Health Technology Assessment 2007; Vol. 11: No. 41

The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation

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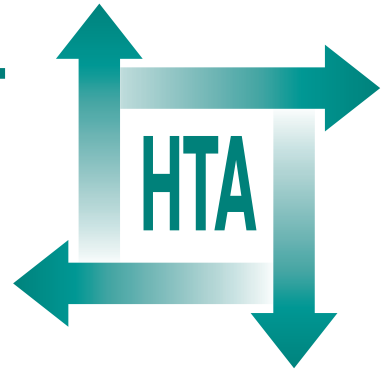
October 2007

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk



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Declared competing interests of authors: none

Published October 2007

This report should be referenced as follows:

Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(41).

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

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The research reported in this monograph was commissioned by the HTA Programme as project number 04/08/02. The contractual start date was in February 2005. The draft report began editorial review in June 2006 and was accepted for publication in April 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. 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 referees 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.

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ISSN 1366-5278

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Abstract

The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation

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Objectives: To assess whether open angle glaucoma (OAG) screening meets the UK National Screening Committee criteria, to compare screening strategies with case finding, to estimate test parameters, to model estimates of cost and cost-effectiveness, and to identify areas for future research.
Data sources: Major electronic databases were searched up to December 2005.
Review methods: Screening strategies were developed by wide consultation. Markov submodels were developed to represent screening strategies. Parameter estimates were determined by systematic reviews of epidemiology, economic evaluations of screening, and effectiveness (test accuracy, screening and treatment). Tailored highly sensitive electronic searches were undertaken.
Results: Most potential screening tests reviewed had an estimated specificity of 85% or higher. No test was clearly most accurate, with only a few, heterogeneous studies for each test. No randomised controlled trials (RCTs) of screening were identified. Based on two treatment RCTs, early treatment reduces the risk of progression. Extrapolating from this, and assuming accelerated progression with advancing disease severity, without treatment the mean time to blindness in at least one eye was approximately 23 years, compared to 35 years with treatment. Prevalence would have to be about 3–4% in 40 year olds with a screening interval of 10 years to approach cost-effectiveness. It is predicted that screening might be cost-effective in a 50-year-old cohort at a prevalence of 4% with a 10-year screening interval. General population screening at any age, thus, appears not to be cost-effective. Selective screening of groups with higher prevalence (family history, black ethnicity) might be worthwhile, although this would only cover 6% of the population. Extension to include other at-risk cohorts (e.g. myopia and diabetes) would include 37% of the general population, but the prevalence is then too low for screening to be considered cost-effective. Screening using a test with initial automated classification followed by assessment by a specialised optometrist, for test positives, was more cost-effective than initial specialised optometric assessment. The cost-effectiveness of the screening programme was highly sensitive to the perspective on costs (NHS or societal). In the base-case model, the NHS costs of visual impairment were estimated as £669. If annual societal costs were £8800, then screening might be considered cost-effective for a 40-year-old cohort with 1% OAG prevalence assuming a willingness to pay of £30,000 per quality-adjusted life-year. Of lesser importance were changes to estimates of attendance for sight tests, incidence of OAG, rate of progression and utility values for each stage of OAG severity. Cost-effectiveness was not particularly sensitive to the

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accuracy of screening tests within the ranges observed. However, a highly specific test is required to reduce large numbers of false-positive referrals. The findings that population screening is unlikely to be cost-effective are based on an economic model whose parameter estimates have considerable uncertainty. In particular, if rate of progression and/or costs of visual impairment are higher than estimated then screening could be cost-effective.

Conclusions: While population screening is not cost-effective, the targeted screening of high-risk groups may be. Procedures for identifying those at risk, for quality assuring the programme, as well as adequate service provision for those screened positive would all be needed. Glaucoma detection can be improved by increasing attendance for eye examination, and improving the performance of current testing by either refining practice or adding in a technology-based first assessment, the latter being the more cost-effective option. This has implications for any future organisational changes in community eye-care services. Further research should aim to develop and provide quality data to populate the economic model, by conducting a feasibility study of interventions to improve detection, by obtaining further data on costs of blindness, risk of progression and health outcomes, and by conducting an RCT of interventions to improve the uptake of glaucoma testing.

Contents

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List of abbreviations

AGIS	Advanced Glaucoma Intervention Study
ASSIA	Applied Social Science Index and Abstracts
BHPS	British Household Panel Survey
C-20°	central 20 degrees of visual field
CCT	Current Controlled Trials
CDR	cup-to-disc ratio
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CNTGS	Collaborative Normal Tension Glaucoma Study
CRD	Centre for Reviews and Dissemination
CrI	credible interval
D	dioptre
DALY	disability-adjusted life-year
DARE	Database of Abstracts of Reviews of Effectiveness
DOR	diagnostic odds ratio
EMGT	Early Manifest Glaucoma Trial
EQ-5D	EuroQol 5 Dimensions
FDT	frequency doubling technology
FN	false negative
FP	false positive
GAT	Goldmann applanation tonometry
GDx VCC	GDx variable corneal compensation
GHT	glaucoma hemifield test
GO	glaucoma optometrist
GPS	glaucoma probability score
HbA_{1c}	glycosylated haemoglobin
HF	Harrington–Flock
HMIC	Health Management Information Consortium
HRQoL	health-related quality of life
HRT	Heidelberg retina tomograph
HSROC	hierarchical summary receiver operating characteristic
IC	incremental cost
ICER	incremental cost-effectiveness ratio
IGA	International Glaucoma Association
IOP	intraocular pressure
ITT	intention-to-treat
MD	mean deviation
MDP	motion detection perimetry
MPT	manual perimetry technique
MRA	Moorfields regression analysis

continued

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List of abbreviations *continued*

NA	not applicable
NCT	non-contact tonometry
NEI	National Eye Institute
NFI	nerve fibre indicator
NFL	nerve fibre layer
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NRR	neuroretinal rim
NS	not stated
NSC	National Screening Committee
NTG	normal tension glaucoma
OAG	open angle glaucoma
OCT	optical coherence tomography
OKP	oculokinetic perimetry
OR	odds ratio
PS	partial sight
QALY	quality-adjusted life-year
QAVY	quality-adjusted year of vision
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
RDOR	relative diagnostic odds ratio
RNFL	retinal nerve fibre layer
RR	relative risk
RTA	retinal thickness analyser
RVM	relevance vector machine
SAP	standard automated perimetry
SCI	Science Citation Index
SD	standard deviation
SE	standard error
SITA	Swedish interactive threshold algorithm
SLP	scanning laser polarimetry
SROC	summary receiver operating characteristic
SSCI	Social Science Citation Index
STV&WS	Sight Test Volume and Workforce Survey
SWAP	short-wavelength automated perimetry
TD	total deviation
TN	true negative
TP	true positive
VCDR	vertical cup-to-disc ratio
VFQ	Visual Function Questionnaire
VI	visual impairment

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

Executive summary

Background

Glaucoma is the leading cause of irreversible blindness worldwide. Open angle glaucoma (OAG) accounts for about 50% of glaucoma blindness. Prior evaluations of screening effectiveness have concluded that there is insufficient evidence to recommend screening for OAG; recent treatments appear effective in delaying progression, but long-term health outcomes are uncertain. Screening programmes for OAG have not been adopted in any country. In the UK, glaucoma is detected by opportunistic case finding, usually by community optometrists.

Objectives

The objectives of this systematic review were:

- to assess whether OAG screening meets the UK National Screening Committee (NSC) criteria
- to develop a model comparing screening strategies with case finding
- to estimate parameters through systematic reviews
- to model estimates of cost and cost-effectiveness
- to identify areas for future research.

Methods

Screening strategies were developed by wide consultation. In the first ('technician') strategy, the cohort 'at risk' would be invited for examination, based on measurement of intraocular pressure (IOP) and a second 'test' (not prespecified). Screen positives would be referred for specialised optometrist assessment. In the second ('glaucoma optometrist') strategy, the cohort would be invited to a specialised optometrist for assessment. Positives from either strategy would be referred for diagnosis, by an ophthalmologist, as occurs in current case finding ('no screening' strategy).

Markov submodels were developed to represent these strategies. Parameter estimates were determined by systematic reviews of epidemiology, economic evaluations of screening, and effectiveness (test accuracy, screening and treatment).

Tailored highly sensitive electronic searches were undertaken. The date of last searches was December 2005.

Results

In the UK, the estimated prevalence of OAG is 2.1% [95% confidence interval (CI) 1.7 to 2.5], ranging from 0.3% in people aged 40 to 3.3% in people aged 70 years. Incidence ranges from 30 to 181 per 100,000 person-years for ages 50 and 70 years, respectively. Of an estimated half a million people affected, 67% are undetected. Several risk factors are identified; for ages 40–75 years, prevalence estimates are: people with myopia 2.7%, people with diabetes 3.3% and family history in a first-degree relative 6.7%. The risk is four times higher among those of African ethnicity. Insufficient data were available to estimate prevalence in other ethnic minority groups in the UK.

Most potential screening tests reviewed had an estimated specificity of 85% or higher. No test was clearly most accurate, with only a few, heterogeneous studies for each test.

No randomised controlled trials (RCTs) of screening were identified. Based on two treatment RCTs, early treatment reduces the risk of progression (hazard ratio 0.65, 95% CI 0.49 to 0.87). Extrapolating from this, and assuming accelerated progression with advancing disease severity, without treatment the mean time to blindness in at least one eye was approximately 23 years, compared to 35 years with treatment.

The main determinant of cost-effectiveness was prevalence. Prevalence would have to be about 3–4% in 40 year olds with a screening interval of 10 years to approach cost-effectiveness. It is predicted that screening might be cost-effective in a 50-year-old cohort at a prevalence of 4% with a 10-year screening interval. General population screening at any age, thus, appears not to be cost-effective. Selective screening of groups with higher prevalence (black ethnicity and family history) might be worthwhile, although this would only cover 6% of the population. Extension to include other at-risk cohorts (e.g. myopia and diabetes)

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would include 37% of the general population, but the prevalence is then too low for screening to be considered cost-effective.

Screening using a test with initial automated classification followed by assessment by a specialised optometrist, for test positives, was more cost-effective than initial specialised optometric assessment. The cost-effectiveness of the screening programme was highly sensitive to the perspective on costs (NHS or societal). In the base-case model, the NHS costs of visual impairment were estimated as £669. If annual societal costs were £8800, then screening might be considered cost-effective for a 40-year-old cohort with 1% OAG prevalence assuming a willingness to pay of £30,000 per quality-adjusted life-year. Of lesser importance were changes to estimates of attendance for sight tests, incidence of OAG, rate of progression and utility values for each stage of OAG severity. Cost-effectiveness was not particularly sensitive to the accuracy of screening tests within the ranges observed. However, a highly specific test is required to reduce large numbers of false-positive referrals.

The findings that population screening is unlikely to be cost-effective are based on an economic model whose parameter estimates have considerable uncertainty. In particular, if rate of progression and/or costs of visual impairment are higher than estimated then screening could be cost-effective.

Conclusions

Implications for healthcare

Screening for OAG met the UK NSC criteria for condition and treatment, but not for test or screening. Population screening is not cost-effective, but targeted screening of high-risk groups may be. Measures systematically to identify those at risk and quality assure the programme would be required. Adequate service provision for those screened positive would be needed.

Glaucoma detection can be improved by increasing attendance for eye examination, and improving the performance of current testing by either refining practice or adding in a technology-based first assessment, the latter being the more cost-effective option. This has implications for any future organisational changes in community eye-care services.

Implications for research

Further research should aim to develop and provide quality data to populate the economic model, by undertaking the following, in order of priority.

First, a feasibility study of interventions to improve detection; input from qualitative researchers, health economists, health psychologists and trialists is required to evaluate components of the care pathway:

- optimal test strategy
- acceptability of interventions to improve attendance and the acceptability of subsequent testing
- harms and benefits associated with enhanced glaucoma detection strategies.

Secondly, a refinement of the parameter estimates in the economic model. In particular, further data on costs of blindness, risk of progression and health outcomes are required. A value for information analysis would inform where primary research should be directed.

Thirdly, an RCT of interventions to improve the uptake of glaucoma testing, informed by the results of the prior feasibility studies.

Chapter 1

The aim of the review

This report was commissioned to evaluate the clinical effectiveness and cost-effectiveness of screening for open angle glaucoma (OAG) in the UK. Specifically, secondary research with economic modelling was required to assess the extent to which screening for OAG would meet the National Screening Committee (NSC) criteria for a screening programme and to identify future research needs.

The specific objectives were:

- to review systematically risk factors for developing OAG, and to determine the prevalence and incidence of OAG according to age
- to review systematically the accuracy of screening tests for OAG
- to review systematically treatment effectiveness and to extrapolate these effects on long-term visual outcome
- to identify any potential benefits and harms of screening and subsequent management
- to determine the clinical and cost-effectiveness of alternative screening strategies
- to assess whether screening for OAG meets specified criteria for a national screening programme
- to describe the impact on the NHS if a population screening programme for OAG were initiated
- to identify and prioritise areas for future research.

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Chapter 2
Background

Introduction

Glaucoma describes a group of eye diseases, in which there is progressive damage to the optic nerve leading to impaired vision and blindness if untreated. The primary glaucomas (those that are not a consequence of other eye or systemic disease) can be classified as OAG or angle closure glaucoma. These two types are distinguished by the anatomy of the anterior segment of the eye, as illustrated in *Figure 1*.

Angle closure glaucoma, although less common than OAG, is more likely to result in bilateral blindness and is estimated to be the cause of 50% of glaucoma blindness worldwide.[1,2] While screening for angle closure glaucoma may be appropriate for other country settings, it is a different disease from OAG, with different risk factors, and different screening tests are required for early detection. The epidemiology of OAG is described in detail in Chapter 5.

This report was commissioned to assess whether screening for OAG would be worthwhile in the UK. Screening for OAG among 'at-risk' target populations with interval screening offered at selected sites has not been adopted in any country, but a number of ad hoc strategies exists, with clinical guidelines for the detection and subsequent management of glaucoma.[3–7]

For screening for OAG to be considered, several criteria should be addressed. In the UK, the NSC provides advice to government on which population screening programmes should be introduced. The NSC uses a set of criteria, based on the original WHO criteria,[8] but developed over the years to take account of new scientific developments. These criteria are available on the NSC website.[9] Not all the criteria are relevant to OAG, but most are. In brief, the condition should be an important public health problem, there needs to be an acceptable test or combination of tests that are able to detect sufficient people at risk of visual impairment to justify testing large numbers of people who are not at risk, early treatment must be effective and acceptable, and appropriate diagnostic and management facilities to care for people with detected glaucoma must be available. The benefits of screening must outweigh the risks, and the programme needs to be cost-effective and practically feasible. The NSC, in cooperation with the Welsh Assembly, convened a workshop on screening for glaucoma in September 2001 and a report has been issued.[10] The current NSC policy is that screening for OAG is not yet recommended, and the topic is due for reconsideration in 2008.[11]

A recent health technology assessment report for the US Preventative Services Task Force found that screening can detect early OAG in adults and that

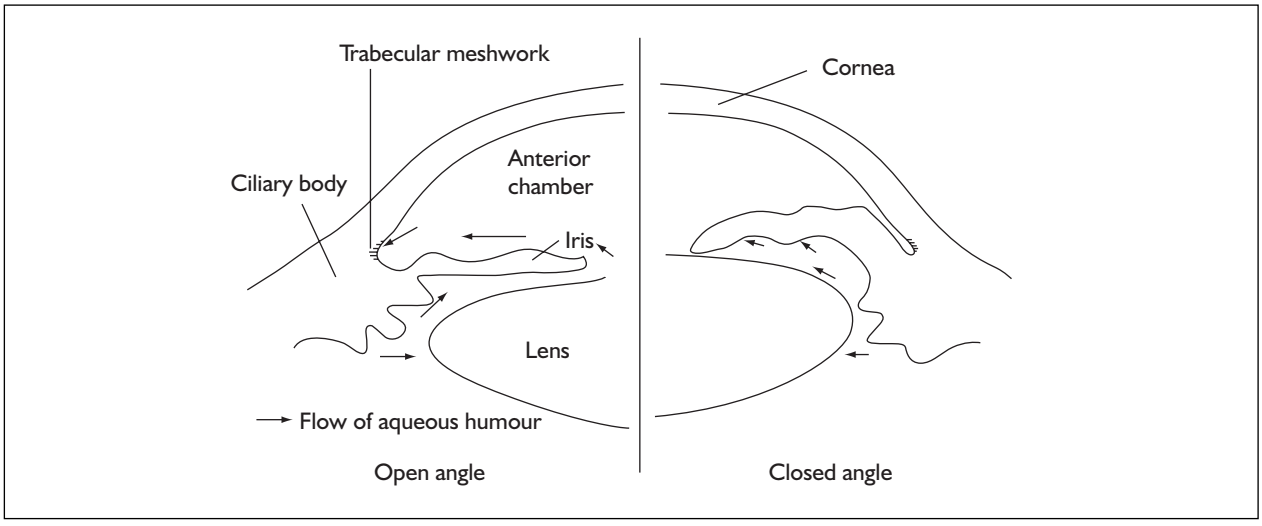

FIGURE 1 *Anterior segment of the eye (open angle and closed angle)*

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early treatment reduces the number of people whose visual field defects progress, but that the evidence was insufficient to determine whether a screening programme would reduce impairment of vision or impairment of quality of life.[12]

New potential screening tests for OAG are available,[13–17] and recent evidence on the effectiveness of treatment[18,19] justifies a further evaluation of the effectiveness of screening for OAG.

The condition

OAG is diagnosed primarily by glaucomatous optic neuropathy (cupping) and a compatible visual field defect, in the presence of an open, normal appearing, anterior chamber angle. Raised intraocular pressure (IOP) of at least 21 mmHg (two standard deviations above the mean) used to be considered as a part of the definition of OAG, but population studies have consistently found that many people with OAG have an IOP below this level.[20–24] The risk of developing glaucoma, and for worsening of existing glaucoma, does, however, increase with increasing IOP.[25–27] More advanced disease at diagnosis is also associated with a higher IOP.[23,28]

Typical early glaucomatous changes in the optic disc include localised or generalised thinning of the neuroretinal rim, with increased enlargement of the optic cup and an increased cup-to-disc ratio (CDR). As glaucoma advances, there is further neuroretinal rim thinning until the cup occupies most of the disc area (*Figure 2*).

Currently, the only treatment for OAG is to lower the IOP. This can be done medically, usually with eye drops, or surgically, by laser, or any combination of these. The effectiveness of OAG treatments is evaluated in a number of ongoing or completed Cochrane reviews,[18,29–31] and is discussed in Chapter 7.

Burden of disease in the UK

Glaucoma is second to age-related macular degeneration as the most common cause of blindness in adults in the UK and Ireland.[32–35]

The statutory definition of blindness is that "a person should be so blind as to be unable to perform any employment". There is no equivalent definition for partial sight, but it refers to people who are not blind, but who are substantially and permanently disabled by defective vision.[36] Ophthalmologists register new cases of blindness and partial sight with the local authorities across the UK. Registration is voluntary; it is a prerequisite for receiving certain social security benefits, but not for all social service concessions. The recommendations for blind and partial sight registration, based on the vision of the better eye, are as described in Box 1.

The frequency of glaucoma as a cause of blindness or partial sight is reported as incidence (new cases) and prevalence (all cases). Registration data are available for England, Scotland and Wales,[37–39] but recent estimates of incident visual impairment are not available for Northern Ireland. In England, Scotland and Wales, 31,676 people were

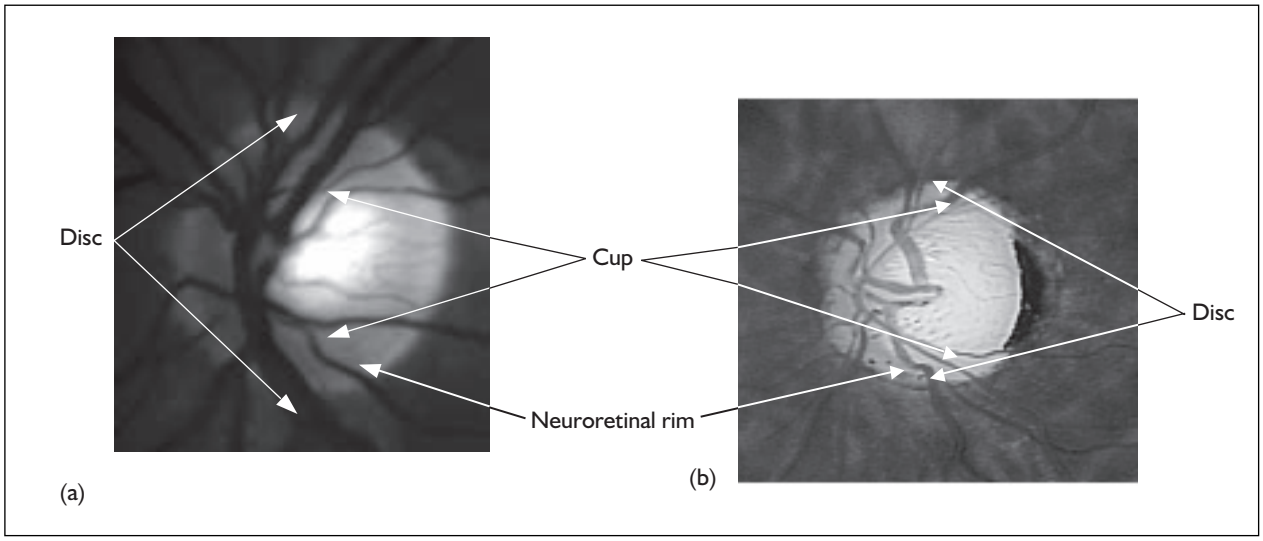

FIGURE 2 *The optic nerve in OAG: (a) healthy optic nerve (reproduced with permission from* AgingEye Times*, www.agingeye.net); (b) advanced glaucoma damage (reproduced courtesy of A Azuara-Blanco)*

Blindness
- Acuity worse than 3/60
- Acuity better than 3/60, but below 6/60 with a very restricted visual field

Partial sight
- From 3/60 to 6/60 with a full visual field
- Up to 6/24 with moderate restriction of the visual field
- 6/18 or better with a gross visual field defect

BOX 1 *Recommendations for blind and partial sight registration*

registered as incident visual impairment (blind and partial sight registrations) in 2002/03, although data were not detailed according to causes of visual impairment.

A detailed analysis of main causes of blindness for England and Wales in 1990/91 found that glaucoma was the main cause in 11.7% of incident blind registrations and 9.6% of partial sight registrations for all ages, and a contributing cause in another 8% of blind and 4% of partial sight registrations.[34] People may be registered using the specific term OAG or simply as 'glaucoma, unspecified'. A more recent analysis of certifications of visual impairment in England and Wales in 1999/2000 found similar proportions, with glaucoma accounting for 10.9% of blindness and 10.2% of partial sight registrations, although the analysis was not detailed according to registrations specifically for OAG.[32] Applying these proportions to registration data for 2002/03, it can be estimated that 3108–3138 people aged over 50 years were newly registered with visual impairment (blind and partial sight) due to glaucoma in England and Scotland in 2002/03. There are at least 1192 new registrations of incident visual impairment due to OAG as the main cause, but the true number may be higher than this, as some OAG cases would have been registered as glaucoma non-specified. Data for Wales were not detailed according to age and are not included.

Data on blind and partial sight registration may not be accurate for several reasons. The criteria for registration are subjective, some eligible people do not wish to be registered and ophthalmologists may not offer registration to those who are eligible. Analyses of people eligible for blind and partial sight registration from attendees at ophthalmology departments in three centres in the UK have estimated that up to 50% of individuals eligible for blind or partial sight registration are not registered.[32,40,41] These studies were consistent in their findings that people eligible for partial sight registration were less likely to be registered than people eligible for blind registration. People with visual field loss alone were less likely to be registered than people with impaired central visual acuity, and people undergoing long-term treatment and follow-up were less likely to be registered or have registration delayed compared with people with a condition that was untreatable and not under long-term follow-up, for example age-related macular degeneration.[32,40,41] It is therefore likely that many more people have visual impairment due to OAG than currently recorded in the UK blind and partial sight registration system.

Vision below the level that is required for driving is a major burden of glaucoma, and is not necessarily reflected in the visual impairment statistics, but is of importance to those affected. The number of people who have been forced to surrender a driving licence on account of glaucoma visual field loss is not captured by national statistics, but would be an important indicator of the burden of glaucoma.

Current practice for glaucoma detection in the UK

In the UK, community optometrists are the key providers of primary eye care; general medical practitioners do not usually have access to specialist equipment or the necessary training and skills to detect glaucoma. The majority (90%) of referrals to secondary care ophthalmology as suspect glaucoma are initiated from an optometrist.[42–44] Current detection strategies are opportunistic, based on optometrist case finding or open access where the population tested is self-selecting. In the UK, apart from Scotland, only select groups qualify for a free sight test; such groups are people aged over 40 years with a family history of glaucoma, people aged over 60 years and those on income support. Guidelines exist for a more detailed eye examination in at-risk groups; the optometrist is advised to undertake an assessment of the optic nerve head, perform tonometry and undertake a central visual field assessment.[45] 'At risk' is not, however, defined and is at the discretion of the practitioner: a sight test may not necessarily include testing for glaucoma, and, as such, cases, particularly early glaucoma, are missed.

In summary, the current service does not constitute a formal attempt to reach and test

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everyone at risk in a defined population and is opportunistic surveillance rather than screening.[46] Guidelines are provided by the College of Optometrists[45] about which tests should be done and when, but these are not mandatory, and as such a sight test often does not detect glaucoma. Uptake of sight testing by the population is variable and members of more deprived communities are less likely to seek testing.[47] The General Ophthalmic Services in Scotland have been reviewed, and as from April 2006, provision has been made to provide free NHS eye examinations for all. The thrust of the new service is to move away from the current emphasis of a sight test on refraction to a broader eye health assessment appropriate to the patient's needs, including a more extensive examination to improve glaucoma detection.

Diagnostic and treatment services

Current, usual practice is that suspect glaucoma cases identified by community optometrists are referred to secondary care for an ophthalmologist's opinion with treatment, observation or discharge as required. People requiring treatment or observation as high-risk suspects remain under review by an ophthalmologist.

With an ageing population and improved detection, the current diagnostic and management service in secondary hospital care is likely to become increasingly overloaded. Several schemes are in operation in the UK, which aim to alleviate the pressure on the hospital eye service and improve glaucoma care, by using glaucoma-trained optometrists, or nurse practitioners in co-managed shared care treatment and monitoring schemes, which may be hospital or community based.[48–50] National initiatives to define and develop clinical care pathways for glaucoma are underway.[51–54] These, together with a review of general ophthalmic services[55] and a connected information technology system in the NHS, provide the basis for a standardised diagnostic and treatment service for glaucoma.

Chapter 3

Screening tests for glaucoma

Description of potential screening tests

Ideally, a screening test for OAG should be safe, easy to administer and interpret, portable, quick, acceptable to the people who are to be tested, and sufficiently valid to distinguish between those who do and do not have OAG.

Tests for glaucoma involve an assessment of structural changes at the optic nerve head, functional visual loss by visual field testing and the level of the IOP. It is not always possible to make a definitive diagnosis using these criteria. A person could have a media opacity precluding a view of the optic disc, or visual field testing may not be possible, and in these circumstances diagnosis is made on only one of these findings or severe visual loss with raised IOP.[56]

Many commercial devices, particularly for assessing structural damage, are now available. The following sections describe candidate screening tests for OAG. The diagnostic performance of the candidate screening tests is reported in Chapter 6.

Intraocular pressure

Measurement: contact and non-contact tonometry

Contact tonometry and non-contact tonometry (NCT) are quick, taking about 1–2 minutes per eye.

Contact tonometry

The most widely used and generally accepted reference standard for measuring the IOP is Goldmann applanation tonometry (GAT). GAT uses a prism to apply an external force to the cornea to indent and flatten its surface.[57] The two general sources of error with Goldmann tonometry can be categorised as those caused by faults in the application of the technique and those related to biological variability of the human eye, both normal and pathological. Of particular note is the error induced by variability in the central corneal thickness. GAT is mounted onto a slit-lamp, which limits its convenience, and is usually performed by trained optometrists, nurses and ophthalmologists. A clinical background is not essential; with training a technician can perform GAT.

The Perkins tonometer is a portable device that is similar to the Goldmann tonometer. Like the other portable devices, it is useful in situations where a patient cannot be seated at a slit-lamp, such as bedside examinations, the operating room, nursing homes, remote areas and mass screenings.

The Tonopen is an automated handheld applanation tonometer based on the MacKay–Marg tonometer.[58] It is small, light and battery operated, but may be less accurate than GAT.

There are potential problems with using contact tonometry in a screening situation in that contact with the tear film and the cornea may raise concerns regarding transmissible disease. Chemical disinfection is required after each test to reduce the risk of cross-infection.

Disposable prisms for Goldmann and Perkins tonometry or disposable covers for the Tonopen tip avoid the risk of cross-infection but incur additional costs. Disposable prism tonometry is, potentially, a reliable alternative to GAT.[59]

Non-contact tonometry

NCTs applanate the cornea with a puff of air.[60] Measurement errors are larger in patients who squeeze their eyelids or who blink rapidly in response to the startling jet of air, and in eyes with moderately elevated IOPs. The advantages of NCT include speed, no anaesthetic and low risk for corneal abrasion (hence more suitable for technician operation) and, since there is no direct contact with the eye, any infection control issues are avoided.

Population distribution of IOP

IOP in the population is normally distributed with an additional tail towards higher levels of IOP (*Figure 3*). The mean IOP in adult populations is consistently estimated at 15–16 mmHg, with a standard deviation (SD) of 2.5–2.8 mmHg.[20–22,61–66] Other factors (ethnicity, diabetes, systolic blood pressure, family history of

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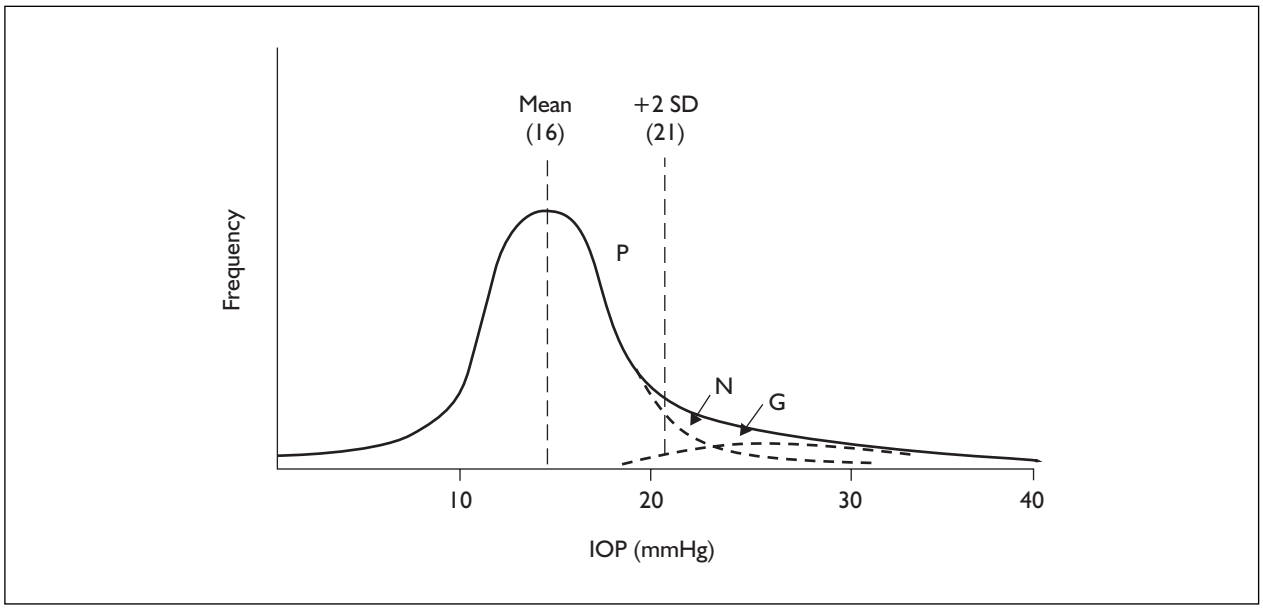

FIGURE 3 *Intraocular pressure (IOP). G, glaucoma population; N, normal distribution; P, frequency of distribution of IOP in population.*

glaucoma, myopia) influence the population IOP distribution.[67] There is a marked overlap of IOP distributions between those with and without glaucoma. In people with glaucoma the median untreated IOP has been estimated to be 26 mmHg.[62,68]

Structural damage

Structural damage is assessed clinically by a subjective assessment of the optic nerve head (the optic disc) and/or by evaluating the retinal nerve fibre layer.

Ophthalmoscopy (direct and indirect)

Direct ophthalmoscopy (i.e. with a direct ophthalmoscope), best performed with the pupils dilated and the room darkened, provides a magnified view of the optic disc. The main disadvantage is the absence of a stereoscopic view. The examiner has to use indirect cues to allow the interpretation of the optic disc as a tridimensional structure. Furthermore, direct ophthalmoscopy does not yield a permanent record, and the examiner is required to draw the optic disc to allow subsequent comparisons.

Binocular ophthalmoscopy has the advantage of stereopsis, allowing a tridimensional observation of the optic disc. Current practice consists of the use of a standard slit-lamp biomicroscopy associated with non-contact lenses (60D or 78D). The possibility of achieving stereopsis depends on the pupil's size, which often needs to be dilated, the image is inverted and additional training is required for accurate interpretation. It is also possible to use the slit-lamp in association with a contact lens (e.g. the Goldmann lens), but this technique requires the use of a topical anaesthetic and a viscoelastic substance between the lens and the cornea. Despite being more uncomfortable, the image provided is excellent with high magnification and is not inverted, making for easier interpretation.

Optic disc photography (monoscopic and stereoscopic)

A wide variety of digital and non-digital cameras is available to provide colour images of the optic disc. Photography has the advantage over ophthalmoscopy of a permanent recording of the optic disc, but has the same limitations of ideally requiring a dilated pupil and clear media, that is, no significant cataract. Monoscopic photographs can be obtained with a standard fundus camera; however, the tridimensional structure of the optic disc can only be assessed by stereophotography. Stereoscopic pictures can be obtained with sequential photographs using a standard fundus camera by horizontal realignment of the camera base when photographing the same retinal image. Alternatively, simultaneous stereoscopic fundus photographs can be obtained using a camera with a beam-splitting prism to capture two images of the fundus taken simultaneously at a fixed relative angle. Digital stereophotographs may be viewed in a number of ways, using either stereoviewers or flicker glasses, which rapidly alternate the image between the left and right eye of the observer.[69]

Population distribution of CDR

Optic disc changes typical of glaucoma include vertical and generalised thinning of the neuroretinal rim, localised thinning and notching, and displacement of the retinal vessels. A consensus definition for glaucomatous optic neuropathy has been proposed whereby a CDR above which 2.5% of the normal population lie defines the upper limit of normal.[56] Optic disc parameters, particularly size of the optic disc, vary for different populations; in European populations, the 97.5% centile typically equates to a vertical cup-to-disc ratio (VCDR) of 0.7[70] and is generally considered to be the most useful parameter for determining glaucoma in the presence of a visual field defect.[56] Cup disc asymmetry of 0.2–0.3 could also be used to define glaucoma.[71,72] For subjects in whom a reliable visual field test is not possible, a cut-off exceeding the 99.5th percentile (i.e. a VCDR $\geqslant$ 0.9), in most populations, would define glaucoma. Cup disc size varies between populations with small discs having small cups that may be pathological, and vice versa for large discs. Thus, the division between normal and abnormal for optic disc parameters is not clear, and therefore a screening test based on a subjective assessment of glaucomatous optic nerve damage would require an experienced observer to diagnose glaucoma accurately.

Retinal nerve fibre layer photography

The appearance of the retinal nerve fibre layer (RNFL) may be documented using high-resolution black and white images, where the fibre bundles are seen as silver striations, most visible in the superior and inferior poles of the optic disc (*Figure 4*). The technique includes the use of a green or blue filter with either standard or digital photography. The quality of RNFL image is poor in eyes with small pupils and media opacities. Furthermore, the technique is subjective and requires an experienced observer for interpretation. A manual with a reference set of RNFL images is available to guide technicians in the reading of such images.[73]

Quantitative analysis of the optic nerve head and RNFL

Scanning laser tomography

Confocal laser scanning imaging technology, used by the Heidelberg retina tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany), exploits the principle of confocal laser scanning to allow quantitative structural information.

The topographic image is derived from multiple optical sections at consecutive focal depth planes. Each image consists of numerous pixels, with each pixel corresponding to the retinal height at its location. The device is operator dependent in that the optic disc margin needs to be defined by a contour line manually placed around the inner margin of the peripapillary scleral ring. The software calculates stereometric parameters within this line. These parameters are computed for the whole of the optic nerve head, and for six predefined sectors.

The HRT II is compact and relatively easy to use, pupil dilation is not required and cataracts do not prevent imaging. Specific training is required in contour line placement, which can be a source of error in image analysis. Measurement time is about 10 minutes per eye.[13,14] HRT III is now available and does not require manual drawing of the contour line.

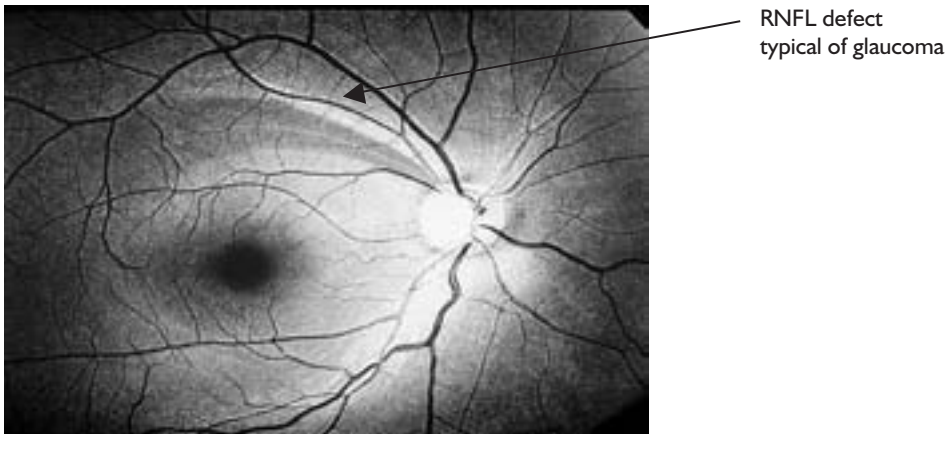

FIGURE 4 *The retinal nerve fibre layer (reproduced courtesy of A Azuara-Blanco)*

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Population distribution of test parameters
The commercially available HRT II device reports the Moorfields regression analysis (MRA) as a classification system for glaucoma. This classification is based on a normative database of 80 normal white participants, with a refractive error of less than 6 dioptres (D).[74] The neuroretinal rim (NRR) is thinned in glaucoma, and the MRA has derived limits for normality based on the area of the NRR, classified for each segment of the optic disc. Three diagnostic classes are given: within normal limits (the NRR area lies within the 95% prediction interval of normal), borderline (between 95% and 99%) and outside normal limits (beyond 99.9%). This is a statistical classification, based on a narrowing of the NRR. The classifications of borderline and outside normal limits are considered as indicative of OAG, but definitive diagnosis requires other relevant clinical data.

However, the normative database is based on small numbers and may not be valid for non-white populations, people with high refractive error and large or tilted optic discs; as such, the results should be interpreted with caution. The HRT III incorporates a new, larger, race-specific database. This new normative database consists of 733 eyes of white people and 215 eyes of black people. The software v3.0 calculates the glaucoma probability score (GPS), a new, automated algorithm that evaluates both optic disc and parapapillary RNFL topography to estimate the probability of glaucoma. The GPS uses a new sophisticated version of artificial intelligence known as a relevance vector machine (RVM) that estimates the likelihood of glaucoma. No contour line or reference plane is used in the GPS calculation, and therefore it is completely an operator-independent analysis.

Data are limited on the distribution of HRT parameters in the general population and this is relevant to the use of the HRT as a screening device for OAG. In the UK, a study evaluating screening for eye disease[75] is ongoing (the Bridlington eye assessment project), where people aged over 65 years receive a comprehensive eye examination by a trained optometrist, with the examination including optic disc imaging using the HRT II. Women were found to have significantly larger rim volume, mean RNFL thickness and cross-sectional area than men, and tended to have smaller cup areas and volumes and cup-to-disc area ratios than men. It is also worth noting that the performance of the HRT is dependent on the optic disc size.[76,77] For HRT II to be used in a screening situation the diagnostic criteria for classification as normal and abnormal need to be appropriately defined. Asymmetrical thinning of the NRR is recognised as one of the diagnostic criteria for OAG. In the same Bridlington population study, a reference range for rim to disc area asymmetry in a normal elderly population was defined, with this measure having the advantage over other HRT parameters of being independent of age, gender and disc size. A measure of between-eye NRR asymmetry could be used to discriminate between normals and abnormals for screening purposes.[78]

Scanning laser polarimetry
Scanning laser polarimetry (SLP) measures the RNFL thickness objectively based on the birefringent properties of the RNFL, which has its neurotubules disposed in an organised, parallel fashion. This peculiar anatomy leads to a rotation of the plane of polarised light as it passes through the RNFL, creating a retardation that is directly proportional to its thickness. The current model (GDx VCC) introduces variable corneal compensation to enhance the accuracy of the measurements. The GDx VCC is user friendly and compact, and pupil dilation is not required. A technician can perform the test. The disadvantage is that eyes with optic disc abnormalities, such as large myopic discs with peripapillary atrophy, cannot be imaged reliably. The GDx VCC can acquire images in less than 3 minutes for both eyes.

Population distribution of test parameters
The normative database characterises the normal tridimensional RNFL thickness, and individual patient profiles are compared with the normative database, thus indicating RNFL loss due to disease. The database also includes data on glaucoma subjects and is the basis of the machine classifier, the nerve fibre indicator (NFI), for indicating OAG damage. There is a wide range of RNFL thickness values among normal individuals, with overlap between normal and eyes with OAG. The GDx NFI is intended to supply the clinician with a method of glaucoma diagnosis, and the higher the NFI the greater the likelihood that the eye has glaucoma. A score of 0–30 is considered normal, 31–70 indicates that the eye is suspect for glaucoma and 71–100 indicates that the eye is glaucomatous. The GDx VCC normative database contains 811 (540 normal, 271 glaucoma) patients. Ethnic minorities are well represented on the database: Caucasians and Hispanics 70%, African-Americans 18% and Asians 12%.[79]

Optical coherence tomography
The RNFL thickness is also measured by optical coherence tomography (OCT). OCT is an optical imaging technique capable of providing high-resolution, cross-sectional, *in vivo* imaging of the human retina in a fashion analogous to B-scan ultrasonography, but using light instead of sound.[80] The first commercial system was available in 1996; the latest generation OCT3 system is Stratus-OCT. Early OCT systems required a pupil size of at least 5 mm. OCT3, however, operates with a 3-mm pupil size, which suggests, like non-mydriatic fundus cameras, that pupil dilation is not required when operated in a darkened room. Posterior subcapsular cataracts and cortical cataracts can impair measurement.[14]

Population distribution of test parameters
A single score of overall RNFL thickness averaged over 12 clock-hour thicknesses is compared with a normative database derived from responses from 350 individuals aged between 20 and 80 years.[81] An abnormal result is defined as below 5% level compared with the normal population. The distribution of OCT parameters has not been described in a population setting.

Retinal thickness analyser
The retinal thickness analyser (RTA), commercially available since 2000 (Talia), combines a colour digital fundus camera with a laser-based system (helium–neon laser, wavelength 543 nm) for measuring nerve fibre layer thickness. One scan covers 3 × 3 mm, which consists of 16 optical capital cross-sections with the laser. Each cross-section is 187 μm apart and 3 mm long. In the posterior pole thickness mode, five such scans at the centre, super temporal and infer temporal, and superonasal and inferonasal areas of the posterior pole, which cover an area of 6 mm × 6 mm, are performed for each measurement. The performance of the RTA is affected by media opacities.

Visual function tests

Frequency doubling technology
The clinical test procedure measures contrast threshold in 19 visual field locations within the central 20 degrees of the visual field (C-20°). It can be used in threshold and suprathreshold screening mode. In the suprathreshold mode it takes about 1 minute per eye. Recently, FDT Matrix, a 24-2 version of frequency doubling technology (FDT), has been introduced. FDT is portable and user friendly, and moderate uncorrected refractive errors, a common finding in the general population, do not appear to interfere with FDT testing.

Population distribution of test parameters
Normative data were based on examination of 407 healthy people, aged between 14 and 85 years, to provide a basis for establishing the probability plots for FDT perimetry.[82] Using the C-20°–1 algorithm, the initial level presented would be detected by 99% of the normal population of a particular age, and is therefore designed to have a high specificity. Using the C-20°–5 algorithm the initial level presented would be detected by 95% of the normal population of a particular age and is therefore a test aimed to optimise sensitivity.

Motion detection perimetry
This test measures the ability to detect movement in the peripheral retina, which may be impaired in glaucoma. There are several types of stimuli that can be used to explore motion sensitivity: a line, a dot or a patch of dots. Motion detection perimetry (MDP) takes longer and may be more difficult for people to perform than standard perimetry, although its reliability appears not to be affected by cataract or pupil size. There is, as yet, no commercially available instrument, and the principle of motion detection as a screening tool for OAG needs further evaluation.[83]

Oculokinetic perimetry
Oculokinetic perimetry (OKP) with the Damato chart is a simple and inexpensive visual field test device. Damato campimetry consists of 20 numbers located on a flat, white card within the central 30 degrees of visual field. The subject is required to refixate from number to number, sequentially reporting whether the central 1.5-mm black spot is visible. There is a 40-cm hinged piece that serves to maintain the appropriate test distance and occludes the non-tested eye. Any point missed, other than the physiological blind spot area, is confirmed once before considering it a true missed point. A modified version is currently available (free of charge) on the Internet.[84,85] This test, either in card form or web based, is quick, simple and available, and if of sufficient diagnostic validity would be valuable as a screening test.

Short-wavelength automated perimetry
Short-wavelength automated perimetry (SWAP) is a modification of automated static threshold perimetry and is purported to detect very early loss of sensitivity in the visual field. SWAP uses a yellow background and large, blue stimuli to test the blue cones. The blue cone system is slower and has a low visual acuity (about 20/200). As a consequence, the stimulus is perceived as fuzzy, and the test is more difficult and time-consuming.

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Uncorrected refractive errors have less of an effect on the thresholds determined by SWAP, but lens opacities tend to result in profoundly depressed fields that are difficult to interpret.

Population distribution of test parameters
Glaucomatous visual field defects include, classically, arcuate scotomas within the central 25 degrees, nasal step, diffuse loss of sensitivity, hemispheric loss and eventually only a central island of vision remaining. There are many definitions of abnormality based on the number of abnormal points, the pattern of visual field loss, the depth of the defect and the glaucoma hemifield test (GHT). Normative databases are established for standard automated perimetry[14,86] and for the more recent Swedish interactive threshold algorithms (SITA) based on 330 people with no evidence of OAG.[87]

The GHT is widely used to distinguish between abnormal and normal results on standard automated perimetry.[88] The GHT is based on a comparison of the expected sensitivity in the superior hemifield to the inferior hemifield. On standard SAP testing, the GHT is reported as abnormally high sensitivity, within normal limits, generalised reduction in sensitivity, borderline/generalised reduction in sensitivity, borderline, and outside normal limits. The latter two classifications generally are taken as suspicious of glaucoma.

Standard automated perimetry
Standard automated perimetry (SAP) is considered to be the reference standard in visual field examination of glaucomatous patients. SAP estimates the threshold sensitivity of several points within the visual field. The target locations remain constant and the brightness is modified in a staircase approach to estimate the sensitivity. SAP is able to quantify the reliability, and compare the actual examination with an age-matched normal database. Examination of the visual field in glaucoma is usually limited to the central 30- or 24-degree area, since almost all clinically relevant defects fall within this area. The most commonly used automated perimeter in the UK in ophthalmology clinics is the Humphrey perimeter, now with SITA, which speeds up the testing process.

Suprathreshold testing with automated perimetry involves the use of stimuli that are of greater intensity than the presumed threshold at each location. This test strategy does not quantify the depth of visual field defects, but is much quicker than threshold testing.

