–0.001	–31,448	Dominated
	(6) OCT & Nurse	54,787	10.472	3230	–0.008	–402,465	Dominated
	(1) FFA & OCT	62,759	10.449	11,202	–0.030	–368,763	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	11,221	–0.031	–361,908	Dominated
	(4) OCT & OCT	67,421	10.442	15,864	–0.038	–416,445	Dominated
	(2) FFA & Ophthalmologist	72,358	10.575	20,801	0.095	218,127	
	(8) Ophthalmologist & Ophthalmologist	72,377	10.575	18	–0.001	–27,506	Dominated
	(5) OCT & Ophthalmologist	77,865	10.567	5507	–0.008	–681,762	Dominated

TABLE 61 One-way sensitivity analysis: ophthalmologist monitoring specificity (*continued*)

Ophthalmologist monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	49,150	10.478				
	(9) Ophthalmologist & Nurse	49,170	10.478	20	–0.001	–31,809	Dominated
	(6) OCT & Nurse	52,102	10.470	2951	–0.008	–366,309	Dominated
	(1) FFA & OCT	62,759	10.449	13,609	–0.029	–470,106	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	13,628	–0.030	–460,768	Dominated
	(2) FFA & Ophthalmologist	66,579	10.575	17,428	0.097	179,997	
	(8) Ophthalmologist & Ophthalmologist	66,597	10.575	19	–0.001	–28,239	Dominated
	(4) OCT & OCT	67,421	10.442	843	–0.133	–6313	Dominated
	(5) OCT & Ophthalmologist	71,481	10.567	4902	–0.008	–601,684	Dominated
0.5	(3) FFA & Nurse	46,769	10.477				
	(9) Ophthalmologist & Nurse	46,789	10.476	20	–0.001	–32,169	Dominated
	(6) OCT & Nurse	49,442	10.469	2673	–0.008	–330,421	Dominated
	(2) FFA & Ophthalmologist	60,922	10.575	14,153	0.098	144,077	
	(8) Ophthalmologist & Ophthalmologist	60,941	10.575	19	–0.001	–28,964	Dominated
	(1) FFA & OCT	62,759	10.449	1837	–0.126	–14,607	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	1856	–0.126	–14,685	Dominated
	(5) OCT & Ophthalmologist	65,219	10.567	4297	–0.008	–522,843	Dominated
	(4) OCT & OCT	67,421	10.442	6500	–0.133	–48,691	Dominated
0.6	(3) FFA & Nurse	44,411	10.476				
	(9) Ophthalmologist & Nurse	44,432	10.475	20	–0.001	–32,527	Dominated
	(6) OCT & Nurse	46,806	10.467	2395	–0.008	–294,806	Dominated
	(2) FFA & Ophthalmologist	55,384	10.575	10,972	0.100	110,175	
	(8) Ophthalmologist & Ophthalmologist	55,403	10.575	19	–0.001	–29,681	Dominated
	(5) OCT & Ophthalmologist	59,076	10.567	3692	–0.008	–445,261	Dominated
	(1) FFA & OCT	62,759	10.449	7375	–0.126	–58,658	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	7394	–0.126	–58,517	Dominated
	(4) OCT & OCT	67,421	10.442	12,038	–0.133	–90,204	Dominated

continued

TABLE 61 One-way sensitivity analysis: ophthalmologist monitoring specificity (*continued*)

Ophthalmologist monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	42,078	10.474				
	(9) Ophthalmologist & Nurse	42,099	10.474	20	–0.001	–32,882	Dominated
	(6) OCT & Nurse	44,195	10.466	2116	–0.008	–259,466	Dominated
	(2) FFA & Ophthalmologist	49,961	10.575	7882	0.101	78,122	
	(8) Ophthalmologist & Ophthalmologist	49,981	10.574	20	–0.001	–30,391	Dominated
	(5) OCT & Ophthalmologist	53,048	10.567	3087	–0.008	–368,955	Dominated
	(1) FFA & OCT	62,759	10.449	12,798	–0.126	–101,847	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	12,817	–0.126	–101,491	Dominated
	(4) OCT & OCT	67,421	10.442	17,461	–0.133	–130,910	Dominated
0.8	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.9	(3) FFA & Nurse	37,483	10.472				
	(9) Ophthalmologist & Nurse	37,504	10.471	21	–0.001	–33,589	Dominated
	(6) OCT & Nurse	39,043	10.463	1560	–0.008	–189,620	Dominated
	(2) FFA & Ophthalmologist	39,446	10.575	1962	0.103	18,981	
	(8) Ophthalmologist & Ophthalmologist	39,466	10.574	21	–0.001	–31,789	Dominated
	(5) OCT & Ophthalmologist	41,322	10.566	1877	–0.009	–220,218	Dominated
	(1) FFA & OCT	62,759	10.449	23,313	–0.125	–185,856	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	23,332	–0.126	–185,082	Dominated
	(4) OCT & OCT	67,421	10.442	27,976	–0.133	–210,099	Dominated

TABLE 61 One-way sensitivity analysis: ophthalmologist monitoring specificity (*continued*)

Ophthalmologist monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(2) FFA & Ophthalmologist	34,347	10.575				
	(8) Ophthalmologist & Ophthalmologist	34,368	10.574	21	–0.001	–32,476	Dominated
	(3) FFA & Nurse	35,221	10.470	874	–0.105	–8357	Dominated
	(9) Ophthalmologist & Nurse	35,242	10.470	895	–0.105	–8507	Dominated
	(5) OCT & Ophthalmologist	35,618	10.566	1271	–0.009	–147,799	Dominated
	(6) OCT & Nurse	36,502	10.462	2155	–0.113	–19,102	Dominated
	(1) FFA & OCT	62,759	10.449	28,412	–0.125	–226,777	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	28,431	–0.126	–225,797	Dominated
	(4) OCT & OCT	67,421	10.442	33,074	–0.133	–248,673	Dominated

TABLE 62 Two-way sensitivity analysis: ophthalmologist monitoring sensitivity and specificity (NMB at £30,000)

Ophthalmologist monitoring						
Sensitivity	Specificity	Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
0.8	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	59,393	10.4103	252,918	
		(3) FFA & Nurse	45,800	10.2925	262,976	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	63,691	10.4027	248,389	
		(6) OCT & Nurse	48,475	10.2850	260,076	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	59,412	10.4097	252,880	
		(9) Ophthalmologist & Nurse	45,820	10.2919	262,938	
0.8	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	54,012	10.4045	258,125	
		(3) FFA & Nurse	43,544	10.2888	265,120	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	57,705	10.3968	254,199	
		(6) OCT & Nurse	45,941	10.2813	262,498	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	54,031	10.4039	258,087	
		(9) Ophthalmologist & Nurse	43,564	10.2882	265,082	
0.8	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	48,762	10.3989	263,206	
		(3) FFA & Nurse	41,315	10.2851	267,238	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	51,851	10.3911	259,883	
		(6) OCT & Nurse	43,434	10.2776	264,893	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	48,782	10.3983	263,168	
		(9) Ophthalmologist & Nurse	41,336	10.2845	267,200	
0.8	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	43,639	10.3935	268,166	
		(3) FFA & Nurse	39,113	10.2815	269,331	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	46,124	10.3856	265,445	
		(6) OCT & Nurse	40,954	10.2739	267,264	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	

TABLE 62 Two-way sensitivity analysis: ophthalmologist monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(8) Ophthalmologist & Ophthalmologist	43,660	10.3929	268,127	
		(9) Ophthalmologist & Nurse	39,134	10.2809	269,294	
0.8	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	38,639	10.3882	273,008	✓
		(3) FFA & Nurse	36,938	10.2779	271,400	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	40,519	10.3803	270,890	
		(6) OCT & Nurse	38,500	10.2703	269,610	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	38,660	10.3876	272,969	
		(9) Ophthalmologist & Nurse	36,959	10.2774	271,362	
0.8	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	33,758	10.3831	277,736	✓
		(3) FFA & Nurse	34,788	10.2744	273,445	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	35,032	10.3751	276,221	
		(6) OCT & Nurse	36,072	10.2668	271,932	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	33,779	10.3825	277,697	
		(9) Ophthalmologist & Nurse	34,809	10.2739	273,407	
0.9	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	60,343	10.5119	255,013	
		(3) FFA & Nurse	46,394	10.4057	265,776	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	64,640	10.5039	250,476	
		(6) OCT & Nurse	49,068	10.3978	262,867	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	60,362	10.5112	254,975	
		(9) Ophthalmologist & Nurse	46,414	10.4051	265,738	
0.9	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	54,861	10.5096	260,425	
		(3) FFA & Nurse	44,074	10.4034	268,026	✓

continued

TABLE 62 Two-way sensitivity analysis: ophthalmologist monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	58,554	10.5015	256,490	
		(6) OCT & Nurse	46,470	10.3955	265,394	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	54,881	10.5089	260,387	
		(9) Ophthalmologist & Nurse	44,095	10.4028	267,988	
0.9	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	49,502	10.5073	265,717	
		(3) FFA & Nurse	41,780	10.4011	270,252	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	52,589	10.4991	262,385	
		(6) OCT & Nurse	43,897	10.3931	267,897	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	49,522	10.5067	265,678	
		(9) Ophthalmologist & Nurse	41,800	10.4005	270,213	
0.9	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,259	10.5051	270,893	
		(3) FFA & Nurse	39,511	10.3988	272,453	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	46,742	10.4969	268,164	
		(6) OCT & Nurse	41,350	10.3908	270,376	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,280	10.5045	270,854	
		(9) Ophthalmologist & Nurse	39,531	10.3982	272,415	
0.9	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	39,130	10.5029	275,957	✓
		(3) FFA & Nurse	37,266	10.3966	274,631	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	41,008	10.4946	273,831	
		(6) OCT & Nurse	38,827	10.3886	272,831	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	39,151	10.5023	275,918	
		(9) Ophthalmologist & Nurse	37,287	10.3960	274,592	