The proportion of people able to undertake the test reliably, and the need for confirmatory testing, could limit the usefulness of standard automated perimetry as a screening test. However, perimetry does have the advantage of its availability, in that most community optometric practices are equipped with automated perimeters.

Chapter 4

Overview of methods and definitions

In this chapter an overview of methods is presented including the clinical pathways and details of the structure of the economic model. This overview is used to provide a structure to the rest of this report. Data related to the issues and methods used are reported in subsequent chapters as described towards the end of the section 'Economic model' (p. 15).

Developing the screening pathways and the economic model

Screening pathways

There are various options for a screening programme. The options were explored by personal communication with UK experts in the diagnosis and management of OAG (ophthalmologists and optometrists).

The key questions asked were:

- Who should be invited for screening and how would these groups be identified?
- Which of the many candidate screening tests or combinations of tests should be used to screen for OAG?
- Should level of IOP be used as part of a screening strategy and, if so, what cut-off of IOP should be used?
- Where should screening take place and who should perform it?
- Should screen-positive people be diagnosed and managed in primary care by optometrists or in secondary care either by ophthalmologists or a supervised care glaucoma diagnostic service?

The pathways were presented to the following patients and professional groups for refinement: a meeting of the European Glaucoma Society in Brussels, October 2005; a meeting with patient representatives from the International Glaucoma Association (IGA) convened in Aberdeen, October 2005; and an advisory group to the NSC on screening for OAG in the UK, convened in November 2005. The latter group consisted of representatives of specialist societies, ophthalmology, optometry, nurses and a patient group.

As described in Chapter 3, many potential screening tests are now available. There was no consensus on which test or combination of tests should be recommended as a screening test. As explained in Chapter 2, the level of IOP does not define OAG, but the risk of OAG increases with increasing IOP and the rate of progression may also correlate with higher IOP. There was a general consensus on the inclusion of IOP level to identify people of high risk of developing severe glaucoma, and an IOP of 26 mmHg was generally agreed as a cut-off. There were concerns that this would miss a significant number of cases of low-pressure OAG and therefore an additional test or tests for people with an IOP below 26 mmHg should be considered.

It was generally agreed that screening should start at 50 years, but for higher risk groups (e.g. people with a family history of OAG or of African ethnicity), screening at 40 years should be considered. It was agreed that identifying siblings of newly diagnosed OAG was not currently feasible. If such an approach to screening were to be implemented a register of incident OAG cases would be required.

The high demand on already stretched hospital eye departments was highlighted as a concern if a population screening programme was introduced. However, for the purpose of this evaluation, the advisory group to the NSC felt that this project should evaluate the performance of the tests and the impact on the number of cases detected, but that this should be modelled through the existing diagnostic pathway where suspected cases are referred to hospital eye departments as if there were the capacity to do this. If screening appeared viable, further research would be needed to evaluate the best strategy for managing the newly diagnosed cases.

The outcomes of these discussions led to the development of two alternative strategies for a screening programme, and the economic model was developed to compare these with the current situation of opportunistic screening.

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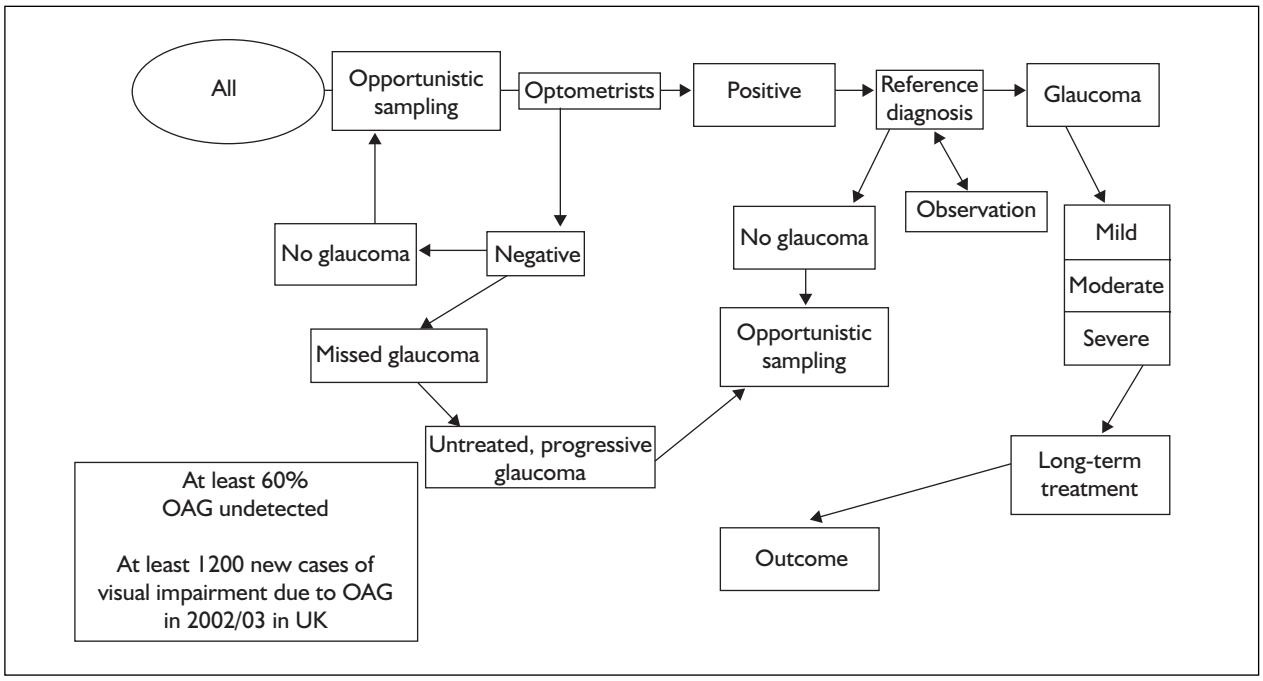

FIGURE 5 *Current case finding*

Current case finding

Current practice involves the opportunistic screening of individuals presenting to community optometrists for an eye test (*Figure 5*). Individuals who test positive are referred to secondary care for diagnosis by an ophthalmologist (i.e. the reference diagnosis).

Screening strategies

Both potential screening strategies considered would involve inviting a prespecified cohort of at-risk individuals for screening. At-risk groups may be identified on the basis of age and another factor such as family history of OAG or ethnicity.

Screening by invitation to a glaucoma-trained optometrist

In the first of the screening strategies considered testing would be performed by a glaucoma optometrist (*Figure 6*). Glaucoma-trained optometrists are optometrists who have received additional training in glaucoma diagnosis and management and have been accredited, usually by assessment by a consultant ophthalmologist specialising in glaucoma. The glaucoma optometrist would perform a full ophthalmic examination, measurement of the IOP, and examination of the optic nerve and visual fields, using the equipment available in the particular optometric practice. People considered to have glaucoma, or to be highly suspect of glaucoma would be referred to an ophthalmologist for a definitive diagnosis, as in current practice. Other significant eye pathology might also be identified by the glaucoma optometrist, although this possibility has not been included in the economic model described below. Furthermore, with this strategy some of the cases of OAG may still be identified by opportunistic screening.

Screening by a technician

In the second screening strategy the population to be screened would be invited to a primary care setting to undergo a measure of IOP and a single screening test by a technician or nurse, who has received some training (*Figure* 7).

This screening pathway incorporates IOP measurement by applanation tonometry, with a cut-off of an IOP of at least 26 mmHg being used to identify groups at higher pretest probability of developing serious OAG. A second test is used for people with an IOP below 26 mmHg. The choice of second test depends on which of the alternative tests has the best balance of diagnostic accuracy, the proportion of people able to do the test and availability. People with an IOP of at least 26 mmHg, and people with an IOP below 26 mmHg and positive on the second test would be referred for diagnostic assessment by a glaucoma-accredited optometrist. People testing negative on the second test are not referred for further testing and are recalled for further screening in the next cycle. As with the first

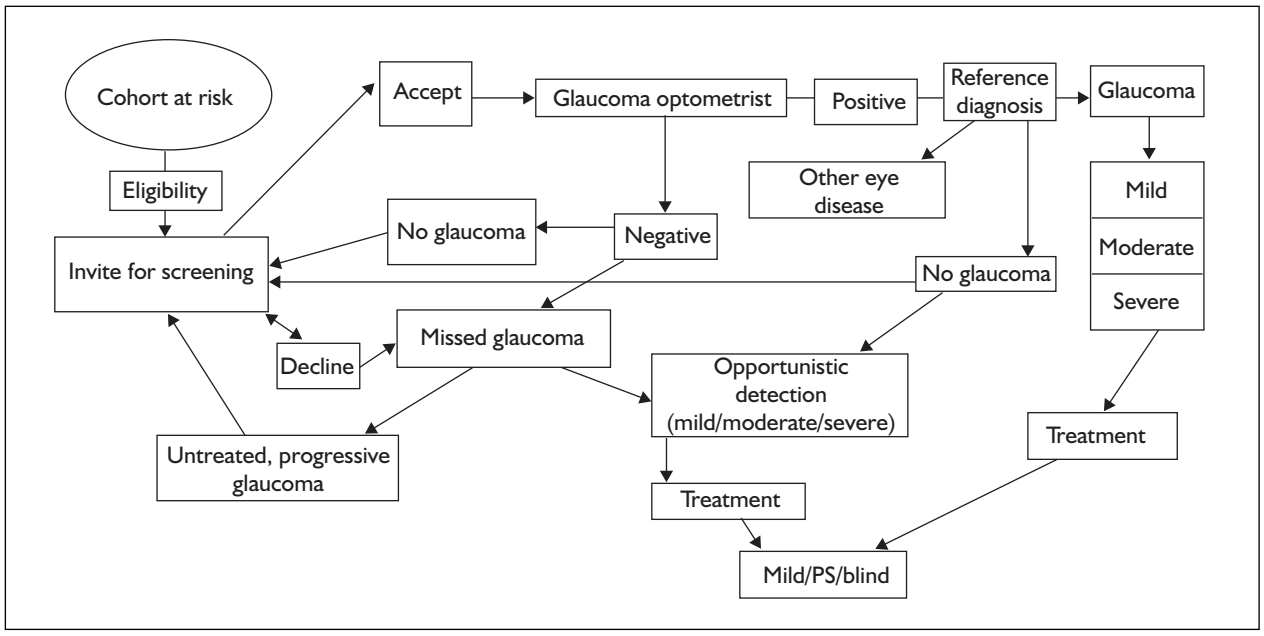

FIGURE 6 *Screening by referral to a glaucoma accredited optometrist. PS, partial sight.*

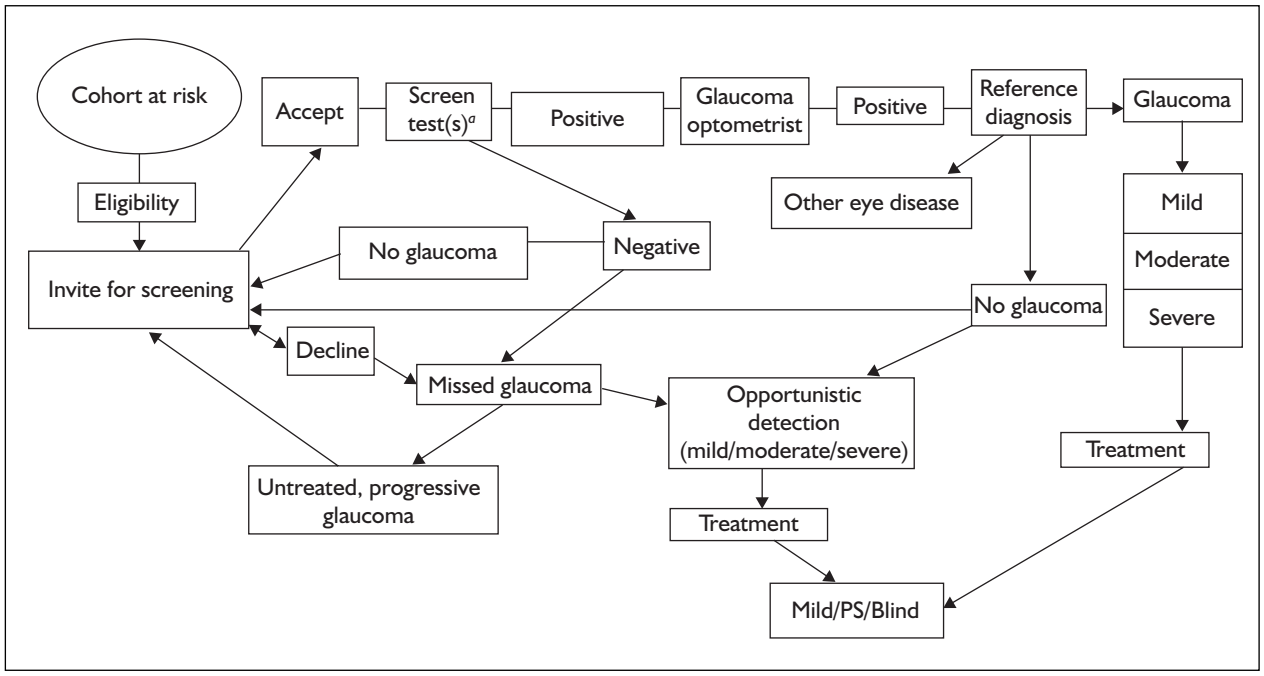

FIGURE 7 *Screening by a technician.* [a] *Test is IOP and technology. The reference standard is an ophthalmologist in all strategies. IOP ⩾ 26 mmHg = screen positive; IOP < 26 mmHg + second technology test positive = screen positive; IOP < 26 mmHg+ second technology test negative = return to standard case finding and rescreen cycle.*

strategy, other significant eye disease would be identified and ongoing case finding by current practice may still identify OAG cases.

Economic model

The economic model was developed to represent the screening pathways described above. The pathways indicate that screening would be best considered as an event that will be repeated at discrete time intervals. Furthermore, as glaucoma is a chronic condition, which progresses slowly over time, the model should reflect timing of both screening and disease progression. For this reason a Markov modelling approach was adopted. A Markov model can be used to represent the logical and temporal sequence of events following the

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implementation of alternative screening strategies. In this study the model is used to provide the estimated costs and outcomes over a selected period of a cohort of patients for different screening and/or non-screening strategies adopted. Three Markov submodels were developed and run in parallel. Each submodel represented one of the three strategies outlined above. The model parameters and the data are presented in the section 'Economic evaluation of screening for OAG' (p. 105). The results of these sub-models presented in this chapter were compared to obtain the final cost-effectiveness results, which are presented in 'Results of base-case analysis and sensitivity analysis on the base' (p. 115).

The model

Typically, Markov models have states (e.g. Markov states) in which individuals stay for a period of time called a 'cycle'. The cycle must be a period relevant to the condition considered (e.g. 6 months, 1 year). At the end of each cycle, individuals can remain in the state in which they started the cycle or move to a different state. The probabilities of moving from one state to another are called transition probabilities. In each state, the model will assign costs and benefits for each individual according to different interventions and/or the time spent in the state. In these models, there must be at least one absorbing state, typically death, from which the person will not be able to leave.

Figure 8 shows a simplified version of the model used for the base-case analysis. In this figure the states are presented as ovals while the arrows show the possible directions in which individuals could move at the end of each cycle, depending on the transition probabilities. The states considered in the model were those thought to reflect possible paths for normal and glaucoma individuals. The top line in *Figure 8* represents the possible path for undiagnosed individuals, while the bottom section of the figure reflects the glaucoma progression for treated patients.

Glaucoma states were defined in terms of severity of disease; namely, observation, glaucoma mild, glaucoma moderate, glaucoma severe and visual impairment. There is no universally agreed staging system for OAG, and there are limited data on utility values according to glaucoma severity (see 'Health state utilities', p. 112, for details). Therefore, an economic project management group, including three economists and three ophthalmologists, agreed the classification of health states. The severity of disease was based on binocular visual field loss. The detailed description of binocular visual field loss was adapted from a scoring system of the integrated visual field, whereby uniocular visual field analyses are integrated into a single binocular field without additional testing, reported by Crabb and colleagues.[89,90] The definitions of health states are described in *Table 1*.

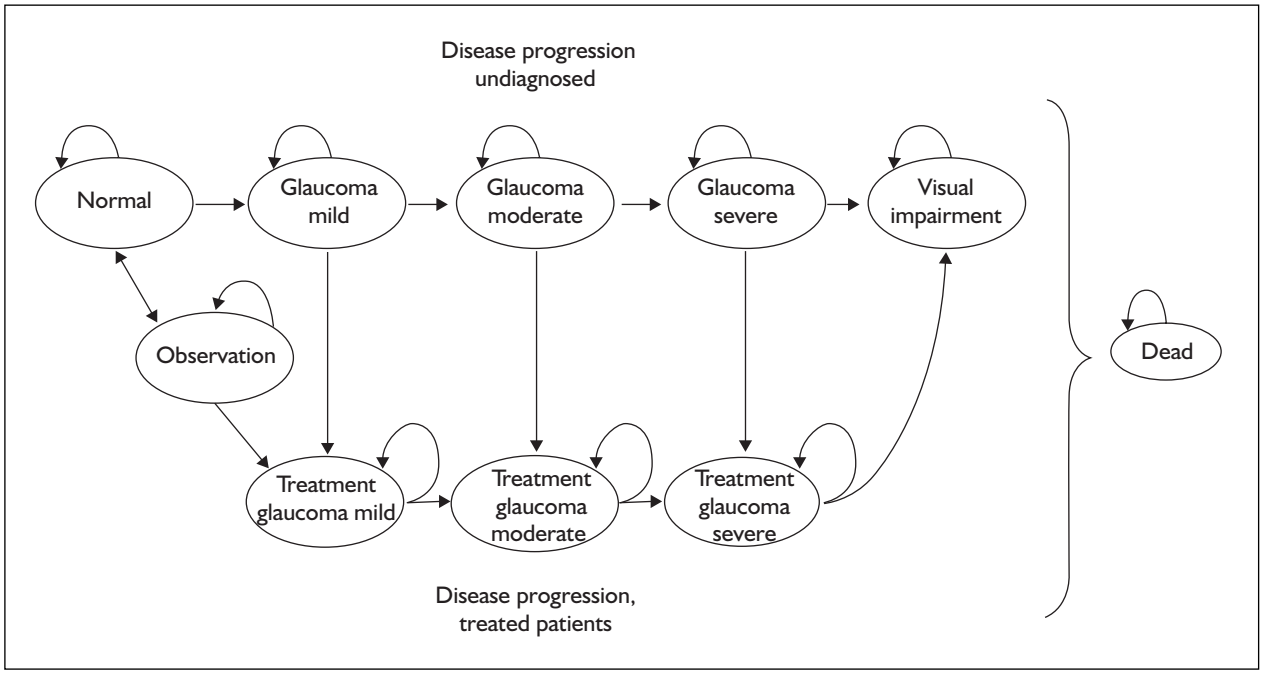

FIGURE 8 *Markov model for OAG*

TABLE 1 *Definitions of glaucoma health states*

No glaucomatous impairment	Under observation as suspect glaucoma but not on medication and no glaucoma visual field defect in either eye
Mild glaucoma	On treatment, no binocular visual field loss, unilateral glaucoma visual field defect present
Moderate glaucoma	Up to five missed points (<10 dB) in the binocular central 20° of visual field
Severe glaucoma	Binocular visual field loss below UK driving standard[a]
Visual impairment (includes partial sight and blind)	As per criteria for 'severe', except binocular visual field loss includes both the upper and lower fields of vision

Adapted from Crabb *et al*.[89,90]

[a] Six or more adjoining missed points (<10 dB), and any additional separate missed point(s) OR a cluster of four or more adjoining missed points (<10 dB), either of which is either wholly or partly within the central 20° superior or inferior hemispheric field.

The treatment states refer to treated disease at each stage. The modality of treatment, either IOP-lowering eye drops, laser or surgery or any combination thereof, is not specified for a treatment state. A treatment state refers to any modality or combination treatment for each stage of severity.

According to whether the individual has or has not got glaucoma, he or she would start in the model in a normal state or in an undiagnosed glaucoma state. As time passes, the normal individuals could develop glaucoma (e.g. new incident cases of glaucoma), while those with glaucoma could progress into further stages of the disease until they eventually become visually impaired. These states represent the true condition of the individual. There are three treatment states in *Figure 8*, which vary according to the severity of glaucoma being treated. An observation state where individuals without a definite diagnosis remain until a further diagnosis decision is made is also included in the model. The observation state was built up as 'tunnel states'; that is, a person is observed for a definite period within which a decision is made about whether or not OAG is present. More details on the observation states are provided below.

OAG is not reversible and this is reflected in the model (*Figure 8*). It is not possible to return to the normal state or to a less severe glaucoma state from any glaucoma state. The absorbing state in the model is death. Any individual can move into this state from any other state within the model.

The model allows for a cohort of the population, some with OAG, to pass through different strategies. The intuitive idea behind the model is to identify the strategy that leads to the largest proportion of individuals with OAG crossing the bridge into treatment (*Figure 8*). *Figures 50–52* in Appendix 1 show complete versions of the model.

The diagnosis of OAG within the model

Ophthalmologist involvement within the model

Four types of professional are explicitly considered in the model. These are the technician, the optometrist, the glaucoma optometrist (GO) and the ophthalmologist. The main difference between them within the model is their ability to diagnose OAG, which varies from a simple reading of an equipment outcome by the technician to the assumed gold-standard assessment by the ophthalmologist used in the base-case analysis.

Ophthalmologists are involved as the final stage of diagnosis in all three strategies and their diagnosis is considered to be the gold standard in the analyses presented in this study. Nevertheless, the model structure allows this assumption to be relaxed if data were to become available. For any person assessed by the ophthalmologist the following decision structure is used (*Figure 9*). If the ophthalmologist's assessment is positive, they will decide to treat the patient, although the model structure allows this to be either a true or a false positive. If the assessment is negative, there will be two options: to discharge or to keep under observation. The decision to place someone under observation would be appropriate if the ophthalmologist felt, for whatever reason, that the individual was at high risk of developing glaucoma.

As stated above, the final stage of the diagnosis is always the ophthalmologist. *Figure 10* shows the possible paths for the normal state. Within the

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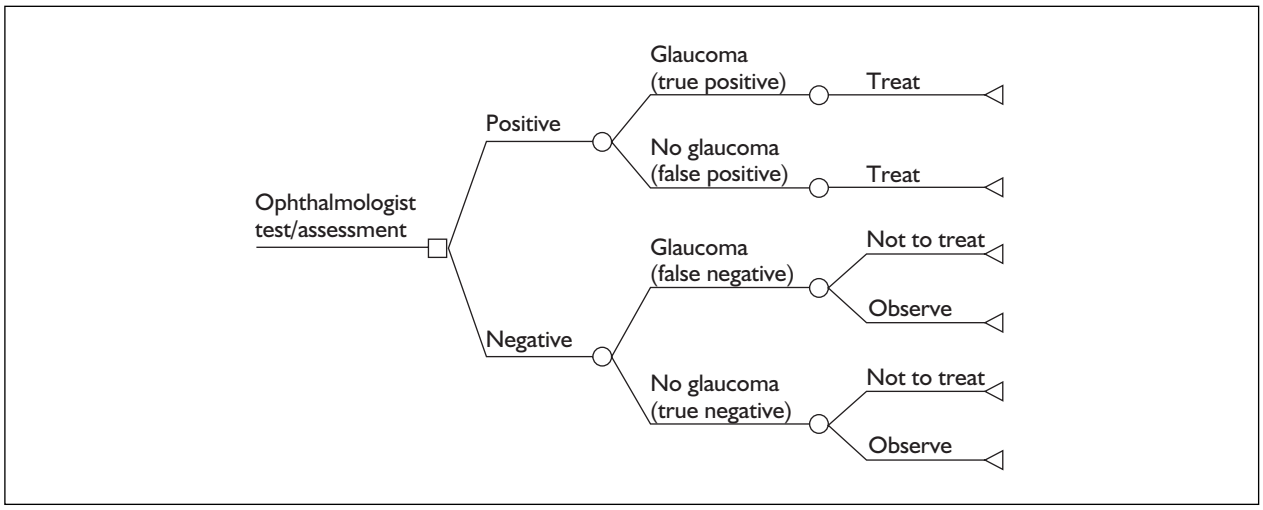

FIGURE 9 *Decision pathways for diagnosis by the ophthalmologist*

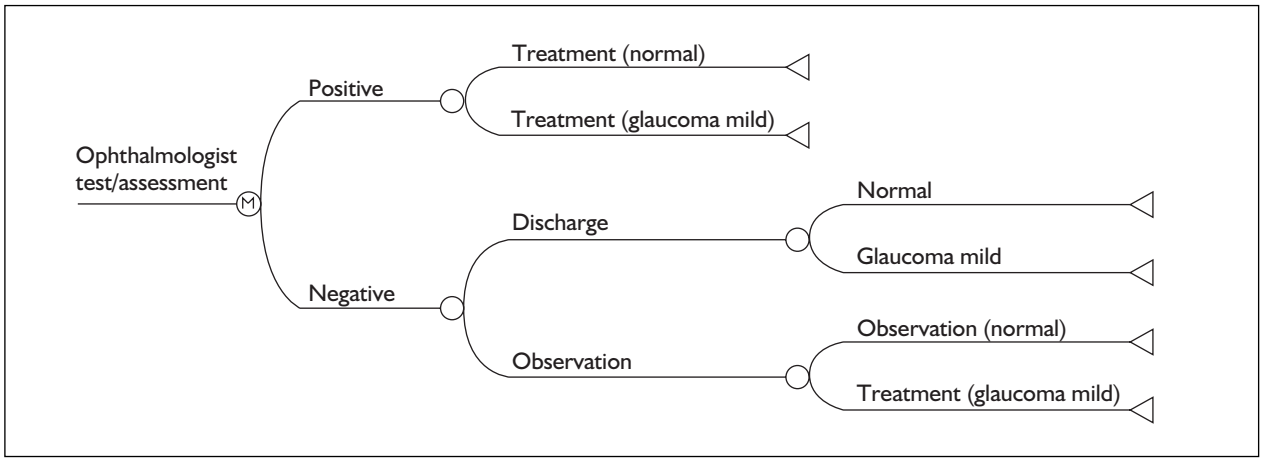

FIGURE 10 *Ophthalmologist involvement Markov tree: normal state*

base case all these people will be correctly identified as negative for OAG.

Conceptually, if the diagnostic ability of the ophthalmologist is less than perfect, then the ophthalmologist might incorrectly identify a person as being positive for OAG and initiate treatment. In such a situation the person would at the end of the cycle move into the 'treatment (normal)' state or progress into 'treatment (glaucoma mild)' state. If the assessment is negative, the ophthalmologist can decide to discharge the patient or keep the person under observation. If the person is discharged it is possible that over the duration of the cycle they may go on to develop OAG. The likelihood of this happening would be dictated by the expected incidence of OAG over the cycle length (i.e. the annual incidence of OAG). For a person kept under observation it is possible that they will develop OAG while under observation. The likelihood of this happening is again dictated by the annual incidence of OAG. Should the person develop OAG then this will be diagnosed by the ophthalmologist and treatment started.

Figure 11 shows a similar Markov tree layout for the 'glaucoma mild' state case. In the analyses presented in this report it has been assumed that all people with mild glaucoma referred to the ophthalmologist will be correctly diagnosed as having OAG and will commence treatment. Treatment, on average, would be expected to delay the progression of disease, but not prevent progression for all people. For this reason people diagnosed with OAG may move into the states of 'treatment (glaucoma mild)' or 'treatment (glaucoma moderate)'. The likelihood of moving to either of these two states will be determined by

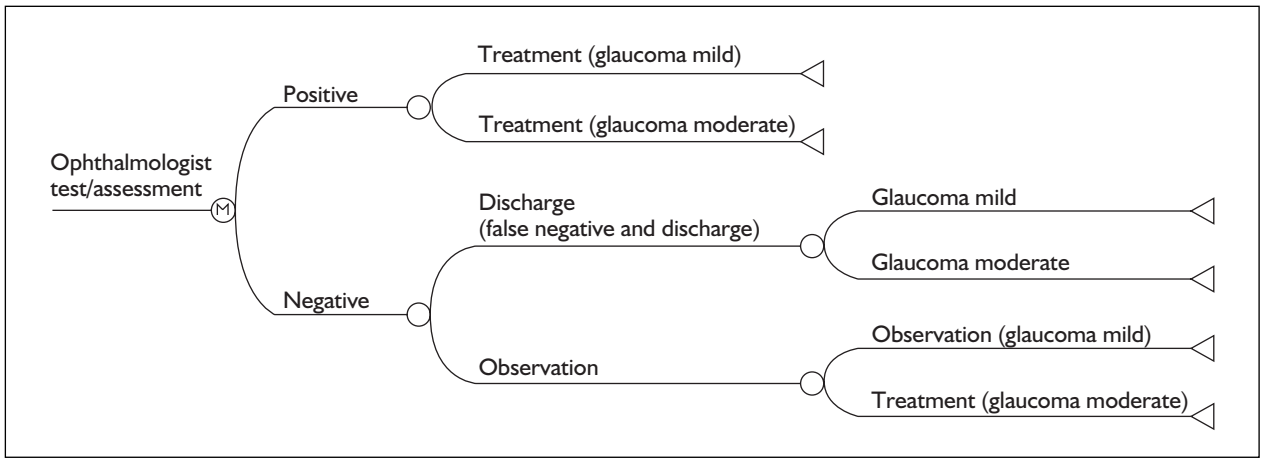

FIGURE 11 *Ophthalmologist involvement Markov tree: glaucoma mild state*

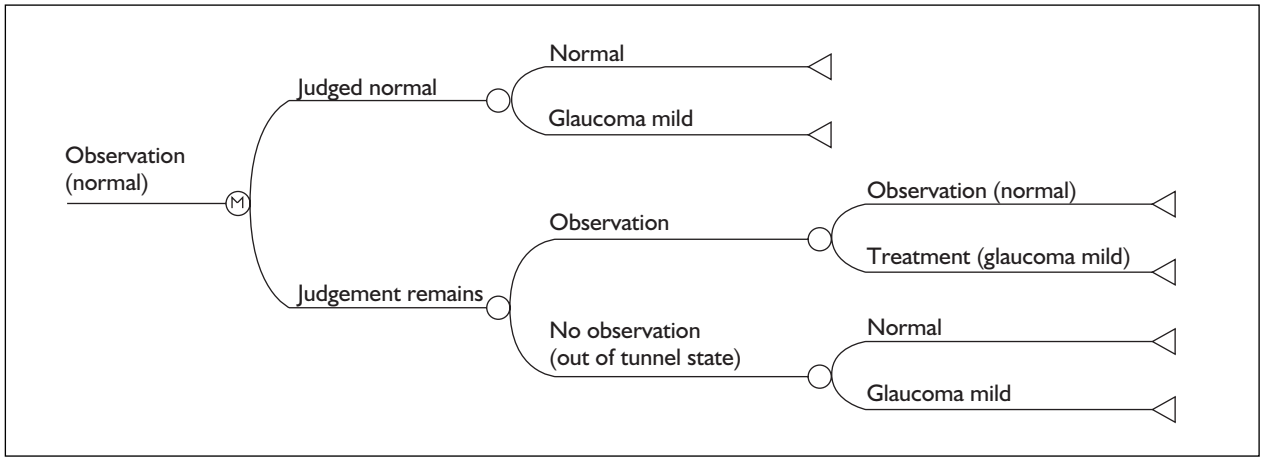

FIGURE 12 *Observation (normal) state Markov tree*

the annual risk of progression from mild to moderate disease for treated cases.

Conceptually, if the diagnostic ability of the ophthalmologist is less than perfect then it might be possible for a person with mild OAG to be incorrectly diagnosed as negative. In such a situation the ophthalmologist might discharge the person, who would then face the risk of progressing to more severe disease. The likelihood of progression would be equal to the annual risk of disease progression for untreated OAG.

Although only considered as a hypothetical option within the model at present, it may be possible that individuals incorrectly diagnosed as negative are still considered by the ophthalmologist as being suspect of OAG. In this situation such people would enter the state 'observation (glaucoma mild)'. In the initial period under observation the patient would have the risk of the disease progressing and moderate OAG developing. If such progression should occur then it might be expected to be identified by the ophthalmologist and treatment initiated. It is for this reason that in *Figure 11* one of the branches following observation progresses to 'treatment (glaucoma moderate)' and not to 'observation (glaucoma moderate)'.

Observation state structure

The tree structure for this state is similar, no matter what health state the person originates from. These states are modelled as a 5-year tunnel state. *Figure 12* shows the structure for the 'observation (normal)' state. As noted above and described in *Figure 8*, this is the only observation state allowed in the analyses presented in this report (owing to the opthalmologist gold standard/perfect information assumption within the model).

A person coming from a normal state, who the ophthalmologist wishes to observe, would enter

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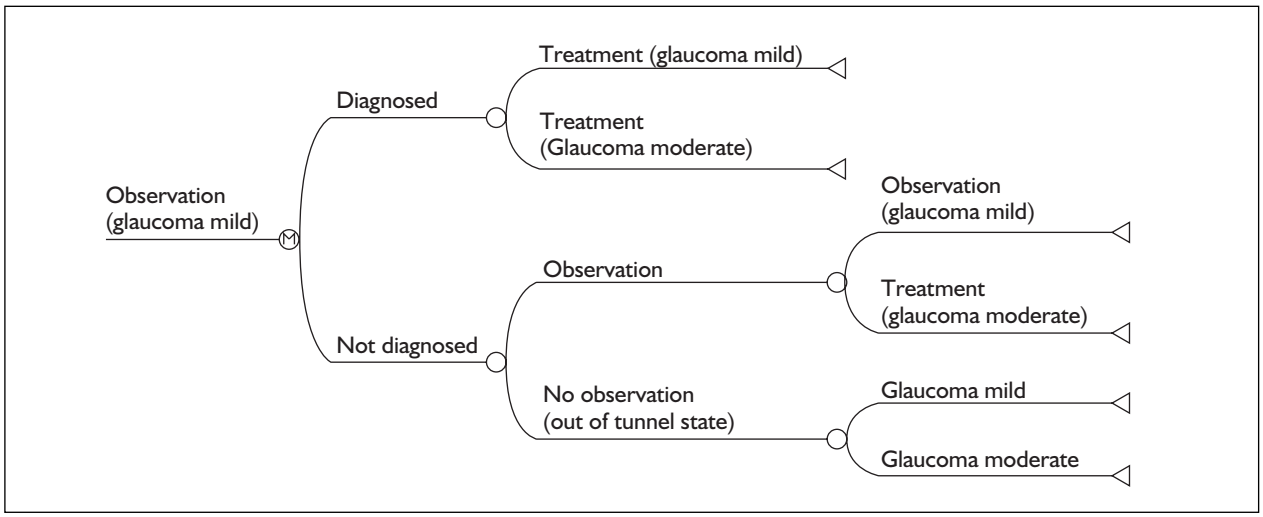

FIGURE 13 *Observation (glaucoma mild) state Markov tree*

this 'observation (normal)' state. During the cycle length of this state the ophthalmologist could decide that the patient under observation does not have OAG, or decide to keep the person under observation. In the first situation, the person would be discharged as 'normal' (i.e. no OAG). However, they would still face the risk of developing OAG (based on likelihood of its incidence) and hence might progress into the state of 'glaucoma mild'. Should this occur then this will not be identified unless presenting to the ophthalmologist at some future date.

If the ophthalmologist's judgement does not change, the person will remain in observation for a maximum of 5 years (five cycles of the model). In any of these years the person would face the risk of developing OAG. If this happens the person will be automatically detected and treatment initiated.

Although this state is not possible in any of the analyses presented in this report, *Figure 13* shows the Markov tree hypothetical situation of people with mild OAG being observed [the 'observation (glaucoma mild)' state]. The difference is that, when diagnosed, in this case as a glaucoma mild patient, the person will not be discharged but will commence treatment [i.e. enter the 'treatment (glaucoma mild)' state]. Furthermore, if the disease progresses to moderate OAG [the 'treatment (glaucoma moderate)' state] then this will be identified and the patient will be treated as a glaucoma moderate patient. The rest of the structure is similar to that depicted in *Figure 12*.

The strategies considered

The model considered one current practice strategy and the two alternative screening strategies as described in *Figures 5–7*. Current practice reflects current glaucoma detection by opportunistic case finding. The two alternative screening strategies vary in how screening would be organised; for example, an invitation for a screening examination by a glaucoma-trained optometrist or for a simple test assessing either visual field loss or structural damage, together with a measurement of the IOP by a technician. The Markov models reflecting these pathways are detailed in Appendix 1 (*Figures 50–52*).

As indicated above, the model has assumed that the ophthalmologist is the gold standard and makes a perfect diagnosis (e.g. specificity and sensitivity equal to 1) but, as described above, the model structure allows for the relaxation of this assumption. If the ophthalmologist assessment result is negative, the individual could be discharged or remain under observation (as described above). If positive, the ophthalmologist initiates treatment.

For all the screening strategies, people are invited for screening at preselected screening intervals (e.g. every 3, 5 or 10 years) and they have the choice of accepting or declining the invitation. Those who accept the invitation would go through the screening process, while those who decline the invitation would follow similar paths to the one they would follow in no-screening years. For the years for which screening does not occur it is

assumed that people might still be diagnosed using the same procedures outlined for current practice (strategy 1).

Populating the model with parameter estimates
To provide estimates of relative effectiveness, cost and cost-effectiveness data, the model requires estimated values for a whole range of different types of parameters. Such parameter estimates should be derived in a systematic and reproducible manner to avoid bias caused by the distorted and selective use of data.[91] The assembly of such data need not necessarily be comprehensive; rather, effort should be focused on identifying the most relevant data to the decision problem, which was in this case the comparison of alternative screening strategies for OAG for a UK setting.

A series of systematic reviews and focused searches covering the different types of data required for the economic model was therefore conducted. The methods and results of these are reported in detail in subsequent chapters of this report. In brief, the broad types of data required to populate the economic model relate to:

- the prevalence, incidence and risk of progression of the disease; that is, its epidemiology and natural history (systematically assessed in Chapter 5)
- the performance of the different strategies in terms of the accuracy of the screening and diagnostic tests used (systematically assessed in Chapter 6); the effectiveness of treatments for those identified as having OAG (systematically reviewed in Chapter 7)
- resource use and unit costs required to estimate the costs of alternative screening strategies; the specific parameters and methods used to provide estimates that are relevant to a UK context are described in the section reporting the detailed methods and results of the economic evaluation ('Economic evaluation of screening for OAG', p. 105)
- Health state utilities; the methods used to identify UK-specific values are also described in 'Economic evaluation of screening for OAG' (p. 105).

In addition to these data, the structure and conduct of the economic evaluation could be usefully informed by any previous economic evaluations. A review of such studies, as reported in 'Systematic review of cost-effectiveness of screening for OAG' (p. 95), should indicate whether further assessment of cost-effectiveness is worthwhile; it might also serve to identify an existing model that could be readily adapted for this study, or if the existing economic evaluations are limited it could provide a firm justification for a new modelling exercise. Thus, a thorough review of the strengths and weaknesses of the existing studies may help to ensure that a model will provide as useful evidence as possible on cost-effectiveness.

Searching for the evidence

Highly sensitive electronic searches were undertaken to identify the evidence for this report. Initial searching was undertaken between January and April 2005, with the major searches updated during November and December 2005. As prespecified in the protocol, electronic searches were restricted to reports published in the English language; reports published only as abstracts were excluded. The following databases were searched:

- MEDLINE: 1966 to November week 3 2005
- EMBASE: 1980 to 2005 week 49
- MEDLINE In Process and Non-indexed Citations: 23 February, 6 December 2005
- Science Citation Index (SCI): 1981 to 3 December 2005
- BIOSIS: 1985 to 30 November 2005
- Cochrane Central Register of Controlled Trials (CENTRAL): Cochrane Library Issue 4 2005
- PsycInfo: 1967 to June week 3 2005
- Social Science Citation Index (SSCI): 1981 to 27 June 2005
- Applied Social Science Index and Abstracts (ASSIA): 28 June 2005
- Science Direct (*American Journal of Ophthalmology, Ophthalmology* only): 1998 to November 2005
- High Wire Journals (*British Journal of Ophthalmology, Investigative Ophthalmology* and *Vision* only): 1998 to November 2005
- *Journal of Glaucoma*: 2001 to November 2005
- NHS Economic Evaluation Database (NHS EED): November 2005
- Health Technology Assessment Database (HTA Database): November 2005
- Database of Abstracts of Reviews of Effectiveness (DARE): November 2005
- Cochrane Database of Systematic Reviews (CDSR): Cochrane Library Issue 4 2005
- Health Management Information Consortium (HMIC): November 2005
- National Research Register: Issue 1 2006
- Current Controlled Trials (CCT): March 2006
- Clinical Trials: March 2006.

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TABLE 2 *Retrieved reports for each component of the review*

Database	Effectiveness of screening	Accuracy and reproducibility of diagnostic tests	Patient acceptability of glaucoma testing	Effectiveness of glaucoma treatment	Epidemiology, risk and progression	Economic evaluation of screening	General search
MEDLINE/EMBASE	985	4939	62	305	3943	349	
SCI	77	401			410	44	
BIOSIS	67	141			30		
CENTRAL	62	26		18			
PsycInfo			35				
SSCI			39				
ASSIA			28				
Science Direct/High Wire/*J Glaucoma*		112					
HMIC							36
NHS EED						38	
HTA							29
DARE							20
CDSR							3
CCT							56
Clinical Trials							0
National Research Register							54
Total	1191	5619	164	323	4383	431	198

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TABLE 3 *Number of reports selected for full-text assessment*

Database	Effectiveness of screening	Accuracy and reproducibility of diagnostic tests	Patient acceptability of glaucoma testing	Effectiveness of glaucoma treatment	Epidemiology, risk and progression	Economic evaluation of screening	Background information
MEDLINE/EMBASE	0	772	5	15	406	48	48
SCI	0	39	–	–	21	4	1
BIOSIS	0	14	–	–	4	–	0
CENTRAL	0	3	–	0	–	–	0
PsycInfo	–	–	0	–	–	–	–
SSCI	–	–	2	–	–	–	–
ASSIA	–	–	3	–	–	–	–
Science Direct/High Wire/*J Glaucoma*	–	3	–	–	–	–	1
HMIC	0	23	0	0	0	8	5
NHS EED	–	–	–	–	–	6	–
HTA	0	13	0	0	0	0	6
DARE	0	0	0	0	0	0	0
CCT	0	0	0	0	0	0	0
National Research Register	0	0	0	0	0	0	0
Web/unpublished	0	0	0	0	2	1	13
Total	0	867	10	15	433	67	74

Specific searches were undertaken separately for each component of the report: effectiveness of screening, accuracy and reproducibility of diagnostic tests, patient acceptance of glaucoma testing, effectiveness of glaucoma treatment, epidemiology, risk factors and progression of glaucoma, and economic evaluation. In addition, general searches on the topic of OAG were undertaken within the reviews and trials databases. *Table 2* details the databases that were searched for each component, with the number of reports retrieved from each search after deduplication against the results of the MEDLINE/EMBASE searches. Appendix 2 details all the search strategies that were used. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies. Web pages of appropriate professional organisations were also searched for additional background material. The details of the main ones consulted are listed in Appendix 2.

The databases were searched using strategies that were tailored to the scope of the individual components of this report:

- Effectiveness of screening: aimed to restrict evidence to randomised controlled trials (RCTs), without language restriction.
- Accuracy and reproducibility of diagnostic tests: aimed to restrict evidence to reports that assessed diagnostic performance of a selected range of tests. This was supplemented with full-text searching of selected ophthalmology journals.
- Patient acceptability of glaucoma testing: additional social science databases were searched.
- Effectiveness of glaucoma treatment: a relevant systematic review,[19] published in 2005, was identified, therefore searching was restricted to updating this review.
- Epidemiology, risk and progression: included, but was not restricted to, specific searching for selected risk factors and known major epidemiological studies.
- Economic evaluation of screening: aimed to restrict evidence to cost-effectiveness and utilities data.

All titles and abstracts identified in these ways were assessed to identify potentially eligible studies. *Table 3* provides details of the number of reports that were selected for full-text assessment.

Chapter 5

Epidemiology of open angle glaucoma

Introduction

The aetiology of the majority of cases of adult-onset OAG is not known. Since OAG has no associated symptoms and is often asymptomatic before the development of established visual field loss, there is a need to identify groups at a high risk of developing glaucoma and quantify the level of risk.

Risk factors have been identified from epidemiological studies. These are increasing age and IOP, ethnicity, family history of OAG in a first-degree relative, myopia and diabetes. Identifiable gene mutations are implicated,[92–96] but account for only about 4% of cases of adult-onset OAG.[97] Although certain genetic subtypes are more likely to progress towards severe disease, based on current knowledge of the inheritance of OAG, genetic screening would not detect a substantial number of the currently undetected cases.

The aim of this systematic review was to determine the incidence and prevalence of OAG in the UK population and to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes.

Methods

Inclusion and exclusion criteria

Types of studies and participants

Population-based studies, namely cohort and cross-sectional studies, investigating the risk of developing OAG and the prevalence in the UK, were included. Meta-analyses and systematic reviews of observational population-based studies were also included. Preliminary searches identified few UK studies and therefore other studies reporting similar populations, such as European, North American, Canadian or Australasian were sought. Studies in which the population was defined at the hospital or clinic-based setting were excluded, as participants were not considered to be representative of the general population. Studies were also excluded when it was not possible to ascertain the type of glaucoma being assessed. The review was restricted to English-language publications.

Types of risk factors and outcomes

The following variables were considered as risk factors for OAG:

- age: 40, 50, 60, 70 years
- myopia: mild/moderate (≥6 D); high (>6)
- ethnicity
- diabetes: types 1 and 2
- family history: one or more first-degree relative(s) with OAG
- IOP.

The following outcome measures were considered:

- number of OAG cases detected
- number of mild, moderate and severe OAG cases detected
- relative risk of OAG for each risk factor reported
- relative risk of mild, moderate and severe OAG for each risk factor
- time to glaucoma diagnosis (mild, moderate and severe) according to level of IOP.

Data extraction strategy

Four reviewers screened the titles and abstracts of all papers identified by the search strategy. Full text copies of all potentially relevant studies were obtained and four reviewers independently assessed them for inclusion. Reviewers were not masked to the names of studies' authors, institutions or sources of the reports. Any uncertainties in the data were resolved by discussion between reviewers.

A data extraction form was developed to record details of the design of included studies, year of publication, year of study, country of study, sample size, participation rate, method of recruitment, eligibility criteria, diagnostic criteria for OAG, overall prevalence and prevalence by the risk factors of interest, relative risk of OAG and incidence (Appendix 3). Data were single data extracted by the same four reviewers.

Quality assessment strategy

Two reviewers (JB, TL) assessed the methodological quality of the included studies. Any disagreements were resolved by consensus or arbitration. The included studies were assessed to

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TABLE 4 *Quality assessment criteria*

Criterion	Type of bias
Were participants sampled adequately? (Random sample obtained from a representative population)	Selection
Was exposure (risk factor) status obtained from a secure record? (Clinical examination or examination records)	Detection
Was the criterion used in the diagnostic classification thorough? (Glaucomatous visual field defect with or without glaucomatous optic neuropathy)	Detection
Was the response rate greater than 75%?	Attrition

see whether they contained the elements shown in *Table 4*. An acceptable diagnosis required a glaucomatous visual field defect with or without glaucomatous optic neuropathy. It was accepted that the classification of glaucoma would vary between studies, and in particular that methods for ascertaining visual field loss would have changed from the studies conducted in the 1960s. A secure record for exposure (risk factor) assessment was considered to be through a clinical examination or the examination of records. The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available.

Data synthesis

Prevalence and incidence reported for an age range were attributed to the age category to which the midpoint was closest. Study estimates of prevalence came from definite cases of OAG excluding probable and/or possible cases. When this information was not provided, it was assumed that the rate presented in studies was for definite cases.

The prevalence of glaucoma was calculated as the number of participants diagnosed with glaucoma divided by the number of participants screened. The prevalence of OAG was calculated for the whole population, and for those aged 40, 50, 60 and 70 years. For each study, a standard error (SE) estimate was produced, using the large sample normal approximation. Prevalence estimates were pooled using the DerSimonian and Laird random effects method.[98] A pooled estimate of the proportion of undetected OAG was produced using the same methods. Since only one study[99] reported the prevalence of undetected OAG by age, the overall estimate of undetected OAG was applied to each age category to produce crude age-specific estimates. A crude age-specific estimate of the prevalence of undetected OAG was calculated by multiplying the pooled prevalence estimate at that age by the pooled estimate of the proportion of previously undetected cases.