TABLE 62 Two-way sensitivity analysis: ophthalmologist monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.9	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	34,111	10.5008	280,913	✓
		(3) FFA & Nurse	35,045	10.3944	276,786	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	35,384	10.4924	279,389	
		(6) OCT & Nurse	36,328	10.3863	275,263	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	34,132	10.5002	280,873	
		(9) Ophthalmologist & Nurse	35,066	10.3938	276,747	
1.0	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	61,151	10.6006	256,868	
		(3) FFA & Nurse	46,920	10.5057	268,253	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	65,449	10.5923	252,322	
		(6) OCT & Nurse	49,592	10.4976	265,334	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	61,170	10.6000	256,829	
		(9) Ophthalmologist & Nurse	46,940	10.5051	268,214	
1.0	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	55,592	10.6015	262,455	
		(3) FFA & Nurse	44,548	10.5047	270,594	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	59,284	10.5932	258,511	
		(6) OCT & Nurse	46,942	10.4965	267,953	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	55,611	10.6009	262,415	
		(9) Ophthalmologist & Nurse	44,568	10.5041	270,555	
1.0	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	50,144	10.6024	267,927	
		(3) FFA & Nurse	42,200	10.5037	272,912	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	53,231	10.5939	264,586	
		(6) OCT & Nurse	44,316	10.4955	270,549	

continued

TABLE 62 Two-way sensitivity analysis: ophthalmologist monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Ophthalmologist monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	50,164	10.6017	267,887	
		(9) Ophthalmologist & Nurse	42,220	10.5031	272,873	
1.0	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,806	10.6031	273,288	
		(3) FFA & Nurse	39,875	10.5028	275,207	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,288	10.5946	270,550	
		(6) OCT & Nurse	41,713	10.4945	273,121	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,827	10.6025	273,248	
		(9) Ophthalmologist & Nurse	39,896	10.5021	275,168	
1.0	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	39,574	10.6038	278,541	✓
		(3) FFA & Nurse	37,574	10.5018	277,480	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	41,450	10.5952	276,407	
		(6) OCT & Nurse	39,133	10.4935	275,671	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	39,595	10.6032	278,501	
		(9) Ophthalmologist & Nurse	37,594	10.5012	277,440	
1.0	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	34,445	10.6045	283,690	✓
		(3) FFA & Nurse	35,295	10.5008	279,730	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	35,716	10.5958	282,159	
		(6) OCT & Nurse	36,576	10.4925	278,198	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	34,466	10.6038	283,650	
		(9) Ophthalmologist & Nurse	35,316	10.5002	279,690	

NMB, net monetary benefit.

TABLE 63 One-way sensitivity analysis: probability ophthalmologist monitoring assessment having unclear results

Ophthalmologist monitoring assessment unclear results (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0	(3) FFA & Nurse	39,548	10.470				
	(9) Ophthalmologist & Nurse	39,569	10.469	21	–0.001	–33,315	Dominated
	(6) OCT & Nurse	41,400	10.462	1852	–0.008	–226,583	Dominated
	(2) FFA & Ophthalmologist	44,524	10.572	4976	0.102	48,739	
	(8) Ophthalmologist & Ophthalmologist	44,544	10.571	20	–0.001	–31,134	Dominated
	(5) OCT & Ophthalmologist	47,035	10.563	2511	–0.008	–298,363	Dominated
	(1) FFA & OCT	62,759	10.449	18,235	–0.122	–148,955	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,254	–0.123	–148,350	Dominated
	(4) OCT & OCT	67,421	10.442	22,897	–0.130	–175,949	Dominated
0.1	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(3) FFA & Nurse	39,991	10.476				
	(9) Ophthalmologist & Nurse	40,012	10.475	21	–0.001	–33,159	Dominated
	(6) OCT & Nurse	41,815	10.468	1824	–0.008	–222,233	Dominated
	(2) FFA & Ophthalmologist	44,778	10.578	4787	0.102	46,820	
	(8) Ophthalmologist & Ophthalmologist	44,798	10.578	20	–0.001	–31,053	Dominated
	(5) OCT & Ophthalmologist	47,231	10.570	2453	–0.008	–289,539	Dominated
	(1) FFA & OCT	62,759	10.449	17,981	–0.129	–139,671	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,000	–0.129	–139,140	Dominated
	(4) OCT & OCT	67,421	10.442	22,643	–0.136	–165,940	Dominated

continued

TABLE 63 One-way sensitivity analysis: probability ophthalmologist monitoring assessment having unclear results (*continued*)

Ophthalmologist monitoring assessment unclear results (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.3	(3) FFA & Nurse	40,214	10.479				
	(9) Ophthalmologist & Nurse	40,234	10.478	21	–0.001	–33,081	Dominated
	(6) OCT & Nurse	42,024	10.471	1811	–0.008	–220,072	Dominated
	(2) FFA & Ophthalmologist	44,911	10.581	4698	0.102	45,894	
	(8) Ophthalmologist & Ophthalmologist	44,931	10.581	20	–0.001	–31,011	Dominated
	(5) OCT & Ophthalmologist	47,335	10.573	2423	–0.009	–285,164	Dominated
	(1) FFA & OCT	62,759	10.449	17,848	–0.132	–135,275	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	17,867	–0.133	–134,778	Dominated
	(4) OCT & OCT	67,421	10.442	22,510	–0.140	–161,186	Dominated
0.4	3) FFA & Nurse	40,437	10.482				
	9) Ophthalmologist & Nurse	40,458	10.482	20	–0.001	–33,003	Dominated
	6) OCT & Nurse	42,234	10.474	1797	–0.008	–217,921	Dominated
	2) FFA & Ophthalmologist	45,048	10.585	4611	0.102	44,991	
	8) Ophthalmologist & Ophthalmologist	45,068	10.584	20	–0.001	–30,969	Dominated
	5) OCT & Ophthalmologist	47,443	10.576	2394	–0.009	–280,815	Dominated
	(1) FFA & OCT	62,759	10.449	17,711	–0.135	–131,033	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	17,730	–0.136	–130,567	Dominated
	(4) OCT & OCT	67,421	10.442	22,373	–0.143	–156,587	Dominated
0.5	(3) FFA & Nurse	40,661	10.485				
	(9) Ophthalmologist & Nurse	40,682	10.485	20	–0.001	–32,926	Dominated
	(6) OCT & Nurse	42,445	10.477	1784	–0.008	–215,780	Dominated
	(2) FFA & Ophthalmologist	45,189	10.588	4528	0.103	44,111	
	(8) Ophthalmologist & Ophthalmologist	45,209	10.587	20	–0.001	–30,925	Dominated
	(5) OCT & Ophthalmologist	47,554	10.579	2365	–0.009	–276,491	Dominated
	(1) FFA & OCT	62,759	10.449	17,570	–0.138	–126,936	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	17,589	–0.139	–126,500	Dominated
	(4) OCT & OCT	67,421	10.442	22,233	–0.146	–152,138	Dominated

TABLE 64 One-way sensitivity analysis: nurse/technician monitoring assessment sensitivity

Nurse monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(3) FFA & Nurse	32,207	8.877				
	(9) Ophthalmologist & Nurse	32,229	8.877	22	0.000	–116,739	Dominated
	(6) OCT & Nurse	34,065	8.874	1859	–0.003	–623,825	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	12,443	1.698	7329	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(3) FFA & Nurse	33,490	9.193				
	(9) Ophthalmologist & Nurse	33,512	9.193	22	0.000	–81,140	Dominated
	(6) OCT & Nurse	35,346	9.189	1856	–0.004	–469,932	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	11,159	1.382	8077	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.3	(3) FFA & Nurse	34,692	9.465				
	(9) Ophthalmologist & Nurse	34,714	9.465	22	0.000	–63,348	Dominated
	(6) OCT & Nurse	36,545	9.460	1853	–0.005	–383,994	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	9957	1.110	8973	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 64 One-way sensitivity analysis: nurse/technician monitoring assessment sensitivity (*continued*)