Incidence was summarised for each age category as the mean and range for cases per 100,000 years at risk. No formal pooling was undertaken. No studies provided data with which to estimate incidence for 40 year olds and therefore the values for 50 year olds were used. Incidence estimates for the UK were determined by dividing the number of cases newly diagnosed by the number of people at risk (population data were obtained from the 2001 UK Census).

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken using the DerSimonian and Laird method. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

A pooled prevalence was also calculated for the prevalence of OAG in the high-risk group under each risk factor. The number at risk in the UK population for each risk factor was determined by applying the pooled estimate to the 2001 UK Census. Data obtained from the A-rated studies contributed to the pooled estimates. Where no A-rated studies were available B-rated studies were used.

High IOP was defined as one or more measurements with readings equal to or above 26 mmHg. Other IOP cut-offs were also investigated. Participants with myopia were defined as having one or more measurements with refractive errors greater than 0.5 D, ascertained by either measurement of present spectacles or a

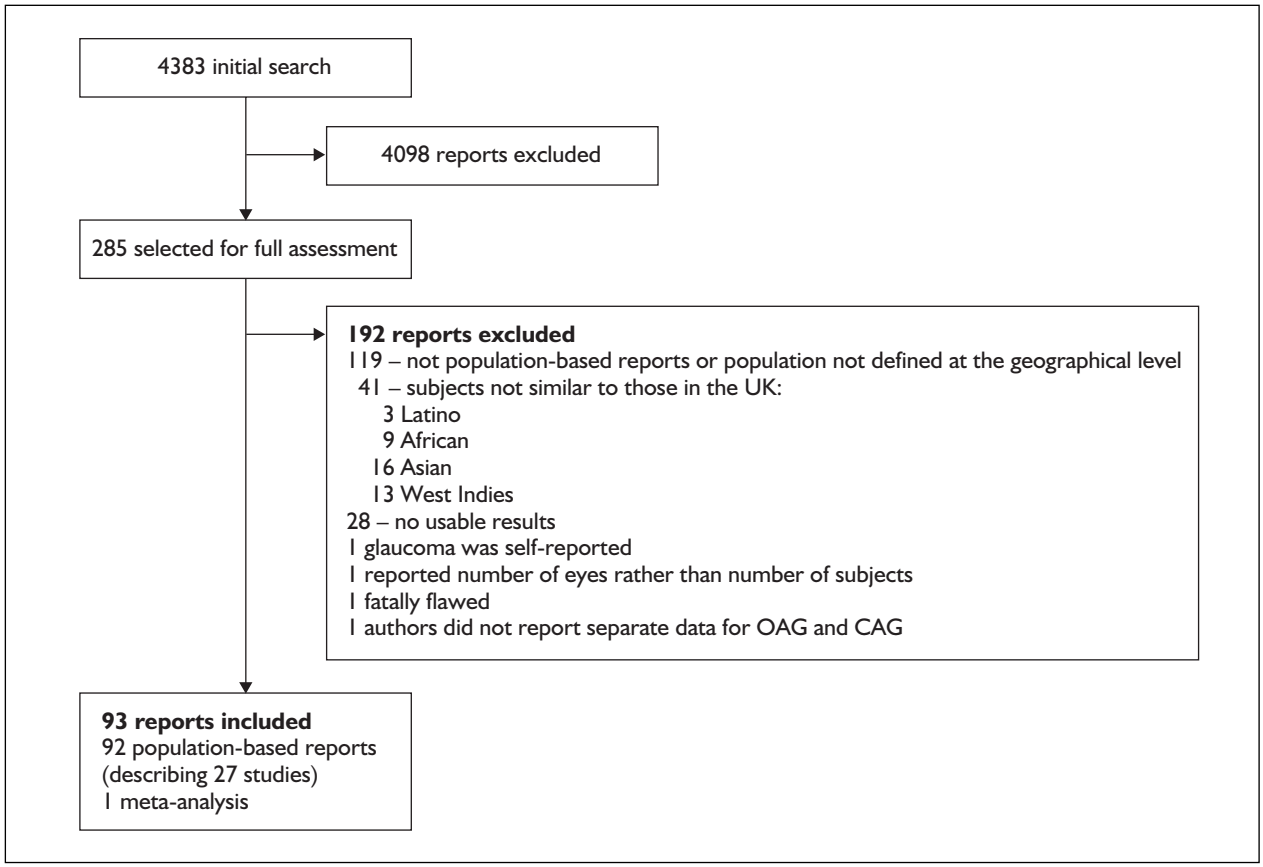

FIGURE 14 *Study selection process*

refraction examination. Family history of OAG was defined as participants having any first-degree relative affected by OAG confirmed by clinical examination. Diabetes was defined as people on treatment for diabetes (type 1 or 2) or those testing positive on urinalysis, glycosylated haemoglobin (HbA_{1c}) or a glucose tolerance test.

Results

Number and type of studies included

The study selection process is summarised in *Figure 14*. In total, 4383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. Ninety-two reports describing 27 studies met the inclusion criteria for the review. In addition, one meta-analysis was identified. The included studies and associated references are listed in Appendix 4.

Number and type of studies excluded, with reasons for specific exclusions

A total of 192 reports was obtained but subsequently excluded because they failed to meet one or more of the inclusion criteria (*Figure 14*). The majority of the exclusions were not population-based studies or the population was not defined at the geographical level. (See Appendix 5 for further details.)

Study quality and characteristics of included studies

Quality of available evidence

The results of the quality assessment of the included studies are summarised in *Table 5*. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, baring of the blind spot, case records, unstandardised criteria) were used in five studies (19%).[100–104] IOP, diabetes and myopia status were obtained from a secure record (examination or examination records) in most studies. However, only one (20%)[105] obtained family history status from a secure source, by examination of first-degree relatives of detected cases. Sixteen (59%) included studies specified the participation rate to be greater than 75%; however, this information was unclear in seven (26%) studies.

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TABLE 5 *Summary of quality assessment of papers (n = 27) reporting cross-sectional studies*

Criterion	A	B	Unclear
Were participants sampled adequately and selected from a relevant population?	22 (81%)	5 (19%)	0
Were the criteria used in the diagnostic classification thorough?	22 (81%)	5 (19%)	0
Was IOP status obtained from a secure record?[a]	9 (90%)	1 (10%)	0
Was family history status obtained from a secure record?[a]	1 (20%)	4 (80%)	0
Was diabetes status obtained from a secure record?[a]	3 (75%)	1 (25%)	0
Was myopia status obtained from a secure record?[a]	3 (100%)	0 (0%)	0
Was the response rate greater than 75%?	16 (59%)	4 (15%)	7 (26%)

[a] As not all studies report all risk factors, the total number of studies does not add up to 26.

Characteristics of included studies

Appendix 6 provides details of the characteristics of all included studies. Only A-rated studies are described in this section (n = 19).[21,22,28,63,64,99,105–117] All but one of the included studies[105] described a population-based cross-sectional study. The remaining eight studies[100–104,118–120] are also described in Appendix 6.

Studies included in the review presented variations in relation to study settings, age of participants, types of exposures measured and the definition of OAG (*Tables 6* and 7). Of the 19 eligible studies, four took place in the UK,[21,64,113,116] three in the USA,[111,114,122] two each in Australia,[63,115] Italy,[106,107] Iceland[110,117] and Sweden,[28,109] and one each in Ireland,[108] Spain,[99] Greece,[112] and The Netherlands.[105]

The participation rate ranged from 67%[121] to 92%.[21] Four studies did not provide information on participation rate. Sample size ranged from 207[116] to 32,918.[28]

All 19 studies gave details of participants' age. Eight studies included participants aged 40 years old and all but seven studies did not have an upper age limit. Most studies involved mainly white populations. However, in one study 45% (n = 2394) of included participants were of black ethnicity.[114]

The majority of studies selected participants from a population register (census in eight, municipal register in three and electoral register in one). One study took participants from another population-based study.[121] Two additional studies drew participants from general medical practice groups[113,116] and one recruited participants after delivering preliminary publicity campaign cards inviting people over 40 years of age in Bedford, UK, for a screening examination.[64]

All studies ascertained glaucoma status by means of a clinical examination. Questionnaires were used to ascertain exposure status of participants in three studies.[63,99,114]

Disease prevalence

Data on prevalence was grouped as undetected OAG and overall OAG. Undetected OAG refers to participants being newly diagnosed at screening. Overall OAG refers to both previously detected and undetected glaucoma. All 19 studies provided information on the prevalence of OAG with the majority reporting undetected prevalence as well as the overall prevalence (*Table 7*). Estimates of the overall prevalence of OAG varied across studies, ranging from 0.4[21] to 6.6%.[117] The pooled prevalence rate from 19 studies was estimated to be 2.1% [95% confidence interval (CI) 1.7 to 2.5]. For previously undetected OAG, the pooled prevalence rate was 1.4% (95% CI 1.0 to 1.9). Fifteen studies contributed to this estimation and values ranged from 0.3[108] to 3.3%.[109] By applying the pooled prevalence estimates to the UK population over 40 years of age, it was estimated that there are approximately 569,000 people affected by OAG, of which 380,000 are undetected cases (*Table 7*, *Figure 15*). (The proportion of people with undetected glaucoma across the studies can be found in Appendix 6.)

Disease incidence

The incidence of OAG was investigated in three studies (*Table 8*).[123–125] Two of the studies estimated the incidence of OAG by conducting a population-based cohort study with an observation period of 5 years. The other study estimated the incidence of OAG from age-specific prevalence data. Based on these studies, the incidence rate

TABLE 6 *Characteristics of included studies (only A-rated studies)*

Study	Country	Participants selection	Age range (years)	No. of participants (% uptake)	Ethnicity (%)		Exposures
					White	Black	
Anton, 2004[99] Segovia Study	Spain	Census	40–79	510 (90)	NR	NR	IOP; family history, age
Bankes, 1968[64] Bedford Glaucoma Survey	UK	All population	40+	5,941	NR	NR	IOP, age
Bonomi, 2001[106] Egna–Neumarkt Glaucoma Study	Italy	National register	40–80+	4,297	NR	NR	Age
Cedrone, 1997[107]	Italy	Census	40–80+	1,034	NR	NR	IOP, age
Coffey, 1993[108]	Ireland	Electoral register	50–80+	2,186	NR	NR	IOP, age
Dielemans, 1996[105] Rotterdam Study	Netherlands	Municipal registry	55–75+	3,062 (72)	98	NR	IOP, family history, diabetes, age
Ekstrom, 1996[109] Tierp Glaucoma Survey	Sweden	Municipal registry	60–74	760 (91)	NR	NR	
Grodum, 2002[28]	Sweden	All population	57–79	32,918 (77)	NR	NR	
Leibowitz, 1980[22] Framingham Eye Study	US	Other population-based study	55–84	2,631 (67)	100		Age
Hollows, 1966[21]	UK	Census	40–75	4,231 (92)	NR	NR	
Jonasson, 1987[117]	Iceland	Census	43–83+	751 (81)	NR	NR	Age
Jonasson, 2003[110] Reykjavik Eye Study	Iceland	Census	50–80+	1,045 (76)	NR	NR	Age
Klein, 1992[111] Beaver Dam Eye Study	US	Census	43–84	4,926 (83)	100	0	IOP, myopia diabetes
Kozobolis, 2000[112]	Greece	Municipal registry	40–80+	1,107 (85)	NR	NR	IOP, age
Mitchell, 1997[122] Blue Mountains Eye Study	Australia	Census	49–80+	3,654 (88)	100	0	IOP, age, family history, myopia
Reidy, 1998[113]	UK	General medical practice groups	65–100	1,547 (84)	NR	NR	Age
Tielsch, 1991[114] Baltimore Eye Survey	US	Census	40–80+	5,308 (79)	54.9	45.1	IOP, diabetes, family history, ethnicity, age
Weih, 2001[115] Visual Impairment Project	Australia	Census	40–90+	4,498 (86)	100	0	IOP, family history, myopia, ethnicity, age
Wormald, 1992[116]	UK	Age–gender register	65+	207 (72)	NR	NR	

NR, not reported.

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TABLE 7 *Prevalence of OAG in population-based studies*

Study ID	Diagnostic criteria for OAG	Participants	Prevalence OAG (%)	
			Undetected	Overall
Anton, 2004[99] Segovia Study	Glaucomatous optic disc stereographs, suprathreshold field and open angle	510	2.1	2.1
Bankes, 1968[64] Bedford Glaucoma Survey	Disc, semi-automated field, open angle slit-lamp examination on suspects	5,941	NR	0.76
Bonomi, 2001[106] Egna-Neumarkt Glaucoma Study	Disc (direct ophthalmoscopy), suprathreshold field, slit-lamp examination	4,297	1.5	1.95
Cedrone, 1997[107]	Suprathreshold field, and one of IOP positive or disc positive	1,034	2.3	2.5
Coffey, 1993[108]	Disc and slit-lamp, suprathreshold field only in suspects	2,186	0.3	1.0
Dielemans, 1996[105] The Rotterdam Study	Threshold field, open angle and one of positive disc or IOP positive	3,062	0.6	1.1
Ekstrom, 1996[109] Tierp Glaucoma Survey	Disc, threshold field, open angle on slit-lamp	760	3.2	5.7
Grodum, 2002[28]	Threshold field, disc, open angle on slit-lamp examination	32,918	1.2	1.5
Leibowitz, 1980[22] The Framingham Eye Study	Glaucoma visual field defect and any of positive IOP, or disc or glaucoma history	2,631	NR	1.0
Hollows, 1966[21]	Disc, field, slit-lamp (open angle)	4,231	0.3	0.4
Jonasson, 1987[117]	Glaucoma visual field defect and any of positive IOP, or disc or glaucoma history	751	NR	6.6
Jonasson, 2003[110] Reykjavik Eye Study	Disc, IOP, threshold fields (two out of three)	1,045	2.4	4.0
Klein, 1992[111] Beaver Dam Eye Study	Disc (stereoscopic photograph), suprathreshold field	4,926	1.9	2.1
Kozobolis, 2000[112]	Open angle (slit-lamp examination), disc, nerve fibre defect and visual field defect	1,107	2.0	2.8
Mitchell, 1997[122] Blue Mountains Eye Study	Disc, open angle, suprathreshold field	3,654	1.2	2.4
Reidy, 1998[113]	Suprathreshold field, disc	1,547	2.3	3.0
Tielsch, 1991[114] Baltimore Eye Survey				
	Slit-lamp examination (open angles), disc, (stereoscopic photography), field	5,308	1.2	2.5
Weih, 2001[115] Visual Impairment Project	Disc, threshold visual field	4,498	1.1	1.8
Wormald, 1992[116]	Disc, suprathreshold fields	207	0.5	4.4
Pooled estimate (95% CI)			1.4 (1.0 to 1.9)	2.1 (1.7 to 2.5)
UK estimate Denominator: Total population over 40 (2001 Census): 27,116,127			**Number affected** 379,626	**Number affected** 569,439

TABLE 8 *Incidence estimates stratified by age*

Age (years)	Study	Incidence rate (per 100,000 per year)
40	Mukesh, 2002[125]	0
50	Mukesh, 2002[125]	20
	Podgor, 1983[123]	40
60	Mukesh, 2002[125]	120
	Podgor, 1983[123]	60
	de Voogd, 2005[124]	60
70	Mukesh, 2002[125]	280
	Podgor, 1983[123]	140
	de Voogd, 2005[124]	124

TABLE 9 *Estimated new OAG cases per year by age cohort*[a]

Age (years)	UK population at risk (*n*)	Mean (per 100,000 per year)	Range (population)	UK estimate	Range
40	878,257	30[b]	20–40	263	176–351
50	717,088	30	20–40	215	144–287
60	556,794	80	60–120	445	334–668
70	486,614	181	124–280	880	603–1408

[a] Population estimate for all people aged 40–70: 11,054 new cases per year in the UK.
[b] Same incidence as 50 year olds was assumed.

for OAG increases with age (*Table 9*). Incidence of OAG ranged from 30 to 181 cases per 100,000 people per year at 40 and 70 years of age, respectively. By applying the pooled estimate for each age to the 2001 UK census population, the number of new cases in the UK is estimated to range from 263 to 880 new cases for 40 and 70 year olds per calendar year, respectively. It is noteworthy that sample sizes in the older age cohorts are usually quite small and therefore the estimates presented in *Table 9* may not reflect the true incidence among older people. In addition, the ageing population in the studies may not be representative of the general ageing population. For those reasons, these incidence estimates should be interpreted with caution.

Disease severity

Five studies provided information on disease severity for participants; however, information was not provided separately for the newly detected cases, and in the majority of cases disease status was unclear (*Table 10*).[71,108,114,117,126] In these cross-sectional studies the percentage of people with moderate disease varies from approximately 9%[114] to 15.4%.[126] Mild disease was reported in only one study and was estimated to be 12.1%.[114] Severe disease was reported in three studies, varying from 4%[117] to 14.6%.[108] Blind from glaucoma was reported in four studies, varying from 3%[71] to 10.6%.[114] There appeared to be heterogeneity between the studies regarding severity definition and therefore these results should be interpreted with caution.

Demographic risk factors

Age

The prevalence of OAG by age was reported in 16 studies (*Table 11*). There was no standardisation of age intervals across studies and therefore direct comparisons were difficult. For the purpose of this review, the focus was on age 40, 50, 60 and 70 years as cut-offs. All studies consistently showed that the prevalence of OAG increases with older age. The overall prevalence of OAG by age was 0.3 (95% CI 0.1 to 0.5) in people aged 40 years and increased steeply with age to 3.3% (95% CI 2.5 to 4.0) in people aged 70 years. As the prevalence of undetected cases stratified by age was not reported in any of the included studies, it was assumed that the proportion of undetected OAG does not vary across age groups. The prevalence of undetected OAG was then estimated to range from 0.2 to 2.1% in people aged 40 and 70 years, respectively (*Table 11*). *Figure 15* shows the estimated number of people with undetected OAG in the UK, steadily rising from 1761 at 40 years to 11,000 people at 70 years of age.

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TABLE 10 *Severity of glaucoma (newly detected and established cases)*

Study	Severity (%)										Definition of severity
	Mild		Moderate		Severe		Blind		Unclear		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Coffey, 1993[108]	NR	NR	NR	NR	3	(15)	1	(7)	37	(78)	Severe: low vision (<6/18) Blind: not reported
Dielemans, 1994[71] Rotterdam Study	NR	NR	2	(6[a])	NR	NR	1	(3)	31	(91)	Moderate: advanced visual field loss in at least one eye Blind: visual acuity ⩽20/200 in the better eye
Jonasson, 1987[117]	NR	NR	NR	NR	2	(4)	3	(6)	45	(90)	Severe: visual field loss Blind: visual acuity ⩽6/60 in the better eye or visual field less than 10° (legally blind)
Lee, 2003[126] Blue Mountains Eye Study	NR	NR	16	(15[a])	6	(6)	NR	NR	82	(79)	Moderate: advanced visual field loss in at least one eye Severe: bilateral advanced visual field loss
Tielsch, 1991[114] Baltimore Eye Survey	16	(12)	12	(9)	NR	NR	14	(11)	90	(68)	Mild: one visual field either typically abnormal or compatible with glaucoma and cupping or nerve fibre layer loss Moderate: at least one abnormal visual field with some but not perfect congruence between fields and a C/D ⩾ 0.8 or a difference between the two eyes of ⩾0.3 Blind: end-stage disease with visual acuity ⩽20/200 and 100% cupping

[a] No details of the other eye were given, so disease severity was assumed to be moderate because it was presumed that the authors would have reported it as bilateral visual field loss (severe disease).

Ethnicity

The relationship between ethnicity and OAG was evaluated in only one study.[114] This study provided a direct comparison of prevalence between black and white ethnicity. Age-specific prevalence rates for OAG among African-Americans ranged from 1.23% (95% CI 0.23 to 2.24) in those aged 40–49 years to 9.15% (95% CI 5.83 to 12.48) in those aged 70–79 years. The relative risk of OAG among the Baltimore over-40 years black population compared with whites is estimated to be 3.80 (95% CI 2.56 to 5.64). The onset of disease appears to be earlier for blacks as the number of cases identified for those aged between 40 and 59 was considerably higher than that observed in whites (2.3% and

TABLE 11 *Pooled prevalence estimate stratified by age*

Age (years)	Study	Prevalence (%) (95% CI)	
		Undetected	**Overall**
40	Anton, 2004[99]	0	0
	Bankes, 1968[64]	NR	2.0 (0 to 0.4)
	Bonomi, 2001[106]	NR	0.4 (0 to 0.8)
	Cedrone, 1997[107]	NR	1.4 (0 to 2.9)
	Kozobolis, 2000[112]	NR	0
	Tielsch, 1991[114]	NR	0.6 (0.1 to 1.0)
	Weih, 2001[115]	NR	0.1 (0 to 0.2)
Pooled prevalence		0.2 (0.1 to 0.4)[a]	0.3 (0.1 to 0.5)
50	Anton, 2004[99]	2.2 (0 to 5.2)	2.2 (0 to 5.2)
	Bankes, 1968[64]	NR	0.3 (0.1 to 0.5)
	Bonomi, 2001[106]	NR	1.4 (0.7 to 2.0)
	Cedrone, 1997[107]	NR	1.3 (0 to 2.8)
	Coffey, 1993[108]	NR	0.7 (0 to 1.3)
	Jonasson, 1987[117]	NR	0.9 (0 to 2.1)
	Jonasson, 2003[110]	NR	0.6 (0 to 1.3)
	Klein, 1992[111]	NR	1.0 (0.5 to 1.5)
	Kozobolis, 2000[112]	NR	2.8 (0.4 to 5.1)
	Mitchell, 1997[122]	NR	0.4 (0 to 0.7)
	Tielsch, 1991[114]	NR	2.1 (1.3 to 2.8)
	Weih, 2001[115]	NR	0.8 (0.3 to 1.3)
Pooled prevalence		0.6 (0.3 to 1.0)[a]	0.9 (0.6 to 1.3)
60	Anton, 2004[99]	2.2 (0 to 4.7)	2.2 (0 to 4.7)
	Bankes, 1968[64]	NR	0.9 (0.4 to 1.4)
	Bonomi, 2001[106]	NR	2.3 (1.4 to 3.1)
	Cedrone, 1997[107]	NR	2.5 (0.8 to 4.3)
	Coffey, 2003[108]	NR	1.8 (0.8 to 2.7)
	Dielemans, 1996[105]	NR	0.2 (0 to 0.4)
	Jonasson, 1987[117]	NR	3.0 (0.6 to 5.3)
	Jonasson, 2003[110]	NR	2.8 (1.1 to 4.5)
	Klein, 1992[111]	NR	1.1 (0.5 to 1.6)
	Kozobolis, 2000[112]	NR	2.5 (0.9 to 4.2)
	Leibowitz, 1980[22]	NR	0.6 (0.1 to 1.0)
	Mitchell, 1997[122]	NR	1.1 (0.5 to 1.6)
	Tielsch, 1991[114]	NR	1.3 (0.9 to 1.8)
	Weih, 2001[115]	NR	1.9 (1.1 to 2.6)
Pooled prevalence		0.9 (0.5 to 1.4)[a]	1.4 (1.0 to 1.9)
70	Anton, 2004[99]	3.3 (0.4 to 6.1)	3.3 (0.4 to 6.1)
	Bankes, 1968[64]	NR	2.8 (1.5 to 4.2)
	Bonomi, 2001[106]	NR	4.6 (3.0 to 6.3)
	Cedrone, 1997[107]	NR	4.3 (1.7 to 6.9)
	Coffey, 2003[108]	NR	3.2 (1.7 to 4.7)
	Dielemans, 1996[105]	NR	1.3 (0.7 to 2.0)
	Jonasson, 1987[117]	NR	6.1 (2.6 to 9.6)
	Jonasson, 2003[110]	NR	8.0 (4.6 to 11.3)
	Klein, 1992[111]	NR	2.8 (1.9 to 3.7)
	Kozobolis, 2000[112]	NR	2.6 (1.1 to 4.1)
	Leibowitz, 1980[22]	NR	1.3 (0.5 to 2.1)
	Mitchell, 1997[122]	NR	4.2 (2.9 to 5.4)
	Reidy, 1998[113]	NR	2.0 (1.0 to 2.9)
	Tielsch, 1991[114]	NR	4.6 (3.3 to 5.9)
	Weih, 2001[115]	NR	4.2 (2.7 to 5.6)
	Wormald, 1992[116]	NR	2.0 (0 to 4.7)
Pooled prevalence		2.1 (1.4 to 3.0)[a]	3.3 (2.5 to 4.0)

[a] Owing to the limited evidence on the prevalence of undetected OAG by age, the overall estimate of undetected OAG was applied to each age category to produce crude age-specific estimates.

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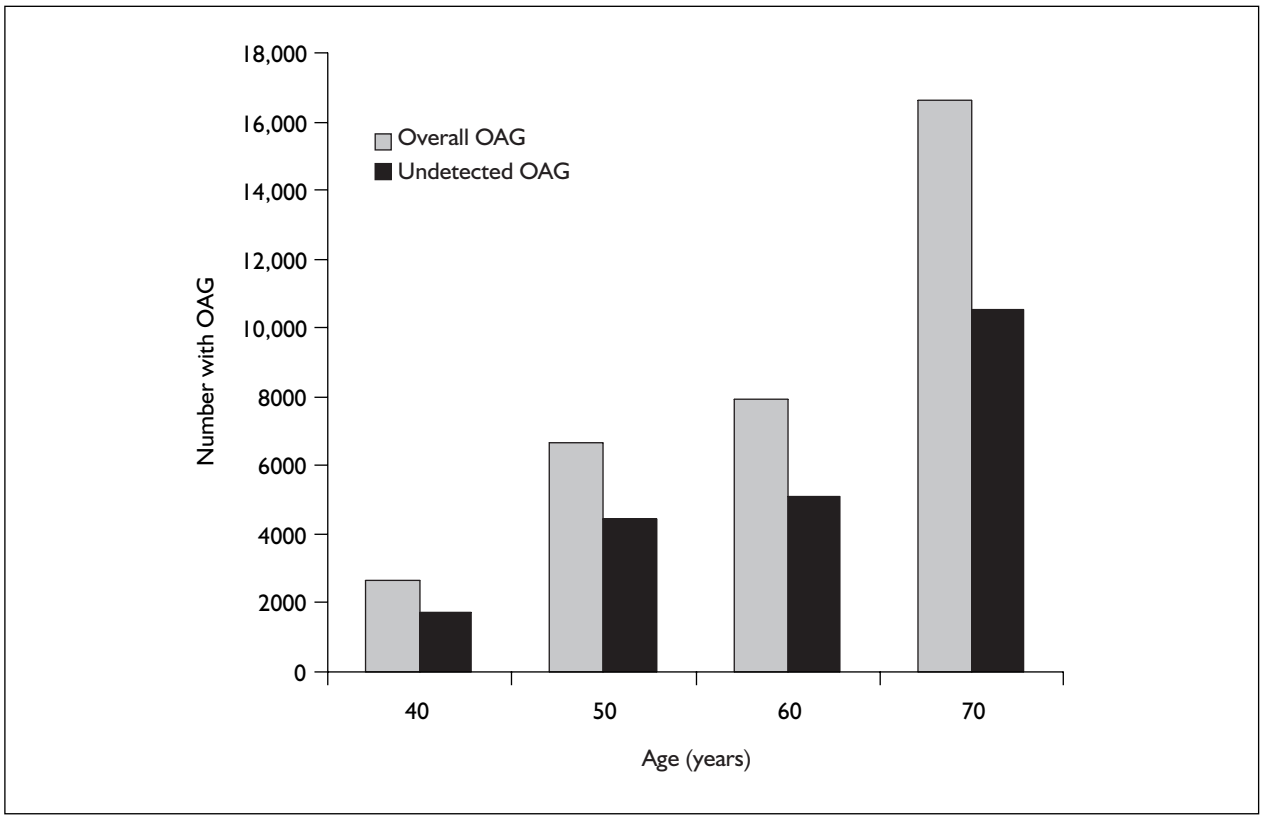

FIGURE 15 *Estimated number of people with OAG in the UK at specific ages*

0.25%, respectively). The number of people of black ethnicity (Caribbean, African, other and mixed) with OAG in the UK is estimated to be approximately 9000 for those aged between 40 and 75 years. No studies reported data for other ethnic populations.

Ocular risk factors

IOP

Seven studies described the prevalence of OAG by a range of IOP levels.[63,99,107,108,111,112,127] Across the studies, the proportion of people with OAG who had an IOP above 21 mmHg was consistently higher than those who had an IOP of 21 mmHg or less (*Table 12*). The proportion of people with high IOP varied widely across studies. However, all but one[99] included cases with previously detected OAG, and thus already under glaucoma therapy, and therefore underestimate the true prevalence of OAG in people with high IOP. The reason for the study by Coffey[108] reporting such a low prevalence of glaucoma among those with high IOP was unclear, although the authors did not report IOP measurements in 12 of the 36 OAG cases. Prevalence of IOP by higher IOP levels (≥26 mmHg) was also investigated. The risk of having glaucoma for those with IOP measurements 26 mmHg or greater is estimated to be 13 times higher than that for those with lower IOP [relative risk (RR) 12.58, 95% CI 5.07 to 31.24]; of note was that only newly detected cases contributed to the estimation of this relative risk.[127]

Myopia

Prevalence rates of OAG for those with and without myopia were available from four studies (*Table 13*).[128–131] The proportion of people with OAG appeared to be higher in participants with myopia than in those without myopia. The prevalence of OAG among people with myopia ranged from 1.4 to 4.3%, with a pooled estimate of 2.7% (95% CI 1.5 to 3.9). The pooled relative risk of OAG among participants with myopia (any definition) compared with non-myopes was estimated to be 1.88 (95% CI 1.53 to 2.31). This result should be treated with caution as there was no standardisation on the definition of myopia across the studies and therefore the risk for low (<–6 D) and moderate (>–6 D) could not be determined.

Non-ocular risk factors

Diabetes

The prevalence of OAG by diabetes status was reported in four studies that established diabetes

TABLE 12 *Prevalence of OAG stratified by IOP*

Study	Age (years)	IOP > 21 mmHg (*n*/*N*)	IOP ⩽ 21 mmHg (*n*/*N*)	Undetected OAG (%)
Anton, 2004[99]	40–79	0.37 (3/8)	0.014 (7/497)	100
Cedrone, 1997[107]	40+	0.34 (21/62)	0.005 (5/1002)	19.2
Coffey, 1993[108]	50+	0.09 (6/65)	0.0087 (15/1734)	66.7
Klein, 1992[111]	43–84	0.31 (71/232)	0.007 (33/4694)	90
Kozobolis, 2000[112]	40+	0.28 (28/101)	0.003 (3/1006)	70
Mitchell, 1996[63]	49+	0.2 (27/135)	0.022 (81/3654)	51
Tielsch, 1994[127]	40+	0.1 (80/775)	0.011 (114/9669)	61

TABLE 13 *Univariate and multivariate odds ratios (OR) reported by studies describing the relationship between glaucoma and myopes*

Study	Crude OR	95% CI	Adjusted OR	95% CI	Comments
Grodum, 2001[128]	1.85	1.4 to 2.4	NR	NR	Myopia: ⩾–2.0 D
Mitchell, 1999[129]	2.1[a]	1.2 to 3.8	2.4	1.3 to 4.1	Adjusted for age, gender, family history of glaucoma, diabetes, hypertension, typical migraine history, steroid use and presence of pseudoexfoliation; myopia: ⩾1.0 to 3.0 D
Weih, 2001[130]	NR	NR	1.6	0.9 to 6.7	Adjusted for age; myopia: ⩾–0.5 D
Wong 2003[131]	NR	NR	1.6	0.9 to 2.6	Adjusted for age and gender; myopia: ⩾–1.0 D

[a] Gender adjusted.

TABLE 14 *Univariate and multivariate odds ratios reported by studies describing the relationship between glaucoma and diabetes*

Study	Crude OR	95% CI	Adjusted OR	95% CI	Comments
Dielemans, 1996[105]	NR	NR	3.11	1.12 to 8.66	Adjusted for age, gender and body mass index
Klein, 1994[132]	NR	NR	1.84	1.09 to 3.11	Adjusted for age and gender
Leibowitz, 1980[22]	1.27	0.5 to 2.9	NR	NR	
Mitchell, 1997[122]	2.07	1.5 to 4.7	2.12	1.18 to 3.79	Adjusted for age and gender

by clinical tests.[22,105,122,132] Three of those provided adjusted estimates for odds ratios[105,122,132] (*Table 14*). The prevalence of OAG among participants with diabetes varied from 1.2%[105] to 5.5%,[122] with a pooled estimate of 3.3% (95% CI 1.8 to 4.8%). As shown in *Table 14*, this investigation demonstrated almost twice the risk of OAG onset among people with diabetes when compared with people without diabetes (RR 1.93, 95% CI 1.38 to 2.69). The number of those with diabetes with OAG in the UK is estimated to be approximately 49,300 for those aged over 45 years.

Family history

The relationship between family history of glaucoma and OAG was investigated in five studies.[99,130,133–135] Only four presented data sufficiently similar to allow for quantitative synthesis.[130,133–135] However, the Rotterdam Study[135] was removed from the analysis because their uptake rate was low (<75%). The included studies reported adjusted odds ratios estimates (*Table 15*). The prevalence of OAG among participants with a positive family history varied from 4.2 to 8.6%, with a pooled estimate of 6.7% (95% CI 5.0 to 8.4). The meta-analysis showed that a family history of glaucoma is associated with a three-fold excess age-adjusted risk of OAG (RR 3.14, 95% CI 2.32 to 4.25) (*Table 16*). These results should be interpreted with caution, as these studies are methodologically weak because family history of glaucoma was based solely on

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TABLE 15 *Univariate and multivariate odds ratios reported by studies describing the relationship between glaucoma and family history*

Study	Crude OR	95% CI	Adjusted OR	95% CI	Comments
Mitchell, 2002[133]	2.7[a]	1.5 to 4.7	3.18	1.8 to 5.6	Adjusted for age, myopia, ocular hypertension, diabetes and IOP
Tielsch, 1994[134]	2.48	1.6 to 3.9	2.85	1.8 to 4.5	Adjusted for age and race
Weih, 2001[130]	NR	NR	3.7	2.0 to 6.7	Adjusted for age
Wolfs, 1998[135]	14.7[a]	1.7 to 130	16.6	1.9 to 147	Adjusted for age, gender, and the presence of diabetes or hypertension

[a] Age and gender adjusted.

TABLE 16 *Pooled prevalence estimates and respective adjusted relative risks stratified by ethnicity, IOP, myopia, diabetes and family history*

Risk factor	Pooled prevalence (%) (95% CI)	Pooled adjusted relative risk	95% CI	Number of studies
Black ethnicity[a]	–	3.80	2.56 to 5.64	1[114]
IOP ⩾ 26 mmHg	–	12.58	5.07 to 31.24	1[127]
Myopia	2.7 (1.5 to 3.9)	1.88	1.53 to 2.31	4[128–131]
Diabetes	3.3 (1.8 to 4.8)	2.08	1.44 to 2.99	3[105,122,132]
Family history	6.7 (5.0 to 8.4)	3.14	2.32 to 4.25	3[130,133,134]

[a] African-American.

participant self-report of family history. This method is suboptimal as it relies on the imperfect knowledge among participants (a form of recall bias).

This association remained statistically significant when data from the Rotterdam Study[135] were also considered (RR 3.23, 95% CI 2.40 to 4.37). This study investigated the relationship of OAG with family history by means of a nested case–control study and was initially excluded from this analysis because of the high degree of uncertainty surrounding the results owing to its small sample size. However, it was the only study that ascertained a positive family history by examining first-degree relatives of patients with glaucoma and control subjects from the population-based Rotterdam Study.

Discussion

In this chapter a systematic review has provided the basis for estimates of the prevalence of OAG in Western countries and associated risk factors were evaluated. The results support an association between OAG and raised IOP, myopia, diabetes, age, family history and black ethnicity. There were insufficient data to estimate the risk of OAG for other ethnic minority groups in the UK.

Inclusion criteria

Given the aetiological focus of this systematic review, study designs such as population-based cross-sectional and cohort studies were considered the most appropriate sources of evidence on the prevalence and incidence of OAG. As Beral[136] and Dickersin[137] pointed out, if associations detected by those studies are causal, even small increased risks are likely to have a large public health impact when exposure is common.[136,137] Study designs such as these are, however, subject to many alternative interpretations because of the scope for the results to be biased or confounded.[138] In addition, the published epidemiological literature is unquestionably heterogeneous.[137] Studies naturally vary in terms of participants' characteristics or on the methods used to assess exposure and outcomes. The presence of major heterogeneity among studies in a systematic review means that the results of any statistical synthesis should be treated with caution.

Only 19 of the 26 studies identified in this review were considered to be similar enough to allow for meaningful pooling. This selection was based on

the consideration that reasonable quality studies that might contribute usable data for evidence synthesis should have an adequate sampling method, an acceptable glaucoma definition, an exposure status obtained from a high-quality data source, and a response rate greater than or equal to 75%.

This systematic review attempted to estimate the current prevalence and incidence of OAG in the UK by applying the pooled estimates to the 2001 UK Census population. There are numerous epidemiological surveys assessing the prevalence of glaucoma, but there are few cohort studies that provide estimates of incidence. Only three studies have been identified to report 5-year incidence rates for a cohort of people. Incidence studies are important to identify the risk of developing OAG and the number of new cases among a population of individuals previously unaffected. Prevalence studies only measure the risk of having the disease. To overcome this problem, some studies derived the incidence from already available prevalence data.[139,140] Using this method, Minassian and colleagues[140] in the UK estimated a higher incidence than that observed in this study (approximately 14,000 as opposed to 11,000). This difference may be because their estimate is based on a much smaller population, including only those aged above 65 years.

The systematic review includes the results of 14 studies conducted in eight different European countries, as well as three in the USA and two in Australia. The breadth of coverage across geographical areas facilitates the consideration of generalisability, although this limited the data available on the risk of glaucoma by ethnicity.

Included studies

Only four UK surveys[21,64,113,116] met the inclusion criteria, two of which were performed during the 1960s. For these two, the level of risk, population structure, disease definition and methods of diagnosis used may no longer be applicable to the current situation. In addition, the results of studies performed outside the UK may not be generalisable to a UK population owing to differences in aetiological and cultural factors. Further studies would be useful to assess directly the prevalence of OAG overall and by the different risk factors deemed important for the UK.

The results of the review may be biased if the participation rates in the included studies are low. In this review, six of the 19 studies included did not provide information on participation rates. In addition, the majority of studies that provided this information did not give details about the characteristics of those who did not participate. This provides a potential for bias if the risk of glaucoma among responders is systematically different from that of non-responders. If non-responders were to be more likely to be glaucoma cases (perhaps because they do not see the benefit of entering the study), then this would lead to underestimation of the prevalence of OAG in the population.

The results of this systematic review must also be interpreted in light of the quality of the included observational studies. A validated checklist was not used to assess the quality of the included studies; instead, a set of fields had to be satisfied in order for a study to be considered good quality with no major flaws. The reason for this is that there are no validated checklists available to assess the quality of cross-sectional studies. Some may find this checklist compact and oversimplified. However, studies failing to provide details on eligibility criteria or where the credibility of study designs was questionable were excluded before the quality assessment stage. For example, a cohort study that did not demonstrate the outcome of interest would have been excluded with no further quality assessment conducted. Nevertheless, despite efforts to focus only on the best available data for some outcomes (e.g. risk of OAG by family history) B-rated studies had to be included because of the lack of available evidence. Furthermore, even where data were available they were not always reported in a format suitable for inclusion in the meta-analysis. For example, Anton and colleagues[99] evaluated the relationship of OAG to family history of glaucoma, but results were presented as a proportion of those with OAG who had a positive family history. No data were provided on the proportion of people with family history in the total sample and, hence, a relative risk could not be estimated.

One of the main difficulties in ascertaining an estimate of population prevalence and risk factors for developing OAG is the lack of a reference standard definition of OAG. Raised IOP is a risk factor for developing OAG, but does not define its presence or absence. In this review, studies were included using a definition of OAG based on glaucomatous visual field loss, but the definition of a glaucomatous visual field defect varied considerably across the studies. Perimetric methods for ascertaining glaucomatous visual field loss have evolved over time. The review included

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several studies conducted in the 1960s, and the studies used a range of criteria to define a positive test; therefore, the definition of a positive case may vary between observers and studies and account for some of the variation in prevalence rates between studies. Differential verification bias was likely in some of the included studies[28,64,106–108,110,112] in that only suspects on the initial screen went on to a more extensive reference standard examination, and therefore some of the cases may have been missed. Therefore, the prevalence may have been underestimated by these studies.

OAG and age

The association between OAG and age is very robust. All included studies show that the prevalence of OAG is higher in older age groups. One of the limitations in the calculation of a pooled estimate of prevalence in this review is the fact that the age cut-offs used were different to those reported in the included studies. In addition, specific age points (40, 50, 60, 70) were chosen rather than age ranges, and therefore the assumption that the prevalence is constant across a particular age range may not be a true representation.

OAG and ethnicity

Only one study included in the review reported data on the relationship between ethnicity and OAG.[114] The risk of having OAG for African-Americans was found to be approximately four times that for whites. OAG is not only more prevalent but also appears to be more severe in black than in white people. This is possibly because the onset of disease is earlier for black people than it is for white people.[114] The relative risk was not adjusted for other risk factors and should therefore be treated with caution. In addition, the UK African Caribbean Eye Survey reported that not only darker skin but also place of origin in Africa are associated with a significantly increased risk of disease.[120] The risk of glaucoma among black Africans was significantly higher than that in black Caribbeans. This study was, however, a B-rated study, in that it was based on a volunteer sample rather than a random sample of the population.

Studies conducted in Africa, South America and Asia were not included, as it was felt that the level of risk in these settings would not necessarily be representative of the risk observed in the same ethnic groups living in the UK. Prevalence rates as high as 13% and 16% have been observed in Congo[141] and Barbados.[142]

The increased risk associated with black ethnicity may be a function of the excess co-morbidities in these populations, including sickle cell disease, systemic hypertension and diabetes.[143] There may also be ethnic differences in optic disc morphology and an increased susceptibility at a given IOP level. However, there is likely to be heterogeneity within an ethnic population, and a common level of attributable risk to being of black ethnicity may not be appropriate for different geographical areas and subgroups within an ethnic group.[144]

People of Hispanic ethnicity are also at increased risk. In a large US population-based study of definite OAG in Latinos of Mexican ancestry, including more than 6000 participants who underwent a complete ophthalmic examination for determining glaucoma, the prevalence pattern of OAG was similar to that observed in those of black ethnic origin in the USA and significantly higher than in non-Hispanic whites.[145]

OAG and IOP

Across the included studies the proportion of people with OAG who had an IOP greater than 21 mmHg was consistently higher than among those who had an IOP less than 21 mmHg. Even though a clear association was found between OAG and high IOP, it is possible that this relationship could be stronger. The reason for this is that the included studies did not provide a separate IOP measurement for those participants who had previously detected glaucoma. It is very likely that these participants will be receiving pressure-lowering therapy, hence the possible underestimation of the prevalence of OAG among those with high IOP. One study provided sufficient data to calculate the relative risk based on previous undiagnosed cases.[127] The sample was small and the estimate was unadjusted for other risk factors and should therefore be treated with caution.

OAG and myopia

There is evidence that people with myopia are more likely to develop OAG. One of the greatest limitations in assessing the relationship between these two conditions is the lack of a consensus across the included studies on the definition of myopia. For example, in the Visual Impairment Project,[115] participants were classified as myopes when they had a refractive error worse than –0.5 D, whereas Grodum and colleagues[28] used a refractive error equal or worse than –2.0 D to classify myopes. In addition, differences in the definition of glaucoma may lead to an

underestimation of the prevalence of OAG among people with myopia. However, overdiagnosis of glaucoma among people with myopia may also be responsible for this association, because myopia is associated with a number of non-glaucomatous visual field defects and myopic discs can be difficult to assess for glaucomatous damage.[131] Owing to limited evidence it was not possible to estimate the risk of glaucoma in people with low and moderate myopia and therefore the pooled estimates should be treated with caution.

Structural differences in the myopic optic nerve may make myopic eyes more susceptible to glaucomatous damage.[129,131,146] Furthermore, glaucoma and myopia have a strong familial basis and therefore they may share a common genetic link.[129] A dose–response relationship between OAG and myopia has been postulated (the higher the myopia the more likely an individual would be to develop OAG). This relationship can be observed in the Blue Mountains Eye Study, reporting an odds ratio of 3.3 for those with moderate to high myopia (≥–3.0 D) compared with 2.3 in those with low myopia (≥–1.0 to <–3.0 D).[129]

OAG and diabetes

Currently available evidence suggests that there is a positive association between people with diabetes and OAG. The present study identified an increased risk of OAG in those with diabetes. These results are consistent with those of a meta-analysis performed in 2004 (OR 1.57; 95% CI 1.13 to 2.20).[147] This meta-analysis had variations in the eligibility criteria used to select studies compared with the present study. Bonovas and colleagues[147] included studies that did not establish diabetes through a clinical examination as well as studies that were conducted in African countries. These were excluded in the review reported in this chapter because, in order to avoid detection bias, exposure should be obtained from a secure record, and also because it is believed that the level of risk of OAG in people in countries of African descent is very different from that observed in other populations.

The results reported in this chapter are consistent with one population-based cohort study performed in Scotland,[102] and with one population-based cross-sectional study performed in England.[116] Ellis and colleagues[102] reported a risk ratio of 1.57 for diabetes, although this result was not statistically significant. This study was excluded from the analysis owing to inadequate methods used to select cases of glaucoma. Wormald and colleagues[120] reported a risk ratio of 2.2 for diabetes, but this result was also not statistically significant (95% CI 0.9 to 5.6). This study was excluded from the analysis because a volunteer sample was used rather than a random sample and therefore it is likely that a healthy volunteer effect was present in the results. The method of sampling is crucial to the avoidance of selection bias, and the observed increased risk in people with diabetes and myopia may reflect this type of bias, in that these groups may be more likely to be tested for glaucoma because they have regular eye tests for diabetic eye disease and for spectacle care for myopia. The impact of this bias would be to elevate artificially the relative risk of OAG.

OAG and family history

All studies identified indicated that an association exists between OAG and a positive family history. However, none of the included studies proved to be high quality (i.e. none was rated as 'A' in the quality assessment). There was no standardisation on the type of family history reported across the four included studies.[115,133–135] It is possible that the level of risk varies according to the type of family history. For example, Tielsch and colleagues[134] and Mitchell and colleagues[133] found some variability in the strength of the association by the type of family member, in which the strongest association was observed between siblings.

Most of the studies relied on verbal reporting of family history of glaucoma rather than a clinical examination of relatives of glaucoma cases, making results prone to misclassification. Such misclassification may be due to an underascertainment of glaucoma cases since the diagnostic criteria used for relatives may have been different from those used to diagnose the cases. Moreover, those who had a previous diagnosis of glaucoma are more likely to recall and therefore report a positive family history.[133,134] In the Rotterdam Study, attempts were made to minimise some of these biases by examining relatives of glaucoma cases. However, a small sample size led to wide confidence intervals surrounding the estimates, giving rise to a high degree of uncertainty.[135]

Even though an increased risk of glaucoma among people with a positive family history has been observed, the population attributable risk is low. This was estimated in two studies.[133,135] Both estimated a population attributable risk of approximately 16%, suggesting that other risk factors largely determine the occurrence of glaucoma in the population.