Nurse monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	35,788	9.699				
	(9) Ophthalmologist & Nurse	35,809	9.699	22	0.000	–52,864	Dominated
	(6) OCT & Nurse	37,638	9.693	1850	–0.006	–330,369	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	8862	0.876	10,115	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(3) FFA & Nurse	36,773	9.900				
	(9) Ophthalmologist & Nurse	36,794	9.900	21	0.000	–46,047	Dominated
	(6) OCT & Nurse	38,620	9.894	1847	–0.006	–294,327	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	7876	0.675	11,672	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.6	(3) FFA & Nurse	37,654	10.074				
	(9) Ophthalmologist & Nurse	37,675	10.074	21	–0.001	–41,312	Dominated
	(6) OCT & Nurse	39,499	10.067	1845	–0.007	–268,779	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	6995	0.501	13,967	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 64 One-way sensitivity analysis: nurse/technician monitoring assessment sensitivity (*continued*)

Nurse monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	38,440	10.225				
	(9) Ophthalmologist & Nurse	38,461	10.225	21	–0.001	–37,863	Dominated
	(6) OCT & Nurse	40,282	10.218	1842	–0.007	–249,932	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	6209	0.350	17,753	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.8	(3) FFA & Nurse	39,142	10.357				
	(9) Ophthalmologist & Nurse	39,162	10.357	21	–0.001	–35,259	Dominated
	(6) OCT & Nurse	40,982	10.349	1840	–0.008	–235,590	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	5507	0.218	25,280	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.9	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 64 One-way sensitivity analysis: nurse/technician monitoring assessment sensitivity (*continued*)

Nurse monitoring assessment sensitivity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	40,332	10.575				
	(9) Ophthalmologist & Nurse	40,352	10.574	20	–0.001	–31,631	Dominated
	(6) OCT & Nurse	42,168	10.566	1836	–0.009	–215,499	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4318	0.000	31,416,455	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 65 One-way sensitivity analysis: nurse/technician monitoring assessment specificity

Nurse monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.1	(2) FFA & Ophthalmologist	44,649	10.575				
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(3) FFA & Nurse	47,769	10.476	3120	–0.099	–31,362	Dominated
	(9) Ophthalmologist & Nurse	47,789	10.475	3140	–0.100	–31,367	Dominated
	(6) OCT & Nurse	50,523	10.467	5874	–0.108	–54,589	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(2) FFA & Ophthalmologist	44,649	10.575				
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(3) FFA & Nurse	46,156	10.475	1507	–0.100	–15,067	Dominated
	(9) Ophthalmologist & Nurse	46,176	10.474	1527	–0.101	–15,174	Dominated
0.2	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(6) OCT & Nurse	48,727	10.467	4078	–0.108	–37,703	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.3	(3) FFA & Nurse	44,550	10.474				
	(9) Ophthalmologist & Nurse	44,570	10.474	20	–0.001	–32,581	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	99	0.101	988	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(6) OCT & Nurse	46,938	10.466	2288	–0.109	–21,050	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 65 One-way sensitivity analysis: nurse/technician monitoring assessment specificity (*continued*)

Nurse monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.4	(3) FFA & Nurse	42,950	10.474				
	(9) Ophthalmologist & Nurse	42,970	10.473	20	–0.001	–32,800	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	1699	0.101	16,809	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(6) OCT & Nurse	45,154	10.466	505	–0.109	–4624	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(3) FFA & Nurse	41,356	10.473				
	(9) Ophthalmologist & Nurse	41,377	10.473	20	–0.001	–33,019	Dominated
	(6) OCT & Nurse	43,378	10.465	2021	–0.008	–247,178	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	3293	0.102	32,401	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.6	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 65 One-way sensitivity analysis: nurse/technician monitoring assessment specificity (*continued*)

Nurse monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.7	(3) FFA & Nurse	38,188	10.472				
	(9) Ophthalmologist & Nurse	38,209	10.472	21	–0.001	–33,454	Dominated
	(6) OCT & Nurse	39,843	10.464	1655	–0.008	–201,701	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	6461	0.103	62,917	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.8	(3) FFA & Nurse	36,614	10.472				
	(9) Ophthalmologist & Nurse	36,635	10.471	21	–0.001	–33,672	Dominated
	(6) OCT & Nurse	38,085	10.464	1472	–0.008	–179,071	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	8035	0.103	77,851	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.9	(3) FFA & Nurse	35,046	10.471				
	(9) Ophthalmologist & Nurse	35,066	10.471	21	–0.001	–33,888	Dominated
	(6) OCT & Nurse	36,334	10.463	1288	–0.008	–156,514	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	9604	0.104	92,575	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 65 One-way sensitivity analysis: nurse/technician monitoring assessment specificity (*continued*)

Nurse monitoring assessment specificity	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1.0	(3) FFA & Nurse	33,484	10.471				
	(9) Ophthalmologist & Nurse	33,505	10.470	21	–0.001	–34,105	Dominated
	(6) OCT & Nurse	34,589	10.463	1105	–0.008	–134,030	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	11,166	0.104	107,095	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000)

Nurse monitoring						
Sensitivity	Specificity	Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
0.6	0.4	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	40,503	10.0787	261,857	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	42,714	10.0718	259,441	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	40,524	10.0782	261,821	
0.6	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	39,074	10.0764	263,218	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,102	10.0696	260,985	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,095	10.0759	263,182	
0.6	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	37,654	10.0742	264,571	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	39,499	10.0673	262,521	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	37,675	10.0737	264,535	
0.6	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	36,242	10.0720	265,917	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	37,903	10.0651	264,049	

continued

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	36,263	10.0714	265,881	
0.6	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	34,837	10.0698	267,256	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	36,316	10.0629	265,571	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	34,858	10.0692	267,219	
0.6	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	33,440	10.0676	268,587	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	34,736	10.0607	267,084	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	33,462	10.0671	268,550	
0.6	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	32,051	10.0654	269,911	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	33,163	10.0585	268,591	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	32,073	10.0649	269,874	
0.7	0.4	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	41,424	10.2286	265,433	
		(4) OCT & OCT	67,421	10.4417	245,830	

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	43,633	10.2212	263,004	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	41,445	10.2280	265,396	
0.6	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	39,928	10.2269	266,879	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,954	10.2196	264,633	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,949	10.2264	266,842	
0.6	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	38,440	10.2253	268,318	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	40,282	10.2179	266,255	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	38,461	10.2247	268,280	
0.6	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	36,959	10.2236	269,750	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	38,618	10.2163	267,869	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	36,980	10.2231	269,712	

continued

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.6	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	35,485	10.2220	271,175	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	36,961	10.2146	269,477	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	35,507	10.2215	271,137	
0.6	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	34,019	10.2204	272,593	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	35,312	10.2130	271,078	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	34,040	10.2198	272,555	
0.6	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	32,560	10.2188	274,004	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	33,669	10.2114	272,672	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	32,581	10.2182	273,966	
0.8	0.4	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	42,235	10.3593	268,545	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	44,441	10.3515	266,105	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	42,255	10.3587	268,506	
0.8	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	40,685	10.3582	270,062	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	42,708	10.3504	267,805	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	40,705	10.3576	270,024	
0.8	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	39,142	10.3571	271,573	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	40,982	10.3493	269,498	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,162	10.3566	271,534	
0.8	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	37,606	10.3561	273,077	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	39,263	10.3483	271,185	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	37,626	10.3555	273,038	
0.8	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	36,076	10.3550	274,574	✓
		(4) OCT & OCT	67,421	10.4417	245,830	

continued

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	37,550	10.3472	272,866	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	36,097	10.3544	274,536	
0.8	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	34,554	10.3540	276,065	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	35,844	10.3461	274,539	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	34,575	10.3534	276,027	
0.8	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	33,038	10.3529	277,550	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	34,145	10.3451	276,207	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	33,059	10.3523	277,511	
0.9	0.4	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	✓
		(3) FFA & Nurse	42,950	10.4739	271,267	
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	45,154	10.4657	268,818	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	42,970	10.4733	271,229	

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
0.9	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	41,356	10.4734	272,845	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	43,378	10.4652	270,578	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	41,377	10.4728	272,806	
0.9	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	39,769	10.4728	274,416	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	41,607	10.4647	272,332	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	39,790	10.4722	274,377	
0.9	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	38,188	10.4723	275,981	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	39,843	10.4641	274,080	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	38,209	10.4717	275,942	
0.9	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	36,614	10.4718	277,540	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	38,085	10.4636	275,822	

continued

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	36,635	10.4712	277,501	
0.9	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	35,046	10.4713	279,092	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	36,334	10.4630	277,557	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	35,066	10.4707	279,053	
0.9	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	33,484	10.4707	280,639	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	34,589	10.4625	279,286	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	33,505	10.4701	280,599	
1.0	0.4	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	43,584	10.5749	273,664	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	45,787	10.5664	271,206	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	43,604	10.5743	273,624	
1.0.	0.5	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	41,955	10.5749	275,292	✓
		(4) OCT & OCT	67,421	10.4417	245,830	