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Conclusions

Key points:

- This systematic review estimates the prevalence of OAG in a predominantly white population aged over 40 years to be 2.1% (95% CI 1.7 to 2.5). An estimated 67% of cases are not currently detected; a prevalence rate of 1.4% (95% CI 1.0 to 1.9) is estimated for those with previously undiagnosed disease.
- The overall prevalence of OAG by age ranges from 0.3 (95% CI 0.1 to 0.5) in people aged 40 years, increasing steeply to 3.3% (95% CI 2.5 to 4.0) in people aged 70 years.
- The incidence of glaucoma is estimated as ranging from 30 to 181 per 100,000 person-years for people aged 50 and 70 years, respectively.
- Approximately 569,000 people are affected by OAG, of whom 380,000 are undetected cases. The number of people with undetected disease steadily rises from 1800 at 40 years, reaching approximately 11,000 at 70 years of age. One can estimate that there are approximately 11,000 new cases of OAG per year.
- The risk of having glaucoma for those with IOP measurements 26 mmHg or greater is estimated to be 13 times higher than that for those with lower IOP.
- The onset of disease appears to be earlier for black people and the relative risk of OAG for people of black ethnicity compared with white people is estimated to be 3.80 (95% CI 2.56 to 5.64).
- There is almost twice the risk of OAG onset in people with diabetes compared with those without diabetes (RR 1.93, 95% CI 1.38 to 2.69).
- A positive family history of glaucoma is associated with OAG (RR 3.14, 95% CI 2.32 to 4.25). The strongest association is for siblings of an affected case.
- The proportion of people with OAG appeared to be higher in participants with myopia compared with those without myopia. The combined relative risk of OAG among participants with myopia compared with those without myopia was estimated to be 1.88 (95% CI 1.53 to 2.31).

Strengths and limitations:

- This comprehensive systematic review identified 19 eligible studies. Data were sparse for some of the review outcomes. For example, only one study provided data on the relationship between OAG and ethnicity. There were few data for the assessment of disease severity. Even though a number of studies reported family history, none of the included studies that contributed to an overall estimate was of high quality. Therefore, more accurate risk information is necessary for better estimates to be developed in relation to family history and ethnicity.
- An extensive literature search was conducted, but only published data in English were sought. It is possible that unpublished and non-English-language studies were missed, with the direction of effect in these studies being unknown.
- Strong associations between OAG and increased age, black ethnicity, high IOP, myopia, diabetes and family history are highlighted. However, the prevalence of glaucoma by certain risk factors may be overestimated, in particular when assessing family history, myopia and diabetes as potential risk factors, as these groups are more likely to have sight tests, and therefore may be more likely to have glaucoma diagnosed. Also, some studies did not adjust relative risk estimates to other risk factor variables.
- Risk factor and OAG definitions varied considerably, causing the exclusion of several studies because of poor reporting and inadequate criteria.

For future epidemiological studies, a standardised definition of OAG and improved reporting on how the suspects and definite cases received the reference standard diagnostic assessment are required. Efforts should be directed to create a collaborative group with the aim of standardising data such that the results can be presented and pooled with similar case definitions for similar populations. Ideally, prevalence studies should report IOP measurements for participants with newly diagnosed (i.e. untreated) glaucoma, to allow the determination of appropriate cut-offs for IOP as a diagnostic or prognostic indicator of OAG.

Chapter 6

Screening and diagnostic tests for open angle glaucoma

Introduction

There are many potential tests or combinations of tests for detecting glaucoma (see Chapter 3). To date, no single test or combination of tests has been identified as a definitive screening test for glaucoma.

The aim of this systematic review was to evaluate the accuracy of candidate screening tests and to provide details of the reliability of the tests and the proportion of people able to complete each test.

Methods

Inclusion and exclusion criteria

Types of study

The following types of study were included:

- direct (head-to-head) studies in which both index test(s), comparator test(s) and reference standard test are done independently in the same group of people
- RCTs in which people are randomised to the index and comparator test(s) and all receive the reference standard test.

Where there was insufficient evidence from direct studies and RCTs, indirect (between-study) comparisons were considered by meta-analysing studies that compared each single test or combination of tests with the reference standard test, and comparing the meta-analyses of the different tests. This type of study design, however, is less reliable than direct studies as differences in test accuracy are susceptible to confounding factors between studies. The following types of study were considered for the indirect comparisons:

- observational studies, including cohort studies, with analysis data on at least 100 participants, in which the sample is created by identifying all people presenting at the point of testing (without any reference to the test results)
- case–control studies in which two groups are created, one known to have the target disease and one known not to have the target disease, where it was reasonable to assume that all included had undergone the index and reference standard tests.

Population-based studies and studies in a primary care or hospital-based setting were considered where the participants were likely to be representative of a screening situation or of a glaucoma suspect population referred from a GP or an optometric practice. Case–control studies where the inclusion criteria were different for cases and controls were excluded; that is, studies comparing severely diseased people with very healthy controls or studies excluding people with other ocular disease such that the spectrum of disease and non-disease was unlike that to be encountered in a screening situation. Also excluded were case reports and studies investigating technical aspects of a test.

Target condition

The target condition was OAG (early, moderate or severe).

Participants

People over 40 years of age and those in the following higher risk subgroups were included:

- family history of glaucoma
- black race
- people with myopia
- people with diabetes.

The criteria for defining myopia and diabetes were loosely applied and definitions used by study authors for these conditions were considered acceptable.

Index and comparator test(s)

The tests to be considered fell within three broad categories:

- structure
  - ophthalmoscopy
  - optic disc photography (including non-digital and digital monoscopic and stereoscopic photography, and planimetric)

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  - RNFL photography
  - HRT version II
  - GDx VCC RNFL analyser (scanning laser polarimetry)
  - OCT
  - RTA
- function:
  - FDT
  - MDP
  - OKP
  - SWAP
  - white-on-white SAP, including suprathreshold and threshold
- IOP:
  - GAT
  - NCT
  - tonopen.

Comparisons both of individual and combinations of tests were considered.

Reference standard test

There is no optimal reference standard for the diagnosis of OAG or the classification of its severity. OAG is a clinical diagnosis, based on structural abnormalities of the optic disc and an associated glaucomatous visual field defect. Progressive structural optic neuropathy has been proposed as a reference standard.[148]

Either of two reference standard tests was considered. The primary reference standard test was confirmed OAG on follow-up. This was considered the best reference standard, although it was anticipated that few studies would use it. Therefore, also considered were studies where the reference standard was ophthalmologist-diagnosed OAG requiring treatment. This diagnosis can be based on an assessment of the visual field and/or the optic disc, but without follow-up confirmation. Each reference standard might include one or more of the screening tests against which it was being compared.

Studies using a technology-based diagnostic test(s) result alone as a reference standard were excluded.

Types of outcome

To be included, studies had to report relevant and interpretable data on one of more of the following types of outcome:

- the absolute numbers of true positives, false positives, false negatives and true negatives, or numbers from which they could be computed, such as the sensitivity and specificity values
- adverse events
- acceptability of the tests to those who receive them
- reliability of the tests.

If the evidence allowed, it was planned to assess test performance in early, moderate and severe glaucoma.

Data extraction strategy

Two reviewers (GM, MARS) 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 (GM, MARS) independently assessed them for inclusion. Any disagreements were resolved by consensus or arbitration by a third party (JB).

A data extraction form was developed and piloted. One reviewer (GM or MARS) extracted details of study design, participants, index, comparator and reference standard tests, participant flow and outcome data. In the event of any uncertainty, a second reviewer (GM or MARS) provided advice and validated the data extraction.

Quality assessment strategy

Quality assessment was performed using the QUADAS tool. QUADAS is a recently developed quality assessment tool for use in systematic reviews of diagnostic studies.[149] It was developed through a formal consensus method and was based on empirical evidence. The original QUADAS checklist contained 14 questions. The QUADAS tool was adapted to make it more applicable to assessing the quality of studies of tests for detecting OAG. (See Appendix 7 for an example of the modified checklist.)

Question 1 concerns the representativeness of the spectrum of people assessed by the test (question 1 of the original QUADAS checklist). This was split into two parts, depending on whether the study sample was (1) taken from an unscreened population with a glaucoma prevalence between >0 and 20% or (2) constructed from previously undiagnosed glaucoma patients but representative of those referred from primary care as suspect glaucoma. Case–control studies were assessed on the basis of whether the cases and controls could be regarded as representative of those detected in primary care.

Question 2, concerning the reference standard (question 3 of the original QUADAS checklist), was reworded to ask whether the reference standard was follow-up confirmation of glaucoma

(i.e. glaucoma confirmed clinically by the longitudinal follow-up of the patient), considered to be the best reference standard against which to measure tests for detecting OAG. Given the nature of the reference standard, the QUADAS question on whether the period between reference standard and index test was short enough to be reasonably sure that the target condition did not change between the two tests was omitted (question 4 of the original QUADAS checklist).

Questions 3 (partial verification bias), 4 (differential verification bias), 5 (incorporation bias), 6 (test review bias), 7 (diagnostic review bias) and 10 (withdrawals from the study) remained unchanged (questions 5, 6, 7, 10, 11 and 14 of the original QUADAS checklist). Partial verification bias occurs when not all of the study participants are verified by a reference standard. Differential verification bias happens when some of the patients receiving the index test are verified by a different reference standard. Incorporation bias occurs when the index test also forms part of the reference standard. Test review bias and diagnostic review bias happen when interpretation of the results of the index test is influenced by knowledge of the results of the reference standard, and vice versa.

It should be noted that in relation to incorporation bias (question 5), in glaucoma a situation may occur whereby the index test may be a test of visual function (e.g. FDT) and the reference standard may include a different test of visual function (e.g. SAP). In such cases question 5 was marked as incorporation bias avoided, taking the view that although both tests were of visual function they were actually different tests. However, in a situation such as this the sensitivity and specificity of the index test may be overestimated as the tests are measuring similar outcomes. The same situation may occur with different tests that assess the structure of the eye when one is the index test and one forms part of the reference standard, e.g. HRT II and ophthalmoscopy.

Question 8 is concerned with whether the same clinical data were available when the test results were interpreted as would be available when the test is used in practice (question 12 of the original QUADAS checklist). This question was split into two parts, depending on whether the study was a screening or diagnostic accuracy study. It was assumed that in a screening situation in practice the index test results alone would be used, but that for studies of diagnostic test accuracy (cohort or case–control) in practice information from ophthalmic examination and/or information on co-morbidity might be used.

Question 9 concerns the reporting of numbers of uninterpretable/intermediate test results (question 13 of the original QUADAS checklist). If uninterpretable/intermediate results occur but are not reported then this may lead to a biased assessment of the test characteristics. Therefore, this question was retained and also amended to include whether incomplete tests were reported.

Items relating to the quality of reporting in terms of the description of the selection criteria, the execution of the index test, and the execution of the reference standard test were omitted (questions 2, 8 and 9 of the original QUADAS checklist). Three questions were added to the checklist on whether the technology of the index test was still current (question 11), whether the study provided a clear definition of what was considered a positive result (question 12), and whether the definition of a positive test result was determined before the study was carried out (question 13).

Two reviewers (GM, MARS) independently assessed the quality of all included studies using the modified version of QUADAS. Each of the 13 questions was checked as 'Yes', 'No' or 'Unclear'. Each item was worded so that a rating of 'Yes' was always optimal in terms of methodological quality. Any disagreements were resolved by consensus or arbitration by a third party (JB). A 'higher quality' study was considered to be one that was checked as 'Yes' to questions 1 (patient spectrum representative), 3 and 4 (partial and differential verification bias avoided) and 6 and 7 (test review bias and diagnostic review bias avoided). Sensitivity analysis was planned to assess whether the results for higher quality studies differed systematically from those of the other included studies.

Data analysis

The results of the individual studies were tabulated and sensitivity, specificity, and diagnostic odds ratios (DORs) calculated. A DOR combines sensitivity and specificity into a single summary of diagnostic performance. If more than one threshold level was reported in a given study a separate 2×2 table was derived for each threshold. Separate 2×2 tables were also produced for relevant subgroups considered in the studies.

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Relative diagnostic odds ratios (RDORs) were calculated for studies comparing two or more tests in the same participants. A 95% confidence interval was calculated under the assumption of two independent groups which will be conservative. Insufficient data were reported, however, to allow a paired analysis to be undertaken.

Summary performance of each test

Summary receiver operating characteristic (SROC) curves were produced for each test where two or more studies reported estimates of sensitivity and specificity. A second set of SROC curves was also produced for a test-specific common cut-off. From each study reporting each test, a cut-off was chosen (the common cut-off) from among the various cut-offs reported. The aim was to select a cut-off that was broadly similar across studies reporting that test. The decision on which cut-off to select was made following discussion by two ophthalmologists (JB and RS). Owing to the limited number of studies identified, statistical investigation of the potential sources of heterogeneity was not undertaken. The *F* distribution method was used for calculating the confidence intervals for sensitivity and specificity for individual studies,[150] which were produced using Metadisc software.[151]

Meta-analysis models were fitted using the hierarchical summary receiver operating characteristic (HSROC) model[152] in WinBUGS 1.4.[153] This model 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 and DORs for each model were reported as median and 95% credible interval (CrI). Credible intervals are the Bayesian equivalent of confidence intervals. Where two or more higher quality studies were available for a test, a model using only these studies was also fitted. A simplified model, which assumed a symmetrical SROC shape, was used where limited data caused convergence problems under the full model.

Indirect comparison between tests

All tests with two or more included studies were modelled together in a single HSROC model to compare formally the performance of the tests. A symmetrical SROC model was assumed for all the tests. Pairwise differences in sensitivity and specificity between tests were assessed from the median difference and the corresponding 95% credible interval.

Results

Number and type of studies included

Appendix 8 lists the 82 studies published in 93 reports that were included.

Accuracy

Forty studies, published in 46 reports, met the inclusion criteria for the screening and diagnostic accuracy review. There were 20 population-based studies representative of a screening setting.[21,72,99,100,106,112,115,154–170] Twenty studies were representative of a glaucoma suspect population referred from primary care, of which eight were cohort studies[22,171–177] and 12 were case–control studies.[178–191]

Uptake, interpretability, time taken to do test and reliability of test

In addition to the studies included in the review of screening and diagnostic test accuracy that contributed information on uptake, interpretability of tests, time taken to do the test and reliability of the test, 47 reports also provided data on these aspects. These studies did not provide usable outcome data in terms of test accuracy, but otherwise met the review's inclusion criteria.[107,109,110,132,192–234] Information on uptake, interpretability and time taken to do the test is given in the results section for each test, while those studies reporting reliability are listed in Appendix 9.

Number and type of studies excluded, with reasons for specific exclusions

For the screening and diagnostic accuracy review, 5918 titles and abstracts from the specific and general searches were screened, from which 877 were selected for full-text assessment. Articles were excluded because they failed to meet one or more of the specified inclusion criteria in terms of study design, participants, index tests, reference standard or outcomes reported. Fifty-seven of the full-text reports excluded were case–control studies whose participants were considered to be unrepresentative of those who would attend for screening and are listed in Appendix 10.

Tabulation of quality of studies, characteristics of studies and evidence rating

Quality of studies

The results of the quality assessment for the individual studies are shown in Appendix 11. The quality assessment of studies reporting the various tests is discussed in the results section for each test.

TABLE 17 *Uptake reported by population-based studies*

Study	Eligible	Attended	%
Anton, 2004[99] (Segovia Study)	569	510	89.6
Bengtsson, 1980[100] (Dalby Population Survey)	1,938	1,511	78.0
Bonomi, 2001[106] (Egna–Neumarkt Study)	5,816	4,237	72.9
Cedrone, 1997[107]	1,226	1,034	84.3
Christoffersen, 1995[154]	196	195	99.5
Ekstrom, 1996[109] (Tierp Glaucoma Survey)	838	760	90.7
Hollows, 1966[21] (Rhondda Valley Study)	4,608	4,231	91.8
Ivers, 2001[157] (Blue Mountains Eye Study)	4,433	3,654	82.4
Jonasson, 2003[110] (Reykjavik Eye Study)	1,379	1,045	75.8
Katz, 1993[159] (Baltimore Eye Survey)	6,705	5,308	79.2
Klein, 1994[132] (Beaver Dam Eye Study)	5,924	4,926	83.2
Kozobolis, 2000[112] (Crete, Greece Glaucoma Study)	1,300	1,107	85.2
Leibowitz, 1980[22] (Framingham Eye Study)	3,977	2,631	66.2
Robin, 2005[163]	2,486	704	28.3
Vernon, 1990[164]	988	874	88.5
Wang, 1998[168]	530	405	76.4
Weih, 2001[115] (Visual Impairment Project)	5,520	4,744	85.9
Wolfs, 1999[169] (Rotterdam Study)	10,275	6,777	66.0
Total	58,708	44,653	76.1

Characteristics of studies

Appendix 12 provides details of the characteristics of the included studies.

The 40 studies enrolled over 48,000 people, with over 39,000 included in the analysis. The earliest study took place in 1963[21] and the latest in 2003/04,[156,176] while 21 studies gave no indication of the period in which they were carried out. Thirteen studies took place in the USA,[22,158,159,162,166,168,170,172,175,181,187–189] nine in the UK,[21,164,176,177,180,182,186,190,191] four in Australia,[115,157,163,173] two each in Italy,[106,174] The Netherlands,[169,183] Spain[99,179] and Sweden,[100,171] one each in Belgium,[155] Canada,[156] Greece,[112] India[161] and Norway,[154] and one in Canada and Finland.[178] Twenty-six studies gave details of the gender of their participants, 51% of whom were women.[21,22,99,106,112,115,154–157,159,161–164,166,168,170,171,173–176,183,186,188] The median age of the participants across studies was 60.5 years, with an age range from 13 years[183] to 97 years.[155,157]

The reports included a number of major population-based prevalence surveys, such as the Baltimore Eye Survey,[72,159] the Blue Mountains Eye Study,[157] the Crete, Greece Glaucoma Study,[112] the Dalby Population Survey,[100] the Egna–Neumarkt Study,[106] the Framingham Eye Study,[22] the Glaucoma Screening Study (GLASS),[158,160] the Groningen Longitudinal Glaucoma Study,[183–185] the Rhondda Valley Study,[21] the Rotterdam Study,[169] the Segovia Study[99] and the Visual Impairment Project.[115]

The included studies reported the following tests: ophthalmoscopy,[115,163,164,168,172,177,191] optic disc photography,[166,169,175,188–190] RNFL photography,[167,178,188,189] HRT II,[156,163,186] OKP,[154,170,180,182] SAP,[157–159,162–164,166,168,174,176,179,181,182,186] FDT,[155,161,163,170,173,176,183–185,187] GAT,[21,22,99,100,106,112,157,168,171] and NCT.[164,165] No studies of GDx VCC, OCT, RTA, SWAP, MDP or Tonopen met the inclusion criteria in terms of reporting of test accuracy outcomes.

Eighteen population-based studies reported uptake (the percentage of those eligible for screening who actually attended).[21,22,99,100,106,107,109,110,112,115,132,154,157,159,163,164,168,169] Out of a total of 58,708 eligible people, 44,653 (76.1%) attended for screening (median 82.8%, range 28.3–99.5%) (*Table 17*). Fifteen of these studies are included in the screening and diagnostic accuracy review. Three others failed to meet the review's inclusion criteria in terms of test accuracy outcomes, but as they provided data on uptake they have also been included in the table.[107,110,132]

Tabulation of results

Tests of structure

Ophthalmoscopy

Quality assessment

Seven studies enrolling 7279 people reported the test accuracy of ophthalmoscopy, including four population-based studies,[115,163,164,168] two cohort studies[172,177] and one case–control study.[191] *Figure 16* summarises the quality assessment for

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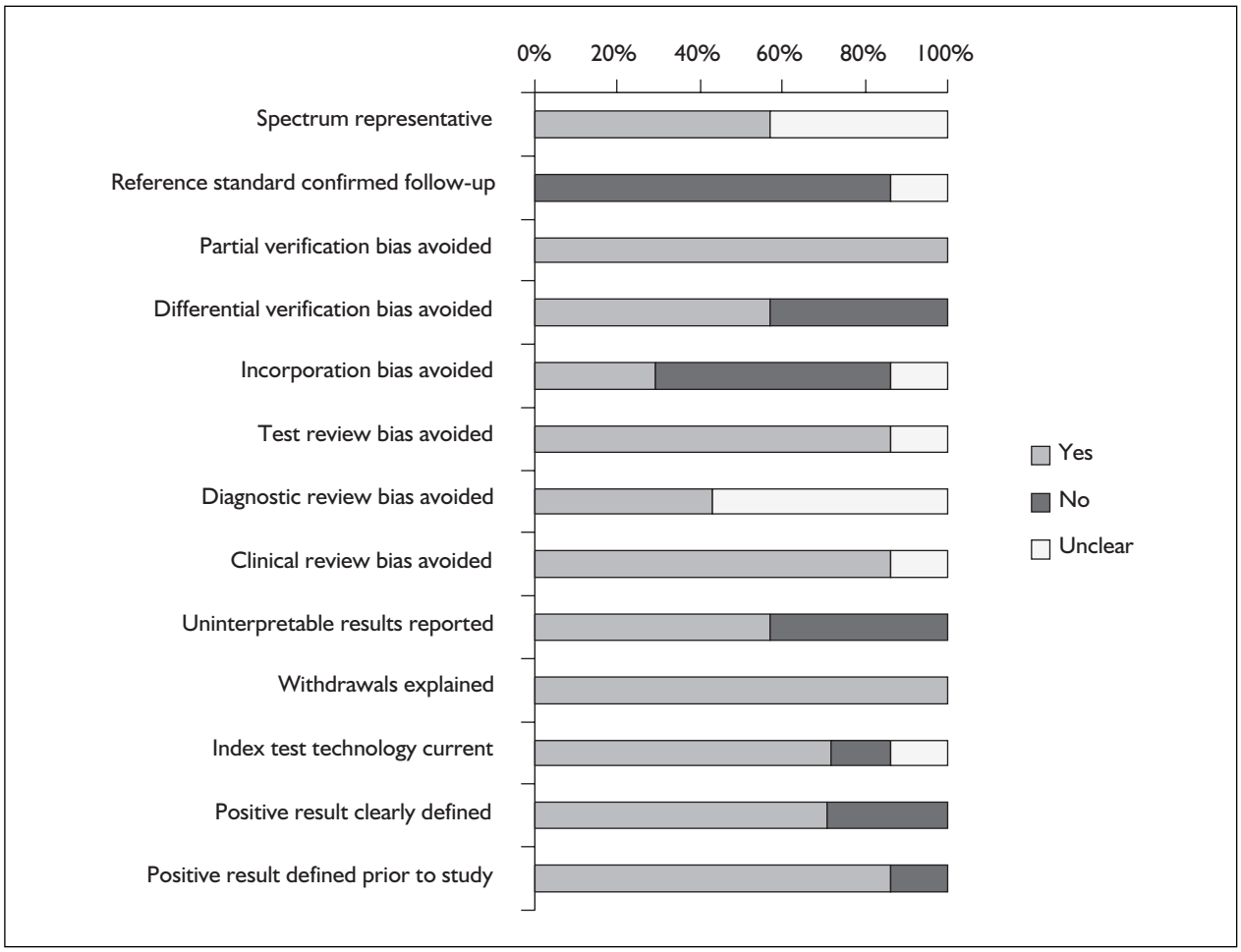

FIGURE 16 *Ophthalmoscopy: summary of quality assessment*

these studies. In four of the seven studies the participants were considered to be representative of a screening setting.[115,163,164,168] Four studies were judged to be free from both partial and differential verification bias.[163,172,177,191] In three of the seven studies both the index test and the reference standard test were interpreted without knowledge of each other's results.[115,163,191] Only the study by Robin and colleagues[163] met all criteria specified for higher quality studies.

Accuracy

Figure 17(c) shows the sensitivity and specificity, with 95% confidence intervals, for the five studies reporting ophthalmoscopy at a common cut-off (for details of the common cut-off selected for ophthalmoscopy see Appendix 13). There was statistically significant heterogeneity across the studies, most obviously due to the study by Theodossiades and colleagues in terms of sensitivity[177] and Theodossiades and colleagues[177] and Wood and colleagues[191] in terms of specificity. Both were small studies using subjective criteria to detect suspect discs in an already suspect population, one being a cohort study[177] and the other a case–control study.[191] In both studies it was unclear whether the spectrum of people was representative of those who would be encountered in primary care. The study by Wood and colleagues[191] was specifically aimed at identifying people with early/moderate glaucoma.

Figure 17(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 11% (cut-off of VCDR $\geq$ 0.9)[163] to 100% (cut-off of VCDR $\geq$ 0.4),[163] while specificity ranged from 57% (cut-off of VCDR $\geq$ 0.4)[163] to 99% (discs subjectively graded as normal or suspicious).[164] For the common cut-off, sensitivity ranged from 41%[115] to 91%,[177] while specificity ranged from 74%[177] to 99%.[164] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 60% (95% CrI 34 to 82%), 94% (95% CrI 76 to 99%) and 25.70 (95% CrI 5.79 to 109.50), respectively (*Figure 17d*).

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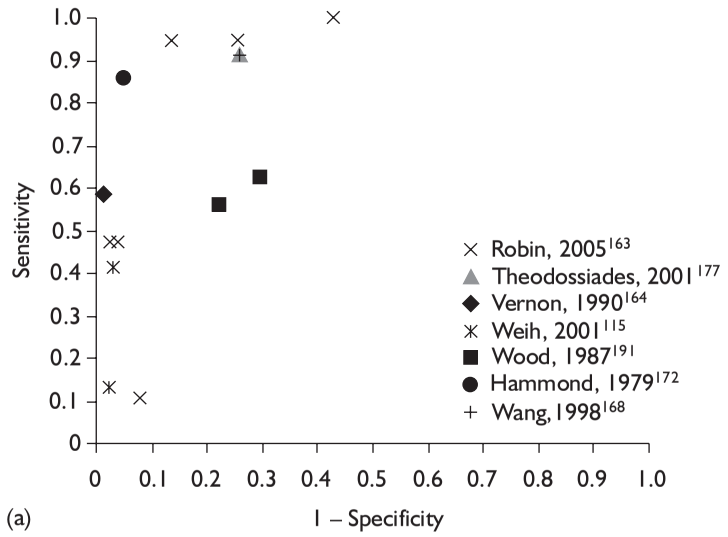

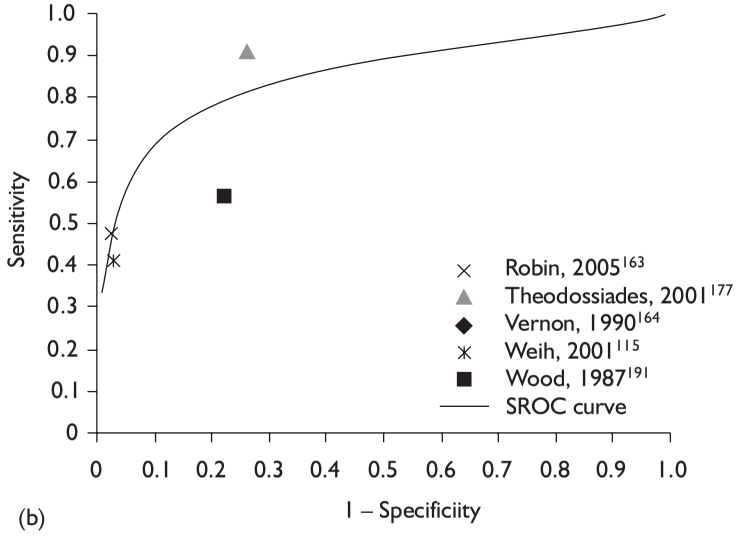

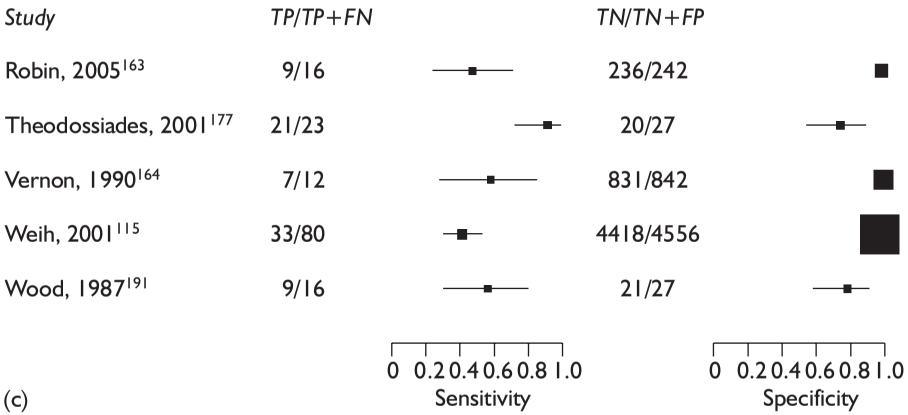

Common cut-off

Number of studies	5
Sensitivity (%) (95% CrI)	60 (34 to 82)
Specificity (%) (95% CrI)	94 (76 to 99)
DOR (95% CrI)	25.70 (5.79 to 109.50)

Higher quality studies

Number of studies	1
Sensitivity (%) (95% CrI)	47 (24 to 71)
Specificity (%) (95% CrI)	98 (95 to 99)
DOR (95% CrI)	35.40 (10.54 to 118.88)

(d)

FIGURE 17 *Ophthalmoscopy: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

TABLE 18 *Type of ophthalmoscopy used*

Study	Type of ophthalmoscopy	Pupils dilated?	Clinical experience of those giving/interpreting the tests
Robin, 2005[163]	Slit-lamp biomicroscopy	Not stated	Not stated
Vernon, 1990[164]	Direct ophthalmoscopy	Undilated	Experienced ophthalmologist
Wang, 1998[168]	Direct ophthalmoscopy	Dilated	Not stated
Weih, 2001[115]	Slit-lamp	Dilated	Trained clinician
Hammond, 1979[172]	Direct ophthalmoscopy	Undilated	Nurses skilled in the use of the ophthalmoscope
Theodossiades, 2001[177]	Direct ophthalmoscopy	Undilated	Not stated (optometrists)
Wood, 1987[191]	Direct ophthalmoscopy	Dilated	Not stated (ophthalmologists)

Table 18 shows, where this information was reported, the type of ophthalmoscopy undertaken, whether or not participants' pupils were dilated and the clinical experience of those giving the tests.

Interpretable results
Ten population-based studies reported that 13,341 (98.0%) of 13,620 participants provided interpretable test results for ophthalmoscopy,[22,100,107,109,112,115,161,163,164,168] while three prospective cohort studies reported that 278 (90.0%) of 309 participants provided interpretable test results,[172,177,200] giving an overall rate of 97.8% for all studies. None of the studies gave details of the time taken to perform the test.

Optic disc photography
Quality assessment
Six studies enrolling over 7800 people reported the test accuracy of optic disc photography, including two population-based studies,[166,169] one cohort study[175] and three case–control studies.[188–190] *Figure 18* summarises the quality assessment for these studies. In four of the six studies the participants were considered to be representative of a screening setting[166,169] or diagnostic setting[175,188] (i.e. people referred from primary care with suspect glaucoma). Five of the six studies were judged to be free from both partial and differential verification bias.[166,169,175,188,189] In four studies both the index test and the reference standard test were interpreted without knowledge of each other's results.[166,169,175,190] The studies by Vitale and colleagues,[166] Wolfs and colleagues[169] and Schultz and colleagues[175] met all of the above criteria specified for higher quality studies.

Accuracy
Figure 19(c) shows the sensitivity and specificity, with 95% confidence intervals, for the six studies reporting optic disc photography at a common cut-off (for details of the common cut-off selected for optic disc photography see Appendix 13). The study by Wollstein and colleagues[190] aimed to detect early-stage glaucoma.

Figure 19(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 35% (cut-off of concave slopes and CDR $\geq$ 0.05 in the vertical than horizontal direction)[189] to 86% (cut-off of VCDR $\geq$ 0.5),[175] while specificity ranged from 59% (cutoff of VCDR $\geq$ 0.59)[166] to 99.5% (cut-off of concave slopes and CDR $\geq$ 0.05 in the vertical than horizontal direction).[189] For the common cutoff, sensitivity ranged from 65%[175] to 77%,[166,188] while specificity ranged from 59%[166] to 98%.[175] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 73% (95% CrI 61 to 83%), 89% (95% CrI 50 to 99%) and 21.74 (95% CrI 3.07 to 148.30), respectively (*Figure 19d*).

Table 19 shows, where this information was reported, details of the optic disc photography, whether or not participants' pupils were dilated and the clinical experience of those giving the tests.

Interpretable results
Seven population-based studies reported that 16,957 (85.0%) of 19,950 participants provided interpretable test results for optic disc photography,[110,155,157,159,166,168,169] while four prospective cohort studies reported that 499 (89.7%) of 556 participants provided interpretable test results,[175,202,207,209] giving an overall rate for all studies of 85.1%. One study reported that the average test duration was 16 minutes per eye (image acquisition and recording requiring

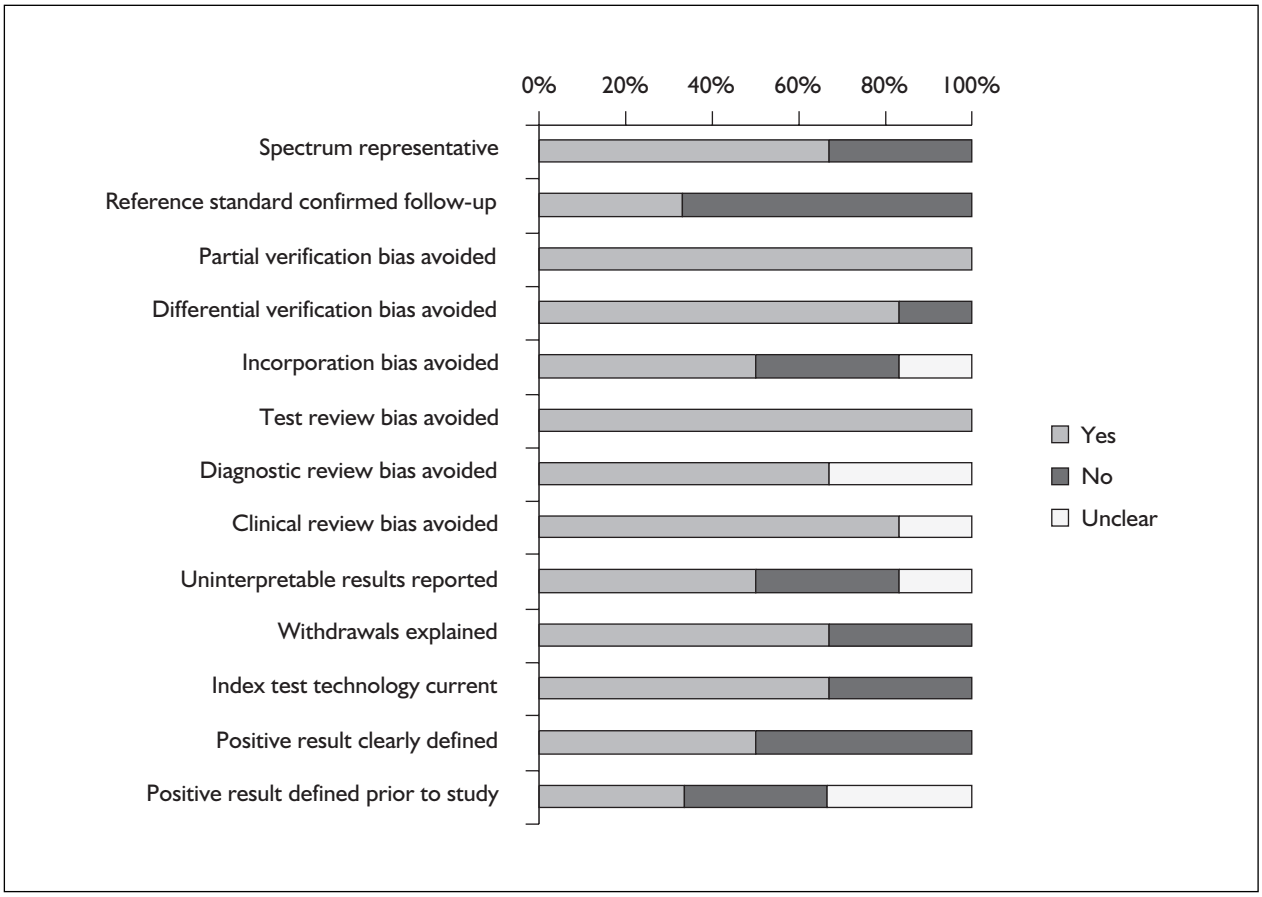

FIGURE 18 *Optic disc photography: summary of quality assessment*

TABLE 19 *Details of optic disc photography*

Study	Type of optic disc photography	Pupils dilated?	Experience of those giving/interpreting the tests
Vitale, 2000[166]	Topcon ImageNet simultaneous stereophotography	Dilated	Technicians with considerable experience carried out the tests
Wolfs, 1999[169]	Topcon TRC-SS2 simultaneous stereophotography	Dilated	Transparencies digitised and analysed by technicians
Quigley, 1980[188]	Colour stereophotographs placed in a stereoviewer	Not stated	Not stated
Schultz, 1995[175]	NIDEK fundus camera for stereophotographs using Kodak Gold 100 35-mm negative film. Also stereo slide transparencies obtained using 35-mm Ektachrome 100 film and examined through a stereoviewer	Dilated	Photographs examined by third-year ophthalmology residents
Sommer, 1979[189]	Colour stereophotographs	Not stated	Not stated
Wollstein, 2000[190]	Canon CF6OU colour non-simultaneous stereophotographs using 35-mm Kodak Ektachrome 150 film	Not stated	Taken by trained technicians, interpreted by experienced observers (glaucoma consultants, glaucoma fellow, clinical glaucoma technician)

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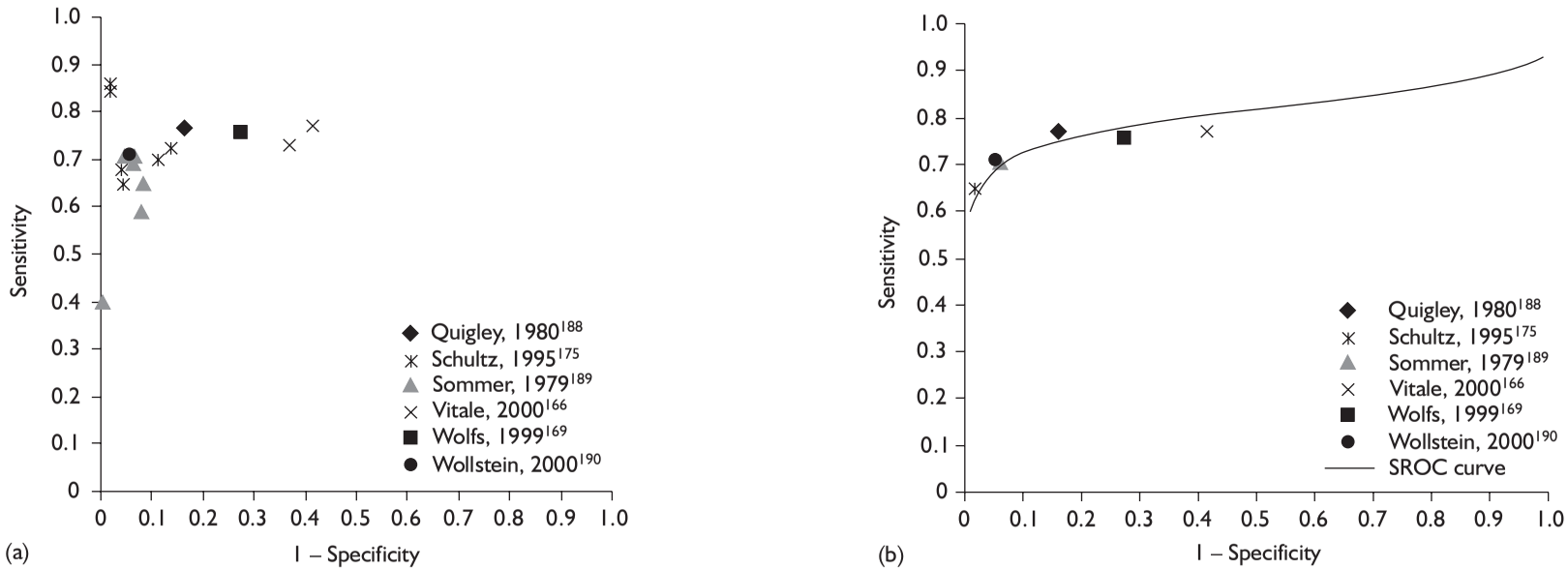

Study	*TP/TP+FN*	*TN/TN+FP*
Quigley, 1980[188]	43/56	200/238
Schultz, 1995[175]	89/137	224/228
Sommer, 1979[189]	12/17	193/206
Vitale, 2000[166]	34/44	81/138
Wolfs, 1999[169]	28/37	3712/5106
Wollstein, 2000[190]	36/51	68/72

0 0.2 0.4 0.6 0.8 1.0 Sensitivity

0 0.2 0.4 0.6 0.8 1.0 Specificity

(c)

Common cut-off	
Number of studies	6
Sensitivity (%) (95% CrI)	73 (61 to 83)
Specificity (%) (95% CrI)	89 (50 to 99)
DOR (95% CrI)	21.74 (3.07 to 148.30)
High-quality studies	
Number of studies	3
Sensitivity (%) (95% CrI)[a]	74 (30 to 95)
Specificity (%) (95% CrI)[a]	82 (45 to 97)
DOR (95% CrI)[a]	13.08 (2.22 to 100.90)

(d)

FIGURE 19 *Optic disc photography: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.* [a] *Based on HSROC model with symmetric SROC curve.*

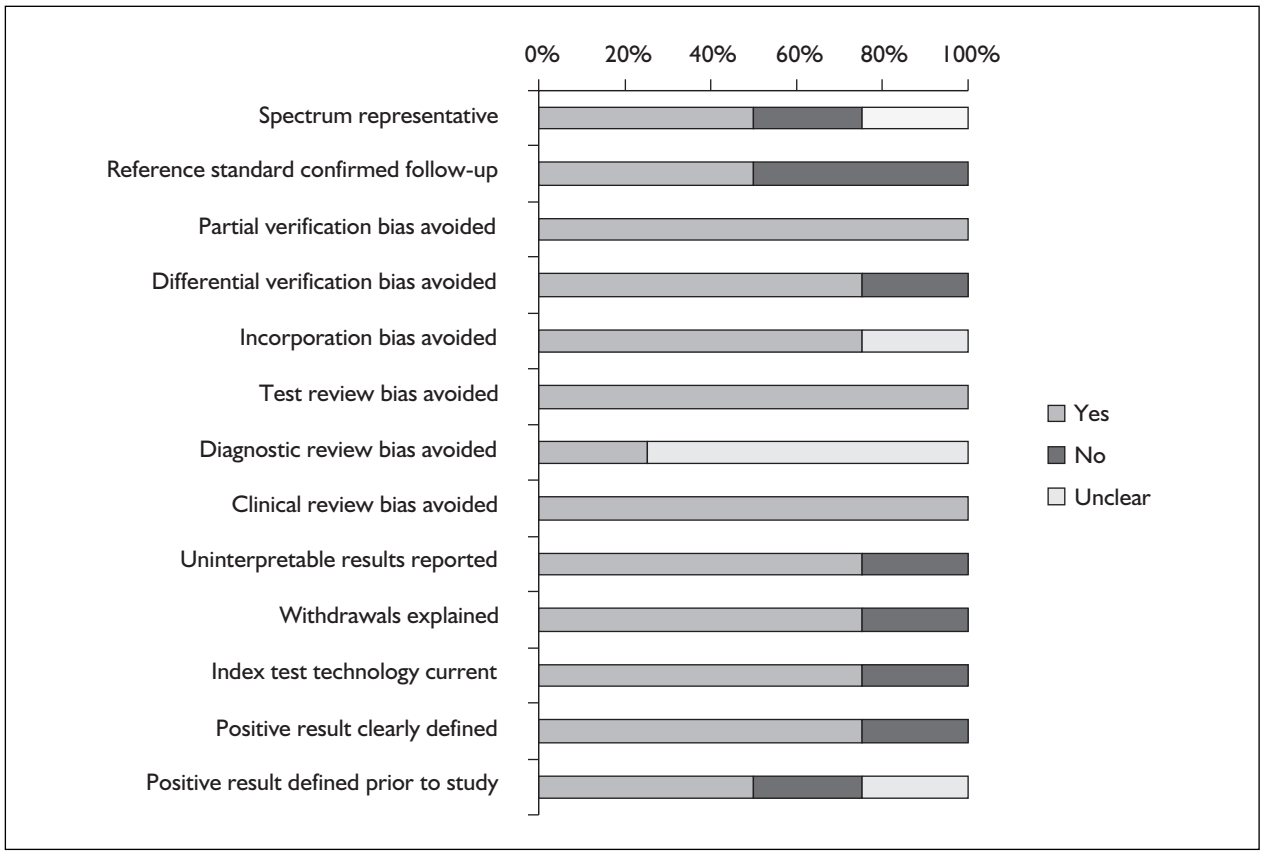

FIGURE 20 *RNFL: summary of quality assessment*

approximately 4 minutes per eye, after which time the presence of the patient was no longer required, with subsequent calculations of topographical and pallor parameters requiring approximately 12 minutes per eye).[197]

RNFL photography

Quality assessment

Four studies enrolling over 700 people reported the test accuracy of RNFL photography, including one population-based study[167] and three case–control studies.[178,188,189] *Figure 20* summarises the quality assessment for these studies. In two of the four studies the participants were considered to be representative of a screening[167] or diagnostic[188] setting. Three studies were judged to be free from both partial and differential verification bias.[178,188,189] In one study both the index test and the reference standard test were interpreted without knowledge of each other's results.[178] No study met all the criteria specified for higher quality studies.

Accuracy

Figure 21(c) shows the sensitivity and specificity, with 95% confidence intervals, for the four studies reporting RNFL photography at a common cut-off (for details of the common cut-off selected for RNFL photography see Appendix 13). Three studies were set in the USA.[167,188,189] The study by Airaksinen and colleagues[178] appeared to have a joint setting of Canada and Finland and it was unclear whether the spectrum of people was representative of those who would be encountered in primary care.

Figure 21(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. Both for all cut-offs and the common cut-off, sensitivity ranged from 59%[189] to 94%,[178] while specificity ranged from 60%[178] to 98%.[189] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 75% (95% CrI 46 to 92%), 88% (95% CrI 53 to 98%) and 23.10 (95% CrI 4.41 to 123.50), respectively (*Figure 21d*).

Interpretable results

One population-based study reported that 136 (79.5%) of 171 participants provided interpretable test results for RNFL photography.[167] None of the studies reported the time taken to perform the test, but it is likely to be similar to optic disc photography.

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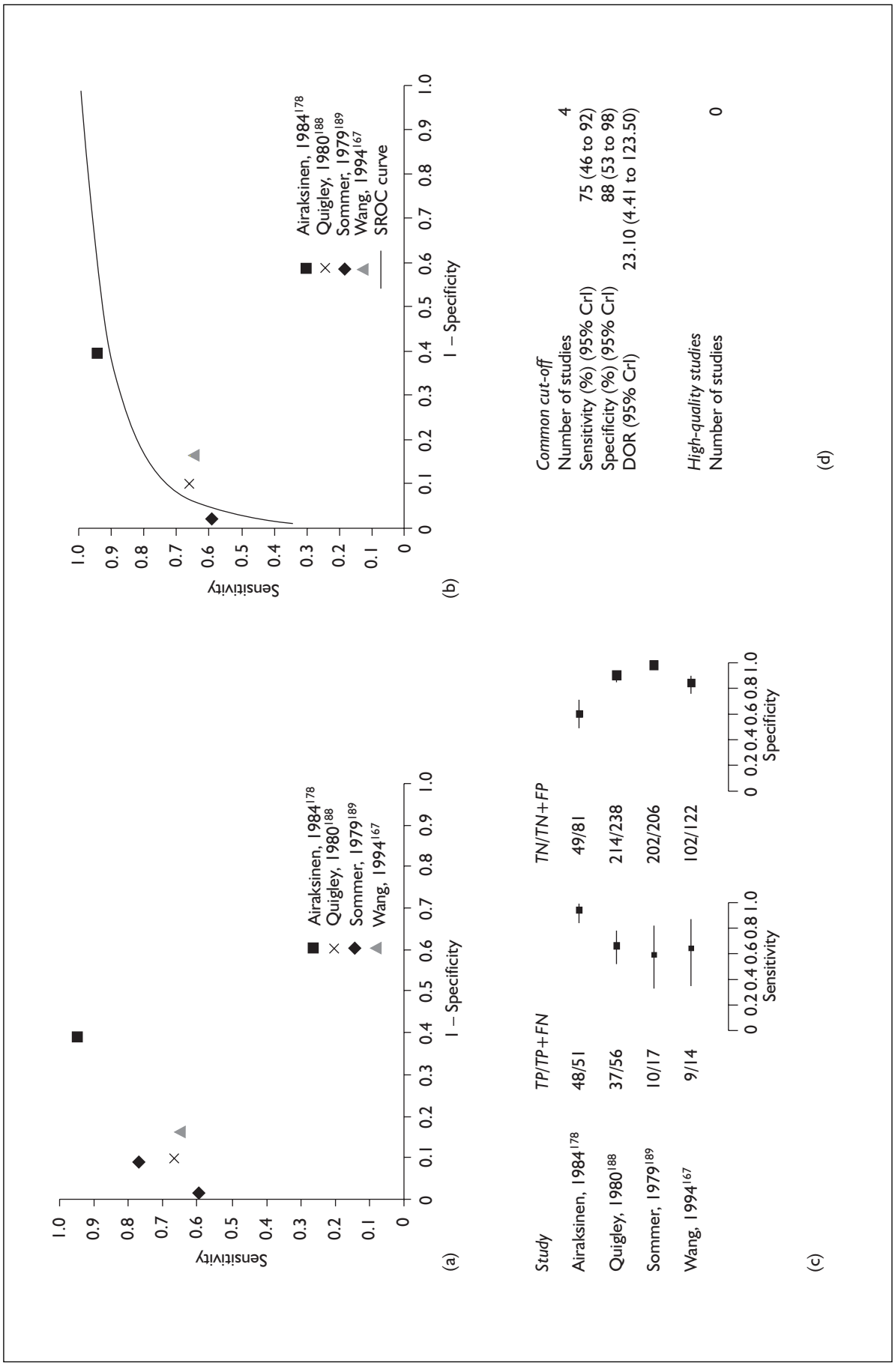

FIGURE 21 *RNFL photography: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

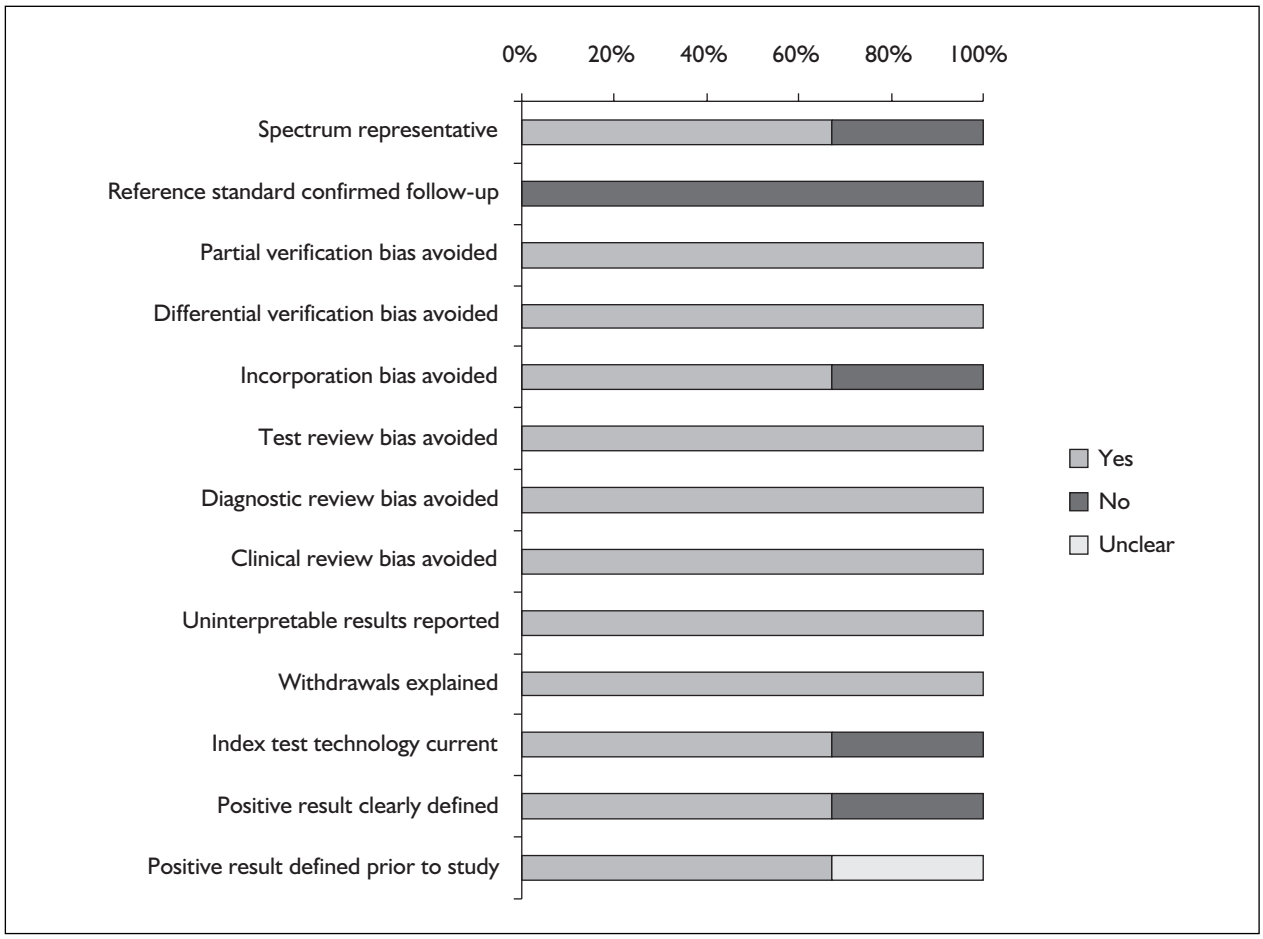

FIGURE 22 *HRT II: summary of quality assessment*

HRT II

Quality assessment

Three studies enrolling 1073 people reported the test accuracy of HRT II, including two population-based studies,[156,163] and one case–control study.[186] *Figure 22* summarises the quality assessment for these studies. In the studies by Harasymowycz and colleagues[156] and Robin and colleagues[163] the participants were considered to be representative of a screening setting. All three studies were judged to be free from both partial and differential verification bias.[156,163,186] In all three studies the index test and the reference standard test were interpreted without knowledge of each other's results.[156,163,186] The studies by Harasymowycz and colleagues[156] and Robin and colleagues[163] met the criteria specified for higher quality studies.

Accuracy

Figure 23(c) shows the sensitivity and specificity, with 95% confidence intervals, for the three studies reporting HRT II at a common cut-off (for details of the common cut-off selected for HRT II see Appendix 13). In the population-based studies by Harasymowycz and colleagues[156] and Robin and colleagues[163] the tests were carried out by an ophthalmic photographer and "appropriately trained staff", respectively, while in the case–control study by Ieong and colleagues[186] the tests were carried out by optometrists and early-stage glaucoma was targeted. The study by Harasymowycz and colleagues[156] focused on groups at high risk of developing glaucoma (people of Caribbean or African descent, or older than 50 years of age, or with a family history of OAG).

Figure 23(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 69%[186] to 100%,[156] while specificity ranged from 81%[163] to 95%.[186] For the common cut-off, sensitivity ranged from 69%[186] to 95%,[163] while specificity ranged from 81%[163] to 95%.[186] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 86% (95% CrI 55 to 97%), 89% (95% CrI 66 to

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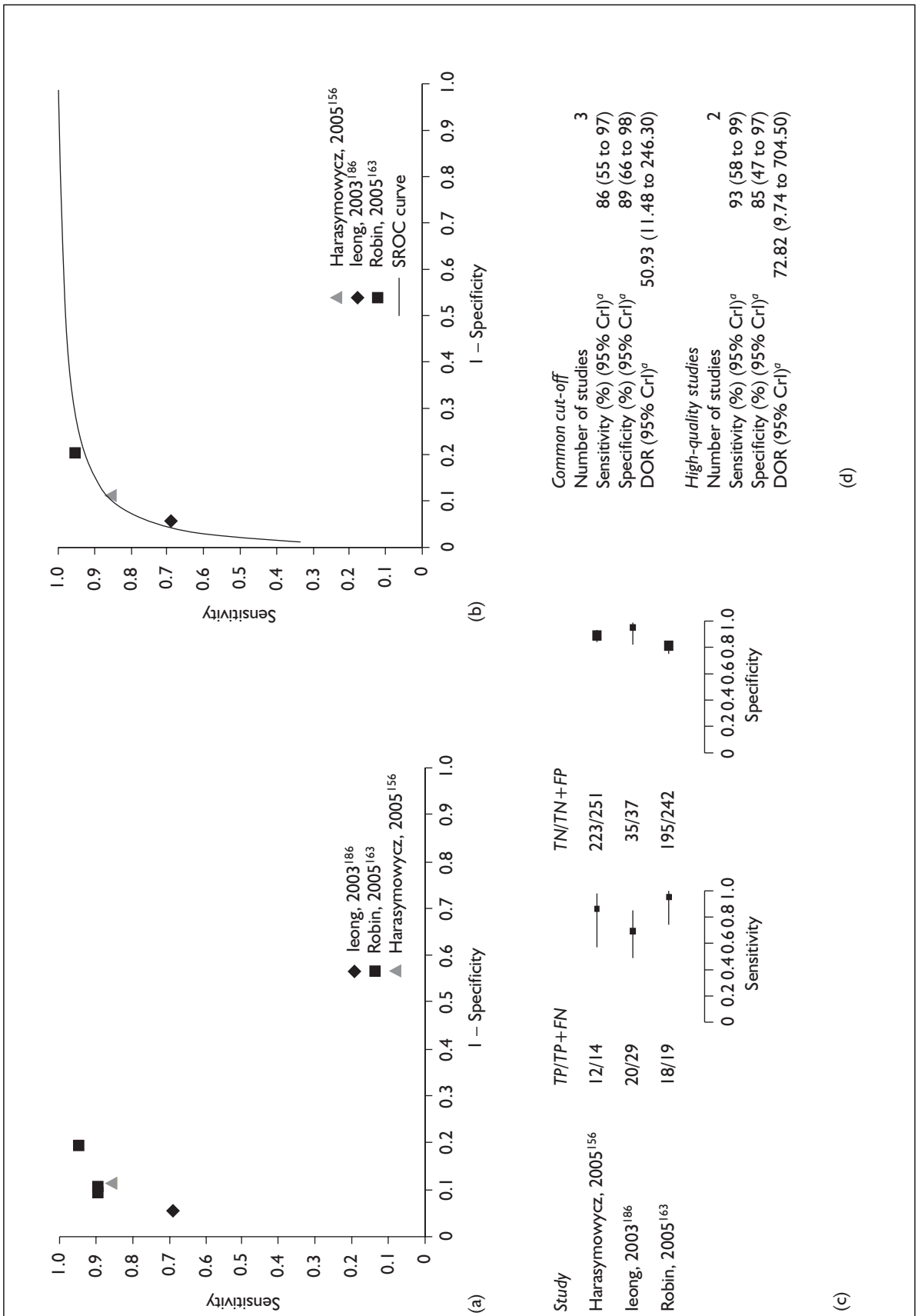

FIGURE 23 *HRT II: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.* [a] *Based on HSROC model with symmetric SROC curve.*

98%) and 50.93 (95% CrI 11.48 to 246.30), respectively (*Figure 23d*).

Interpretable results
Two population-based studies reported that 536 (94.2%) of 569 participants provided interpretable test results for HRT II.[156,163] None of the studies reported the time taken to perform the test.

Tests of function

FDT (C-20-1)

Quality assessment
Three studies involving 575 people reported the test accuracy of the FDT C-20-1 test, including one population-based study[170] and two case–control studies.[185,187] *Figure 24* summarises the quality assessment for these studies. In two of the three studies the participants were considered to be representative of a screening[170] or diagnostic[185] setting. The study by Yamada and colleagues[170] was the only one judged to be free from both partial and differential verification bias and also the only one in which both the index test and the reference standard test were interpreted without knowledge of each other's results, thereby meeting the criteria specified for higher quality studies.

Accuracy
Figure 25(c) shows the sensitivity and specificity, with 95% confidence intervals, for the three studies reporting FDT C-20-1 at a common cut-off (for details of the common cut-off selected for FDT C-20-1 see Appendix 13). The heterogeneity in terms of specificity is mainly due to the high value reported by Johnson and colleagues.[187] In this study both eyes of normal participants (mean age 46 years) and one eye of participants with glaucoma (mean age 64 years) were tested.

Figure 25(a) and *(b)* show, respectively, the SROC plots for all cut-offs with multiple abnormal test points for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 65% at five abnormal test points[185] to 93% at one abnormal test point,[187] while specificity ranged from 86% at one abnormal test point[170] to 100% at one abnormal test point, two abnormal test points or two clustered abnormal test points.[187] For a common cut-off of one abnormal test point, sensitivity ranged from 91%[185] to 93%,[187] while specificity ranged from 86%[170] to 100%.[187] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 92% (95% CrI 65 to 95%), 94% (95% CrI 73 to

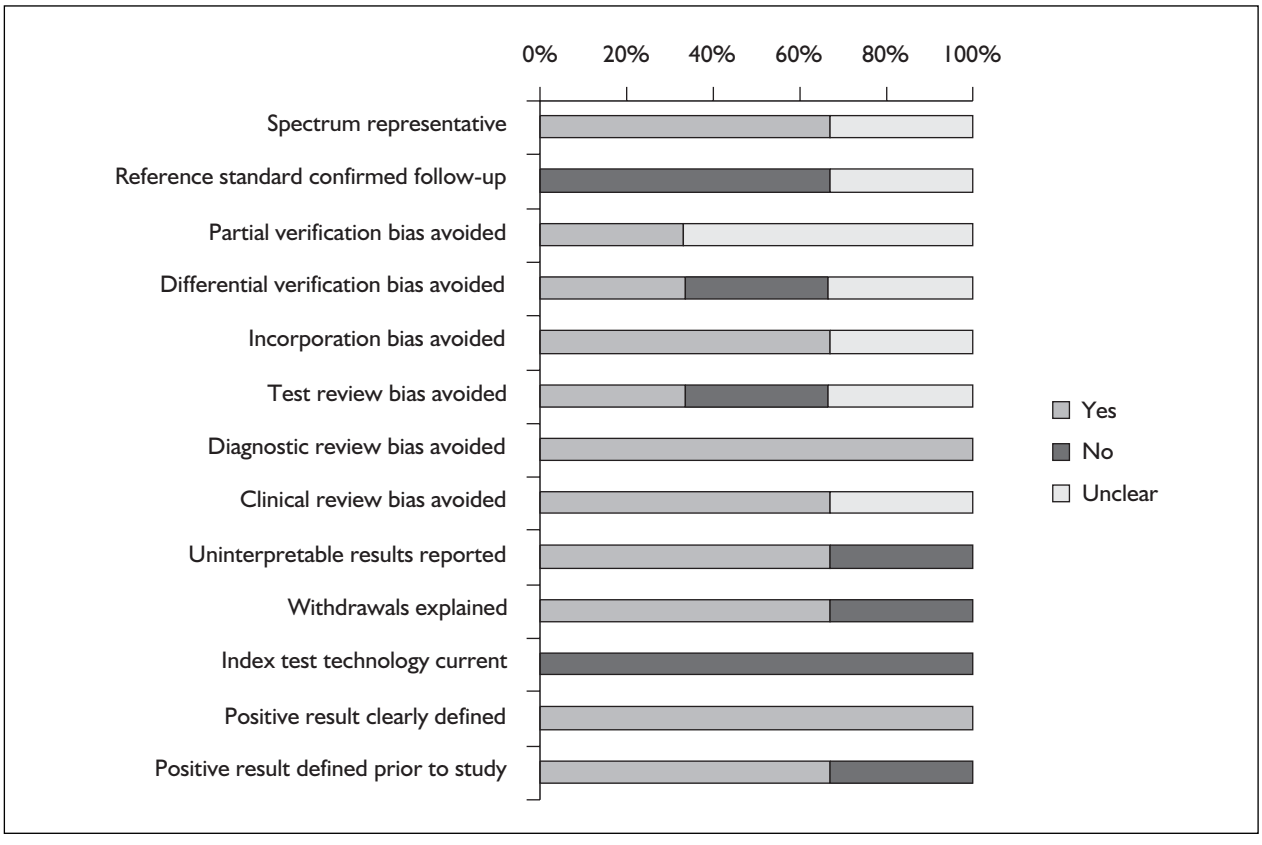

FIGURE 24 *FDT C-20-1: summary of quality assessment*

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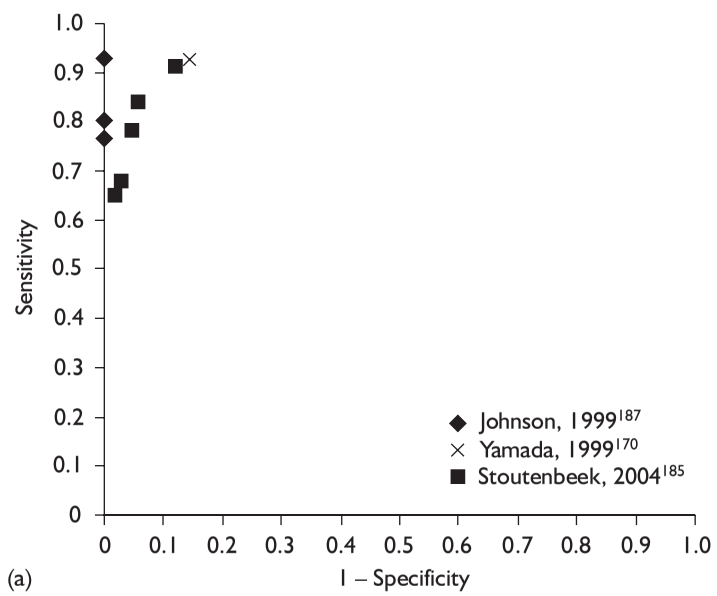
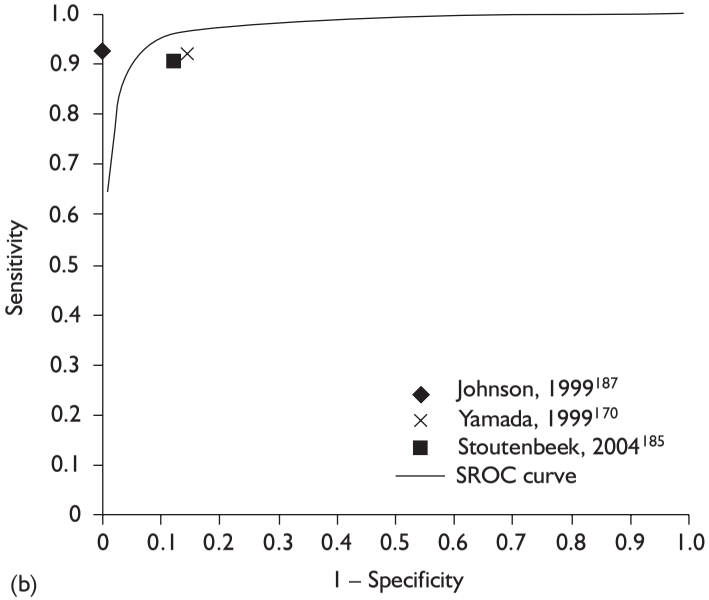


(a)



(b)

Study	*TP/TP+FN*	*TN/TN+FP*
Johnson, 1999[187]	52/56	104/104
Stoutenbeek, 2004[185]	91/100	95/108
Yamada, 1999[170]	24/26	183/214

(c)

Common cut-off	
Number of studies	3
Sensitivity (%) (95% CrI)[a]	92 (65 to 99)
Specificity (%) (95% CrI)[a]	94 (73 to 99)
DOR (95% CrI)[a]	181.20 (25.49 to 2139.00)

High-quality studies	
Number of studies	1
Sensitivity (%) (95% CrI)	92 (75 to 99)
Specificity (%) (95% CrI)	86 (80 to 90)
DOR (95% CrI)	70.84 (15.94 to 314.91)

(d)

FIGURE 25 *FDT C-20-1: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

99%) and 181.20 (95% CrI 25.49 to 2139.00), respectively (*Figure 25d*).

Interpretable results
Two population-based studies reported that 14,569 (96.8%) of 15,057 participants provided interpretable test results for FDT C-20-1,[170,210] while one prospective cohort study reported that 27 (87.1%) of 31 participants provided interpretable test results,[214] giving an overall rate of 96.7% for all studies. Four studies reported the time taken to perform the test,[170,185,187,214] which ranged from less than 45 seconds per eye for normal participants to approximately 2 minutes per eye for those with advanced glaucoma.[187]

FDT (C-20-5)
Quality assessment
Five studies involving 2956 people reported the test accuracy of the FDT C-20-5 test, including three population-based studies[155,161,163] and two case–control studies.[173,187] *Figure 26* summarises the quality assessment for these studies. In two of the five studies the participants were considered to be representative of a screening setting.[155,163] Four of the five studies were judged to be free from both partial and differential verification bias.[155,161,163,173] In three of five studies[155,161,163] both the index test and the reference standard test were interpreted without knowledge of each other's results. Two of five studies met the criteria specified for higher quality studies.[155,163]

Accuracy
Figure 27(c) shows the sensitivity and specificity, with 95% confidence intervals, for the five studies reporting FDT C-20-5 at a common cut-off (for details of the common cut-off selected for FDT C-20-5 see Appendix 13). There was marked statistically significant heterogeneity across the studies. In particular, the study by Mansberger and colleagues[161] reported extremely low sensitivity (7%) compared with the other studies. The setting for this study was rural villages in India. Ophthalmological diagnosis was based on review of optic disc photographs and this may have overdiagnosed glaucoma.

Figure 27(a) and *(b)* show, respectively, the hierarchical SROC plots for all cut-offs with multiple abnormal test points for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 7% at one abnormal test point[161] to 100% at one abnormal test point on repeat

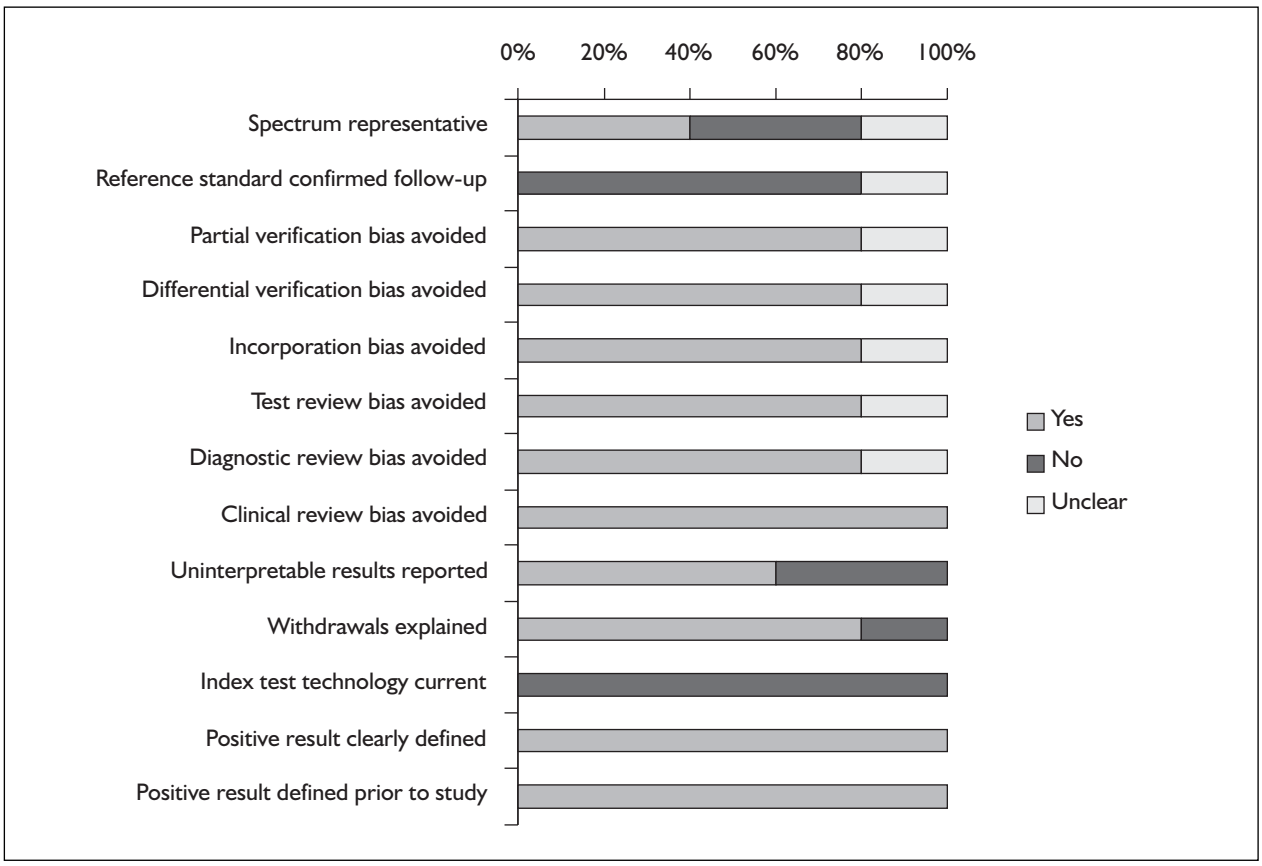


FIGURE 26 *FDT C-20-5: summary of quality assessment*

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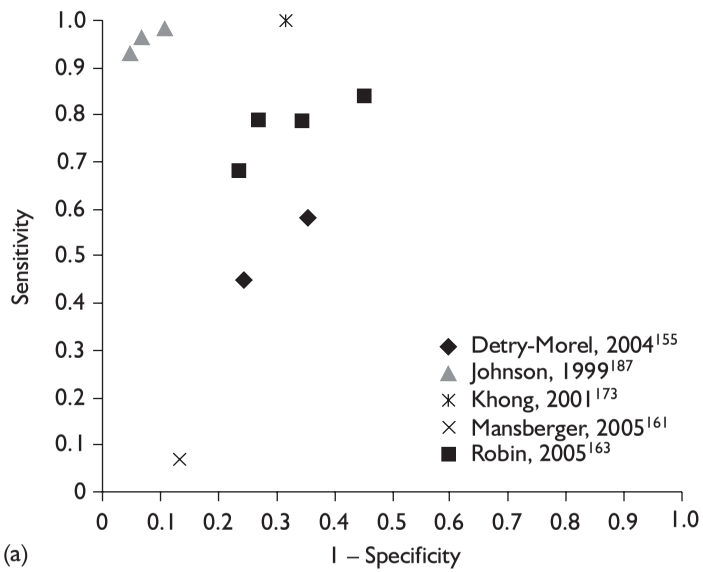
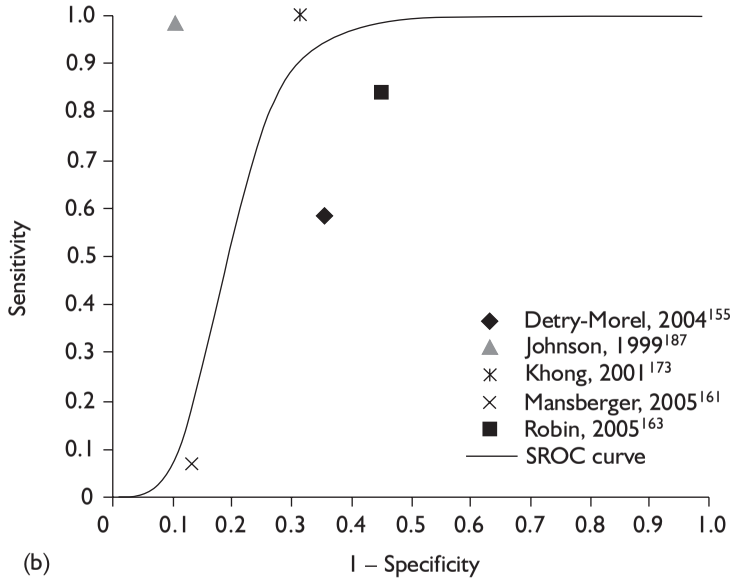


(a)



(b)

Study	*TP/TP+FN*	*TN/TN+FP*
Detry-Morel, 2004[155]	39/67	2027/3144
Khong, 2001[173]	2/2	76/111
Johnson, 1999[187]	55/56	93/104
Mansberger, 2005[161]	4/57	168/194
Robin, 2005[163]	16/19	133/242

(c)

Common cut-off	
Number of studies	5
Sensitivity (%) (95% CrI)	78 (19 to 99)
Specificity (%) (95% CrI)	75 (57 to 87)
DOR (95% CrI)	10.14 (0.72 to 249.00)
High-quality studies	
Number of studies	2
Sensitivity (%) (95% CrI)[a]	72 (26 to 96)
Specificity (%) (95% CrI)[a]	60 (17 to 92)
DOR (95% CrI)[a]	3.84 (0.70, 23.81)

(d)

FIGURE 27 *FDT C-20-5: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.* [a] *Based on HSROC model with symmetric SROC curve.*

testing,[173] while specificity ranged from 55% at one abnormal test point[163] to 95% at two clustered abnormal test points.[187] For a common cut-off of one abnormal test point, sensitivity ranged from 7%[161] to 100%,[173] while specificity ranged from 55%[163] to 89%.[187] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 78% (95% CrI 19 to 99%), 75% (95% CrI 57 to 87%) and 10.14 (95% CrI 0.72 to 249.00), respectively (*Figure 27d*).

Interpretable results

Three population-based studies reported that 2164 (91.8%) of 2357 participants provided interpretable test results for FDT C-20-5,[155,161,163] while one prospective cohort study[173] reported that 223 (97.8%) of 228 participants provided interpretable test results, giving an overall rate of 92.3% for all studies. Two studies[155,187] reported the time taken to perform the test, which ranged from less than 45 seconds per eye for normal participants to approximately 2 minutes per eye for those with advanced glaucoma.[187]

FDT (C-20 full threshold and C-20 matrix)

Heeg and colleagues,[183,184] in a case–control study set in The Netherlands, reported the accuracy of the FDT C-20 full threshold test. An abnormal test result was defined as more than one depressed test point, $p < 0.01$, in the total deviation probability plot (TD > 1). *Table 20* shows the sensitivity and specificity of the FDT C-20 full threshold test, both for all participants and for a subgroup excluding those with early glaucoma, at cut-offs of TD greater than 1, 2 and 3. As would be expected, for both the whole group and also the subgroup, sensitivity was highest (90% and 100%, respectively) at a cut-off of TD greater than 1, while specificity was highest (both 88%) at TD greater than 3. In terms of quality assessment, the cases and controls were judged as being representative of a diagnostic setting.

Spry and colleagues,[176] in a cohort study set in the UK, reported the test accuracy of the FDT C-20 matrix (Humphrey matrix 24-2). An abnormal test result was defined as a GHT outside the normal limit and/or $p < 0.05$ with the pattern standard deviation global index in one or both eyes. The study reported sensitivity of 100% and specificity of 27%. In terms of the quality of the study, the spectrum of people was considered to be representative of a diagnostic setting, it was judged to be free from both partial and differential verification bias, and both the index test and the reference standard test were interpreted without knowledge of each other's results, thereby meeting the criteria specified for higher quality studies.

OKP

Quality assessment

Four studies enrolling 768 people reported the test accuracy of OKP, including two population-based studies,[154,170] and two case–control studies.[180,182] *Figure 28* summarises the quality assessment for these studies. In three of the four studies the participants were considered to be representative of a screening[154,170] or diagnostic[182] setting. The study by Yamada and colleagues[170] was the only one judged to be free from both partial and differential verification bias and was also the only study in which both the index test and the reference standard test were interpreted without knowledge of each other's results, thereby meeting the criteria specified for higher quality studies.

Accuracy

Figure 29(c) shows the sensitivity and specificity, with 95% confidence intervals, for the four studies reporting OKP at a common cut-off (for details of the common cut-off selected for OKP see Appendix 13). There was statistically significant heterogeneity, in terms of sensitivity, mainly due to the study by Harper and colleagues.[182] There was no obvious explanation for this heterogeneity in

TABLE 20 *Sensitivity and specificity of FDT C-20 full threshold for whole group and subgroup excluding patients with early glaucoma*

Cut-off TD		Sensitivity (%)	Specificity (%)
>1	All participants	90	81
	Early glaucoma excluded	100	81
>2	All participants	86	85
	Early glaucoma excluded	99	85
>3	All participants	82	88
	Early glaucoma excluded	97	88

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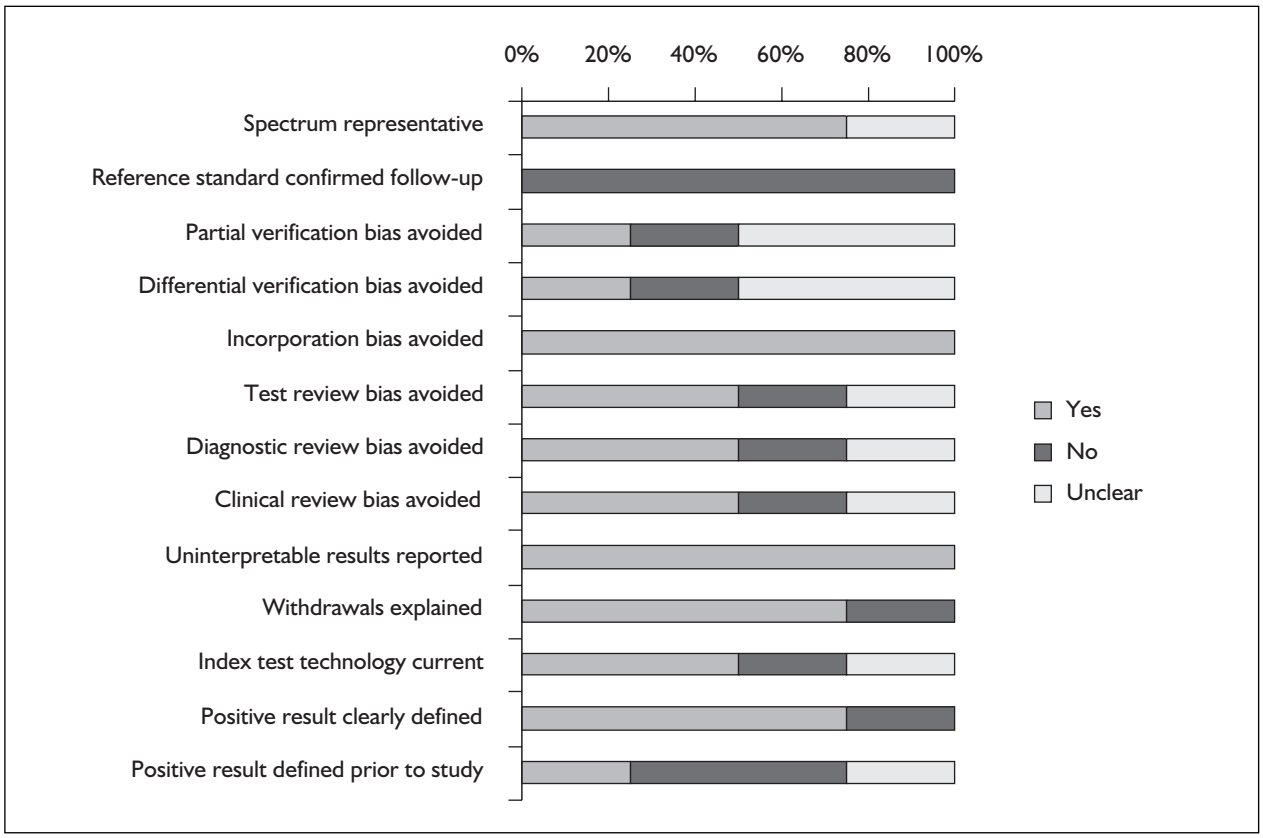

FIGURE 28 *OKP: summary of quality assessment*

terms of the spectrum of people. In three of the four studies, including the study by Harper and colleagues, the participants were considered to be representative of a screening[154,170] or diagnostic[182] setting, while the representativeness of the participants was unclear in the case-control study by Damato and colleagues.[180] However, in contrast to the other three studies, in the study by Harper and colleagues[182] there was minimal instruction and supervision. In preparation for the test, the participants were asked to read the test instructions with no further assistance given, following which they self-administered the test, unsupervised.[182]

Figure 29(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies and the common cut-off. For both all cut-offs and the common cut-off, sensitivity ranged from 25%[182] to 100%,[154] while specificity ranged from 78%[170] to 94%.[154,182] One reason for the high sensitivity reported by Christoffersen and colleagues[154] was that test negatives did not receive a reference standard test to confirm this but were assumed to be true negatives, so that the study reported no false negatives and therefore a sensitivity of 100%. Yamada and colleagues[170] also reported a high sensitivity rate (95%). However, this study contained a higher than average prevalence of glaucoma (10.7%) and it would be expected that the sensitivity of the test would therefore be higher in such a population compared with an average prevalence population. The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 86% (95% CrI 29 to 100%), 90% (95% CrI 79 to 96%) and 57.54 (95% CrI 4.42 to 1585.00), respectively (*Figure 29d*).

Interpretable results

Two population-based studies reported that 362 (97.1%) of 373 participants provided interpretable test results for OKP,[154,170] while one prospective cohort study reported that 16 (94.1%) of 17 participants provided interpretable test results,[212] giving an overall rate of 96.9% for all studies. Three studies reported the time taken to perform the test,[154,170,212] which ranged from approximately 3 minutes[170] to 4 minutes[212] per eye.

SAP (suprathreshold)

Quality assessment

Nine studies enrolling over 10,200 people reported the test accuracy of the SAP

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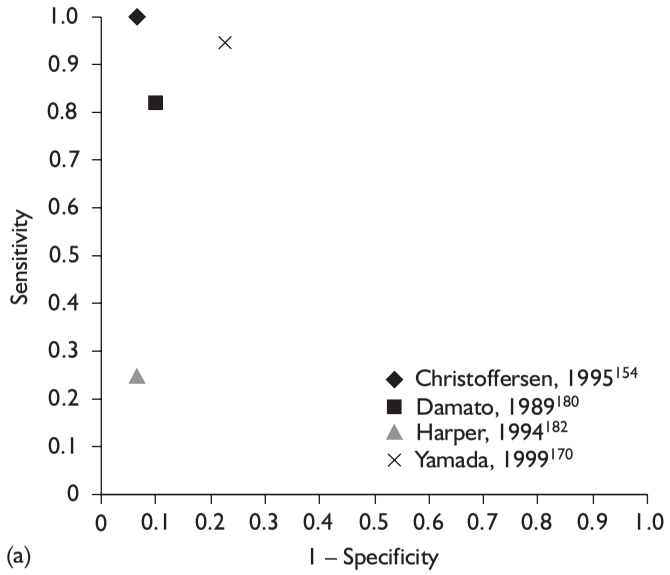
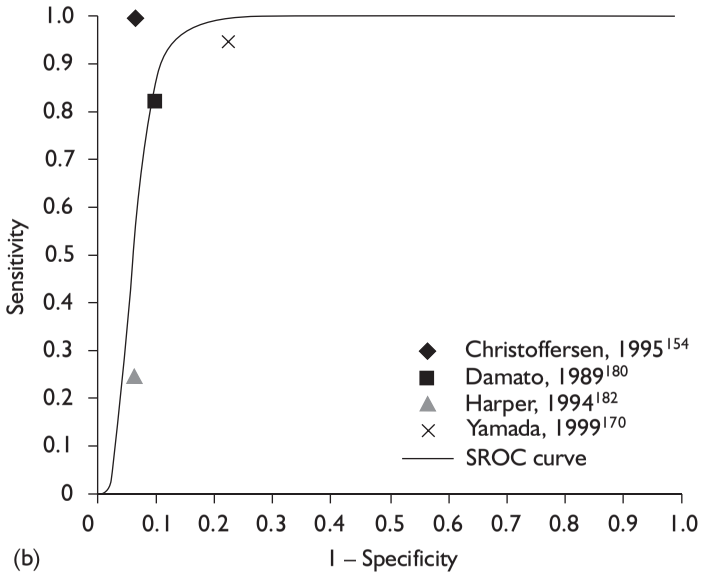
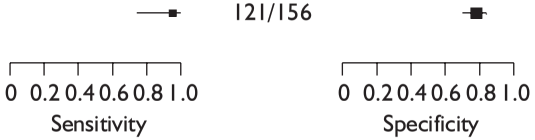


(a)



(b)

Study	*TP/TP+FN*	*TN/TN+FP*
Christoffersen, 1995[154]	16/16	160/171
Damato, 1989[180]	42/51	46/51
Harper, 1994[182]	13/52	132/141
Yamada, 1999[170]	18/19	121/156



(c)

Common cut-off	
Number of studies	4
Sensitivity (%) (95% CrI)	86 (29 to 100)
Specificity (%) (95% CrI)	90 (79 to 96)
DOR (95% CrI)	57.54 (4.42 to 1585.00)

High-quality studies	
Number of studies	1
Sensitivity (%) (95% CrI)	95 (74 to 100)
Specificity (%) (95% CrI)	78 (70 to 84)
DOR (95% CrI)	62.23 (8.02 to 482.67)

(d)

FIGURE 29 *OKP: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

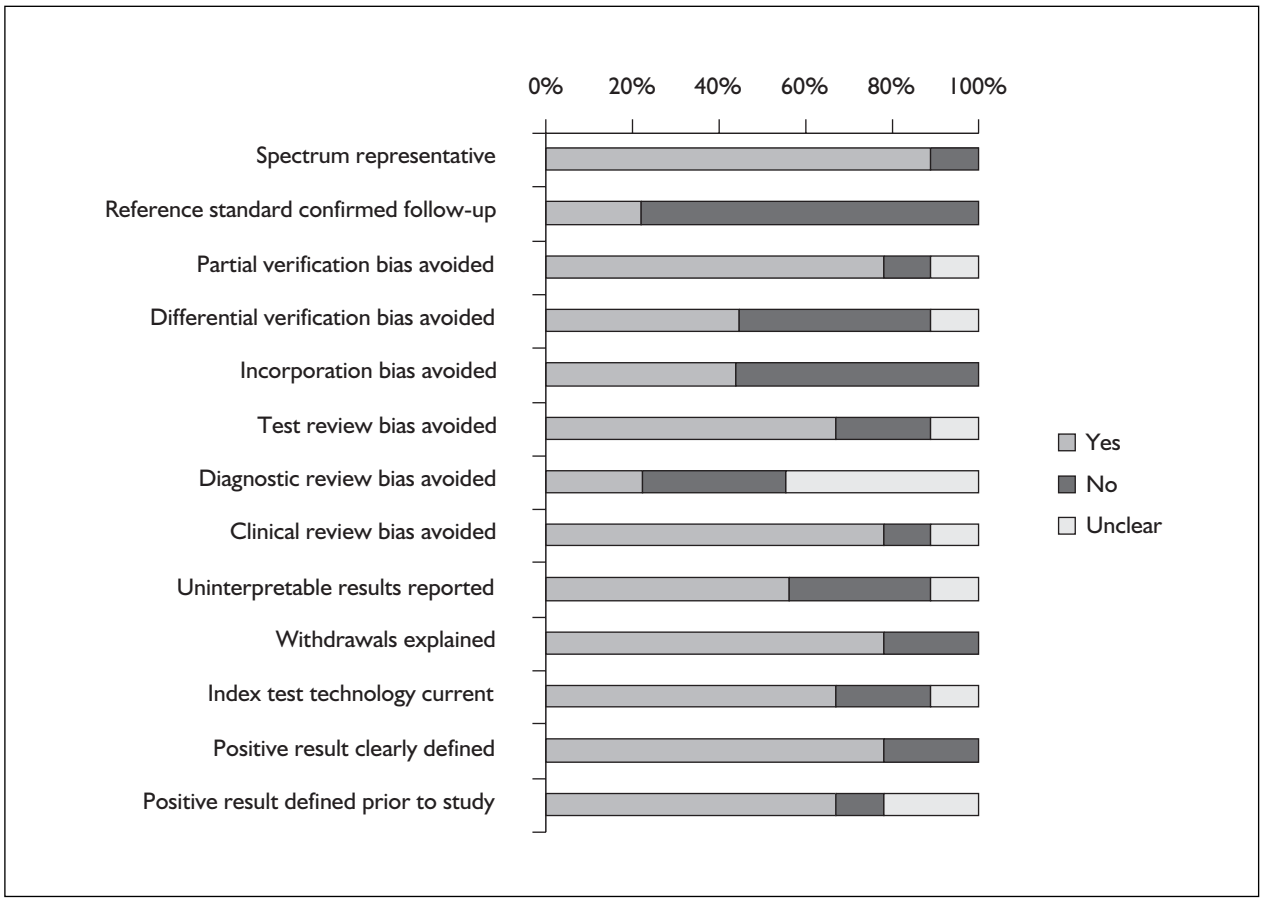


FIGURE 30 *SAP: summary of quality assessment*

suprathreshold test, including six population-based studies,[157,159,162,164,166,168] one cohort study[174] and two case–control studies.[182,186] *Figure 30* summarises the quality assessment for these studies. In eight of nine studies the participants were considered to be representative of a screening[157,159,162,164,166,168] or diagnostic[174,182] setting. Four of the nine studies were judged to be free from both partial and differential verification bias.[162,166,174,186] In two of the nine studies both the index test and the reference standard test were interpreted without knowledge of each other's results.[166,186] Only the study by Vitale and colleagues[166] met the criteria specified for higher quality studies.

Accuracy

Figure 31(c) shows the sensitivity and specificity, with 95% confidence intervals, for the nine studies reporting SAP suprathreshold at a common cut-off (for details of the common cut-off selected for SAP suprathreshold see Appendix 13). There was statistically significant heterogeneity across the studies that could not be explained by differences in study design, participants or equipment used. However, the two largest population-based studies, the Blue Mountains Eye Study[157] and the Baltimore Eye Survey,[159] involving more than 3600 and 4700 people, respectively, reported similar sensitivities and specificities. Of note in the study by Vernon and colleagues,[164] is that the definition of glaucoma excluded people with IOP of 22 mmHg or below.

Figure 31(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. For all cut-offs, sensitivity ranged from 25% (sufficient points to drop the indicator into the suspicious zone or below)[164] to 100% (one or more points missing),[157] while specificity ranged from 50% (one or more points missing)[157] to 96% (sufficient points to drop the indicator into the suspicious zone or below).[164] For the common cut-off, sensitivity ranged from 25% (sufficient points to drop the indicator into the suspicious zone or below)[164] to 90% (at least four abnormal points in any single quadrant),[162] while specificity ranged from 67% (absolute or relative defects $\geqslant$17)[168] to 96% (sufficient points to drop the indicator into the suspicious zone or below).[164] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off

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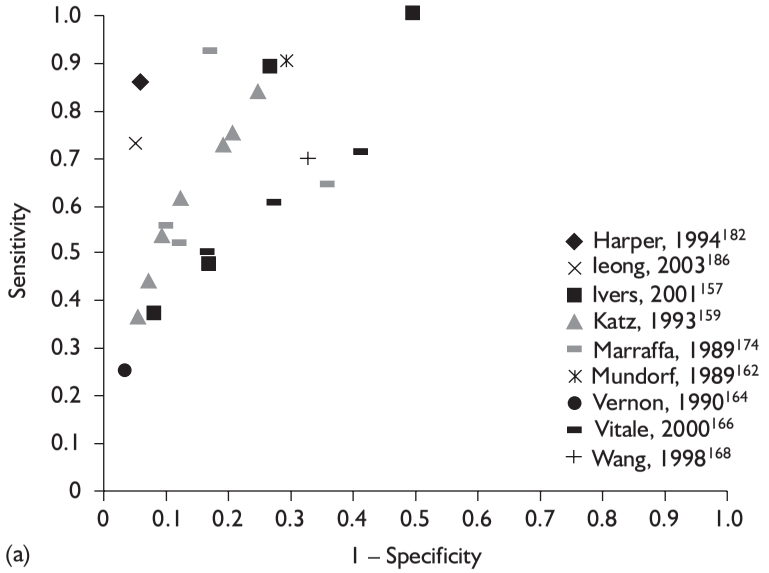

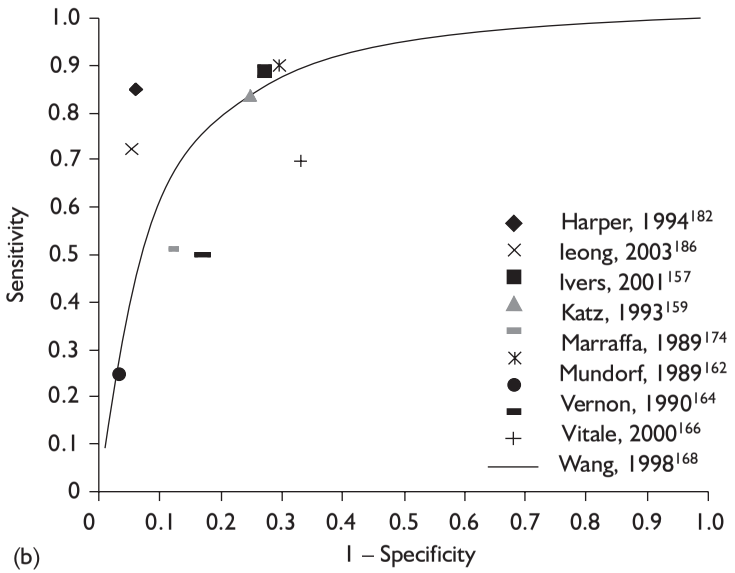

Study	*TP/TP+FN*	*TN/TN+FP*
Harper, 1994[182]	57/67	136/145
Ieong, 2003[186]	21/29	35/37
Ivers, 2001[157]	77/87	2587/3567
Katz, 1993[159]	122/146	3439/4587
Marraffa, 1989[174]	72/140	37/42
Mundorf, 1989[162]	9/10	95/135
Vernon, 1990[164]	3/12	813/843
Vitale 2000[166]	29/58	141/170
Wang 1998[168]	48/69	97/145

(c)

Common cut-off	
Number of studies	9
Sensitivity (%) (95% CrI)	71 (51 to 86)
Specificity (%) (95% CrI)	85 (73 to 93)
DOR (95% CrI)	14.42 (6.39 to 33.73)
High-quality studies	
Number of studies	1
Sensitivity (%) (95% CrI)	50 (37 to 63)
Specificity (%) (95% CrI)	83 (76 to 88)
DOR (95% CrI)	4.86 (2.53 to 9.33)

(d)

FIGURE 31 *SAP suprathreshold: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

were 71% (95% CrI 51 to 86%), 85% (95% CrI 73 to 93%) and 14.42 (95% CrI 6.39 to 33.73), respectively (*Figure 31d*).