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Sensitivity	Specificity					
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	43,974	10.5664	273,017	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	41,975	10.5742	275,252	
1.0	0.6	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	40,332	10.5749	276,914	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	42,168	10.5663	274,823	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	40,352	10.5742	276,875	
1.0	0.7	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	38,714	10.5748	278,531	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	40,367	10.5663	276,622	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	38,735	10.5742	278,491	
1.0	0.8	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	37,103	10.5748	280,141	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	38,573	10.5663	278,415	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	37,124	10.5742	280,101	

continued

TABLE 66 Two-way sensitivity analysis: nurse- or technician-led monitoring sensitivity and specificity (NMB at £30,000) (*continued*)

Nurse monitoring						
Sensitivity	Specificity	Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
1.0	0.9	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	35,498	10.5748	281,746	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	36,784	10.5662	280,203	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	35,518	10.5741	281,706	
1.0	1.0	(1) FFA & OCT	62,759	10.4494	250,724	
		(2) FFA & Ophthalmologist	44,649	10.5750	272,601	
		(3) FFA & Nurse	33,898	10.5748	283,345	✓
		(4) OCT & OCT	67,421	10.4417	245,830	
		(5) OCT & Ophthalmologist	47,131	10.5666	269,866	
		(6) OCT & Nurse	35,001	10.5662	281,984	
		(7) Ophthalmologist & OCT	62,778	10.4488	250,686	
		(8) Ophthalmologist & Ophthalmologist	44,669	10.5744	272,561	
		(9) Ophthalmologist & Nurse	33,919	10.5741	283,305	

NMB, net monetary benefit.

TABLE 67 One-way sensitivity analysis: probability nurse/technician monitoring assessment unclear

Nurse monitoring assessment unclear (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0	(3) FFA & Nurse	39,518	10.460				
	(9) Ophthalmologist & Nurse	39,539	10.460	21	–0.001	–33,469	Dominated
	(6) OCT & Nurse	41,306	10.452	1788	–0.008	–219,099	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	5131	0.115	44,737	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,919	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.1	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.2	(3) FFA & Nurse	40,027	10.485				
	(9) Ophthalmologist & Nurse	40,048	10.485	21	–0.001	–33,009	Dominated
	(6) OCT & Nurse	41,915	10.477	1888	–0.008	–229,688	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4622	0.090	51,428	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,958	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

continued

TABLE 67 One-way sensitivity analysis: probability nurse/technician monitoring assessment unclear (*continued*)

Nurse monitoring assessment unclear (%)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0.3	(3) FFA & Nurse	40,292	10.497				
	(9) Ophthalmologist & Nurse	40,312	10.497	21	–0.001	–32,787	Dominated
	(6) OCT & Nurse	42,230	10.489	1938	–0.008	–234,954	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4357	0.078	55,983	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,978	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.4	(3) FFA & Nurse	40,563	10.509				
	(9) Ophthalmologist & Nurse	40,584	10.508	20	–0.001	–32,570	Dominated
	(6) OCT & Nurse	42,552	10.501	1989	–0.008	–240,202	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4086	0.066	61,882	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,998	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.5	(3) FFA & Nurse	40,841	10.521				
	(9) Ophthalmologist & Nurse	40,862	10.520	20	–0.001	–32,358	Dominated
	(6) OCT & Nurse	42,880	10.512	2039	–0.008	–245,435	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	3808	0.054	69,925	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–294,018	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated

TABLE 68 One-way sensitivity analysis: OCT unit cost

OCT unit cost (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
30	(9) Ophthalmologist & Nurse	37,446	10.472				
	(3) FFA & Nurse	37,446	10.473	1	0.001	835	
	(6) OCT & Nurse	39,071	10.465	1625	–0.008	–198,353	Dominated
	(8) Ophthalmologist & Ophthalmologist	42,317	10.574	4870	0.102	47,980	
	(2) FFA & Ophthalmologist	42,318	10.575	1	0.001	1398	
	(5) OCT & Ophthalmologist	44,586	10.567	2268	–0.008	–268,648	Dominated
	(7) Ophthalmologist & OCT	60,434	10.449	18,116	–0.126	–143,560	Dominated
	(1) FFA & OCT	60,436	10.449	18,118	–0.126	–144,295	Dominated
	(4) OCT & OCT	64,885	10.442	22,567	–0.133	–169,320	Dominated
40	(3) FFA & Nurse	38,538	10.473				
	(9) Ophthalmologist & Nurse	38,548	10.472	9	–0.001	–15,184	Dominated
	(6) OCT & Nurse	40,263	10.465	1725	–0.008	–210,601	Dominated
	(2) FFA & Ophthalmologist	43,414	10.575	4875	0.102	47,723	
	(8) Ophthalmologist & Ophthalmologist	43,423	10.574	9	–0.001	–13,878	Dominated
	(5) OCT & Ophthalmologist	45,783	10.567	2369	–0.008	–280,538	Dominated
	(1) FFA & OCT	61,528	10.449	18,114	–0.126	–144,264	Dominated
	(7) Ophthalmologist & OCT	61,536	10.449	18,122	–0.126	–143,608	Dominated
	(4) OCT & OCT	66,078	10.442	22,664	–0.133	–170,044	Dominated
50	(3) FFA & Nurse	39,630	10.473				
	(9) Ophthalmologist & Nurse	39,650	10.472	19	–0.001	–31,202	Dominated
	(6) OCT & Nurse	41,456	10.465	1825	–0.008	–222,848	Dominated
	(2) FFA & Ophthalmologist	44,510	10.575	4879	0.102	47,763	
	(8) Ophthalmologist & Ophthalmologist	44,529	10.574	19	–0.001	–29,154	Dominated
	(5) OCT & Ophthalmologist	46,979	10.567	2469	–0.008	–292,428	Dominated
	(1) FFA & OCT	62,620	10.449	18,110	–0.126	–144,233	Dominated
	(7) Ophthalmologist & OCT	62,638	10.449	18,128	–0.126	–143,656	Dominated
	(4) OCT & OCT	67,270	10.442	22,760	–0.133	–170,767	Dominated

continued

TABLE 68 One-way sensitivity analysis: OCT unit cost (*continued*)

OCT unit cost (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
60	(3) FFA & Nurse	40,722	10.473				
	(9) Ophthalmologist & Nurse	40,752	10.472	29	–0.001	–47,221	Dominated
	(6) OCT & Nurse	42,648	10.465	1926	–0.008	–235,095	Dominated
	(2) FFA & Ophthalmologist	45,606	10.575	4884	0.102	47,803	
	(8) Ophthalmologist & Ophthalmologist	45,635	10.574	29	–0.001	–44,429	Dominated
	(5) OCT & Ophthalmologist	48,176	10.567	2569	–0.008	–304,319	Dominated
	(1) FFA & OCT	63,712	10.449	18,106	–0.126	–144,201	Dominated
	(7) Ophthalmologist & OCT	63,740	10.449	18,134	–0.126	–143,703	Dominated
	(4) OCT & OCT	68,462	10.442	22,856	–0.133	–171,491	Dominated
70	(3) FFA & Nurse	41,814	10.473				
	(9) Ophthalmologist & Nurse	41,854	10.472	39	–0.001	–63,240	Dominated
	(6) OCT & Nurse	43,840	10.465	2026	–0.008	–247,342	Dominated
	(2) FFA & Ophthalmologist	46,702	10.575	4888	0.102	47,842	
	(8) Ophthalmologist & Ophthalmologist	46,741	10.574	39	–0.001	–59,705	Dominated
	(5) OCT & Ophthalmologist	49,372	10.567	2670	–0.008	–316,209	Dominated
	(1) FFA & OCT	64,805	10.449	18,102	–0.126	–144,170	Dominated
	(7) Ophthalmologist & OCT	64,842	10.449	18,140	–0.126	–143,751	Dominated
	(4) OCT & OCT	69,655	10.442	22,953	–0.133	–172,214	Dominated