Interpretable results
Six population-based studies reported that 8368 (80.1%) of 10,444 participants provided interpretable test results for SAP suprathreshold,[157,159,162,164,166,168] while two prospective cohort studies involving 504 participants reported that all provided interpretable test results,[174,208] giving an overall rate of 81.0% for all studies. Four studies reported the time taken to perform the test,[159,162,164,174] which ranged from approximately 3 minutes[164] to 15 minutes[157,159,162,164,166,168] for both eyes.

SAP (threshold)
Quality assessment
Five studies enrolling 1457 people reported the test accuracy of the SAP threshold test, including two population-based studies,[158,163] one cohort study[176] and two case–control studies.[179,181] *Figure 32* summarises the quality assessment for these studies. In three of the five studies the participants were considered to be representative of a screening[163] or diagnostic[176,179] setting. Four of the five studies were judged to be free from both partial and differential verification bias.[158,163,176,179] In one study both the index test and the reference standard test were interpreted without knowledge of each other's results.[163] Only the study by Robin and colleagues[163] met the criteria specified for higher quality studies.

Accuracy
Figure 33(c) shows the sensitivity and specificity, with 95% confidence intervals, for the five studies reporting SAP threshold at a common cut-off (for details of the common cut-off selected for SAP threshold see Appendix 13). There was statistically significant heterogeneity across the studies. There was no obvious explanation for the heterogeneity, although there were differences across the studies in terms of study design and setting. The same types of study (population-based,[158,163] case–control[179,181]) appeared to be homogeneous in terms of specificity but not sensitivity.

Figure 33(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and the common cut-off. For all cut-offs for all studies, sensitivity ranged from 58% [mean deviation + pattern SD (least significant), significance level cut-off 0.005] to 97% (mirror image method),[181] (clusters, Low Tension Glaucoma Study,

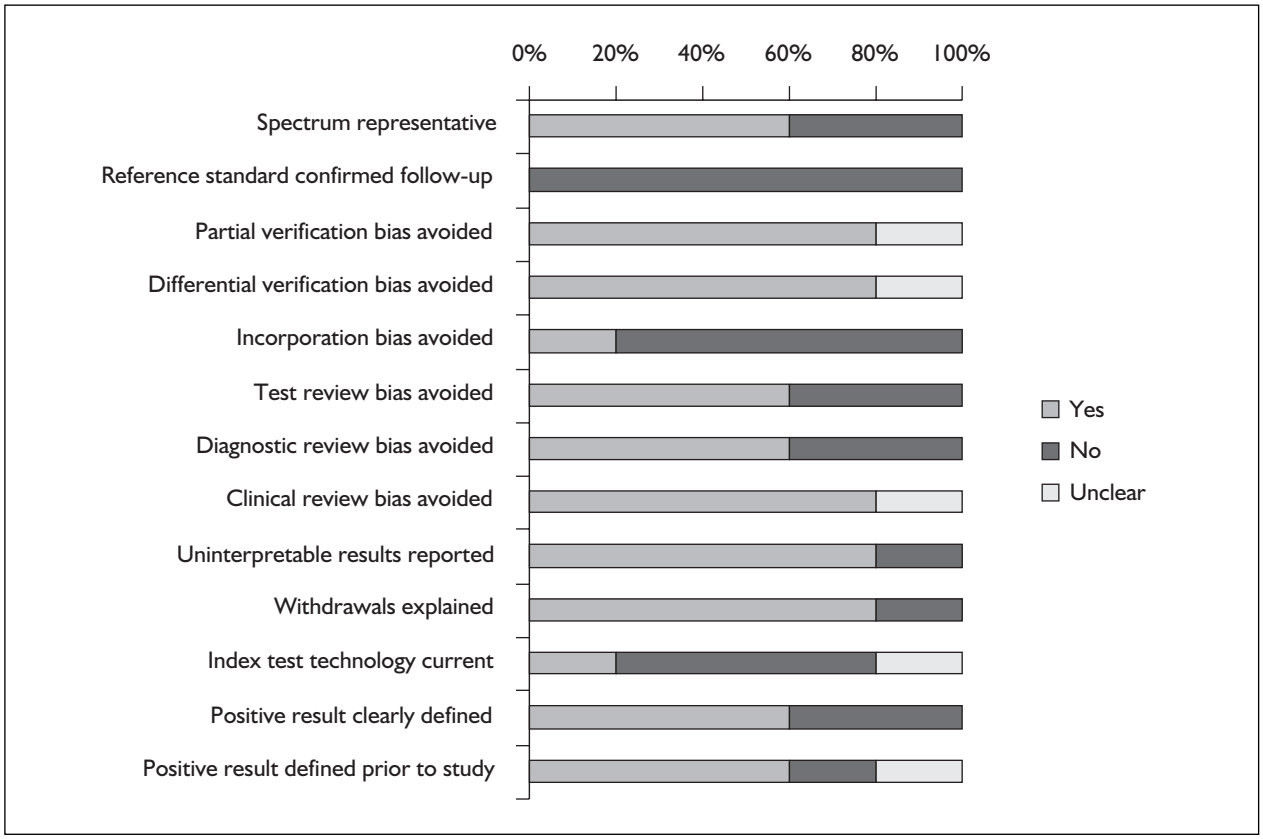

FIGURE 32 *SAP threshold: summary of quality assessment*

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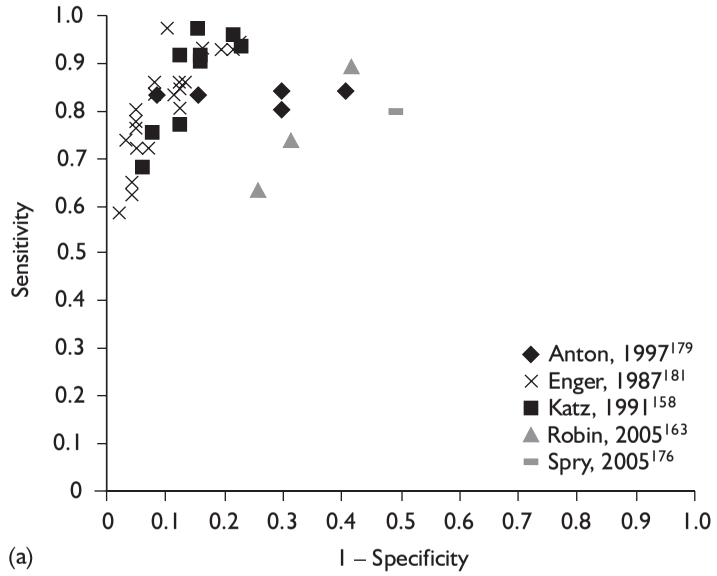

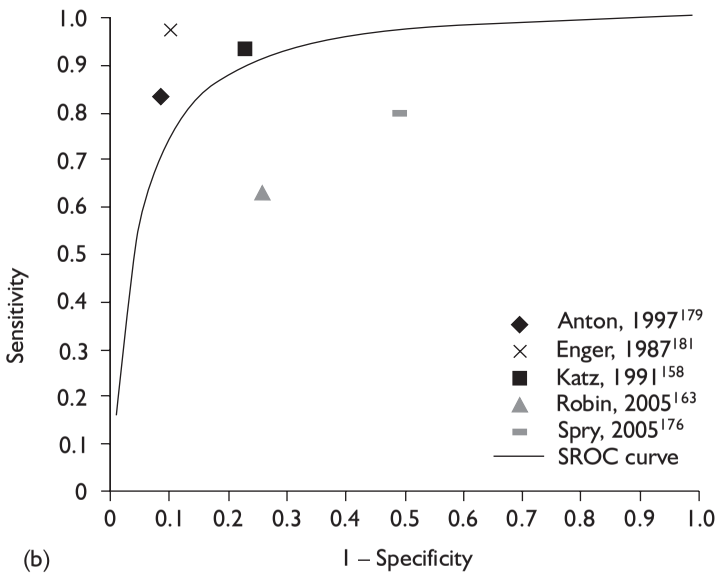

Study	*TP/TP+FN*	*TN/TN+FP*
Anton, 1997[179]	80/96	77/84
Enger, 1987[181]	70/72	88/98
Katz, 1991[158]	99/106	192/249
Robin, 2005[163]	12/19	180/242
Spry, 2005[176]	12/15	17/33

(c)

Common cut-off	
Number of studies	5
Sensitivity (%) (95% CrI)	88 (65 to 97)
Specificity (%) (95% CrI)	80 (55 to 93)
DOR (95% CrI)	29.87 (5.59 to 159.30)
High-quality studies	
Number of studies	2
Sensitivity (%) (95% CrI)[a]	73 (28 to 95)
Specificity (%) (95% CrI)[a]	64 (22 to 92)
DOR (95% CrI)[a]	4.91 (0.82 to 31.25)

(d)

FIGURE 33 *SAP threshold: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.* [a] *Based on HSROC model with symmetric SROC curve.*

p-values),[158] while specificity ranged from 52% (GHT "outside normal limit" and/or pattern SD $p < 0.05$ in one or both eyes)[176] to 98% [mean deviation + pattern SD (least significant), significance level cut-off 0.005].[181] For the common cut-off, sensitivity ranged from 63% [Advanced Glaucoma Intervention Study (AGIS) score ⩾3][158,163] to 97% (mirror image method),[181] while specificity ranged from 52% (GHT "outside normal limit" and/or pattern SD $p < 0.05$ in one or both eyes)[176] to 92% (logistic discriminant analysis applied to 59 points).[179] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off were 88% (95% CrI 65 to 97%), 80% (95% CrI 55 to 93%) and 29.87 (95% CrI 5.59 to 159.30), respectively (*Figure 33d*).

Interpretable results

Seven population-based studies reported that 4459 (98.7%) of 4520 participants provided interpretable test results for SAP threshold,[100,107,109,112,158,163,164] while seven prospective cohort studies involving 940 participants reported that all provided interpretable test results,[176,192,194,195,198,201,206] giving an overall rate of 98.9% for all studies. Four studies reported the time taken to perform the test,[176,195,198,206] which ranged from approximately 5 minutes[176] to 18 minutes[206] for both eyes. All four studies used SITA standard or SITA fast.

Tests of IOP

GAT

Quality assessment

Nine studies involving 20,308 people reported the test accuracy of GAT for detecting OAG, including seven population-based studies[21,99,100,106,112,157,168] and two cohort studies.[22,171] *Figure 34* summarises the quality assessment for these studies. In eight of the nine studies the participants were considered to be representative of a screening[21,99,100,106,112,157,168] or diagnostic[22] setting. Two of the nine studies were judged to be free from both partial and differential verification bias.[21,100] In no study were both the index test and the reference standard test interpreted without knowledge of each other's results and no study met the criteria specified for higher quality studies.

Accuracy

Figure 35(c) shows the sensitivity and specificity, with 95% confidence intervals, for the nine studies reporting GAT at a common cut-off (for details of

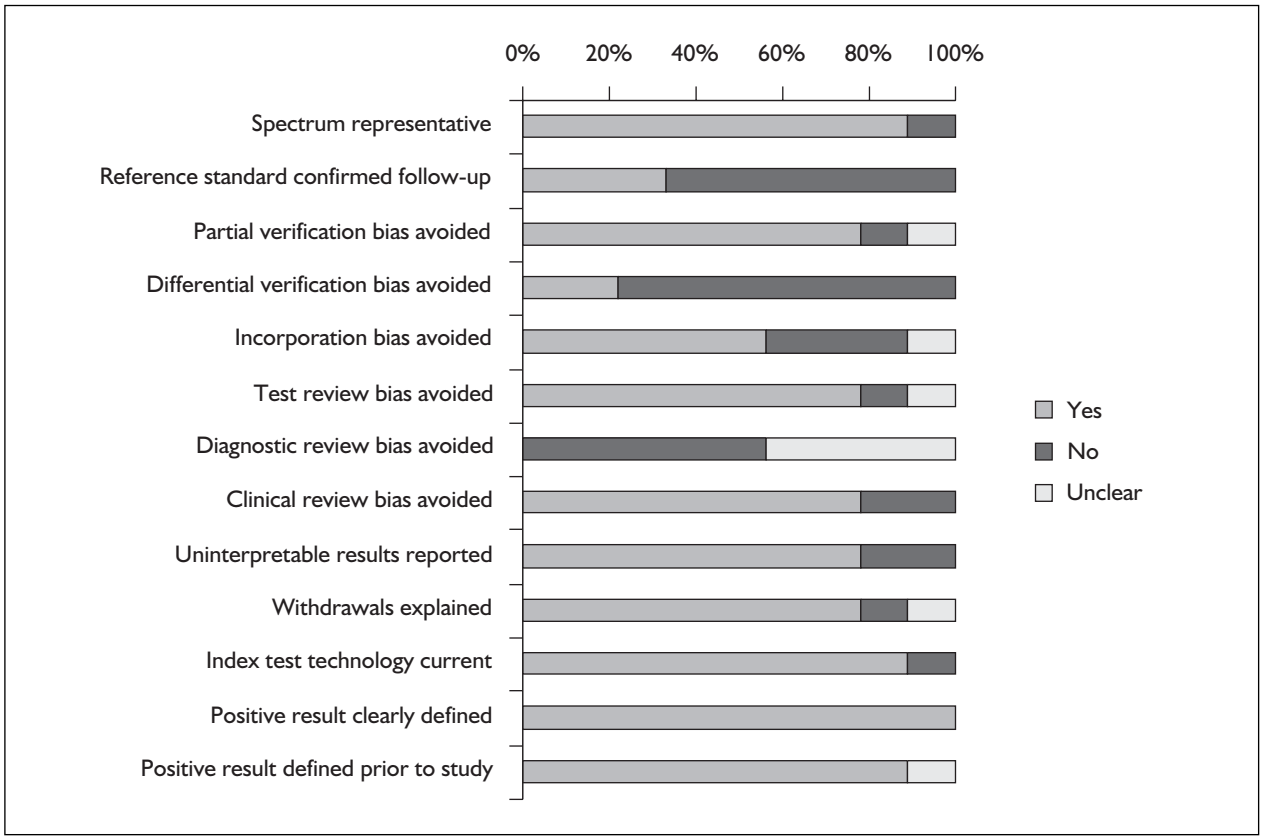

FIGURE 34 *GAT: summary of quality assessment*

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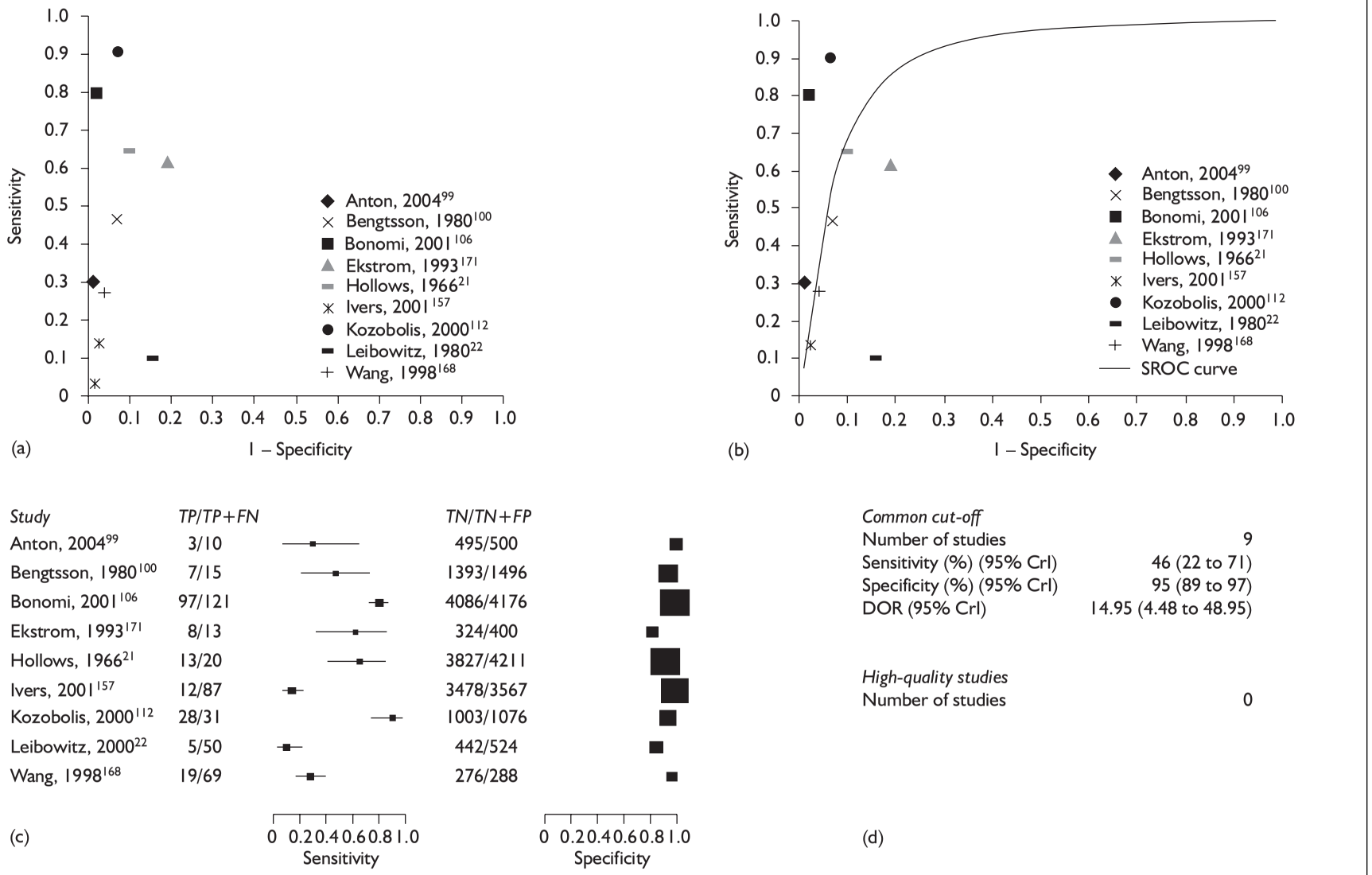

FIGURE 35 *GAT: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

the common cut-off selected for GAT see Appendix 13). There was statistically significant heterogeneity across the studies, especially for sensitivity, with no obvious explanation.

Figure 35(a) and *(b)* show, respectively, the SROC plots for all cut-offs for all studies, and for the common cut-off. For all cut-offs, sensitivity ranged from 3% (IOP > 28 mmHg)[157] to 90% (IOP > 21 mmHg),[112] while specificity ranged from 81% (IOP ⩾ 21 mmHg)[171] to 99% (IOP > 21 mmHg,[99] IOP > 28 mmHg).[157] For the common cut-off, sensitivity ranged from 10% (IOP > 21 mmHg)[22] to 90% (IOP > 21 mmHg),[112] while specificity ranged from 81% (IOP ⩾ 21 mmHg)[171] to 99% (IOP > 21 mmHg).[99] The pooled sensitivity, specificity and DOR from the meta-analysis models for the common cut-off of above 21 mmHg were 46% (95% CrI 22 to 71%), 95% (95% CrI 89 to 97%) and 14.95 (95% CrI 4.48 to 48.95), respectively (*Figure 35d*).

Interpretable results

Thirteen population-based studies reported that 25,422 (99.1%) of 25,650 participants provided interpretable test results for GAT,[21,22,99,100,106,107,109,112,157,159,168,199,205] while two prospective cohort studies[193,204] involving 135 participants reported that all provided interpretable test results, giving an overall rate of 99.1% for all studies. None of the studies reported the time taken to perform the test.

NCT

Quality assessment

One population-based study involving 874 people reported NCT for detecting OAG.[164,165] *Figure 36* summarises the quality assessment for this study. The participants were considered to be representative of a screening setting. The study was judged to be free from partial verification bias but not differential verification bias. Furthermore, the index test was interpreted without knowledge of the results of the reference standard test, but not vice versa. It should be noted that the reference standard was suboptimal for several reasons: the authors' definition of glaucoma excluded people with IOP of 22 mmHg or below and included people with IOP above 30 mmHg and 'required treatment' without other evidence of glaucoma damage, and optic nerve evaluation was based on direct ophthalmoscopy through undilated pupils. This study did not meet the criteria required for a higher quality study.

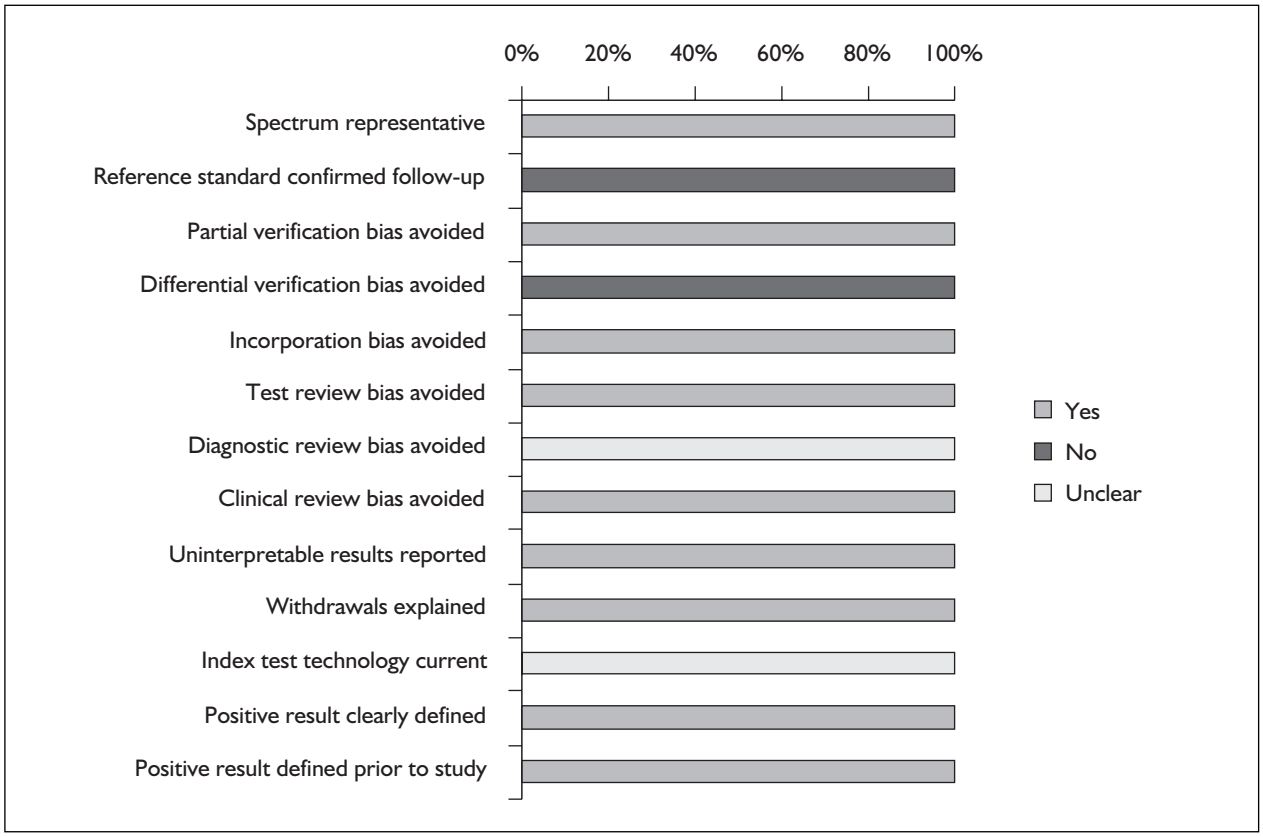

FIGURE 36 *NCT: summary of quality assessment*

Accuracy
Vernon and colleagues[164,165] reported IOP at a range of cut-offs from above 21 mmHg to above 26 mmHg and from one to four pulses per eye. *Figure 37(a)* and *(b)* show, respectively, the SROC plots for all cut-offs, and a common cut-off (for details of the common cut-off selected for NCT see Appendix 13). For all cut-offs, sensitivity ranged from 42% (IOP > 26 mmHg, four pulses per eye) to 92% (IOP > 21 mmHg, IOP > 22 mmHg, both four pulses per eye), while specificity ranged from 93% (IOP > 21 mmHg, one pulse per eye) to 99.7% (IOP > 26 mmHg, four pulses per eye). For the common cut-off of >21 mmHg, sensitivity was 92% (95% CrI 62 to 100%), specificity was 92% (95% CrI 90 to 94%) and the DOR was 134.88 (95% CrI 17.15 to 1061.10) (*Figure 37c* and *d*).

Interpretable results
In addition to the study by Vernon and colleagues,[164] five population-based studies, although not providing usable data for NCT in terms of test accuracy, otherwise met the review's inclusion criteria and provided information on interpretable results.[110,155,161,196,203] The six studies reported that 6126 (97.1%) of 6308 participants provided interpretable test results for NCT, while one prospective cohort study[211] involving 105 participants reported that all provided interpretable test results, giving an overall rate of 97.2% for all studies. One study reported that it took approximately 2 minutes to perform the test for both eyes.[164]

Summary
Table 21 shows the summary performance for each test at the common cut-off. Sensitivity and specificity are derived from the 40 included studies, while the information on interpretable results and time taken to perform the test also includes data, where reported, from other population-based studies and prospective cohort studies that did not report usable outcomes in terms of accuracy, but otherwise met the review's inclusion criteria. Appendix 13 provides details of the sensitivity and specificity for each study, by type of test.

Only one study reporting true and false positives and negatives for NCT met the inclusion criteria. Vernon and colleagues[164] reported 92% sensitivity and also 92% specificity for NCT at a cut-off of IOP above 21 mmHg. However, the high sensitivity reported was influenced by the fact that the authors' definition of glaucoma excluded normal tension glaucoma (NTG). The performance estimates should be viewed with caution as the reference standard was suboptimal. Interpretable results were provided by 97% of those taking the test, while the time taken to perform the test averaged 2 minutes for both eyes.

In many of the tests there was statistical heterogeneity across studies. The FDT C-20-1 test was associated with the highest sensitivity (92%) and was among the tests with the highest specificity (94%) (ophthalmoscopy 94%; GAT 95%), as well as being associated with a relatively high percentage (97%) of interpretable test results and short length of time taken to perform the test (<1–2 minutes per eye).

Higher quality studies
Eight studies met the criteria for higher quality studies, including six population-based studies[155,156,163,166,169,170] and two cohort studies.[175,176] Sensitivity analysis was undertaken by examining separately the results of the higher quality studies, using HSROC analysis where more than one higher quality study reported the same test (*Table 22*). For both SAP threshold and FDT C-20-5, the higher quality studies reported lower values for both sensitivity and specificity when compared with all studies, while two FDT C-20-5 studies not meeting the criteria for higher quality[173,187] reported very high sensitivity values (98% and 100%, respectively). For optic disc photography, compared with all studies, the higher quality studies reported similar sensitivity (74% versus 73%), with slightly lower specificity (82% versus 89%). For HRT II, compared with all studies, the higher quality studies reported higher sensitivity (93% versus 86%) but slightly lower specificity (85% versus 89%).

Studies reporting combinations of tests
Two population-based studies reported the sensitivity and specificity of combinations of tests for detecting OAG.[163,164] Robin and colleagues[163] compared the sensitivity and specificity of sequential testing with FDT C-20-5 followed by HRT II in a population-based study set in Australia involving 261 people. For FDT, participants with any miss of any severity repeated the test. Three definitions of abnormal HRT II were assessed: one or more borderline or severe abnormalities, two or more borderline or one or more severe abnormalities, or three or more borderline or one or more severe abnormalities. The definitions were based on MRA, which takes into account the global and sectorial rim area

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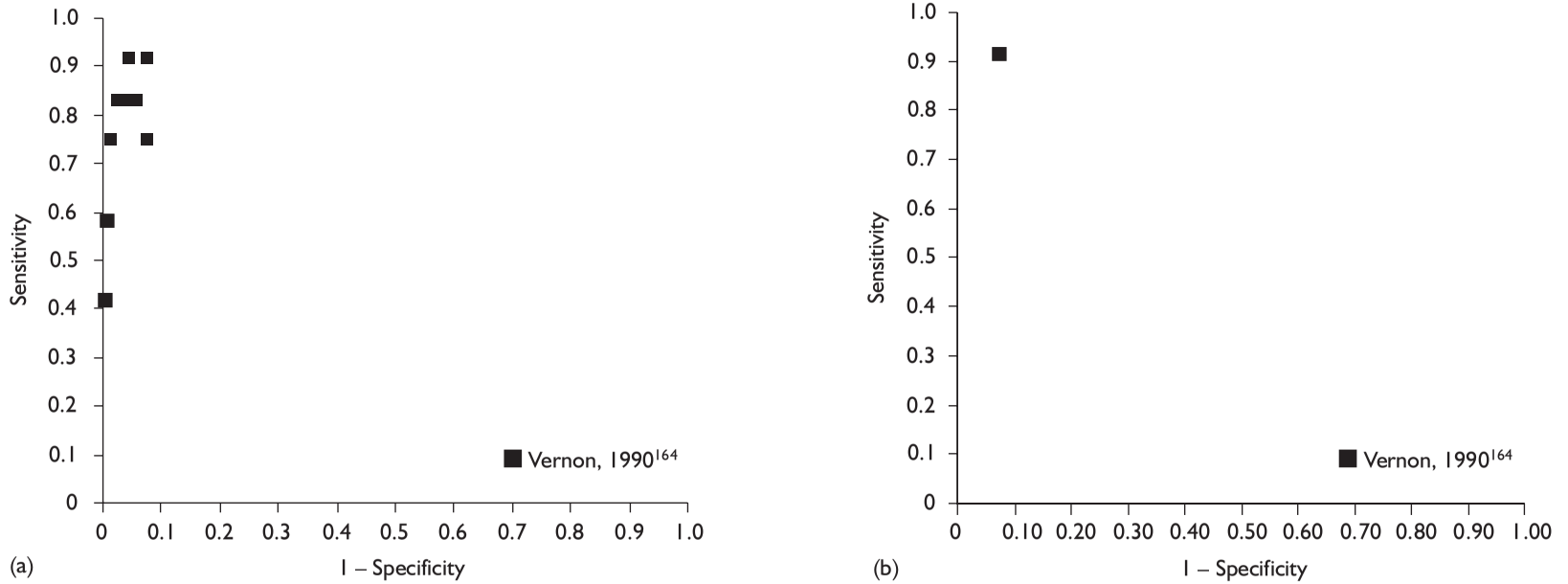

FIGURE 37 *NCT: (a) SROC plot: all studies, all cut-offs; (b) SROC plot: common cut-off; (c) sensitivity and specificity at common cut-off; (d) pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

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TABLE 21 *Summary information for tests included in the HSROC meta-analysis models*[a]

Test	No. of studies	Sensitivity (%) (95% CrI)	Specificity (%) (95% CrI)	DOR[c] (95% CI)	Mean % interpretable results (range)	Time taken to perform test, per eye (minutes) (range)
Ophthalmoscopy	5	60 (34 to 82)	94 (76 to 99)	26 (6 to 110)	98 (86 to 100)	Not stated
Optic disc photography	6	73 (61 to 83)	89 (50 to 99)	22 (3 to 148)	85 (73 to 100)	16
RNFL photography[b]	4	75 (46 to 92)	88 (53 to 98)	23 (4 to 124)	80	Not stated
HRT II	3	86 (55to 97)	89 (66 to 98)	51 (11 to 246)	94 (91 to 97)	Not stated
FDT C-20-1	3	92 (65 to 99)	94 (73 to 99)	181 (25 to 2139)	97 (87 to 99)	<1 to 2
FDT C-20-5	5	78 (19 to 99)	75 (57 to 87)	10 (0.7 to 249)	92 (86 to 98)	<1 to 2
OKP	4	86 (29 to 100)	90 (79 to 96)	58 (4 to 1585)	97 (94 to 98)	3 to 4
SAP suprathreshold	9	71 (51 to 86)	85 (73 to 93)	14 (6 to 34)	81 (60 to 100)	2 to 8
SAP threshold[d]	5	88 (65 to 97)	80 (55 to 93)	30 (6 to 159)	99 (91 to 100)	3 to 9
GAT	9	46 (22 to 71)	95 (89 to 97)	15 (4 to 49)	99 (97 to 100)	Not stated
NCT	1	92 (62 to 100)	92 (90 to 94)	135 (17 to 1061)	97 (90 to 100)	1

[a] Summary data across all studies irrespective of quality.
[b] One study provided data on interpretable results.[167]
[c] DORs are based on all studies using a common cut-off.
[d] Four studies reported the time taken to perform the test, all of which used SITA standard or SITA fast.[176,195,198,206]

TABLE 22 *HSROC analysis: all studies compared with higher quality studies*

	Optic disc photography		HRT II		FDT C-20-5		SAP threshold	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
All studies	73	89	86	89	78	75	88	80
Higher quality	74	82	93	85	72	60	73	64

corrected for global and sectorial disc area and uses three grades: 'normal' if all of the measurements fall within the 95% confidence intervals, 'borderline' if at least one falls between the lower 95% and 99.9% confidence intervals, and 'outside normal limits' if at least one rim area measurement is less than the lower 99.9% confidence interval. The reference standard consisted of a full clinical ophthalmic examination by an ophthalmologist; a panel of nine glaucoma experts determined the final diagnosis of glaucoma. The combinations of tests reported were: (a) FDT (at least one abnormality) then HRT II (at least one abnormality); (b) FDT (at least one abnormality) then HRT II (at least two abnormalities); (c) FDT (at least two abnormalities) then HRT II (at least one abnormality); and (d) FDT (at least two abnormalities) then HRT II (at least two abnormalities). The highest sensitivity, 79%, was reported for both (a) and (b) with specificities of 88% and 93%, respectively, while the highest specificity, 95%, was reported for (d) with a sensitivity of 74%.

The study by Vernon and colleagues[164] also reported the sensitivity and specificity of sequential testing of NCT (Keeler Pulsair) followed by SAP (Henson CFS 2000 26-point suprathreshold screening programme) for detecting OAG. For NCT, the criterion used to define a positive result was mean IOP of at least 22 mmHg. For SAP, a missed point on the 26-point suprathreshold programme required the operator to extend to a 66-point test. A failed test was defined as occurring when sufficient points had been missed to drop the indicator on the screen into the suspicious zone or below. The reference standard consisted of all participants having their optic discs graded by an experienced ophthalmologist. There was verification bias in that those who tested positive on the index tests had a more extensive evaluation. Glaucoma was defined as IOP greater than 22 mmHg plus pathologically cupped disc with field loss, or IOP greater than 22 mmHg on two occasions in association with two or more of six pathological disc parameters despite normal fields, or IOP greater than 30 mmHg on two occasions. The authors reported a sensitivity of 92% and specificity of 93% for sequential testing of IOP followed by the Henson 26-point suprathreshold screening programme. It should be noted, however, that the reference standard is suboptimal as reported for this study when reporting the accuracy of NCT alone in the previous section.

Studies assessing accuracy for different stages of glaucoma

One population-based study[158] and six case–control studies[181,182,184,186,190,191] reported the accuracy of tests for detecting glaucoma at different stages of the disease. Although some of these studies did not specifically state this as an aim, they were considered to do so by either including or excluding people with certain stages of glaucoma. While the present review's inclusion criteria aimed to ensure that study participants would be representative of a screening population, some studies were accepted that excluded very severe loss, for example hemispheric loss, or hemianopia or that applied exclusion criteria on vision that were not judged as being unduly restrictive. These studies were accepted on the basis that they were in effect providing information on test accuracy for different stages of glaucoma and that the categories of people excluded would generally have already been detected owing to the severity of their vision loss. For example, Katz and colleagues[158] excluded people with hemispheric or greater loss, Enger and colleagues[181] excluded those with advanced glaucoma and Harper and colleagues[182] excluded people with more advanced glaucomatous visual field defects, while all participants with glaucoma in the study by Wood and colleagues[191] possessed early/moderate visual field defects. Ieong and colleagues[186] included people with minimal glaucomatous field loss, while Wollstein and colleagues[190] included those with visual field defects defined as 'mild glaucoma'.

As these studies aimed to assess test accuracy in different stages of glaucoma, their participants were representative of a specific severity rather than a broad spectrum of disease. *Table 23* provides details of those studies assessing the accuracy of tests for different stages of glaucoma, the tests used, the sensitivity and specificity reported by the individual studies, and the pooled sensitivity and specificity from the meta-analysis models for all studies reporting the tests (for all stages of glaucoma) at the common cut-off (as shown in *Table 21*).

In two studies[186,190] assessing early-stage glaucoma and reporting optic disc photography, HRT II and SAP suprathreshold, sensitivity ranged from 69% (HRT II) to 72% (SAP suprathreshold), while specificity ranged from 94% (optic disc photography) to 95% (HRT II; SAP suprathreshold). Sensitivity was similar for SAP suprathreshold (72% versus 71%) and optic disc photography (71% versus 73%), but lower for

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TABLE 23 *Studies reporting different stages of glaucoma*

Study	Stage of glaucoma	Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Pooled sensitivity (%) (95% CrI)	Pooled specificity (%) (95% CrI)
Ieong, 2003[186]	Early	HRT II	69 (49 to 85)	95 (82 to 99)	86 (55 to 97)	89 (66 to 98)
		SAP suprathreshold	72 (53 to 87)	95 (82 to 99)	71 (51 to 86)	85 (73 to 93)
Wollstein, 2000[190]	Early	Optic disc photography	71 (56 to 83)	94 (86 to 98)	73 (61 to 83)	89 (50 to 99)
Enger, 1987[181]	Early/moderate	SAP threshold	97 (90 to 100)[a]	98 (93 to 100)[a]	88 (65 to 97)	80 (55 to 93)
Harper, 1994[182,186]	Early/moderate	OKP	25 (14 to 39)	94 (88 to 97)	86 (29 to 100)	90 (79 to 96)
Katz, 1991[158]	Early/moderate	SAP threshold	97 (92 to 99)[b]	94 (90 to 97)[b]	88 (65 to 97)	80 (55 to 93)
Wood, 1987[191]	Early/moderate	Ophthalmoscopy	56 (30 to 80)	78 (58 to 91)	60 (34 to 82)	94 (76 to 99)
Heeg, 2005[184]	Moderate/severe	FDT C-20 full threshold	100 (99 to 100)	81 (75 to 86)	NA	NA

NA, not applicable.
[a] Sensitivity of 97% and specificity of 98% are from different algorithms.
[b] Sensitivity of 97% and specificity of 94% are from different algorithms.

HRT II (69% versus 86%), when compared with the pooled data from the meta-analysis models for all studies reporting the tests at a common cut-off. The specificities reported by the individual studies for each test were higher compared with the pooled data.

In four studies[158,181,182,191] assessing early/moderate-stage glaucoma and reporting ophthalmoscopy, OKP and SAP threshold, sensitivity ranged from 25% (OKP) to 97% (SAP threshold), while specificity ranged from 78% (ophthalmoscopy) to 98% (SAP threshold). In these studies, compared with the pooled data from the meta-analysis models, sensitivity was higher for SAP threshold (97% versus 88%) but lower for ophthalmoscopy (56% versus 60%) and especially for OKP (25% versus 86%), while specificity was higher for OKP (94% versus 90%) and SAP threshold (98% and 94% versus 80%), but lower for ophthalmoscopy (78% versus 94%). One possible explanation for the low sensitivity of OKP put forward by the study authors was that the test was self-administered and unsupervised, and relied on self-assessment by the participants.[182]

In the one study[184] reporting a subgroup of the study population with moderate/severe-stage glaucoma, sensitivity for the FDT C-20 full threshold test was higher (100% versus 90%) with similar specificity (both 81%) when compared with the whole study group.

Studies directly comparing tests

Overview

Six studies directly compared two or more of the following tests that were considered to be potentially feasible for use in a screening programme for detection of OAG: optic disc photography, HRT II, SAP, FDT and GAT.[157,163,166,168,176,186] All of the studies compared SAP with one or more of the other tests (*Table 24*).

SAP compared with optic disc photography

Vitale and colleagues[166] compared SAP (suprathreshold programme 1 of the Dicon LD 400 Autoperimeter) with optic disc photography (Topcon ImageNet) in a case–control study set in the USA involving 249 people. The participants were selected from survivors of a population-based sample included in the Baltimore Eye Survey Follow-up Study.[235] Three definitions of an abnormal SAP test were assessed: two adjacent points missed, three adjacent points missed, or two or more points missed in any location. Criteria used to define a positive test result for optic disc photography were VCDR greater than 0.59 or rim area/disc area less than 0.66. Overall, optic disc photography performed better than SAP in terms of sensitivity but worse in terms of specificity. Sensitivity for SAP ranged from 50% [three adjacent points missed (common cut-off)] to 71% (two or more points missed, any location), while specificity ranged from 58% (two or more points missed, any location) to 83% [three adjacent points missed (common cut-off)]. Sensitivity for optic disc photography ranged from 73% (rim area/disc area <0.66) to 77% [VCDR > 0.59 (common cut-off)], while specificity ranged from 59% [VCDR > 0.59 (common cut-off)] to 62% (rim area/disc area <0.66). In terms of the methodological quality of the study, the spectrum of people was seen as representative of those who would attend for screening, there was no evidence of partial or differential verification bias, and the results of the index tests were interpreted without knowledge of the results of the reference standard test, and vice versa. The reference standard for this study was glaucoma expert opinion based on slit-lamp examination, and dilated ophthalmoscopy to assess the optic disc and nerve fibre layer. Therefore, the estimates for the accuracy of optic disc photography as the index test may overestimate the accuracy of the test, as the reference standard, although a different test, is also a test of structure.

SAP compared with HRT II

Two studies compared SAP with HRT II, with Robin and colleagues[163] reporting HRT II as the better test, and Ieong and colleagues[186] reporting broadly similar results for both tests. Robin and

TABLE 24 *Studies directly comparing two or more of: optic disc photography, HRT II, FDT, SAP and GAT*

Study	Optic disc photography	HRT II	FDT	SAP	GAT
Ivers, 2001[157]				×	×
Ieong, 2003[186]		×		×	
Robin, 2005[163]		×	×	×	
Spry, 2005[176]			×	×	
Vitale, 2000[166]	×			×	
Wang, 1998[168]				×	×

colleagues[163] compared SAP (Central 24-2 threshold screening programme of the Humphrey field analyser) with HRT II in a population-based study set in Australia involving 261 people. The SAP test was analysed using the AGIS visual field test scoring method. Three definitions of abnormal HRT II were assessed: one or more borderline or severe abnormalities, two or more borderline or one or more severe abnormalities, or three or more borderline or one or more severe abnormalities. The reference standard was a full clinical ophthalmic examination and a panel of nine glaucoma experts determined the final diagnosis of glaucoma. Overall, HRT II performed better than SAP in terms of both sensitivity and specificity. Sensitivity for HRT II ranged from 90% (at least two borderline or one severe abnormality; at least three borderline or one severe abnormality) to 95% [at least one borderline or one severe abnormality (common cut-off)], while specificity ranged from 81% [at least one borderline or one severe abnormality (common cut-off)] to 91% (at least three borderline or one severe abnormality). Sensitivity for SAP ranged from 63% [AGIS score ⩾3 (common cut-off)] to 90% (AGIS score ⩾1), while specificity ranged from 58% (AGIS score ⩾1) to 74% [AGIS score ⩾3 (common cut-off)]. In this study the spectrum of people was seen as representative of those who would attend for screening, there was no evidence of partial or differential verification bias, and the results of the index tests were interpreted without knowledge of the results of the reference standard test, and vice versa. The accuracy of both SAP and HRT II as index tests may have been overestimated as visual field testing and estimates of CDRs also formed part of the reference standard.

Ieong and colleagues[186] compared SAP suprathreshold (DICON) with HRT II in a case–control study set in the UK involving 29 participants with OAG (including 15 NTG) and 37 normal participants, with the tests being carried out by eight optometrists. This study aimed to target those with early-stage glaucoma. OAG participants with minimal field loss were recruited through glaucoma clinics at Moorfields Eye Hospital. Normal participants were spouses or partners of those with OAG. The reference standard was glaucoma expert opinion. In terms of the criteria used to define a positive result, for SAP, decisions on whether visual plots were truly defective were left to the optometrists' judgement, while for HRT II if either the global or one of six segments was flagged abnormal the optic disc was regarded as suspicious, with borderline classifications taken as normal. The less affected eye of OAG participants was analysed, while for normal participants the eyes analysed alternated right then left in order of presentation. At the common cut-off, sensitivity for SAP and HRT II was 72% and 69%, respectively, while specificity for both tests was 95%. In terms of quality, the spectrum of people was not regarded as representative of screening or diagnosis in that only early disease was targeted, there was no evidence of partial or differential verification bias, and the results of the index tests were interpreted without knowledge of the results of the reference standard test, and vice versa. The accuracy of both SAP and HRT II as index tests may have been overestimated, as both visual field testing and optic nerve examination formed part of the reference standard.

SAP compared with FDT

Two studies compared SAP with FDT, with both Robin and colleagues[163] and Spry and colleagues[176] reporting FDT as better than SAP in terms of sensitivity, but worse in terms of specificity. Robin and colleagues[163] compared SAP (Central 24-2 threshold screening programme of the Humphrey field analyser) with FDT C-20-5 in a population-based study set in Australia involving 261 people. The SAP test was analysed using the AGIS visual field test scoring method. Four definitions of abnormal FDT C-20-5 were assessed: one abnormal point, two abnormal points, three abnormal points and one abnormal point at moderate or severe level. The reference standard was a full clinical ophthalmic examination and a panel of nine glaucoma experts determined the final diagnosis of glaucoma. Overall, FDT C-20-5 performed better than SAP in terms of sensitivity but worse in terms of specificity. Sensitivity for FDT C-20-5 ranged from 68% (one abnormal point at moderate or severe level) to 84% [one abnormal point (common cut-off)], while specificity ranged from 55% [one abnormal point (common cut-off)] to 76% (one abnormal point at moderate or severe level). Sensitivity for SAP ranged from 63% [AGIS score ⩾3 (common cut-off)] to 90% (AGIS score ⩾1), while specificity ranged from 58% (AGIS score ⩾1) to 74% [AGIS score ⩾3 (common cut-off)]. In this study the spectrum of people was seen as representative of those who would attend for screening, there was no evidence of partial or differential verification bias, and the results of the index tests were interpreted without knowledge of the results of the reference standard test, and vice versa. The accuracy of both SAP and FDT C-20-5 as index tests may have been overestimated as

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visual field testing also formed part of the reference standard.