TABLE 69 One-way sensitivity analysis: FFA unit cost

FFA unit cost (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
80	(3) FFA & Nurse	39,503	10.473				
	(9) Ophthalmologist & Nurse	39,533	10.472	30	–0.001	–47,802	Dominated
	(6) OCT & Nurse	41,360	10.465	1857	–0.008	–226,713	Dominated
	(2) FFA & Ophthalmologist	44,207	10.575	4704	0.102	46,042	
	(8) Ophthalmologist & Ophthalmologist	44,236	10.574	29	–0.001	–44,992	Dominated
	(5) OCT & Ophthalmologist	46,690	10.567	2483	–0.008	–294,041	Dominated
	(1) FFA & OCT	62,721	10.449	18,514	–0.126	–147,446	Dominated
	(7) Ophthalmologist & OCT	62,749	10.449	18,542	–0.126	–146,934	Dominated
	(4) OCT & OCT	67,417	10.442	23,210	–0.133	–174,147	Dominated
90	(3) FFA & Nurse	39,575	10.473				
	(9) Ophthalmologist & Nurse	39,602	10.472	27	–0.001	–43,865	Dominated
	(6) OCT & Nurse	41,427	10.465	1852	–0.008	–226,089	Dominated
	(2) FFA & Ophthalmologist	44,326	10.575	4751	0.102	46,509	
	(8) Ophthalmologist & Ophthalmologist	44,353	10.574	27	–0.001	–41,236	Dominated
	(5) OCT & Ophthalmologist	46,809	10.567	2482	–0.008	–294,013	Dominated
	(1) FFA & OCT	62,731	10.449	18,405	–0.126	–146,577	Dominated
	(7) Ophthalmologist & OCT	62,757	10.449	18,430	–0.126	–146,050	Dominated
	(4) OCT & OCT	67,418	10.442	23,092	–0.133	–173,258	Dominated
100	(3) FFA & Nurse	39,647	10.473				
	(9) Ophthalmologist & Nurse	39,672	10.472	25	–0.001	–39,929	Dominated
	(6) OCT & Nurse	41,494	10.465	1847	–0.008	–225,465	Dominated
	(2) FFA & Ophthalmologist	44,446	10.575	4799	0.102	46,975	
	(8) Ophthalmologist & Ophthalmologist	44,470	10.574	24	–0.001	–37,479	Dominated
	(5) OCT & Ophthalmologist	46,928	10.567	2482	–0.008	–293,985	Dominated
	(1) FFA & OCT	62,741	10.449	18,295	–0.126	–145,707	Dominated
	(7) Ophthalmologist & OCT	62,765	10.449	18,319	–0.126	–145,165	Dominated
	(4) OCT & OCT	67,420	10.442	22,974	–0.133	–172,370	Dominated

continued

TABLE 69 One-way sensitivity analysis: FFA unit cost (*continued*)

FFA unit cost (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
110	(3) FFA & Nurse	39,719	10.473				
	(9) Ophthalmologist & Nurse	39,741	10.472	22	–0.001	–35,992	Dominated
	(6) OCT & Nurse	41,560	10.465	1842	–0.008	–224,840	Dominated
	(2) FFA & Ophthalmologist	44,565	10.575	4847	0.102	47,442	
	(8) Ophthalmologist & Ophthalmologist	44,587	10.574	22	–0.001	–33,723	Dominated
	(5) OCT & Ophthalmologist	47,047	10.567	2482	–0.008	–293,958	Dominated
	(1) FFA & OCT	62,752	10.449	18,186	–0.126	–144,837	Dominated
	(7) Ophthalmologist & OCT	62,772	10.449	18,207	–0.126	–144,281	Dominated
	(4) OCT & OCT	67,421	10.442	22,855	–0.133	–171,481	Dominated
120	(3) FFA & Nurse	39,791	10.473				
	(9) Ophthalmologist & Nurse	39,811	10.472	20	–0.001	–32,056	Dominated
	(6) OCT & Nurse	41,627	10.465	1837	–0.008	–224,216	Dominated
	(2) FFA & Ophthalmologist	44,685	10.575	4894	0.102	47,908	
	(8) Ophthalmologist & Ophthalmologist	44,704	10.574	19	–0.001	–29,967	Dominated
	(5) OCT & Ophthalmologist	47,167	10.567	2482	–0.008	–293,930	Dominated
	(1) FFA & OCT	62,762	10.449	18,077	–0.126	–143,968	Dominated
	(7) Ophthalmologist & OCT	62,780	10.449	18,095	–0.126	–143,396	Dominated
	(4) OCT & OCT	67,422	10.442	22,737	–0.133	–170,593	Dominated
130	(3) FFA & Nurse	39,863	10.473				
	(9) Ophthalmologist & Nurse	39,880	10.472	17	–0.001	–28,119	Dominated
	(6) OCT & Nurse	41,694	10.465	1831	–0.008	–223,592	Dominated
	(2) FFA & Ophthalmologist	44,805	10.575	4942	0.102	48,374	
	(8) Ophthalmologist & Ophthalmologist	44,822	10.574	17	–0.001	–26,211	Dominated
	(5) OCT & Ophthalmologist	47,286	10.567	2482	–0.008	–293,903	Dominated
	(1) FFA & OCT	62,772	10.449	17,968	–0.126	–143,098	Dominated
	(7) Ophthalmologist & OCT	62,788	10.449	17,984	–0.126	–142,512	Dominated
	(4) OCT & OCT	67,423	10.442	22,618	–0.133	–169,704	Dominated

TABLE 69 One-way sensitivity analysis: FFA unit cost (*continued*)

FFA unit cost (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
140	(3) FFA & Nurse	39,934	10.473				
	(9) Ophthalmologist & Nurse	39,949	10.472	15	–0.001	–24,182	Dominated
	(6) OCT & Nurse	41,761	10.465	1826	–0.008	–222,967	Dominated
	(2) FFA & Ophthalmologist	44,924	10.575	4990	0.102	48,841	
	(8) Ophthalmologist & Ophthalmologist	44,939	10.574	15	–0.001	–22,454	Dominated
	(5) OCT & Ophthalmologist	47,405	10.567	2481	–0.008	–293,875	Dominated
	(1) FFA & OCT	62,783	10.449	17,859	–0.126	–142,229	Dominated
	(7) Ophthalmologist & OCT	62,796	10.449	17,872	–0.126	–141,627	Dominated
	(4) OCT & OCT	67,424	10.442	22,500	–0.133	–168,815	Dominated

TABLE 70 One-way sensitivity analysis: ranibizumab unit cost (per injection)

Unit cost for ranibizumab (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
0	(1) FFA & OCT	15,064	10.449				
	(7) Ophthalmologist & OCT	15,087	10.449	23	–0.001	–36,724	Dominated
	(2) FFA & Ophthalmologist	16,110	10.575	1047	0.126	8335	
	(8) Ophthalmologist & Ophthalmologist	16,133	10.574	23	–0.001	–35,089	Dominated
	(4) OCT & OCT	16,226	10.442	116	–0.133	–867	Dominated
	(5) OCT & Ophthalmologist	17,364	10.567	1254	–0.008	–148,531	Dominated
	(3) FFA & Nurse	17,386	10.473	1276	–0.102	–12,486	Dominated
	(9) Ophthalmologist & Nurse	17,409	10.472	1298	–0.103	–12,633	Dominated
	(6) OCT & Nurse	18,647	10.465	2537	–0.110	–22,993	Dominated
50	(2) FFA & Ophthalmologist	18,033	10.575				
	(8) Ophthalmologist & Ophthalmologist	18,055	10.574	23	–0.001	–34,820	Dominated
	(1) FFA & OCT	18,277	10.449	244	–0.126	–1944	Dominated
	(7) Ophthalmologist & OCT	18,300	10.449	267	–0.126	–2114	Dominated
	(3) FFA & Nurse	18,894	10.473	861	–0.102	–8427	Dominated
	(9) Ophthalmologist & Nurse	18,916	10.472	884	–0.103	–8597	Dominated
	(5) OCT & Ophthalmologist	19,370	10.567	1337	–0.008	–158,327	Dominated
	(4) OCT & OCT	19,675	10.442	1642	–0.133	–12,320	Dominated
	(6) OCT & Nurse	20,194	10.465	2161	–0.110	–19,586	Dominated
100	(2) FFA & Ophthalmologist	19,955	10.575				
	(8) Ophthalmologist & Ophthalmologist	19,978	10.574	22	–0.001	–34,551	Dominated
	(3) FFA & Nurse	20,402	10.473	446	–0.102	–4368	Dominated
	(9) Ophthalmologist & Nurse	20,424	10.472	469	–0.103	–4561	Dominated
	(5) OCT & Ophthalmologist	21,375	10.567	1420	–0.008	–168,123	Dominated
	(1) FFA & OCT	21,490	10.449	1535	–0.126	–12,222	Dominated
	(7) Ophthalmologist & OCT	21,513	10.449	1557	–0.126	–12,339	Dominated
	(6) OCT & Nurse	21,741	10.465	1786	–0.110	–16,180	Dominated
	(4) OCT & OCT	23,124	10.442	3168	–0.133	–23,772	Dominated

TABLE 70 One-way sensitivity analysis: ranibizumab unit cost (per injection) (*continued*)

Unit cost for ranibizumab (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
250	(3) FFA & Nurse	24,926	10.473				
	(9) Ophthalmologist & Nurse	24,948	10.472	22	–0.001	–35,686	Dominated
	(2) FFA & Ophthalmologist	25,723	10.575	798	0.102	7810	
	(8) Ophthalmologist & Ophthalmologist	25,745	10.574	22	–0.001	–33,743	Dominated
	(6) OCT & Nurse	26,381	10.465	658	–0.110	–5962	Dominated
	(5) OCT & Ophthalmologist	27,391	10.567	1668	–0.008	–197,512	Dominated
	(1) FFA & OCT	31,130	10.449	5406	–0.126	–43,056	Dominated
	(7) Ophthalmologist & OCT	31,151	10.449	5428	–0.126	–43,014	Dominated
	(4) OCT & OCT	33,471	10.442	7748	–0.133	–58,129	Dominated
500	(3) FFA & Nurse	32,465	10.473				
	(9) Ophthalmologist & Nurse	32,487	10.472	21	–0.001	–34,442	Dominated
	(6) OCT & Nurse	34,115	10.465	1650	–0.008	–201,441	Dominated
	(2) FFA & Ophthalmologist	35,337	10.575	2871	0.102	28,107	
	(8) Ophthalmologist & Ophthalmologist	35,358	10.574	21	–0.001	–32,397	Dominated
	(5) OCT & Ophthalmologist	37,418	10.567	2081	–0.008	–246,492	Dominated
	(1) FFA & OCT	47,196	10.449	11,859	–0.126	–94,447	Dominated
	(7) Ophthalmologist & OCT	47,216	10.449	11,879	–0.126	–94,138	Dominated
	(4) OCT & OCT	50,716	10.442	15,379	–0.133	–115,391	Dominated
750	(3) FFA & Nurse	40,005	10.473				
	(9) Ophthalmologist & Nurse	40,026	10.472	21	–0.001	–33,198	Dominated
	(6) OCT & Nurse	41,849	10.465	1844	–0.008	–225,146	Dominated
	(2) FFA & Ophthalmologist	44,950	10.575	4945	0.102	48,404	
	(8) Ophthalmologist & Ophthalmologist	44,970	10.574	20	–0.001	–31,052	Dominated
	(5) OCT & Ophthalmologist	47,445	10.567	2495	–0.008	–295,472	Dominated
	(1) FFA & OCT	63,262	10.449	18,312	–0.126	–145,838	Dominated
	(7) Ophthalmologist & OCT	63,281	10.449	18,331	–0.126	–145,263	Dominated
	(4) OCT & OCT	67,962	10.442	23,011	–0.133	–172,653	Dominated

continued

TABLE 70 One-way sensitivity analysis: ranibizumab unit cost (per injection) (*continued*)

Unit cost for ranibizumab (£)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	ICER	Dominated
1000	(3) FFA & Nurse	47,545	10.473				
	(9) Ophthalmologist & Nurse	47,565	10.472	20	–0.001	–31,954	Dominated
	(6) OCT & Nurse	49,583	10.465	2038	–0.008	–248,850	Dominated
	(2) FFA & Ophthalmologist	54,564	10.575	7018	0.102	68,701	
	(8) Ophthalmologist & Ophthalmologist	54,583	10.574	19	–0.001	–29,706	Dominated
	(5) OCT & Ophthalmologist	57,472	10.567	2908	–0.008	–344,453	Dominated
	(1) FFA & OCT	79,328	10.449	24,765	–0.126	–197,229	Dominated
	(7) Ophthalmologist & OCT	79,346	10.449	24,782	–0.126	–196,387	Dominated
	(4) OCT & OCT	85,207	10.442	30,643	–0.133	–229,914	Dominated
1500	(3) FFA & Nurse	62,625	10.473				
	(9) Ophthalmologist & Nurse	62,643	10.472	18	–0.001	–29,466	Dominated
	(6) OCT & Nurse	65,052	10.465	2427	–0.008	–296,260	Dominated
	(2) FFA & Ophthalmologist	73,790	10.575	11,166	0.102	109,294	
	(8) Ophthalmologist & Ophthalmologist	73,808	10.574	18	–0.001	–27,014	Dominated
	(5) OCT & Ophthalmologist	77,526	10.567	3735	–0.008	–442,414	Dominated
	(1) FFA & OCT	111,461	10.449	37,670	–0.126	–300,011	Dominated
	(7) Ophthalmologist & OCT	111,476	10.449	37,685	–0.126	–298,636	Dominated
	(4) OCT & OCT	119,697	10.442	45,907	–0.133	–344,438	Dominated

TABLE 71 One-way sensitivity analysis: cycle number from which ranibizumab injection is assumed to have zero unit cost

Cycle number (month)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs
20	(2) FFA & Ophthalmologist	20,496	10.575		
	(8) Ophthalmologist & Ophthalmologist	20,516	10.574	–31,610	Dominated
	(3) FFA & Nurse	21,096	10.473	–5877	Dominated
	(9) Ophthalmologist & Nurse	21,117	10.472	–6046	Dominated
	(1) FFA & OCT	21,383	10.449	–7064	Dominated
	(7) Ophthalmologist & OCT	21,403	10.449	–7186	Dominated
	(5) OCT & Ophthalmologist	21,928	10.567	–169,602	Dominated
	(6) OCT & Nurse	22,455	10.465	–17,749	Dominated
	(4) OCT & OCT	23,010	10.442	–18,867	Dominated
30	(2) FFA & Ophthalmologist	22,099	10.575		
	(8) Ophthalmologist & Ophthalmologist	22,119	10.574	–31,597	Dominated
	(3) FFA & Nurse	22,341	10.473	–2374	Dominated
	(9) Ophthalmologist & Nurse	22,362	10.472	–2563	Dominated
	(5) OCT & Ophthalmologist	23,608	10.567	–178,823	Dominated
	(6) OCT & Nurse	23,735	10.465	–14,830	Dominated
	(1) FFA & OCT	24,137	10.449	–16,237	Dominated
	(7) Ophthalmologist & OCT	24,157	10.449	–16,313	Dominated
	(4) OCT & OCT	25,990	10.442	–29,197	Dominated
40	(3) FFA & Nurse	23,536	10.473		
	(9) Ophthalmologist & Nurse	23,557	10.472	–33,809	Dominated
	(2) FFA & Ophthalmologist	23,639	10.575	1004	
	(8) Ophthalmologist & Ophthalmologist	23,659	10.574	–31,582	Dominated
	(6) OCT & Nurse	24,964	10.465	–12,010	Dominated
	(5) OCT & Ophthalmologist	25,223	10.567	–187,585	Dominated
	(1) FFA & OCT	26,785	10.449	–25,054	Dominated
	(7) Ophthalmologist & OCT	26,805	10.449	–25,086	Dominated
	(4) OCT & OCT	28,851	10.442	–39,107	Dominated
50	(3) FFA & Nurse	24,684	10.473		
	(9) Ophthalmologist & Nurse	24,705	10.472	–33,789	Dominated
	(2) FFA & Ophthalmologist	25,118	10.575	4251	
	(8) Ophthalmologist & Ophthalmologist	25,139	10.574	–31,565	Dominated
	(6) OCT & Nurse	26,144	10.465	–9296	Dominated
	(5) OCT & Ophthalmologist	26,772	10.567	–195,899	Dominated

continued

TABLE 71 One-way sensitivity analysis: cycle number from which ranibizumab injection is assumed to have zero unit cost (*continued*)

Cycle number (month)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs
	(1) FFA & OCT	29,327	10.449	–33,518	Dominated
	(7) Ophthalmologist & OCT	29,347	10.449	–33,507	Dominated
	(4) OCT & OCT	31,596	10.442	–48,603	Dominated
60	(3) FFA & Nurse	25,784	10.473		
	(9) Ophthalmologist & Nurse	25,805	10.472	–33,766	Dominated
	(2) FFA & Ophthalmologist	26,537	10.575	7368	
	(8) Ophthalmologist & Ophthalmologist	26,557	10.574	–31,546	Dominated
	(6) OCT & Nurse	27,275	10.465	–6686	Dominated
	(5) OCT & Ophthalmologist	28,258	10.567	–203,778	Dominated
	(1) FFA & OCT	31,764	10.449	–41,629	Dominated
	(7) Ophthalmologist & OCT	31,784	10.449	–41,578	Dominated
	(4) OCT & OCT	34,226	10.442	–57,687	Dominated
70	(3) FFA & Nurse	26,837	10.473		
	(9) Ophthalmologist & Nurse	26,858	10.472	–33,742	Dominated
	(2) FFA & Ophthalmologist	27,895	10.575	10,356	
	(8) Ophthalmologist & Ophthalmologist	27,916	10.574	–31,526	Dominated
	(6) OCT & Nurse	28,357	10.465	–4181	Dominated
	(5) OCT & Ophthalmologist	29,679	10.567	–211,234	Dominated
	(1) FFA & OCT	34,097	10.449	–49,392	Dominated
	(7) Ophthalmologist & OCT	34,117	10.449	–49,302	Dominated
	(4) OCT & OCT	36,741	10.442	–66,365	Dominated
80	(3) FFA & Nurse	27,844	10.473		
	(9) Ophthalmologist & Nurse	27,865	10.472	–33,717	Dominated
	(2) FFA & Ophthalmologist	29,194	10.575	13,217	
	(8) Ophthalmologist & Ophthalmologist	29,215	10.574	–31,506	Dominated
	(6) OCT & Nurse	29,391	10.465	–1780	Dominated
	(5) OCT & Ophthalmologist	31,037	10.567	–218,279	Dominated
	(1) FFA & OCT	36,327	10.449	–56,808	Dominated
	(7) Ophthalmologist & OCT	36,347	10.449	–56,682	Dominated
	(4) OCT & OCT	39,143	10.442	–74,642	Dominated
90	(3) FFA & Nurse	28,805	10.473		
	(9) Ophthalmologist & Nurse	28,825	10.472	–33,691	Dominated
	(6) OCT & Nurse	30,377	10.465	–191,957	Dominated
	(2) FFA & Ophthalmologist	30,434	10.575	15,951	
	(8) Ophthalmologist & Ophthalmologist	30,454	10.574	–31,484	Dominated