Spry and colleagues[176] compared SAP threshold (SITA fast) with FDT C-20 matrix (Humphrey matrix 24-2) in a cohort study set in the UK involving 48 people. The reference standard consisted of an ophthalmic examination including the SAP threshold test. The definition of an abnormal test for both SAP and FDT was a GHT outside the normal limit and/or $p < 0.05$ with the pattern standard deviation global index in one or both eyes. At the common cut-off, the study reported sensitivity for SAP and FDT of 80% and 100%, respectively, while specificity was 52% and 27%, respectively. In terms of the quality of the study, the spectrum of people was considered representative of a diagnostic setting, there was no evidence of partial or differential verification bias, and the results of the index tests were interpreted without knowledge of the results of the reference standard. The results of the reference standard were interpreted without knowledge of the FDT test results, but with knowledge of the SAP test results as this test formed part of the reference standard. Sensitivity and specificity may be overestimated as both index tests were visual field tests, with one (SAP) also forming part of the reference standard, resulting in incorporation bias for this test.

SAP compared with GAT

Two studies[157,168] compared SAP suprathreshold with GAT, with both reporting that SAP performed better than GAT in terms of sensitivity but worse in terms of specificity. Ivers and colleagues[157] compared SAP (Humphrey 76-point suprathreshold screening test) with GAT in a population-based study set in Australia (Blue Mountains Eye Study) involving 3654 people. Criteria for a positive SAP test included one, three, five or ten or more points missing, while GAT was assessed at IOP greater than 22 mmHg and IOP greater than 28 mmHg. The reference standard for all participants was a detailed eye examination and a screening visual field test. Glaucoma suspects received a more thorough reference standard consisting of a full threshold visual field test. Sensitivity for SAP ranged from 37% (ten or more points missing) to 100% (one or more points missing), while specificity ranged from 50% (one or more points missing) to 92% (ten or more points missing). At the common cut-off sensitivity and specificity for SAP was 89% and 73%, respectively. Sensitivity for GAT ranged from 3% (IOP > 28 mmHg) to 14% [IOP > 22 mmHg (common cut-off)], while specificity ranged from 98% [IOP > 22 mmHg (common cut-off)] to 99% (IOP > 28 mmHg). In terms of the quality of the study, the spectrum of people was seen as representative of those who would attend for screening, there was no evidence of partial verification bias in that everyone received a reference standard test, but there was evidence of differential verification bias in that only test positives on the index tests went on to receive a more thorough reference standard. Although the results of the index tests were interpreted without knowledge of the results of the reference standard test, thereby avoiding test review bias, diagnostic review bias may have occurred in that the final diagnosis of glaucoma was made with knowledge of the results of the SAP and GAT index tests, potentially biasing the assessment of glaucoma status. The accuracy of both SAP and GAT as index tests may have been overestimated, as visual field testing and IOP measurement formed part of the reference standard, so that it was not wholly independent of the index tests, leading to incorporation bias.

Wang and colleagues[168] compared SAP suprathreshold (Humphrey full field 120 screening programme) with GAT in a population-based study set in the USA involving 510 people. The participants were selected from those attending an adult primary care clinic at the Johns Hopkins Hospital. SAP was assessed at 17 or more absolute or relative defects, while GAT was assessed at IOP above 21 mmHg. The reference standard for all participants was a full ophthalmological examination. Only screen positives were referred for a further definite diagnosis of glaucoma. At the common cut-off, the study reported sensitivity for SAP and GAT of 70% and 28%, respectively, while specificity was 67% and 96%, respectively. In terms of the quality of the study, the spectrum of people was seen as representative of those who would attend for screening, there was no evidence of partial verification bias in that all participants received a reference standard test, but there was evidence of differential verification bias in that only test positives on the index tests went on to receive a more thorough reference standard. Although the results of the index tests were interpreted without knowledge of the results of the reference standard test, avoiding test review bias, it was unclear whether the reference standard test was interpreted without knowledge of the results of the index tests. The accuracy of both SAP and GAT as index tests may have been overestimated, as visual field testing and IOP measurement formed part of the reference standard, so that it was not wholly

TABLE 25 *Sensitivity, specificity, DOR and RDOR at the common cut-off for studies directly comparing tests*

Study	Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	RDOR (95% CI)
Ivers, 2001[157]	SAP suprathreshold	89 (80 to 94)	73 (71 to 74)	20 (10 to 39)	1
	GAT	14 (7 to 23)	98 (97 to 98)	6 (3 to 12)	0.31 (0.12 to 0.78)
Ieong, 2003[186]	SAP suprathreshold	72 (53 to 87)	95 (82 to 99)	46 (9 to 237)	1
	HRT II	69 (49 to 85)	95 (82 to 99)	39 (8 to 198)	0.85 (0.08 to 8.54)
Robin, 2005[163]	SAP threshold	63 (38 to 84)	74 (68 to 80)	5 (2 to 13)	1
	HRT II	95 (74 to 100)	81 (75 to 85)	75 (10 to 574)	15.01 (1.57 to 143.82)
	FDT C-20-5	84 (60 to 97)	55 (49 to 61)	7 (2 to 23)	1.31 (0.27 to 6.43)
Spry, 2005[176]	SAP threshold	80 (52 to 96)	52 (34 to 69)	4 (1 to 18)	1
	FDT C-20 matrix	100 (78 to 100)	27 (13 to 46)	12 (1 to 222)	2.83 (0.11 to 72.91)
Vitale, 2000[166]	SAP suprathreshold	50 (37 to 63)	83 (76 to 88)	5 (3 to 9)	1
	Optic disc photography	77 (62 to 89)	59 (50 to 67)	5 (2 to 11)	0.99 (0.36 to 2.75)
Wang, 1998[168]	SAP suprathreshold	70 (57 to 80)	67 (59 to 74)	5 (2 to 9)	1
	GAT	28 (17 to 40)	96 (93 to 98)	9 (4 to 19)	1.89 (0.70 to 5.13)

RDOR = index test DOR/SAP DOR. RDOR calculated as all direct studies had SAP as one of the tests. Values of RDOR > 1 indicate that the test performed better than SAP in the study and values < 1 indicate that the test performed worse than SAP.
For details of the common cut-off selected for each test see Appendix 13.

independent of the index tests, leading to incorporation bias.

Summary

Table 25 shows the sensitivity, specificity, DOR and relative RDOR at the common cut-off for the tests being compared directly within studies. In terms of sensitivity, SAP performed better than GAT,[157,168] broadly similar[186] or worse[163] than HRT II and worse than optic disc photography,[166] FDT C-20-5[163] or FDT C-20 matrix.[176] In terms of specificity, SAP performed better than optic disc photography,[166] FDT C-20-5[163] or FDT C-20 matrix,[176] broadly similar[186] or worse than HRT II[163] and worse than GAT.[157,168] DORs for the tests ranged from 4 for SAP threshold[176] to 75 for HRT II,[163] with higher DORs indicating more convincing diagnostic evidence.

In terms of RDORs, compared with SAP, GAT performed better[168] or worse,[157] HRT II performed better[163] or worse,[186] FDT C-20-5[163] and FDT C-20 matrix[176] performed better, while optic disc photography[166] showed a broadly similar performance. The RDORs in the study by Ivers and colleagues[157] were statistically significant in favour of SAP suprathreshold over GAT, while those in the study by Robin and colleagues[163] were statistically significant in favour of HRT II over SAP threshold.

The studies by Robin and colleagues,[163] Vitale and colleagues[166] and Spry and colleagues[176] met the criteria specified for higher quality studies.

However, incorporation bias occurred in the study by Robin and colleagues[163] and Spry and colleagues[176] as the SAP test also formed part of the reference standard. There was a possibility of incorporation bias in the study by Vitale and colleagues[166] as one index test (optic disc photography) and tests that formed part of the reference standard (slit-lamp biomicroscopy) were tests of structure.

Indirect comparisons in a single HSROC model

The results of the indirect comparison of the ten tests are given in *Table 26*. Out of the large number of comparisons only four for sensitivity and two for specificity showed a statistically significant difference between tests. There was evidence that the sensitivity of FDT C-20-1 was higher than ophthalmoscopy (–30, 95% CrI –62 to –0.01) and GAT (45, 95% CrI 17 to 68), and that SAP threshold (41, 95% CrI 14 to 64) and HRT II (39, 95% CrI 3 to 64) had a higher sensitivity than GAT. For specificity, there was evidence of a higher level for GAT than for FDT C-20-5 (–19, 95% CrI –53 to –0.2) and SAP threshold (–14, 95% CrI –37 to –1). Several other comparisons were close to being statistically significant. No one test (or group of tests) was clearly more accurate than the others.

Discussion of results

Main findings

The included studies reported tests of structure (ophthalmoscopy; optic disc photography, RNFL

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TABLE 26 *Pairwise indirect comparisons of the 10 tests*

Comparison[a]	Difference between tests	
	Sensitivity, median (95% CrI)	**Specificity, median (95% CrI)**
Ophthalmoscopy versus		
Optic disc photography	–12 (–46 to 20)	6 (–7 to 21)
RNFL photography	–14 (–50 to 26)	6 (–7 to 30)
HRT II	–24 (–57 to 14)	5 (–9 to 30)
FDT C-20-1	–30 (–62 to –0.01)*	0.3 (–11 to 18)
FDT C-20-5	–11 (–49 to 32)	19 (–2 to 53)
OKP	–20 (–54 to 19)	4 (–9 to 26)
SAP suprathreshold	–10 (–43 to 20)	9 (–4 to 22)
SAP threshold	–26 (–58 to 2)	14 (–2 to 37)
GAT	15 (–22 to 47)	–0.06 (–12 to 7)
Optic disc photography versus		
RNFL photography	–2 (–31 to 34)	–0.05 (–17 to 24)
HRT II	–12 (–38 to 22)	–1 (–18 to 24)
FDT C-20-1	–18 (–42 to 6)	–6 (–21 to 12)
FDT C-20-5	1 (–30 to 40)	12 (–10 to 47)
OKP	–8 (–35 to 27)	–2 (–18 to 21)
SAP suprathreshold	2 (–23 to 25)	3 (–13 to 17)
SAP threshold	–14 (–38 to 7)	8 (–11 to 31)
GAT	27 (–4 to 53)	–6 (–21 to 3)
RNFL photography versus		
HRT II	–10 (–45 to 25)	–1 (–25 to 24)
FDT C-20-1	–16 (–50 to 10)	–5 (–29 to 13)
FDT C-20-5	3 (–36 to 44)	12 (–16 to 47)
OKP	–6 (–43 to 30)	–1 (–26 to 22)
SAP suprathreshold	4 (–31 to 29)	3 (–21 to 18)
SAP threshold	–12 (–46 to 12)	8 (–17 to 32)
GAT	29 (–10 to 57)	–6 (–30 to 4)
HRT II versus		
OKP	4 (–29 to 38)	–1 (–26 to 22)
FDT C-20-1	–6 (–38 to 17)	–4 (–29 to 14)
FDT C-20-5	12 (–23 to 52)	13 (–16 to 49)
SAP suprathreshold	14 (–18 to 36)	4 (–21 to 19)
SAP threshold	–2 (–34 to 18)	9 (–18 to 33)
GAT	39 (3 to 64)*	–5 (–30 to 5)
OKP versus		
FDT C-20-1	–10 (–42 to 14)	–3 (–26 to 14)
FDT C-20-5	9 (–29 to 49)	14 (–13 to 49)
SAP suprathreshold	10 (–24 to 34)	5 (–18 to 19)
SAP threshold	–6 (–39 to 16)	10 (–15 to 34)
GAT	35 (–2 to 62)	–4 (–26 to 5)
SAP suprathreshold versus		
FDT C-20-1	–20 (–40 to 3)	–8 (–22 to 9)
FDT C-20-5	–1 (–29 to 38)	10 (–12 to 45)
SAP threshold	–16 (–37 to 5)	5 (-12 to 28)
GAT	25 (–2 to 50)	–9 (–22 to 0.3)
SAP threshold versus		
FDT C-20-1	–4 (–23 to 18)	–13 (–36 to 6)
FDT C-20-5	15 (–11 to 53)	5 (–23 to 41)
GAT	41 (14 to 64)*	–14 (–37 to –1)*
FDT C-20-1 versus		
FDT C-20-5	19 (–10 to 57)	18 (–6 to 53)
GAT	45 (17 to 68)*	–0.4 (–18 to 8)
FDT C-20-5 versus GAT	26 (–16 to 57)	–19 (–53 to –0.2)*

[a] A versus B = A – B.
* Statistically significant difference.

photography, HRT II), visual function (FDT, OKP, SAP) and IOP (GAT, NCT). Other tests were considered, including those of structure (GDx VCC, OCT, RTA), visual function (SWAP, MDP) or using Tonopen to measure IOP. However, no studies using these tests met the inclusion criteria in terms of reporting of test accuracy outcomes.

Despite the huge volume of literature, no good-quality studies were found providing a positive response to all questions on the modified QUADAS checklist. Eight studies were rated as higher quality in that the spectrum of people was considered representative of a screening or diagnostic setting, and partial and differential verification bias and test and diagnostic review bias were avoided.

Analyses were performed at a number of different levels:

- HSROC model for each test at all cut-offs and a common cut-off
- HSROC model for tests reported by two or more higher quality studies at a common cut-off
- analysis of studies reporting combinations of tests
- analysis of studies reporting the accuracy of tests for stages of glaucoma
- analysis of studies directly comparing two or more tests in the same population
- indirect comparison of all tests from all included studies at a common cut-off.

From the available data, the following tests were considered to be potentially feasible for use in a screening programme for detection of OAG: optic disc photography, HRT II, FDT, SAP and GAT. Direct comparison studies provide the most robust estimates of comparative test accuracy. Only six studies directly compared two or more of these tests, with all studies including SAP as one of the tests.[157,163,166,168,176,186] In these studies, at the common cut-off, in terms of sensitivity, SAP performed better than GAT,[157,168] broadly similar[186] or worse[163] than HRT II and worse than optic disc photography,[166] FDT C-20-5[163] or FDT C-20 matrix.[176] At the common cut-off, in terms of specificity, SAP performed better than optic disc photography,[166] FDT C-20-5[163] or FDT C-20 matrix,[176] broadly similar[186] or worse than HRT II[163] and worse than GAT.[157,168] Three direct comparison studies met the criteria for higher quality studies.[163,166,176]

The pooled estimate of the sensitivity of the tests in detecting OAG ranged from 46% (GAT) to 92% (FDT C-20-1), while specificity ranged from 75% (FDT C-20-5) to 95% (GAT). The FDT C-20-1 test was associated with the highest sensitivity (92%) and was one of the tests associated with the highest specificity (94%), along with ophthalmoscopy (94%) and GAT (95%). The pooled estimate for FDT C-20-1 showed higher sensitivity and specificity than the pooled estimate for FDT C-20-5 and also the single FDT C-20 full threshold study. This is unexpected (i.e. better sensitivity of C-20-1 than C-20-5). These findings were based on only three FDT C-20-1 studies, five FDT C-20-5 studies and one FDT C-20 full threshold study, with heterogeneity evident especially in the FDT C-20-5 studies. Forest plots showing sensitivity and specificity with 95% confidence intervals revealed statistical heterogeneity across studies for most tests, other than for the sensitivity of optic disc photography (number of studies, $n = 6$), sensitivity and specificity of HRT II ($n = 3$), and sensitivity of FDT C-20-1 ($n = 3$). Empirically, there was no obvious single cause for the heterogeneity, but potential contributory factors include differences in populations, study design, setting, prevalence and severity of glaucoma within studies. Other factors include differences in reference standard, and in tests included within the same category (e.g. different types of perimetry and ophthalmoscopy have a large number of variants, potentially leading to heterogeneity in discriminatory power across studies reporting those tests), and the extent to which studies were affected by other potential biases (e.g. partial and differential verification bias, incorporation bias, test and diagnostic review bias). Owing to the imprecision in the estimates from the pooled meta-analysis models for the diagnostic performance of each test it was not possible to identify a single test (or even a group of tests) as the most accurate.

Based on the pairwise indirect comparisons, in terms of statistically significant differences in test performance, there was evidence that GAT had a lower sensitivity than HRT II, SAP threshold and FDT C-20-1, but a higher specificity than SAP threshold and FDT C-20-5. FDT C-20-1 also seemed to have a better sensitivity than ophthalmoscopy. Other differences in accuracy between tests may well exist which could not be detected because of the high level of uncertainty. The wide credible intervals reflected the small number of studies reporting each test and the generally high level of heterogeneity.

Potential biases

Reference standard

OAG is a clinical diagnosis, based on structural abnormalities of the optic disc and an associated

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glaucomatous visual field defect. There is no universally agreed optimal reference standard for the diagnosis of OAG, although progressive structural optic neuropathy has been proposed as the best possible reference standard.[148,236] Variations in the reference standard used to define OAG directly affect the estimates of test accuracy.[237,238] In addition, the different tests become abnormal at different stages of the disease and at a single time-point agreement between tests is likely to be poor owing to these differences.

In this review either of two reference standard tests was considered. The primary reference standard was confirmed OAG on follow-up and was considered to be the best reference standard although, as anticipated, few studies used it. Therefore, another reference standard, cross-sectional ophthalmologist-diagnosed OAG, was also considered. The diagnosis from this second reference standard could be based on assessment of the visual field and/or the optic disc without requiring follow-up confirmation. Of the 40 studies included in this review, seven used a reference standard of follow-up confirmation of glaucoma.[22,106,166,171,174,178,189] However, there was no obvious pattern in terms of the sensitivity and specificity of the tests reported by studies using a reference standard of follow-up confirmation of glaucoma compared with those studies using a reference standard of ophthalmologist-diagnosed glaucoma.

Severity of the disease

The majority of the studies did not stratify test accuracy on the basis of disease severity. In general, tests become more sensitive as the disease becomes more severe. Hence, a study including participants with advanced disease should report better sensitivity. However, unless the distribution of disease severity in the examined population is explicitly reported in primary studies, it is not possible to evaluate the impact of any spectrum bias that might have occurred. In addition, if an adequate sample size for subgroups is not achieved, within-study comparisons of test performance may result in a loss of power to detect significant differences.[239] Seven studies reporting test accuracy in different stages of glaucoma were included in this review.[158,181,182,184,186,190,191] However, no consistent pattern of sensitivities and specificities for different stages of glaucoma emerged from the studies. One reason for this was that the studies mostly reported different tests. Of those reporting the same tests for different stages of glaucoma, Ieong and colleagues[186] reported a sensitivity of 72% for SAP suprathreshold for early-stage glaucoma, while Enger and Sommer[181] and Katz and colleagues[158] both reported a sensitivity of 97% for early/moderate-stage glaucoma. It is not unexpected that a visual field test such as SAP would increase in sensitivity as the disease progresses. Variations in the results between other studies can be explained by the use of non-uniform and non-standardised definitions for various stages of glaucoma. Some studies used structural damage to define these stages (early, moderate, severe), while others used functional damage. However, it could be argued that once functional damage is detectable on standard perimetry, then by definition the disease has progressed beyond early stage.[229,240,241]

Incorporation bias

In glaucoma diagnosis the concept of incorporation bias is complex. For example, it has been suggested that inclusion of any optic disc criteria in the reference standard when evaluating another optic disc test (e.g. HRT) introduces incorporation bias.[242] In such studies it may seem logical to use only visual field examination as a reference standard test. This, however, assumes that structural (e.g. optic disc) and functional (e.g. visual field) damage occur simultaneously in glaucoma pathogenesis, whereas there is evidence that disc damage precedes manifest visual field loss.[229,240,241] Up to 30% of optic nerve fibre damage occurs before visual field damage becomes detectable. Hence, using visual field assessment alone as a reference standard may report an unfairly low accuracy of an imaging test, especially if more people with early glaucoma are included in the study. For example, if visual field damage alone is used as a reference standard and a study is conducted at time-point A (*Figure 38*) to evaluate an imaging test, it will report many false positives, as detectable visual field damage has not yet occurred. However, if a similar study is performed at time-point B, there will be greater agreement between reference standard and index test and hence the test accuracy will be much higher.

Hospital-based studies (including case–control studies)

Twenty of the 40 studies included in this review were hospital based. A hospital population is, by nature, an enriched population and the prevalence of the disease will be higher than that in the community. This population may also include a disproportionate number of patients with high IOP and a disproportionately small number of patients with small optic discs, potentially leading to overoptimistic performance

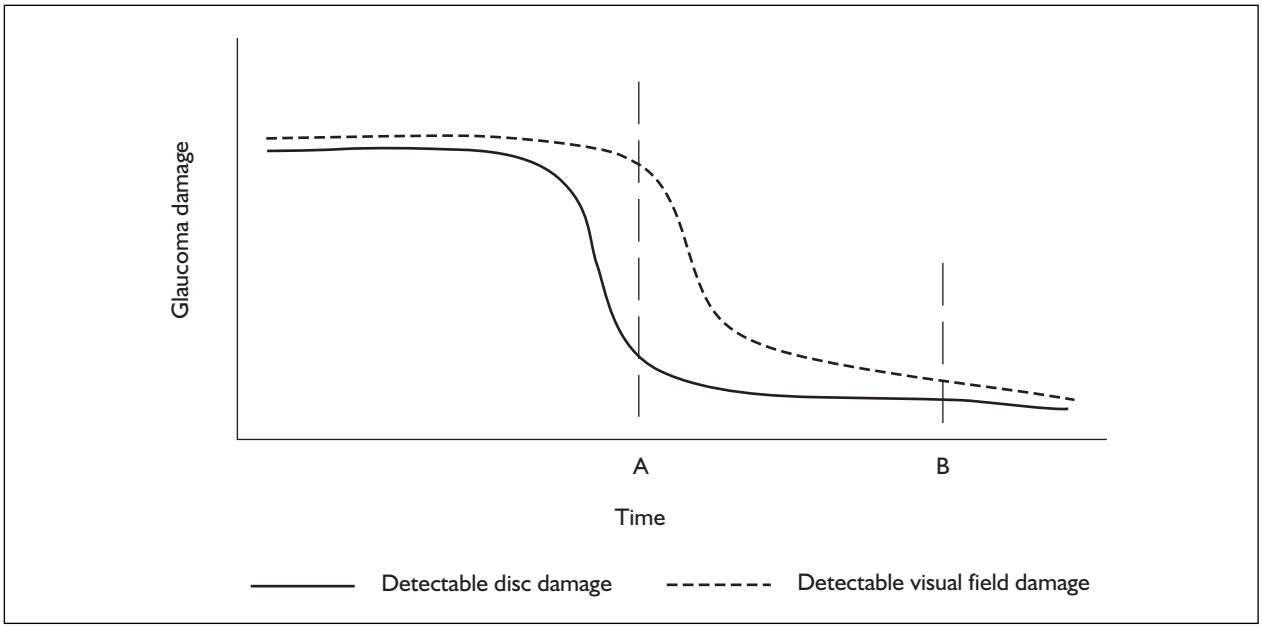

FIGURE 38 *Structural versus functional damage and effect on cross-sectional diagnostic studies*

estimates. In addition, hospital-based studies generally recruit participants from glaucoma clinics who have previous experience of tests and therefore these studies cannot account for the learning effect in those unfamiliar with such tests, unlike the case in a screening situation.[243–246] However, only hospital-based studies whose participants were considered to be representative of those referred from primary care were included in the review.

Diagnostic case–control studies are useful at the initial stages of validating a test. To test the applicability of a new test it should be applied directly to the population of its intended use. Case–control studies recruit participants with a clear disease status, that is, either with or without the target disease. Indeterminate and intermediate results are common, and often coexisting disease produces a positive test result. The majority of the case–control studies identified applied stringent criteria for inclusion such as visual acuity of 6/9, or no other ocular disease. Rutjes and colleagues[247] evaluated various potential sources of bias in diagnostic studies. The factor with the highest impact on estimates of test accuracy was a case–control study design with severely diseased cases and healthy controls. Fifty-seven case–control studies where the participants were considered unrepresentative of a case-mix found in a general population where OAG screening would be carried out were excluded from the review (see Appendix 10).

Prevalence of the disease

The accuracy of a test may vary according to the population in which it is performed. Although absolute sensitivity and specificity of a diagnostic test are independent of the prevalence of a disease, a diverse spectrum of the disease is encountered in different prevalence levels. With increasing prevalence more cases of moderate to severe disease are expected, and since it is easier to differentiate between severely diseased and non-diseased people, a test would be expected to report improved (apparent) sensitivity and specificity. Therefore, studies with a significantly higher prevalence than the UK estimates should be interpreted with this limitation in mind.[156,161–163,168,170] These studies tended to recruit their participants through media advertising rather than contacting individuals in a predefined population. These studies, including two that met the criteria for higher quality studies,[163,170] may be considered to be more representative of screening in higher risk populations.

Higher quality studies

Only eight studies met the criteria specified for higher quality studies, of which six were population based[155,156,163,166,169,170] and two were cohort studies.[175,176] For FDT C-20-5 and SAP threshold, the higher quality studies reported lower values for both sensitivity and specificity compared with all studies, while two studies not meeting the criteria for higher quality[173,187]

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reported very high sensitivity values. For optic disc photography, compared with all studies, the higher quality studies reported similar sensitivity, with slightly lower specificity. For HRT II, compared with all studies, the higher quality studies reported higher sensitivity but slightly lower specificity.

Issues relevant to screening

Uptake and time taken to perform the test

In addition to the sensitivity and specificity of the test(s), other factors may impact on the success of a screening programme, including the percentage of people invited who attend for screening (uptake), the percentage of those taking part who provide interpretable test results and the time taken to perform the test. Uptake levels ranged from 28.3[163] to 99.5%,[154] with a median rate across studies of 82.8%. The difference may be explained at least in part by differences in the way in which the studies made their targeted audience aware of the screening programme. For example, Robin and colleagues[163] advertised their programme through the media, while other studies with greater uptake adopted a more proactive approach in identifying their target population and inviting them to attend for screening.[21,99] The percentage of participants providing interpretable test results ranged from 79.5% for RNFL photography to 99.1% for GAT, with ophthalmoscopy (97.8%), OKP (96.9%), SAP threshold (98.9%), FDT C-20-1 (96.7%) and NCT (97.2%) all reporting rates of interpretable test results greater than 95%.

Few included studies gave details of the time taken to perform the test (see *Table 21*). None of the included studies of ophthalmoscopy, RNFL photography, HRT II or GAT reported the time taken to perform the test. One study reported this information for optic disc photography,[197] three for OKP,[154,170,212] four for SAP suprathreshold,[159,162,164,174] four for SAP threshold, all of which used SITA standard or SITA fast,[176,195,198,206] four for FDT C-20-1,[170,185,187,214] two for FDT C-20-5[155,187] and one for NCT.[164] The information provided on time taken to perform the test should be interpreted with this limitation in mind.

What stage of glaucoma should be targeted for screening?

It is important to determine the severity of glaucoma that screening should detect. This is important as tests that perform better in moderate to severe disease but have low diagnostic yield in early glaucoma could have an overall superior diagnostic utility as screening tests. Identifying large numbers of people with early disease that may never progress to significant visual impairment or reduction in quality of life may result in greater harm than benefit from screening.

Damage caused by OAG typically occurs slowly and over a long period. Many people diagnosed with glaucoma will never develop a significant visual impairment during their lifetime. Current case detection identifies only around half the number of people with OAG and thus prevents only a limited number from progressing to significant visual impairment. Introducing OAG screening with a test that is sensitive for moderate disease will prevent significant visual impairment in an additional number of people but will still miss some cases. Using a highly sensitive test for OAG will identify all those who are at risk of developing significant visual field loss and blindness; however, it will also identify a large proportion of people who are not at risk of developing severe glaucoma during their lifetime. Treating these otherwise asymptomatic individuals could result in the unnecessary use of limited healthcare resources. In addition, labelling asymptomatic individuals as 'diseased' may well cause unnecessary anxiety.

Most of the visual disability in glaucoma is related to visual field loss. Therefore, it is reasonable to target glaucoma with early visual field loss (i.e. perimetric glaucoma) in OAG screening. It is worth noting that this does not rule out structural tests from glaucoma screening. A structural test such as HRT may have a better diagnostic performance than a functional test such as SAP in the perimetric stage of glaucoma because, in this stage, the disc damage would have progressed beyond early stage and would therefore be easier to detect.

Strengths and limitations of the review

The field of systematic reviews of diagnostic tests is a nascent one and the methodology for these complex reviews is currently still evolving. Bearing these limitations in mind, this review is one of the largest systematic reviews of screening and diagnostic tests in glaucoma. Several levels of analyses were undertaken, including HSROC analysis on all studies and higher quality studies, analysis of studies reporting combinations of tests, studies reporting accuracy of tests for detecting stages of glaucoma and studies directly comparing two or more tests. In addition, all the tests were modelled simultaneously (in one model)

using a Bayesian approach. This allowed direct estimates of differences in sensitivities and specificities to be calculated. To be included, studies had to meet specific inclusion criteria. The validity of indirect comparisons does depend on assumptions regarding the characteristics of the included studies; however, the indirect method is formally performing the comparison that users of the report are likely to make when assessing the pooled results for the individual tests. As such, this method of indirect comparisons serves an important purpose and reaffirms the lack of certainty about which test is indeed the best.

In terms of limitations, relatively few studies were identified for each test and it was not possible to perform sensitivity analysis based on study design. Owing to the small number of studies for each test, different study designs (population-based studies and studies including an already suspect population) were pooled together in the HSROC meta-analysis models. Only six of the 40 studies directly compared two or more of the tests that were considered to be potentially feasible for use in a screening programme. There were too few studies on the individual tests for the indirect comparison to identify what was the best test. Only eight studies met the criteria for higher quality studies. The studies were lacking in evidence of test accuracy in high-risk groups and those most likely to be targeted for OAG screening. There is a lack of a generally agreed reference standard test for OAG against which other tests can be evaluated. Studies not providing sufficient information to allow the calculation of 2×2 tables were excluded, although they may have contributed information in terms of sensitivity and specificity. Case–control studies where the participants were not considered representative of a screening population were also excluded, even if the same inclusion and exclusion criteria were applied to both cases and controls, although they may have contributed information on test accuracy in a clinic situation.

Conclusions

Implications for practice

For a low-prevalence disease a screening test needs to be highly specific. In the meta-analysis models the following tests provided a specificity of 85% or higher: ophthalmoscopy (94%), optic disc photography (89%), RNFL photography (88%), HRT II (89%), FDT C-20-1 (94%), OKP (90%), SAP suprathreshold (85%) and GAT (95%). In this review the FDT C-20-1 test was associated with the highest combination of sensitivity and specificity for detecting OAG. As pointed out earlier, there was a wide variation in the reference standards among included studies. Variations in the reference standards may partly account for varied diagnostic accuracies: a stricter reference standard within a study will lead to a higher specificity and vice versa. However, owing to the strongly heterogeneous nature of the data overall and the relatively small number of studies, it was not possible to conclude with certainty whether any one test was definitely superior in terms of accuracy.

Implications for future research

Future research should focus on a consensus OAG definition and reference standard. As a significant proportion of visual morbidity in glaucoma is directly related to visual field loss, a definition with emphasis on visual field damage may be more appropriate. The possibility of a consensus reference standard test should also be explored. The definition of different severities of glaucoma is important, and the stage of glaucoma that is important to be detected by screening should be agreed. There is a need for high-quality primary studies comparing candidate screening tests in an appropriate population.

The accuracy of the various screening tests should be evaluated in a sufficiently large population-based study. Initially, a cross-sectional study to evaluate the relative accuracies of comparator tests would be preferable. The main advantage of a cross-sectional study is a quick outcome. A diagnostic cross-sectional study could be an RCT where patients are randomised to one or the other test(s), or it may be a paired study where each patient receives both (several/all) tests. The advantage of a paired study is that a smaller sample size is required. However, for logistical reasons, it may not be practical for every participant to receive all tests. The study should have a predetermined sample size for assessment of test accuracies in high-risk subgroups and for populations in whom glaucoma screening is thought to be cost-effective. Different combination algorithms combining structural and functional tests need further exploration. In this review the common cut-off chosen for each test was the one most frequently reported by the studies, which may not necessarily be the most appropriate. For example, IOP testing was considered an integral part of a screening strategy, but studies generally reported data only for a cut-off of above 21 mmHg, although also providing data for other, additional, cut-offs would have been more informative.

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Chapter 7

Evidence of effectiveness

Screening for prevention of optic nerve damage due to OAG

Introduction

A Cochrane systematic review of screening for OAG, led by the Cochrane Eyes and Vision group, is in the final stages of completion[248] (and Cochrane Collaboration Eyes and Vision Group: personal communication, 2006). A summary is provided in this section.

The aim of this review was to determine the impact of screening, in terms of benefits and harms, compared with opportunistic case finding. Effectiveness of screening can be assessed by the prevalence of and degree of optic nerve damage due to OAG in screened and unscreened populations, assuming that successful detection and subsequent treatment of OAG lead to lower prevalence of advanced optic nerve damage in screened versus unscreened populations.

Methods

Inclusion and exclusion criteria

RCTs of screening versus no screening for OAG were eligible for inclusion. The reference strategy of no screening included case finding; that is, opportunistic detection. Trials comparing different screening strategies were not included. Any method of randomisation was considered, including that in which individuals, locations or practices were randomised, and differences in study quality were taken into account in the analysis. Ideally, trials should have analysed data on an intention-to-treat (ITT) basis. It was planned to include other types of analysis provided all randomised patients were accounted for and to use an available case-based analysis.

Types of participant

Studies from any population were considered, but major differences in the populations studied such as age at screen and race would be reported when analysing the results. People already known to have glaucoma or already under the care of an eye specialist, or known to be visually impaired for other reasons were not expected to be included in routine screening. Screening is likely to detect other degenerative eye conditions and other forms of glaucoma, although these were not included as the primary outcome of the review.

Types of intervention

Studies of any screening modality for OAG were eligible.

Types of outcome measure

Primary outcomes

Any or all of the following three primary outcomes were considered for this review:

- Prevalence of any degree of characteristic visual field loss in screened and non-screened populations as diagnosed by any method of visual field assessment (excluding confrontation). The proportion of people with a predetermined severity of field loss (attributable to glaucoma) was to be compared in the screened and unscreened populations.
- Prevalence of optic nerve damage in screened and non-screened populations as diagnosed by any method of imaging. The difference in the prevalence of a prespecified degree of structural optic nerve damage would have been examined in screened and unscreened populations.
- Prevalence of visual impairment in screened and non-screened populations as defined by number of subjects certified or registered according to national or regional standards (where the study was conducted) as:
  - blind
  - partially sighted
  - vision below standard for driving.

Secondary outcomes

Screening may lead to more treatment and subsequently a lower mean IOP in screened than in unscreened populations. IOP is a surrogate outcome but, nevertheless, indirect evidence of effectiveness of screening might be derived from the reduction in the severity of the most well-established and modifiable risk factor. Reporting of any differences in mean IOP in screened and unscreened populations was planned.

Adverse effects

False negatives are people with glaucoma who pass screening and go on to lose vision. False

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positives are people without glaucoma who fail screening and are referred for further investigation but who do not undergo any treatment. Referral causes excess burden on health services and unnecessary inconvenience and anxiety for the patient.

Quality of life measures
Reporting of any measures of quality of life or health status attributable to the screening or OAG was planned.

Economic data
Reporting of any economic data on the costs and cost-effectiveness of programme implementation, cost per case identified or other costs relating to the screening programme was planned.

Other outcomes
The technical differences between the screening and control interventions, the quality of the intervention including any quality control measures, rates of participation, contamination and follow-up were measured among screening and control arms.

Follow-up
A minimum follow-up of 1 year postscreening was required for all studies.

Search strategy for identification of studies
Any RCTs evaluating population-based screening programmes for OAG with a minimum 1-year follow-up were included.

Electronic searches
The searches outlined in Chapter 4 were used; however, for this review no language or date restrictions were applied, according to Cochrane methodology. No manual searches were undertaken for this review.

Results
The search generated 1191 records of studies relevant to the search criteria, but none was an RCT of screening and hence no data extraction or analysis was conducted.

Discussion
No RCTS were identified, the applied search strategy (detailed in Appendix 2) was comprehensive, with in this case no language restrictions, and as such it is very unlikely to have missed any existing trials. Two major sources of bias that will otherwise distort the findings of observational studies can only be dealt with by randomised trials of screening.

Lead-time bias occurs when the condition is detected at an earlier stage through screening, although no influence on ultimate outcome is achieved as a result of that earlier detection. The survival is apparently greater because the condition is known about for longer, but an otherwise similar unscreened individual goes blind at the same rate, although spending less time being aware of the problem. In such a circumstance, it is fair to conclude that screening has done harm.

Length bias occurs because interval screening is more likely to detect slowly progressive and indolent disease than aggressive, rapidly progressing glaucoma. Apparently, screening has led to more people with early-stage disease being identified who are at much lower risk of blindness. This apparent benefit may actually be harmful if the risk of the adverse effects of disease in these mild cases is very low, and the number of people with aggressive, blinding glaucoma may remain the same and the blindness rates unchanged.

Hence, this review specifically searched for RCTs of screening in that it is the only study design that can adequately deal with these two sources of bias. However, the organisation and conduct of such studies is demanding and long-term follow-up is required on large numbers of people if there is to be any likelihood of detecting an effect. It is perhaps not surprising that no such trials were identified. Justification for such a study will depend on refinement of screening test strategies and economic modelling of potential benefit and cost.

Conclusions
Effectiveness of screening for OAG can only be established by high-quality randomised trials. Some preliminary issues need to be dealt with before such trials can be undertaken. A better understanding of testing technologies is needed and high-quality studies in different populations are required to delineate optimum screening strategies in terms of individuals, tests, combinations of tests and test frequency. It is recognised that 1-year follow-up, included as a minimum in this review, is extremely short in the course of glaucoma. Ideally, much longer follow-up is required; however, surrogate outcomes such as IOP at 1 year can be indicators of prognosis. Modelling alongside a trial can be used to predict long-term costs and benefits. Better monitoring of health outcomes in large populations using registers of blindness by cause can provide surveillance for the observation of the impact of prevention strategies over time.

Effectiveness of glaucoma treatment

Introduction

Treatment aims to prevent visual disability and preserve overall wellbeing for patients with glaucoma. The visual loss in glaucoma is due to the death of retinal ganglion cells. Vascular and/or mechanical factors at the optic nerve head may precipitate cell death and IOP may be implicated in either or both of these mechanisms.[249] Currently, IOP is the only risk factor that can be treated.

Medical treatment, to lower IOP, is administered topically as eye drops. These treatments are commonly topical β-blockers, and more recently newer topical agents including carbonic anhydrase inhibitors, α_2-agonists and prostaglandin analogues have been introduced. β-Blockers and prostaglandin analogues are the most commonly used medications. Reduced rates of surgery for glaucoma are felt to be a consequence of the introduction of these new eye drops.[250] An alternative or additive treatment to the use of medications is laser trabeculoplasty with discrete laser ablation to the trabecular meshwork of the drainage angle. The effectiveness of alternative medical interventions for OAG and of laser trabeculoplasty is being assessed in two Cochrane reviews that are currently in progress.[30,31]

Glaucoma drainage surgery aims to lower the IOP by creating an alternative route for aqueous humour outflow. Trabeculectomy is the most common glaucoma surgical procedure. In a Cochrane review of medical versus surgical interventions for OAG, evidence from one trial suggests, for mild OAG, that visual field deterioration up to 5 years is not significantly different whether treatment is initiated with medication or trabeculectomy. There was no evidence to determine the effectiveness of contemporary medication (prostaglandin analogues, α_2-agonists and topical carbonic anhydrase inhibitors) compared with surgery in severe OAG.[29]

The aim of this part of the project was to undertake a systematic review to determine the effectiveness of any IOP-lowering treatment (medical, laser or surgery or any combination thereof), compared with no treatment in preventing glaucoma progression in terms of reduced visual field loss and progressive optic nerve damage (a surrogate outcome for visual field loss), and on patient-reported health status.

Methods

Inclusion and exclusion criteria

Systematic reviews and RCTs of treatment versus no treatment for participants with OAG were included. Studies where the participants had ocular hypertension (i.e. raised IOP but no evidence of glaucoma damage) were excluded.

Data extraction

One reviewer screened the titles and abstracts of the identified reports.

Quality assessment

A previously validated ten-item checklist developed by Oxman was used to assess the methodological quality of systematic reviews meeting the inclusion criteria.[251,252] The checklist contains nine criteria, scored as 'Yes', 'Partially' or 'No', depending on the extent to which they are met. The checklist also provides one summary criterion for overall scientific quality, scored on a seven-point scale, where 1 indicates 'extensive flaws' and 7 indicates 'minimal flaws'.

Results

Number and type of studies included

In total, 323 reports were identified, and 15 full-text papers were selected for assessment. One systematic review of RCTs of treatment versus no treatment for ocular hypertension and OAG was identified.[19] No further RCTs of treatment effectiveness for OAG: other than those included in the systematic review and also separately identified by the search strategy, were identified. One additional RCT[253] was identified where participants had ocular hypertension, but this did not meet the inclusion criteria of this specific review and was excluded.

Characteristics of included study

The systematic review by Maier and colleagues[19] included seven studies; however, five of these related to the treatment of ocular hypertension and therefore are not relevant to this review. Thus, this review reports the results of the two included trials of treatment versus no treatment for participants with OAG: the Early Manifest Glaucoma Trial (EMGT),[27] where participants had been identified as having manifest OAG with or without raised IOP, and the Collaborative Normal Tension Glaucoma Study (CNTGS),[254] where participants had OAG but the IOP had not been recorded as over 24 mmHg in either eye.

The CNTGS was a 5-year study in the 1990s across 24 centres in the USA, Canada, The Netherlands and Finland. One eye of 145 participants with

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progressive NTG was randomised to treatment or no treatment. In the treatment arm, treatment could be medical or surgical and aimed for a 30% reduction in IOP. The end-point of the study was documented progression either in terms of visual field or optic disc changes compatible with progression. The rate of development of cataracts in the untreated participants was significantly lower than in the surgically treated group. In a survival analysis there was no significant difference in the risk of progression between the two groups; however, after censoring for cataract development the treated group had a significantly lower risk of progression. The mean survival time to progression in the treated arm was 6 years, and 5 years in the no-treatment arm.

The EMGT had a different spectrum of participants from CNTGS, recruiting newly detected OAG cases identified from a population-screening programme with 255 participants randomised to treatment or no treatment. Participants with very high IOPs (mean IOP >30 mmHg) were excluded. All eyes randomised to treatment received a full 360-degree trabeculoplasty plus a selective β-blocker eye drop (Betaxalol). Additional therapy was added if the IOP exceeded 25 mmHg on two consecutive occasions. At the final analysis (median follow-up of 6 years), 78 (62%) of the 126 control eyes versus 58 (45%) of the 129 treated eyes progressed (log-rank $p = 0.007$). The median time to progression was 5.5 years in the treated patients and 4 years in the no-treatment group. More patients in the treatment arm developed cataract than in the no-treatment group ($p = 0.004$). Health-related quality of life (HRQoL) was measured using a Swedish translation of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), but was not measured at baseline, as the questionnaire was not available at that time. There was no significant difference in composite scores between the treated and untreated group at 6-year follow-up. The results of this study therefore suggest that treatment, whether by randomisation or received during follow-up, was not related to vision-targeted HRQoL. However, the analysis of the HRQoL data was not an ITT analysis.

Quality assessment

The systematic review was assessed as having only minor flaws, in that the criteria used to assess the methodological quality of the included trials were not stated, the search strategy was deemed to be reasonably comprehensive in that there were no language restrictions, reference lists were searched and authors were contacted for further details if required, but there was no handsearching (see Appendix 14 for the detailed results of the quality assessment of the systematic review). As the systematic review had not assessed the methodological quality of the included trials, the quality of the two included RCTs was assessed according to criteria developed by the Cochrane Collaboration Eyes and Vision Group. These criteria assess quality in terms of likelihood of selection, performance, detection and attrition bias. In CNTGS it was unclear whether allocation was adequately concealed, participants and clinicians were not masked to treatment assignment, the person assessing outcomes was unaware of the assigned treatment, it was unclear whether follow-up rates were similar in comparison groups, and the analysis was ITT. Thus, this study can be considered as potentially prone to selection, performance and possibly attrition bias. EMGT was graded as low risk of bias for selection, detection and attrition bias (except for the HRQoL outcome), but there was a possibility of performance bias in that clinicians and participants were not masked to treatment allocation. The nature of the study was such that clinicians needed to be aware of treatment allocation to decide on clinical management during the study.

Assessment of effectiveness

The analysis by Maier and colleagues[19] combined the results of these two studies using a DeSimonian and Laird random effects model and showed a significant pooled treatment effect of lowering IOP to prevent glaucoma progression (hazard ratio 0.65, 95% CI 0.49 to 0.87, $p = 0.003$). There was no significant statistical heterogeneity between the studies ($\chi^2 = 0.13$, $p = 0.72$).

Discussion

In both studies the definition of glaucoma progression was based on either or both of progressive glaucomomatous optic disc changes or progressive visual field loss and progression was determined by a reading committee masked to the intervention. The criteria defining progression of visual field loss and optic disc changes differed between studies but in both studies there was a strict definition of progression, visual field assessment was on automated perimetry and in both studies visual field loss had to be confirmed on repeat testing. In both studies, of those participants progressing, the majority were based on progressive visual field loss with all bar one participant in the EMGT, and three participants in the CNTGS, progressing on optic disc criteria alone.

The results suggest a beneficial treatment effect; however, neither study was graded as high quality on all criteria, and as such the effects may be subject to bias, and the results should be interpreted with this in mind.

Conclusions

Evidence from the included, good-quality, systematic review suggests that treatment is effective at slowing the rate of progression of OAG. It is less certain as to how this translates into the effectiveness of treatment on reducing long-term visual impairment and maintaining quality of life.

Probability of glaucoma deterioration from mild disease to visual impairment

Introduction

As described in the previous section, OAG is typically a slowly progressive disease. The purpose of this section is not systematically to describe all issues and studies that have investigated progression *per se*, but to describe specifically for the purposes of the economic modelling the approximate probability of progressing from mild disease to visual impairment. OAG was defined using a visual field glaucoma staging system that had four stages: mild, moderate, severe and visually impaired (partial sight and blind). The details are described below. Progression was assumed to follow a linear course, implying that a newly diagnosed glaucoma patient would start with mild disease and progress through every stage until visually impaired.

The aim of this component of the study was to estimate the yearly probability of progressing from mild to moderate, moderate to severe and severe to visually impaired.

Grading of disease severity

There is no accepted scale of glaucoma severity. Automated threshold perimetry is a widely accepted method of assessing uniocular glaucoma severity and for monitoring progression in each eye, but there is no standardised definition of severity and progression on automated perimetry. There is also limited evidence on the correlation between the severity of visual field loss and patient-reported visual disability and quality of life.

RCTs for OAG[27,255,256] each developed different scoring systems for defining severity and progression. These scoring systems were event based, in that progression was confirmed when a preset threshold was exceeded. When each of these scales was applied to the same cohort of patients the rates of apparent progression varied according to which scoring scale and definition of progression were used.[257,258]

A modified version of the glaucoma severity scale used by a study group examining the costs of glaucoma treatment by stage in Europe and the USA was used for this study[259,260] (*Table 27*). This scale itself was a modification of the Hodapp–Anderson–Parrish scale.[261] For the purposes of this study a commonly reported measure of the depth of the glaucomatous visual field defect was used; this was the mean defect or mean deviation (MD) on standard automated perimetry. The MD refers to the average deviation in decibels (dB) of the measured threshold values from the age-corrected normal value. One problem with using the MD alone to classify severity is that other non-glaucomatous disease, mainly the presence of cataract, affects the MD. Other glaucoma severity scales are based on the MD, but also take into account other characteristics of visual field loss such as the location and clustering of the defect, the pattern deviation and the corrected pattern standard deviation to categorise the extent of the focal loss of visual field (i.e. correcting for diffuse loss that may be caused by the presence of cataract). After preliminary searching of the literature, it became clear that the pattern deviation and the corrected pattern standard deviation could not be incorporated into the severity scale used, since studies rarely reported these items in detail.