TABLE 71 One-way sensitivity analysis: cycle number from which ranibizumab injection is assumed to have zero unit cost (*continued*)

Cycle number (month)	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs
	(5) OCT & Ophthalmologist	32,333	10.567	–224,925	Dominated
	(1) FFA & OCT	38,455	10.449	–63,882	Dominated
	(7) Ophthalmologist & OCT	38,475	10.449	–63,720	Dominated
	(4) OCT & OCT	41,433	10.442	–82,523	Dominated
100	(3) FFA & Nurse	29,719	10.473		
	(9) Ophthalmologist & Nurse	29,740	10.472	–33,665	Dominated
	(6) OCT & Nurse	31,316	10.465	–194,908	Dominated
	(2) FFA & Ophthalmologist	31,615	10.575	18,559	
	(8) Ophthalmologist & Ophthalmologist	31,636	10.574	–31,462	Dominated
	(5) OCT & Ophthalmologist	33,567	10.567	–231,184	Dominated
	(1) FFA & OCT	40,482	10.449	–70,616	Dominated
	(7) Ophthalmologist & OCT	40,502	10.449	–70,420	Dominated
	(4) OCT & OCT	43,612	10.442	–90,013	Dominated
110	(3) FFA & Nurse	30,589	10.473		
	(9) Ophthalmologist & Nurse	30,610	10.472	–33,638	Dominated
	(6) OCT & Nurse	32,208	10.465	–197,680	Dominated
	(2) FFA & Ophthalmologist	32,739	10.575	21,043	
	(8) Ophthalmologist & Ophthalmologist	32,759	10.574	–31,439	Dominated
	(5) OCT & Ophthalmologist	34,740	10.567	–237,067	Dominated
	(1) FFA & OCT	42,409	10.449	–77,015	Dominated
	(7) Ophthalmologist & OCT	42,428	10.449	–76,787	Dominated
	(4) OCT & OCT	45,683	10.442	–97,119	Dominated
120	(3) FFA & Nurse	31,413	10.473		
	(9) Ophthalmologist & Nurse	31,434	10.472	–33,611	Dominated
	(6) OCT & Nurse	33,054	10.465	–200,280	Dominated
	(2) FFA & Ophthalmologist	33,804	10.575	23,404	
	(8) Ophthalmologist & Ophthalmologist	33,825	10.574	–31,416	Dominated
	(5) OCT & Ophthalmologist	35,853	10.567	–242,585	Dominated
	(1) FFA & OCT	44,236	10.449	–83,080	Dominated
	(7) Ophthalmologist & OCT	44,256	10.449	–82,822	Dominated
	(4) OCT & OCT	47,645	10.442	–103,844	Dominated
	(2) FFA & Ophthalmologist	20,496	10.575		

TABLE 72 Two-way sensitivity analysis: discount rates for cost and QALYs (NMB at £30,000)

Discount rate						
Costs (%)	QALYs (%)	Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
0	0	(1) FFA & OCT	88,482	14.665	351,465	
		(2) FFA & Ophthalmologist	62,690	14.867	383,317	
		(3) FFA & Nurse	55,747	14.702	385,326	✓
		(4) OCT & OCT	94,956	14.654	344,673	
		(5) OCT & Ophthalmologist	66,141	14.855	379,520	
		(6) OCT & Nurse	58,304	14.691	382,433	
		(7) Ophthalmologist & OCT	88,501	14.664	351,420	
		(8) Ophthalmologist & Ophthalmologist	62,711	14.866	383,270	
		(9) Ophthalmologist & Nurse	55,767	14.702	385,280	
0.01	0.01	(1) FFA & OCT	79,586	13.211	316,729	
		(2) FFA & Ophthalmologist	56,451	13.385	345,109	
		(3) FFA & Nurse	50,221	13.243	347,070	✓
		(4) OCT & OCT	85,439	13.201	310,588	
		(5) OCT & Ophthalmologist	59,569	13.375	341,676	
		(6) OCT & Nurse	52,532	13.233	344,454	
		(7) Ophthalmologist & OCT	79,605	13.210	316,686	
		(8) Ophthalmologist & Ophthalmologist	56,471	13.385	345,065	
		(9) Ophthalmologist & Nurse	50,242	13.242	347,026	
0.02	0.02	(1) FFA & OCT	72,037	11.974	287,173	
		(2) FFA & Ophthalmologist	51,156	12.126	312,623	
		(3) FFA & Nurse	45,532	12.002	314,529	✓
		(4) OCT & OCT	77,358	11.965	281,589	
		(5) OCT & Ophthalmologist	53,990	12.116	309,502	
		(6) OCT & Nurse	47,631	11.993	312,151	
		(7) Ophthalmologist & OCT	72,056	11.973	287,133	
		(8) Ophthalmologist & Ophthalmologist	51,176	12.125	312,581	
		(9) Ophthalmologist & Nurse	45,552	12.001	314,487	
0.03	0.03	(1) FFA & OCT	65,588	10.915	261,863	
		(2) FFA & Ophthalmologist	46,633	11.049	284,824	
		(3) FFA & Nurse	41,526	10.940	286,671	✓
		(4) OCT & OCT	70,452	10.907	256,757	
		(5) OCT & Ophthalmologist	49,223	11.040	281,970	
		(6) OCT & Nurse	43,444	10.931	284,497	
		(7) Ophthalmologist & OCT	65,607	10.914	261,824	

TABLE 72 Two-way sensitivity analysis: discount rates for cost and QALYs (NMB at £30,000) (*continued*)

Discount rate		Strategy	Expected cost (£)	Expected QALYs	NMB (£)	Maximum NMB
Costs (%)	QALYs (%)					
		(8) Ophthalmologist & Ophthalmologist	46,653	11.048	284,784	
		(9) Ophthalmologist & Nurse	41,547	10.939	286,631	
0.04	0.04	(1) FFA & OCT	60,045	10.003	240,053	
		(2) FFA & Ophthalmologist	42,746	10.121	260,886	
		(3) FFA & Nurse	38,083	10.025	262,674	✓
		(4) OCT & OCT	64,514	9.996	235,362	
		(5) OCT & Ophthalmologist	45,124	10.113	258,265	
		(6) OCT & Nurse	39,845	10.017	260,676	
		(7) Ophthalmologist & OCT	60,064	10.003	240,016	
		(8) Ophthalmologist & Ophthalmologist	42,766	10.120	260,848	
		(9) Ophthalmologist & Nurse	38,104	10.025	262,635	
0.05	0.05	(1) FFA & OCT	55,252	9.213	221,149	
		(2) FFA & Ophthalmologist	39,384	9.318	240,151	
		(3) FFA & Nurse	35,106	9.233	241,879	✓
		(4) OCT & OCT	59,377	9.206	216,817	
		(5) OCT & Ophthalmologist	41,579	9.310	237,731	
		(6) OCT & Nurse	36,731	9.226	240,035	
		(7) Ophthalmologist & OCT	55,271	9.213	221,113	
		(8) Ophthalmologist & Ophthalmologist	39,404	9.317	240,114	
		(9) Ophthalmologist & Nurse	35,127	9.232	241,842	
0.06	0.06	(1) FFA & OCT	51,083	8.525	204,668	
		(2) FFA & Ophthalmologist	36,460	8.618	222,087	
		(3) FFA & Nurse	32,517	8.542	223,756	✓
		(4) OCT & OCT	54,908	8.519	200,652	
		(5) OCT & Ophthalmologist	38,495	8.611	219,843	
		(6) OCT & Nurse	34,023	8.536	222,047	
		(7) Ophthalmologist & OCT	51,102	8.525	204,634	
		(8) Ophthalmologist & Ophthalmologist	36,481	8.618	222,051	
		(9) Ophthalmologist & Nurse	32,538	8.542	223,720	

NMB, net monetary benefit.

TABLE 73 One-way sensitivity analysis: prevalence for nAMD

nAMD prevalence	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	Strategy	Expected cost (£)
0.1	(9) Ophthalmologist & Nurse	9785	11.109				
	(3) FFA & Nurse	9820	11.109	34	0.000	388,603	
	(8) Ophthalmologist & Ophthalmologist	10,979	11.130	1159	0.021	55,404	
	(2) FFA & Ophthalmologist	11,013	11.130	34	0.000	370,944	
	(7) Ophthalmologist & OCT	15,389	11.106	4376	–0.024	–184,037	Dominated
	(1) FFA & OCT	15,424	11.107	4411	–0.024	–186,193	Dominated
	(6) OCT & Nurse	15,524	11.108	4511	–0.022	–204,863	Dominated
	(5) OCT & Ophthalmologist	18,663	11.130	7650	–0.001	–12,771,991	Dominated
	(4) OCT & OCT	29,660	11.107	18,647	–0.023	–813,472	Dominated
0.2	(9) Ophthalmologist & Nurse	14,786	11.003				
	(3) FFA & Nurse	14,811	11.003	25	0.000	142,530	
	(8) Ophthalmologist & Ophthalmologist	16,594	11.038	1783	0.034	51,892	
	(2) FFA & Ophthalmologist	16,619	11.038	25	0.000	136,422	
	(6) OCT & Nurse	19,871	11.001	3252	–0.037	–88,510	Dominated
	(7) Ophthalmologist & OCT	23,288	10.997	6668	–0.041	–163,248	Dominated
	(1) FFA & OCT	23,313	10.997	6694	–0.041	–164,599	Dominated
	(5) OCT & Ophthalmologist	23,408	11.036	6789	–0.002	–3,561,016	Dominated
	(4) OCT & OCT	35,954	10.996	19,334	–0.041	–467,969	Dominated
0.3	(9) Ophthalmologist & Nurse	19,787	10.897				
	(3) FFA & Nurse	19,803	10.897	16	0.000	60,505	
	(8) Ophthalmologist & Ophthalmologist	22,209	10.945	2406	0.048	50,354	
	(2) FFA & Ophthalmologist	22,225	10.945	16	0.000	58,248	
	(6) OCT & Nurse	24,218	10.894	1993	–0.051	–38,729	Dominated
	(5) OCT & Ophthalmologist	28,152	10.942	5927	–0.003	–1,844,329	Dominated
	(7) Ophthalmologist & OCT	31,186	10.887	8960	–0.058	–154,713	Dominated
	(1) FFA & OCT	31,202	10.888	8977	–0.058	–155,725	Dominated
	(4) OCT & OCT	42,247	10.885	20,022	–0.060	–335,328	Dominated

TABLE 73 One-way sensitivity analysis: prevalence for nAMD (*continued*)

nAMD prevalence	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	Strategy	Expected cost (£)
0.4	(9) Ophthalmologist & Nurse	24,787	10.791				
	(3) FFA & Nurse	24,794	10.791	7	0.000	19,493	
	(8) Ophthalmologist & Ophthalmologist	27,824	10.852	3030	0.061	49,491	
	(2) FFA & Ophthalmologist	27,831	10.853	7	0.000	19,161	
	(6) OCT & Nurse	28,565	10.786	734	–0.066	–11,095	Dominated
	(5) OCT & Ophthalmologist	32,897	10.848	5066	–0.005	–1,120,483	Dominated
	(7) Ophthalmologist & OCT	39,084	10.778	11,253	–0.075	–150,064	Dominated
	(1) FFA & OCT	39,091	10.778	11,260	–0.075	–150,889	Dominated
	(4) OCT & OCT	48,541	10.775	20,710	–0.078	–265,161	Dominated
0.5	(3) FFA & Nurse	29,786	10.685				
	(9) Ophthalmologist & Nurse	29,788	10.685	2	0.000	–5,114	Dominated
	(6) OCT & Nurse	32,913	10.679	3127	–0.006	–539,595	Dominated
	(2) FFA & Ophthalmologist	33,437	10.760	3651	0.075	48,610	
	(8) Ophthalmologist & Ophthalmologist	33,439	10.760	2	0.000	–4,291	Dominated
	(5) OCT & Ophthalmologist	37,642	10.754	4205	–0.006	–721,367	Dominated
	(1) FFA & OCT	46,981	10.668	13,543	–0.092	–147,846	Dominated
	(7) Ophthalmologist & OCT	46,982	10.668	13,545	–0.092	–147,138	Dominated
	(4) OCT & OCT	54,834	10.664	21,397	–0.096	–221,744	Dominated
0.6	(3) FFA & Nurse	34,778	10.579				
	(9) Ophthalmologist & Nurse	34,789	10.578	11	–0.001	–21,519	Dominated
	(6) OCT & Nurse	37,260	10.572	2482	–0.007	–354,998	Dominated
	(2) FFA & Ophthalmologist	39,043	10.668	4266	0.089	48,125	
	(8) Ophthalmologist & Ophthalmologist	39,054	10.667	11	–0.001	–19,926	Dominated
	(5) OCT & Ophthalmologist	42,386	10.660	3343	–0.007	–468,497	Dominated
	(1) FFA & OCT	54,870	10.559	15,827	–0.109	–145,754	Dominated
	(7) Ophthalmologist & OCT	54,880	10.558	15,837	–0.109	–145,128	Dominated
	(4) OCT & OCT	61,128	10.553	22,085	–0.115	–192,228	Dominated

continued

TABLE 73 One-way sensitivity analysis: prevalence for nAMD (*continued*)

nAMD prevalence	Strategy	Expected cost (£)	Expected QALYs	Incremental cost (£)	Incremental QALYs	Strategy	Expected cost (£)
0.7	(3) FFA & Nurse	39,769	10.473				
	(9) Ophthalmologist & Nurse	39,790	10.472	21	–0.001	–33,237	Dominated
	(6) OCT & Nurse	41,607	10.465	1838	–0.008	–224,403	Dominated
	(2) FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768	
	(8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	–0.001	–31,094	Dominated
	(5) OCT & Ophthalmologist	47,131	10.567	2482	–0.008	–293,938	Dominated
	(1) FFA & OCT	62,759	10.449	18,110	–0.126	–144,229	Dominated
	(7) Ophthalmologist & OCT	62,778	10.449	18,129	–0.126	–143,662	Dominated
	(4) OCT & OCT	67,421	10.442	22,772	–0.133	–170,859	Dominated
0.8	(3) FFA & Nurse	44,761	10.367				
	(9) Ophthalmologist & Nurse	44,790	10.366	30	–0.001	–42,025	Dominated
	(6) OCT & Nurse	45,954	10.357	1194	–0.009	–127,138	Dominated
	(2) FFA & Ophthalmologist	50,255	10.482	5494	0.116	47,495	
	(8) Ophthalmologist & Ophthalmologist	50,284	10.482	29	–0.001	–39,470	Dominated
	(5) OCT & Ophthalmologist	51,876	10.473	1620	–0.010	–166,190	Dominated
	(1) FFA & OCT	70,648	10.340	20,393	–0.143	–143,066	Dominated
	(7) Ophthalmologist & OCT	70,676	10.339	20,421	–0.143	–142,545	Dominated
	(4) OCT & OCT	73,715	10.331	23,460	–0.152	–154,673	Dominated
0.9	(3) FFA & Nurse	49,752	10.261				
	(9) Ophthalmologist & Nurse	49,791	10.260	39	–0.001	–48,860	Dominated
	(6) OCT & Nurse	50,302	10.250	549	–0.011	–51,888	Dominated
	(2) FFA & Ophthalmologist	55,861	10.390	6109	0.129	47,279	
	(8) Ophthalmologist & Ophthalmologist	55,900	10.389	38	–0.001	–45,984	Dominated
	(5) OCT & Ophthalmologist	56,620	10.379	759	–0.011	–68,648	Dominated
	(1) FFA & OCT	78,537	10.230	22,676	–0.160	–142,151	Dominated
	(7) Ophthalmologist & OCT	78,574	10.230	22,713	–0.160	–141,666	Dominated
	(4) OCT & OCT	80,009	10.220	24,147	–0.170	–141,988	Dominated

TABLE 74 Alternative utility weights based on Czoski-Murray *et al.*[78]

Strategy	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£)
(3) FFA & Nurse	39,769	–	8.582	0.000	0
(9) Ophthalmologist & Nurse	39,790	21	8.582	0.000	–51,961
(6) OCT & Nurse	41,607	1838	8.577	–0.005	–354,384
(2) FFA & Ophthalmologist	44,649	4880	8.649	0.067	72,717
(8) Ophthalmologist & Ophthalmologist	44,669	20	8.649	0.000	–49,222
(5) OCT & Ophthalmologist	47,131	2482	8.644	–0.005	–474,382
(1) FFA & OCT	62,759	18,110	8.578	–0.071	–255,538
(7) Ophthalmologist & OCT	62,778	18,129	8.578	–0.071	–254,352
(4) OCT & OCT	67,421	22,772	8.574	–0.076	–301,288

–, there is no incremental cost in this option.
Utility weight used: $> 6/12 = 0.706$; $\leq 6/12$ to $> 6/24$ state $= 0.681$; $\leq 6/24$ to $> 6/60$ state $= 0.511$; $\leq 6/60$ to $> 3/60$ state $= 0.511$; $\leq 3/60 = 0.314$.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library