Methods

To estimate the rate of glaucoma progression, a study would require a random sample of people with glaucoma, and who have not been treated. This sample would be prospectively followed up without treatment for many years and visual field tested at regular intervals. Recognising that such an approach is ethically and practically difficult, it

TABLE 27 *Visual field-based glaucoma staging system common cut-off for studies directly comparing tests*

	MD score (dB)
Mild glaucoma	–0.01 to –6.00
Moderate glaucoma	–6.01 to –12.00
Severe glaucoma	–12.01 to –20.00
Visual impairment (partial sight/blind)	–20.01 or worse

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was decided to use two complementary approaches to estimating progression:

- Approach 1: systematically identify RCTs of OAG treatment versus control and predict yearly progression rates (by stage of OAG) beyond the current trial follow-up period.
- Approach 2: partially validate approach 1 estimates and systematically identify any studies that provide yearly estimates of progressing to each of the defined stages of OAG for treated patients.

Inclusion and exclusion criteria

Types of study

The following types of study were included:

- Approach 1: RCTs in which people diagnosed with OAG are randomised to either treatment or no-treatment control groups.
- Approach 2: any comparative or observational studies, including cohort studies, with analysis data on at least 100 participants.

To be considered for inclusion in approach 1, the study had to report the group average baseline MD and follow-up MD measure for treated patients, or to have categorised progression in terms of the present grading system. For approach 2, the study should have categorised progression in terms of the grading system used in this study (or provided enough information to be categorised into the grading system).

Target condition

The target condition was OAG (mild, moderate or severe).

Participants

People over 40 years of age were included.

Outcomes

Studies reporting relevant and interpretable data on the following outcomes were considered:

- average MD in decibels at study entry
- average MD in decibels at follow-up
- average yearly MD reduction
- probability of progressing from mild to moderate disease
- probability of progressing from moderate to severe disease
- probability of progressing from severe disease to visual impairment
- probability of progressing to unilateral blindness.

Data extraction strategy

Two reviewers 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 one reviewer assessed them for inclusion. One reviewer extracted details of study design, participants and outcome data. In the event of any uncertainty, a second reviewer provided advice and validated the data extraction. A list of the included studies is given in Appendix 15.

Data analysis

Approach 1

The baseline MD score was used to categorise study participants into mild, moderate or severe disease. The reduction in MD score at follow-up was used to approximate a yearly rate of reduction. The yearly reduction was applied to each follow-up year. At each follow-up year, the current stage of glaucoma was determined by the MD score as given in the present grading system. The probability of progression per year was estimated by 1 divided by the number of years in the same grade of OAG. For example, if baseline average MD score was –4.0 dB the group would be considered mild disease. If the group were to progress at –0.5 dB per year, it would take 5 years for the group to progress to moderate disease (<–6.0 dB). The probability of yearly progression from mild to moderate disease would be 1/5 = 0.2 for this cohort of patients. The average MD at diagnosis was assumed to be –4.0 dB in the projections.

Approach 2

Study participants were categorised into mild, moderate or severe disease according to either baseline MD scores or study reported severity. The percentage of people progressing was converted into an approximate yearly probability of progressing by dividing the percentage by the average length of follow-up.

Results

Approach 1

As described in the section 'Effectiveness of glaucoma treatment' (p. 87), two randomised trials were identified that compared a treated group with a no-treatment control group.[27,254] *Table 28* describes the type of participants in each group, progression in terms of MD changes and percentage who progressed according to each study definition of progression. Further details can be found in Appendix 16. The results from the EMGT suggested that the average rate (treated and untreated) of progression was approximately

TABLE 28 *Studies included in approach 1*

Study	Treatment	Visual field at baseline (dB)	Length of follow-up	Visual field at follow-up (dB)
CNTGS[254]	Treated (*n* = 61) Control (*n* = 79)	Mean (SD): –8.38 (5.26) Mean (SD): –7.54 (4.31) (moderate)	5 years	Mean defects, mean (SD) (slope per year): –0.4992 (1.97) –0.4018 (3.65) Progressed at end of follow-up 22 (33%) = 6.6% per year 31 (39%) = 7.8% per year
EMGT[27]	Treated (*n* = 129) Control (*n* = 126)	Mean (SD): –5.0 (3.7) Mean (SD): –4.4 (3.3) (mild)	6 years	Mean defects, mean (SD) (dB change per month): –0.03 (0.05) –0.05 (0.07) Progressed at end of follow-up 58 (45%) = 7.5% per year 78 (62%) = 10.3% per year

TABLE 29 *Estimates of probability of progressing per year for treated and untreated patients*

	No. of years (treated)	Probability progressing per year (treated)	No. of years (untreated)	Probability progressing per year (untreated)
Mild to moderate	5	0.2	4	0.25
Moderate to severe	14	0.07	9	0.11
Severe to visually impaired	16	0.06	10	0.10
Total number of years from diagnosis to visual impairment	35		23	

–0.4 dB per year (12 × –0.03 dB per month) for mild OAG patients and the CNTGS suggested that the average rate in moderate OAG patients might be –0.45 dB per year (average of two groups).

There were no included studies within a severe disease OAG population, therefore it was assumed that the rate of MD progression in a severe population was –0.5 dB year (a linear projection from the mild and moderate estimates). The three estimates of MD progression per year for treated patients were used to derive a probability of progressing between mild to moderate, moderate to severe and severe to visual impairment using methods described previously (*Table 29*).

Interpretation

The average treated patient population would progress from mild OAG disease to moderate disease in 5 years, resulting in a yearly probability of progression of 0.2. The population would be moderate OAG for 14 years and remain with severe disease for a further 16 years, resulting in a cumulative time to become visually impaired of 35 years.

Reflecting the uncertainty in these estimates, for the economic modelling, a triangular distribution was used and assumes the rate of progression may be half this rate or as much as triple this rate.

Approach 2

Two additional randomised trials[255,262] and seven cohort studies[259,263–268] met the inclusion criteria and were included. *Table 30* describes the type of participants in each group, and progression percentage who progressed according to each study definition of progression. Further details can be found in Appendix 17.

From the results presented in *Table 30*, it was possible to estimate the yearly probability of progressing from the various OAG stages.

- the yearly probability of progressing from mild to moderate disease from five studies was 0.028,[255] 0.05,[268] 0.066,[265] 0.10[266] and 0.11[263] (median = 0.066)
- the yearly probability of progressing from moderate to severe disease from six studies was

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TABLE 30 *Studies included in approach 2*

Study	Treatment	Visual field at baseline (dB)	Length of follow-up	Visual field at follow-up (dB)
CIGTS[255]	Medicine (n = 307) Surgery (n = 300)	Mean (SD): 4.6 (4.2) Mean (SD): 5 (4.3) Visual field scoring scale (mild)	5 years 63% had data at 5 years	Mean: 5.0 (SE 0.4) Mean: 5.2 (SE 0.4) Visual field scoring scale Progressed at end of follow-up (visits not patients): 314 (10.7%) = 2.1% per year 372 (13.5%) = 2.8% per year
Nouri-Mahdavi, 2005 (AGIS)[262]	AGIS study subset (n = 591, eyes = 789) with a number of different types of progression criteria compared	AGIS study patients had mean of 9 on VF scale (moderate)	Mean = 7.4 years (SD 1.7)	–2.07 (SD 0.86) dB per year in those that progressed only (conservatively assuming that all non-progressed patients had 0-dB per year slopes, the population mean = –0.6 dB per year) Progressed at end of follow-up 30% = 4% per year
Sponsel, 2001[267]	Beaver Dam Study; 120 treated patients	(Moderate)	5 years	Mild/moderate and no progression: 11/120 Progressed a category: 44/120 Improved a category: 22/120 Severe and stayed severe: 43/120 Progressed at end of follow-up 44 (37%) = 7.5% per year
Eid, 2003[263]	102 treated patients	Stage at presentation Grade I: 45 Grade II: 31 Grade III: 17 Grade IV: 9 (mild/moderate)	Mild to moderate: 7 years Moderate to severe: 6 years Severe to visually impaired: 14 years	Stable: 19/102 ⩾1 stage loss: 83 ⩾2 stages lost: 39 3 stages lost: 9 Mild to moderate: (36/45): 11% per year Moderate to severe: (32/48): 11% per year Severe to visually impaired: (4/9): 3% per year
Hattenhauer, 1998[264]	Olmsted county Study: 114 'classic' glaucoma cases	(Mild/moderate)	15 years (SD 8)	Taking only 'classic' glaucoma patients Bilateral blindness: 22% (8–38%) Unilateral blindness: 54% (42–72%)
Quigley, 1996[266]	151 patients from the Baltimore Eye Study used to develop a model of progression	(Mild/moderate)		Progression was 0.23 of a grading scale per year 95% CI (0.04 to 0.50) (i.e. two grades progressed in 10 years) Using the present criteria the probability of progressing would be 10% per year for each stage
Traverso, 2005[259]	194 patients across Europe	Stage 0: 33/194 Stage 1: 32/194 Stage 2: 34/194 Stage 3: 33/194 Stage 4: 31/194 Stage 5: 31/194 (moderate)	5 years	29.6% progressed at least one stage = 6% per year

continued

TABLE 30 *Studies included in approach 2 (cont'd)*

Study	Treatment	Visual field at baseline (dB)	Length of follow-up	Visual field at follow-up (dB)
Spry, 2005[268]	108 patients	AGIS score = 3.3 (mild cases)	3.6 years (SD 1.3)	19% progressed = 5% per year
Olivius, 1978[265]	160 eyes (119 patients)	Grade I: 27 Grade II: 34 Grade III: 39 Grade IV: 24 Grade V: 16 Grade VI: 5 Grade VII: 12 Grade VIII: 3 (mild/moderate)	5 years	Mild to moderate (20/61 = 6.6% per year) Moderate to severe (19/31 = 12% per year) Severe to blind (13/16 = 16% per year)

0.04,[262] 0.06,[259] 0.075,[267] 0.10,[266] 0.11[263] and 0.12[265] (median = 0.087)
- the yearly probability of progressing from severe to visually impaired disease from three studies was 0.03,[263] 0.10[266] and 0.16[265] (median = 0.10).

The Olmsted County study[264] suggested that unilateral blindness in a treated population at 15-year follow-up was 54%. Applying a simple linear progression assumption, it would take 28 years (15/0.54, 95% CI 21 to 36 years) for the entire population to progress to blindness.

Interpretation

There was significant heterogeneity between study probabilities. The study-estimated probabilities of yearly progression for moderate to severe and for severe to visually impaired provided no evidence that approach 1 estimates were clearly wrong. Indeed, the median estimates were within 0.02. The approach 1 estimated probability for mild to moderate progression was significantly higher than for approach 2. This difference may be partly explained by the assumption of severity of mild disease at diagnosis. On the grading scale used in this review, assuming a baseline MD of –4 dB implied that the eye needed to progress by –2 dB to become moderate. Clearly, if more mild disease were diagnosed, the probability of progression to moderate disease would decrease (e.g. –3 dB would decrease the probability of progression to 12%).

Discussion

Approximate estimates for the probability of progression from mild to moderate, moderate to severe and severe to visually impaired were derived. Approach 1 used a simple linear extrapolation of the results from the CNTGS and EMGT studies. The model suggested that it would take 35 years for a treated population to progress to unilateral blindness. Such an estimate is plausible if the Olmsted County study is extrapolated to the entire population[264] (35 years is contained within the Olmsted County study 95% confidence interval) and is similar to the estimate derived by Quigley and colleagues,[266] which suggested that progression to blindness would take approximately 40 years.

Strengths and limitations

Extrapolating trial outcomes from short-term follow-up to longer term outcome risks serious underestimation or overestimation if the assumption of linear progression is incorrect. Using two complementary approaches enabled partial validation of the extrapolation in this study. There is, therefore, some confidence that the estimated probabilities of progression between stages for the entire population of glaucoma patients are approximately correct. The risk of blindness is based on risk estimates for one eye, driven by the available primary data, and is therefore not necessarily representative of the risk of bilateral blindness.

A 'black box' approach was taken to estimate progression. That is, a 'precise' treatment path was not formulated for different stages of glaucoma and differing presenting prognostic factors. Therefore, it is recognised that there may be some inaccuracy in the estimates for specific subgroups of glaucoma patients. This imprecision has been partially taken into account in the economic modelling by assuming that the rate of progression may be as little as half the estimated rates or as much as triple this rate. Using these assumptions, the modelling considered probabilities of progression that were bigger and smaller than any published estimates.

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Some studies[269–272] have tried to predict progression using various prognostic factors. There is some evidence that rate of progression increases with age (e.g. an odds ratio of 1.3 has been suggested for every 5-year increase in age),[270] but it is conflicting and some prospective studies have not found such a relationship.[273] A similar scenario has also been observed for IOP.[274,275] It was decided to ignore such estimates within the economic model. The rationale for this was that one aspect of the economic modelling was to identify which components of the economic model had the most significant impact on the results before adding any further complexities to the model.

Using MD to classify progression was not entirely satisfactory. It is known that other non-glaucomatous disease, such as the presence of cataract, affects the MD. MD was used in this study because a continuous measure of progression was desirable, but studies rarely reported progression on a continuous scale. The more commonly used stage models (event-based models) for progression have a major limitation: all patients within a specific stage are considered to be at the same severity of disease and therefore stage models fail to identify eyes that may be progressing but have not yet reached the threshold to change a stage. The stage approach gives little information on the rate and magnitude of change within patients.[276] A better approach to estimating progression might be trend-based approaches where progression rate is examined on individual visual field points using regression analysis. Some studies have suggested that such an approach is more sensitive than event-based methods.[256,258,262]

Conclusions

Main findings

Using RCTs of treatment versus no treatment, the pooled hazard ratio of progression for treatment versus no treatment was 0.65 (95% CI 0.49 to 0.87). Extrapolating the trial results predicted that a treated person would progress from mild to at least unilateral blindness in approximately 35 years. Untreated, the time to progression is estimated as 23 years.

Future research

The lack of consensus on an appropriate definition of 'progression' is a major impediment to understanding the rate and magnitude of change in glaucoma patients and consequently the long-term effects of various treatments. A comparison of event-based and trend-based scoring systems needs to be undertaken in a large prospective cohort of glaucoma patients who represent the spectrum of glaucoma disease.

Chapter 8
Economic analysis

This chapter has three main sections: an outline of the principles of economic evaluation, a systematic review reporting economic evaluations of OAG screening strategies and a final section reporting the economic evaluation, using a Markov model, the structure of which was outlined in the section 'Economic model' (p. 15), to assess the cost-effectiveness of screening for OAG.

Principles of economic evaluation

The decision to use resources to provide one method of identifying OAG would mean that the opportunity to use them in other desirable ways (either to provide another method of identification or to meet an entirely different health need) is given up. The cost of this decision is the benefits (health gains, etc.) that could have been obtained had the resources been used another desirable way. This is the economic notion of 'opportunity cost'. Strictly speaking, the opportunity cost of a decision to use resources in one way is equivalent to the benefits forgone in the next best alternative use of these resources. Economic evaluation is a method of providing decision-makers with information about the opportunity cost of the decisions that could be made. It is the comparative analysis of alternative courses of action in terms of both their costs (resource use) and effectiveness (health effects).[277] An economic evaluation, in this context, would involve assessing the relative costs and benefits associated with alternative identification strategies, including screening, for OAG. The objective of such an economic evaluation would be to provide information to assist decision-makers in the allocation of the available resources so that benefits can be maximised. How an economic evaluation brings together information on costs and effects is illustrated in *Figure 39*. The vertical axis represents the difference in costs between an experimental (e.g. screening for OAG) and a control treatment (e.g. no formal screening for OAG). An evaluation of alternative strategies for identifying OAG cost estimates might typically be expected to include the value of the resources used to provide the strategy as well as the resource consequences of that strategy (e.g. the costs of treatment). The horizontal axis represents differences in effectiveness between the two approaches. The effectiveness of the alternative strategies might be measured in clinical terms (e.g. reductions in IOP), natural terms (e.g. cases of visual impairment avoided) or more economic measures, such as quality-adjusted life-years (QALYs). The latter combines estimates of both quality of life and length of life. The wider the definition of benefit used, the more likely it is to measure outcomes of importance to individuals.

In the north-west and south-east quadrants of *Figure 39* a clear decision about which treatment should be preferred is provided because one or other treatment dominates. In the north-west quadrant the experimental treatment is more costly and provides less benefit and therefore the control treatment is more efficient (is dominant). In the south-east quadrant the opposite situation occurs and the experimental treatment is more efficient (is dominant) as it is less costly and provides more benefit. The circle in the centre of the figure represents the possibility that no meaningful differences in costs or benefits exist between the treatments and for practical purposes the two interventions are equally efficient. In the two remaining areas of the figure, the north-east and south-west quadrants, a judgement is required as to whether the more effective treatment is worth the extra cost. To aid these judgements, information can be provided in terms of an incremental cost-effectiveness ratio (ICER). The higher the ICER of one intervention compared with another, the less likely it is that this intervention will be considered efficient.

Systematic review of cost-effectiveness of screening for OAG

Aims and objectives

The aim of this systematic review is to address the following research questions. From the perspective of the UK NHS, is screening for OAG cost-effective and which method of screening is most likely to be cost-effective? These questions were addressed by:

- systematically identifying and quality assessing all the economic evaluations comparing alternative methods of screening for OAG

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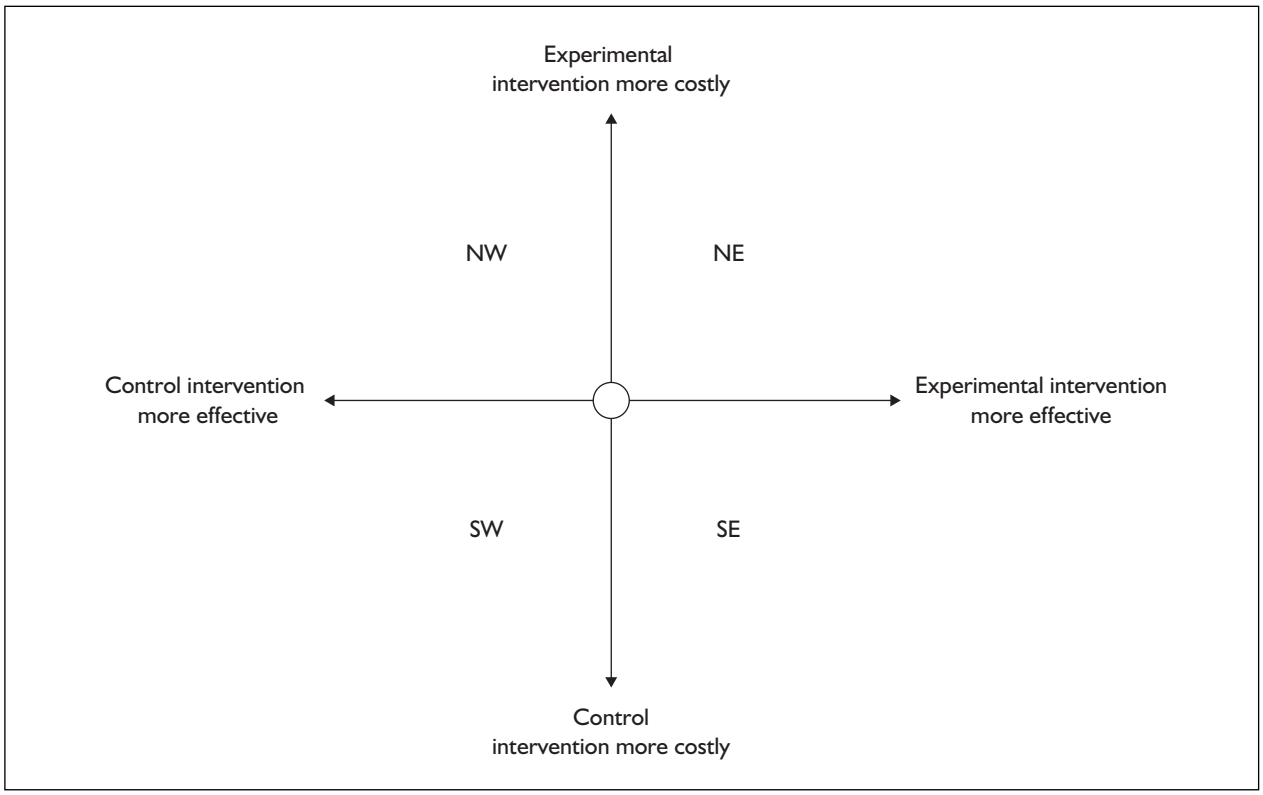

FIGURE 39 *Relationship between the difference in costs and effects between a new (experimental) intervention and a standard (control) intervention*

- summarising the evidence from the review of these studies for and against the alternative interventions.

Methods

Inclusion and exclusion criteria

Types of study

Studies that compare both costs and outcomes for OAG screening were included. Studies were excluded if they did not attempt to relate cost to outcome data. The following types of paper were also excluded: methodological papers, papers that reviewed economic evaluations (although their reference lists were checked), discursive analysis of costs/benefits, partial evaluation studies such as cost analyses, efficacy or effectiveness evaluations and cost of treatment/burden of illness papers.

Study population

Studies had to be performed in adult populations.

Types of intervention

Any intervention used for the screening of OAG.

Types of outcome

The outcomes of the review were costs (regardless of how estimated) and effects (no matter how these had been specified). Additional, more specific, secondary outcomes of the review were:

- incremental costs per case of visual impairment (e.g. loss of vision below driving standard) prevented
- incremental costs per year of visual impairment (e.g. loss of vision below driving standard) prevented
- incremental costs per case of blindness prevented
- incremental costs per additional QALY gained
- incremental costs per number of case of OAG detected.

Search strategy

The search strategy used to identify relevant studies is described in detail in Chapter 4.

Data extraction strategy

One reviewer extracted the data according to the guidelines produced by the Centre for Reviews and Dissemination (CRD) for the critical appraisal of economic evaluations.[91,278] Data extraction focused on two key areas: the results of the economic evaluations in terms of estimates of costs and effects, and the methods used to derive the

results and their interpretation. Where the economic evaluation had been based on a modelling exercise, additional data extraction was performed to describe the source of parameter estimates and the methods used to combine these estimates in the economic model. The criteria used were based on those developed by Philips and colleagues.[91] Where included studies had previously been included in NHS EED, these abstracts were also used to inform the review.

Examples of the type of data extracted from the included studies are described below.

- study characteristics
  - the research question
  - the study design
  - the comparison
  - the setting
  - the time-horizon of the study
  - the basis of costing
- characteristics of the study population
  - numbers receiving or randomised to each intervention
  - other systematic differences in clinical management
  - inclusion/exclusion criteria
  - dates to which data on effectiveness and costs related
- duration of follow-up for both costs and effectiveness
- results
  - summary of effectiveness and costs (point estimate and if reported range or standard deviation)
  - summary of cost-effectiveness/utility (point estimate and if reported range or standard deviation)
  - sensitivity analysis
- conclusions as reported by the authors.

To estimate the secondary outcomes described above, data were also extracted for each intervention considered on:

- number of cases of visual impairment (e.g. loss of driving vision) prevented
- average number of years of visual impairment (e.g. loss of driving vision) prevented
- number of cases of blindness prevented
- average total cost per person screened
- number of cases of OAG
- average number of QALYs.

Quality assessment strategy

The quality of the studies was assessed using Figures 1–11 of the CRD report.[278] Study quality was summarised in terms of how the literature on effectiveness was retrieved, how the effectiveness data were derived from the studies, justification provided for the strategies assessed, how costs were determined, whether all relevant costs were included, the perspective of the analysis (i.e. whose costs and benefits were considered important to the decision-maker), the measures used to determine cost-effectiveness and the nature of the sensitivity analysis performed.

Data synthesis

No attempt was made to synthesise quantitatively the studies that were identified. Data from the included studies were summarised to identify common results, variations and weaknesses across studies. If a study only reported average cost-effectiveness ratios then, where possible, the data were reanalysed to provide estimates of incremental cost-effectiveness. The ICERs were obtained by calculating the difference in costs (ΔC) between one non-dominated strategy and its preceding non-dominated strategy, and dividing it by the difference in effectiveness (ΔE) between these two strategies. It is important to note that the strategies were compared only for the same age groups. It was considered likely that the identified studies would provide data for different patient groups (e.g. those aged 45 and over, those aged 65 and over), a range of pretesting risks (e.g. general population risk, strong pretest suspicion of OAG) and a range of screening and diagnostic interventions. Therefore, separate summaries were developed for each set of studies that considered the same patient group, pretesting risk and diagnostic intervention. Where possible, the data extracted from the included studies were used to provide estimates of the secondary outcomes described above.

Results

Number of studies identified

As described in Chapter 4, a total of 431 titles or abstracts were identified by the searches conducted for the economic evaluation of screening (*Table 2*) and a further 65 titles or abstracts were identified from the general search of databases such as Health Management Information Consortium and HTA. Sixty-seven full-text papers were retrieved for assessment. From these, five eligible reports were identified.[279–283] One study was reported in two separate reports[279,280] and the journal version was used as the primary publication.[280] The four eligible studies used modelling techniques of varying levels of complexity to arrive at estimates of cost-effectiveness. These studies are listed in Appendix 18 and summarised in Appendix 19.

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TABLE 31 *Description of screening strategies considered by each of the studies*

Study	Strategy	Screening interval
Gottlieb, 1983[282]	Ophthalmoscopy, with positives referred to ophthalmology	Once only
	Tonometry ⩾21 mmHg, with positives referred to ophthalmology	Once only
	Tonometry ⩾24 mmHg, with positives referred to ophthalmology	Once only
	HF fields, with positives referred to ophthalmology	Once only
	MPT fields, with positives referred to ophthalmology	Once only
	Globuck fields, with positives referred to ophthalmology	Once only
	Goldmann fields, with positives referred to ophthalmology	Once only
Boivin, 1996[280]	Tonometry (cut-off not stated), fundoscopy, with positives for either getting gonioscopy and perimetry	1, 3 or 5 years
	Tonometry (cut-off not stated), with positives getting fundoscopy, gonioscopy and perimetry	1, 3 or 5 years
Gooder, 1995[281]	Opportunistic screening at the time of a routine eye test	Once only
	Tonometry	Once only
Tuck, 1997[283]	Tonometry and Henson fields	Once only
	Tonometry and perimetry if IOP > 20 mmHg	Once only
	Tonometry and perimetry if IOP > 22 mmHg	Once only
	Tonometry at thresholds of IOP > 22 mmHg	Once only
	Ophthalmoscopy (sv)	Once only
	Perimetry	Once only
	Ophthalmoscopy and tonometry (sv)	Once only
	Ophthalmoscopy and tonometry, positives referred to perimetry (sv)	Once only
	Ophthalmoscopy and tonometry, positives referred to perimetry (lx)	Once only
	Ophthalmoscopy and perimetry (sv)	Once only
	Ophthalmoscopy and tonometry (lx)	Once only
	Ophthalmoscopy and tonometry, 'high-risk' candidates referred to perimetry (sv)	Once only
	Tonometry at thresholds of IOP > 20 mmHg	Once only
	Ophthalmoscopy and tonometry, 'high-risk' candidates referred to perimetry (lx)	Once only
	Ophthalmoscopy and perimetry (lx)	Once only
	Ophthalmoscopy and tonometry and perimetry (sv)	Once only
	Ophthalmoscopy and tonometry and perimetry (lx)	Once only
	Ophthalmoscopy (lx)	Once only

HF, Harrington–Flock; lx, lax referral criteria; MPT, manual perimetry technique; sv, severe referral criteria.

The following section critiques and summarises the included studies.

Characteristics of the included studies

All four studies assessed cost-effectiveness of screening for primary OAG. There was one study each from the USA,[282] and Canada[280] and two studies from the UK.[281,283] The analysis by Gottlieb and colleagues compared hypothetical screening programmes for a population of one million individuals aged between 40 and 79 years.[282] Boivin and colleagues considered the introduction of screening programmes for those aged 40 and 79 years in the Province of Quebec in Canada.[280] In 1991 the population of this province was estimated to be 2.6 million.[280] Gooder considered the implications of adopting screening for a 100,000 cohort of the UK general population aged 40 years or more.[281] In the final study, by Tuck and Crick, the screening strategies were compared for a hypothetical cohort of 10,000 Caucasians aged 40 years and above.[283] In all four studies the screening strategies considered would be implemented in a community setting. The characteristics of the included studies are summarised in Appendix 19.

Screening strategies considered in the studies

A description of the strategies considered by each of the studies is provided in Appendix 19 and summarised in *Table 31*. In only one of these studies was screening compared with current, no screening, practice.[281]

Gottlieb and colleagues considered seven different screening strategies: ophthalmoscopy, tonometry (at two different thresholds of >21 mmHg and >24 mmHg), manual perimetry (using HF, MPT, Globuck or Goldmann fields) and automated perimetry.[282] Boivin and colleagues considered

two main strategies.[280] In the first, initial screening was with tonometry (although the cut-off values were not stated) and fundoscopy, and if there were abnormal findings in either, individuals were then investigated with gonioscopy and perimetry. The second strategy was to screen the population initially with tonometry alone followed by gonioscopy, fundoscopy and perimetry in those with abnormal IOP. A total of 12 scenarios was assessed by varying the age range, participation, compliance and treatment efficacy rates for these two main strategies.[280] Gooder compared two active screening strategies with opportunistic screening performed at the time of a routine eye test (current standard UK practice). The first screening strategy considered was tonometry and the second involved non-contact tonometry and field tests. People testing positive were then referred on to hospital services.[281] Tuck and Crick considered 18 different screening strategies.[283] These strategies varied in terms of the tests used (ophthalmoscopy, tonometry and perimetry), the cut-off values used for tonometry (IOP > 20 or IOP > 22 mmHg) and the severity of referral criteria. Referral criteria depended on IOP, visual field defects (defined as "a failure on the 66-point test, suspicious zone or below, of a Henson suprathreshold field"), CDRs, an assessment of risk based on family history of glaucoma or high myopia. Severity was defined as relatively lax or severe. An example of severe criteria for referral would be that patients with IOP between 26 and 30 mmHg would only be referred if the CDR was >0.4 or if there was a visual field defect. Lax referral criteria would refer all patients with an IOP between 26 and 30 mmHg regardless of the results of the other tests.

As described in *Table 31*, only Boivin and colleagues assessed cost-effectiveness based on a cyclical screening mode (i.e. once every year, every 3 years or every 5 years).[280] The other studies assumed that the screening was to be done only once.[281–283]

Quality of included studies

All studies were based on models, but none specified the type of model used. Two studies dealt with cost-effectiveness of diagnosis and treatment combined[280,282] and one study reported the results in terms of two different measures of cost-effectiveness as well as one measure of cost–utility.[281] The final study considered the costs and effects of diagnosis only (i.e. it excluded the costs and effects consequent on diagnosis).[283] None of the studies implicitly or explicitly justified the screening strategies compared.

All the included studies derived their literature on effectiveness from ad hoc searching, rather than from a systematic review. The estimates of effectiveness of diagnostic and treatment measures were arbitrarily determined in all four studies by assumptions made from data from previous studies and on expert opinion. None of the studies clearly stated how they derived estimates of effectiveness from the included studies. Three studies clearly stated the sensitivities and specificities of the diagnostic tests used in their modelling,[281–283] whereas one did not.[280]

The measures used to determine the effectiveness of the different strategies compared varied between studies. The measures included quality-adjusted years of vision (QAVYs) saved (with quality adjustment based on a subjective assessment of the number of years of vision that someone would forgo to avoid the side-effects of treatment),[282] disability-adjusted life-years (DALYs),[281] years of blindness prevented (although in the study by Boivin and colleagues it was unclear how these were calculated: no values were reported, but number of years of blindness appeared to be the same as the number of cases of blindness avoided)[280,281] and number of true positives identified.[281,283]

All four studies reported detailed data on how the costs were derived and the price year to which costs related (*Table 32*). One study reported costs in Canadian dollars,[280] and two others reported costs in US dollars, one for the year 1980[282] and one for 1995.[283] The fourth study reported costs in 1995 UK pounds sterling.[281] In the study by Tuck and Crick costs were expressed in US dollars but were originally calculated in UK pounds sterling and converted to US dollars using an exchange rate of £1 to US$1.55.[283] Only Boivin and colleagues reported resource quantities and costs separately.[280]

Although there were variations between the studies, the type of resource use considered relevant to include in the costing was generally similar. However, none of the studies included the costs of the organisation of the screening programme such as personnel costs and costs for inviting the participants.

In the study by Gottlieb and colleagues, the costs for diagnosis and treatment in this analysis were estimated from the Massachusetts Blue Cross/Blue Shields average daily hospital reimbursement rates in Massachusetts in the year 1980.[282] The average cost of medications was estimated by doubling

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TABLE 32 *Study characteristics and quality*

Study and setting	Population assessed	Year of costs	Method of literature retrieval	Source of effectiveness data	Costs included in the analysis	Discounting	Type of sensitivity analysis
Gottlieb, 1983[282] USA	1,000,000 Age: 40–79 years	1980	Ad hoc	Average values from studies and expert opinion	Diagnostic, treatment and complication of treatment costs	Yes 5% per annum	One-way
Boivin, 1996[280] Canada	2,607,210 Age: 40–79 years	Professional fees, 1994 prices; drug prices,1993; aids for the blind, 1992; disability pensions, 1993	Ad hoc	Average values from studies and expert opinion	Diagnostic, treatment and societal costs	Not performed	One-way
Gooder, 1995[281] UK	100,000 Age: ⩾40 years	1995	Ad hoc	Average values from studies and expert opinion	Diagnostic costs only	Not performed	None
Tuck, 1997[283] UK	10,000 Age: ⩾40 years	1995	Ad hoc	Average values from studies and expert opinion	Diagnostic costs only	Not performed	One-way

their wholesale prices. The costs included those of screening tests, drugs, diagnostic evaluation, physician visits with and without treatment, surgery for glaucoma and surgery for cataracts as a complication of glaucoma treatment. Indirect societal costs were not taken into account in the analysis. The analysis by Boivin and colleagues included costs for diagnostic tests and treatment (by both the clinician and optometrist), societal costs for the blind in terms of aids (reading, writing and mobility) and disability pensions.[280] The clinician costs were based on fees for procedures performed in a private healthcare setting. Societal costs for blindness were obtained from the budgets for the ten rehabilitation agencies in the Quebec provinces and disability pension costs were obtained from the Régie des rentes du Quebec. The costs were not adjusted for inflation. Treatment costs were based on a hypothetical model of disease progression, which was based on data from selected studies. Gooder included the cost of standard optometrist cost for an eye test and assumed costs for the other tests performed.[281] The only other cost included was the cost of a first outpatient visit. Tuck and Crick assumed that the costs were based on screening conducted as part of a general eye examination by an ophthalmologist or optometrist, usually in conjunction with prescribing lenses.[283] The main assumption was that the initial screening of 10,000 people would be performed by a single professional examiner over a 6-year period. The cost analysis covered cost per hour of optometrist (including all overheads for premises, etc.), capital costs (tonometer and field screener) and cost of secondary examination at a clinic per patient visit (before diagnosis). The cost analysis only covered the costs of diagnosis and not the costs of subsequent treatment and monitoring. The authors of the economic analysis did not take indirect (societal) costs into account.

Only two studies performed discounting,[282,283] although it was relevant to all. In one study future costs were discounted at a rate of 5% per annum[282] and in the other, reusable equipment costs were annualised using a 6% discount rate.[282,283] Only one of the studies clearly stated the time-horizon of the analysis.[281]

In all four studies the assessment of cost-effectiveness was presented from a government perspective. Two studies reported average cost per year of blindness avoided[280,281] and one the average cost per true positive case found.[281,283] Gottlieb and colleagues reported average and incremental cost per quality-adjusted year of vision saved[282] and Gooder reported incremental (versus current practice) cost per DALY saved.[281]

Three studies performed some form of sensitivity analysis, although this was limited to simple one-way analysis (i.e. changing only one parameter at a time; such an approach ignores interactions between different parameters).[280,282,283] Sensitivity analyses were performed around age, disease prevalence and treatment effectiveness rates. The specifics of the sensitivity analyses varied between studies reflecting the different data, outcome measures and model structure used. For example, Gottlieb and colleagues assessed the impact of varying the prevalence of raised IOP, disease progression, treatment effectiveness, variations in surgery refusal rate and proportion of patients controlled with primary medications or surgery alone.[282] In the study by Boivin and colleagues sensitivity analysis was performed with variations in patient age range, frequency of screening, tests used, participation rate and the rate of effectiveness.[280] Tuck and Crick, in their sensitivity analysis, considered varying the prevalence of primary OAG, sensitivity values, predictive values, the costs of examination and the definition of true-positive cases.[283]

Summary of the results of the included studies

As described above the included studies were broadly similar with respect to population, screening and treatment costs and their results are summarised in *Tables 33–38* (and reported in more detail in Appendix 20). Where necessary, the ICERs presented in the tables were calculated, by the reviewers, from data provided in the included studies. Nevertheless, data were not reported in sufficient detail to reinterpret the results of the studies in terms of a common outcome measure.

Tables 33 and *34* report the results of the cost–utility analysis conducted. *Table 33* reports the findings from Gottlieb and colleagues.[282] In this table the results are only presented for three of the seven age groups considered and all screening strategies that were dominated (i.e. less effective than less costly alternatives) have been omitted. Ophthalmoscopy was the least costly but least effective strategy for all age groups except for the 70–74 year olds (*Table 33*). As the table shows, out of the seven strategies considered (see *Table 31*) only between three and four strategies were not dominated. The ordering of the interventions varied between age groups and this indicates the likely importance of age on estimates of cost-effectiveness. It also indicates that the optimal

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TABLE 33 *Incremental cost (IC) per QAVY saved from screening model produced by Gottlieb*[282a]

Strategy	Age range (years)	Total costs (1980 US$)	QAVY	Incremental costs (1980 US$)	Relative difference in cost (%)	Incremental QAVYs	Relative difference in effects (%)	ICER compared to	IC per QAVY
Ophthalmoscopy	40–44	9.3 m	2,750						
Tonometry >24	40–44	14.4 m	5,600	5.1 m	155	2,850	204	Ophthalmosocopy	1,789
Tonometry >21	40–44	21.0 m	11,150	6.6 m	146	5,550	199	Tonometry >24	1,189
Ophthalmoscopy	60–64	16.9 m	15,420						
Globuck fields	60–64	28.8 m	18,160	11.9 m	170	2,740	118	Ophthalmoscopy	4,343
Tonometry >21	60–64	39.9 m	24,800	11.1 m	139	6,640	137	Globuck fields	1,672
Tonometry >24	75–79	23.1 m	10,120						
Ophthalmoscopy	75–79	26.1 m	18,680	3.0 m	113	8,560	185	Tonometry >24	350
Globuck fields	75–79	38.7 m	21,230	12.6 m	148	2,550	114	Ophthalmoscopy	4,941
Goldmann fields	75–79	50.1 m	23,400	11.4 m	129	2,170	110	Globuck fields	5,253

[a] All costs reported in 1980 US dollars.

TABLE 34 *Incremental cost per DALY saved from screening model produced by Gooder*[281a]

Strategy	Total costs (1995 UK£)	DALYs	Incremental costs (1995 UK£)	Relative difference in cost (%)	Incremental DALYs	Relative difference in effects (%)	ICER compared to	IC per DALY
Current practice	308,660[b]	66						
Tonometry	1,905,800	100	1,597,140	517	34	152	Current practice	46,975
NCT and fields	2,923,294	183.4	1,017,494	153	83.4	183	Tonometry	12,200

[a] All costs reported in 1995 UK pounds sterling.
[b] This assumes that opportunistic eye tests would not be displaced by the screening strategy as they are conducted for other reasons, but that costs of referral and subsequent treatment following opportunistic case finding are relevant for inclusion.

choice of strategy might vary by age at screening. Gooder found that both screening strategies considered were more effective but more costly than current practice.[281] However, screening with tonometry might not be considered cost-effective while screening using NCT and fields might be considered worthwhile (the incremental cost per DALY saved compared with current practice was estimated to be approximately £22,000).

The values reported for the cost–utility analyses are difficult to interpret because of the different years and countries to which the data relate as well as differences in the technologies considered and outcome measures used. Presenting the relative difference in costs and effects provides more comparative information. For example, in Gottlieb and colleagues the cost of screening with tonometry with a threshold IOP of 24 mmHg is 155% of the cost of ophthalmoscopy.[282] These estimates put into context the increases in costs and effects that accrue from adopting a more effective but more costly screening strategy.

The results in terms of incremental cost per year of blindness avoided are presented using the same approach as those described for the cost–utility analyses described above. Using the data from Boivin and colleagues, the incremental costs per year of blindness were estimated (*Table 35*).[280] With these data it is unclear whether any of the more costly but effective strategies are worthwhile compared with the strategy of tonometry or tonometry and fundoscopy as initial tests followed by fundoscopy, gonioscopy and perimetry. The data from Gooder suggest lower incremental costs per year of blindness avoided (*Table 36*),[281] and indicate that screening is more likely to be cost-effective compared with data from Boivin and colleagues.[280] However, the data are more difficult to interpret because of the differences between the two studies, in terms of comparators, methods and source data. Without further information it is not possible to disentangle which factor or factors is most important.

In terms of incremental cost per case detected data were available from two studies.[281,283] Both screening strategies considered by Gooder were considerably more effective than current practice, but also more costly (*Table 37*).[281] Tonometry was the least effective and least costly of the two active strategies considered, but as it was compared with the relatively inexpensive current practice the cost per case detected was relatively high. In contrast, the incremental cost per case detected for NCT and field testing strategy compared with tonometry was relatively modest. The data from Tuck and Crick also suggest that tonometry was the least costly but also least effective screening strategy test (*Table 38*). This is because it was associated with a poor sensitivity (69% at an IOP cut-off of 20 mmHg).[283] Screening strategies involving ophthalmoscopy alone or in combination with either tonometry or perimetry were dominated (i.e. less effective and more costly) and have not been included in *Table 38*, although they are presented in Appendix 20. The use of either tonometry followed by perimetry or ophthalmoscopy followed by tonometry and perimetry was more effective than tonometry alone. However, the cost rapidly increased and it would require society to pay an additional US $18,500 per additional case detected associated with adopting a strategy of ophthalmoscopy, tonometry and perimetry for referral candidates with lax referral criteria for further evaluation compared with a screening strategy of perimetry alone.

Discussion

Despite an extensive systematic search of the literature only four studies that assessed the cost-effectiveness of screening strategies for glaucoma were identified. The latest of the included studies was published in 1997 and it analysed costs based on 1995 prices.[283] As a basis for decision-making about the desirability of adopting screening for OAG, our judgement is that this evidence base is insufficient: the diagnostic tests and treatment interventions available for primary OAG have changed since the identified studies were conducted and the tests and treatment interventions used in routine clinical practice now may have different effects from those that were assessed in the included studies. It is quite possible that the cost-effectiveness of glaucoma screening, using currently available tests and treatment options, may differ markedly from the estimates provided by the studies described in this review. Moreover, some of the screening tests used in the studies, such as manual perimetry techniques (HF, MPT and Globuck field tests), are no longer routinely used in clinical practice. There have been developments in diagnostic tests such as SAP, which is currently the choice for visual field testing. Only Gottlieb and colleagues and Gooder included an automated perimetry test in their assessment.[281,282] New treatments are available, with the introduction of prostaglandin analogues, α_2 agonists and topical carbonic anhydrase inhibitors. These were not treatments considered in the reviewed studies.

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TABLE 35 *Incremental cost per year of blindness avoided from screening model produced by Boivin and colleagues*[280a,b]

Strategy no.	Initial test(s)	Subsequent tests	Frequency (years)	Age range (years)	Treatment efficacy (%)	Prevalence reduction (no. of cases)	Relative difference in incremental effects (%)	Total costs (Can$)	Relative difference in incremental cost (%)	ICER compared to which strategy no.?	IC per year of blindness avoided
1	T[a]	F, G, P	3	65–79	50	209		7,763,604			
2	T, F	G, P	3	65–79	50	287	137	12,574,620	162	1	61,680
3	T	F, G, P	3	40–79	50	248		19,154,063			
4	T, F	G, P	5	40–79	50	354	143	28,679,520	150	3	89,863
9	T, F	G, P	3	40–79	70	496	140	36,385,066	127	4	54,264

[a] All costs reported in 1994 Canadian dollars.
[b] Based on a compliance rate of 75% and a participation rate of 75%.
F, fundoscopy; G, gonioscopy; P, perimetry; T, tonometry.

TABLE 36 *Incremental cost per year of blindness avoided from screening model produced by Gooder*[281a]

Strategy	Total costs (£)	Years of blindness avoided	Incremental costs (£)	Relative difference in cost (%)	Incremental years of blindness avoided	Relative difference in effects (%)	ICER compared to	IC per year of blindness avoided
Current practice	308,660[b]	165						
Tonometry	1,905,800	250	1,597,140	517	34	152	Current practice	18,790
NCT and fields	2,923,294	458.5	1,017,494	153	117.6	183	Tonometry	4,880

[a] All costs reported in 1995 UK pounds sterling.
[b] This assumes that opportunistic eye tests would not be displaced by the screening strategy as they are conducted for other reasons, but that costs of referral and subsequent treatment following opportunistic case finding are relevant for inclusion.

A further limitation of the four studies is that only one included a 'no-screening' strategy.[281] Unfortunately, the method of assembling data for use in this economic evaluation was flawed as it was not based on any systematic assembly and relied on indirect comparisons. Therefore, none of the studies was able reliably to address the question as to whether any form of screening would be worthwhile.

It is also important to be aware of the methodological limitations of the included studies. First, it is unclear whether the studies used the best available evidence for the diagnostic performance of the tests and the effectiveness of treatments. The methods used to derive estimates of sensitivity and specificity of screening tests as well as the effectiveness of treatment interventions used in the economic model were poor. They were based on ad hoc searching, rather than on a systematic review. Such an approach has been recognised to be subjective and therefore prone to bias and error.[284] Hence, it is possible that the selection of evidence in the included studies may have been biased. This is a weakness observed in economic evaluations of other treatment conditions.[285] Furthermore, all the studies considered different measures of effectiveness for the cost-effectiveness analysis. Again, this makes it difficult to draw comparisons between studies.

Two of the studies considered screening in countries other than the UK and differences in reimbursement strategies and costs complicate the interpretation from a UK perspective.[280,282] Current UK prices are markedly different from the prices quoted in the two included UK studies. While all four studies explained in detail how the costs for the different strategies were derived, only one study presented resource use and costs separately.[280] This makes it difficult to judge whether these data are applicable to the UK. Only one study considered a cyclical screening strategy (i.e. once every 3 years, etc.),[280] and the failure of the others to consider such an approach is unrealistic as the incidence of glaucoma increases with age (see Chapter 5).

The effectiveness of screening is not just dependent on the sensitivity and specificity of the test used. It also depends on a range of other parameters, such as acceptance of screening, treatment efficacy rate and compliance. A variety of different values was used across the studies and these values were either implicit (e.g. assuming 100% compliance with treatment) or explicit (e.g. Boivin and colleagues assumed a 75% compliance rate with treatment).[280]

The uncertainty surrounding estimates of cost-effectiveness was also very poorly addressed by all four studies. The simple one-way sensitivity analysis used in three studies is unlikely to have fully explored the full extent of the uncertainty present in each evaluation.[280,282,283]

Conclusions

Very few economic evaluations comparing alternative screening strategies (including no screening) for OAG are available. Those studies that were identified suffered from numerous weaknesses that would limit their usefulness for decision-making in the UK at this time. Furthermore, the differences between the studies in terms of tests, populations, assumed effectiveness of tests and treatment as well as costs makes it difficult to disentangle which factors are the key determinants of cost-effectiveness. On the basis of the data summarised in this review there is an insufficient evidence base for judging whether screening for OAG should take place, and if it should take place, how it should be performed. These findings confirm that further research is required on the cost-effectiveness of alternative screening strategies and such work should be based on the systematic consideration of the evidence on acceptability, effectiveness and cost of alternative screening strategies relevant to current practice. This evaluation is described in the next section.

Economic evaluation of screening for OAG

The cost-effectiveness of screening for OAG was assessed using a Markov model. The structure of the model was described in the section 'Economic model' (p. 15). The interventions compared within the model are first briefly described, before the methods used to obtain the necessary data to populate the model are presented. The methods used to present estimates of cost-effectiveness for the base-case analysis and the key areas of uncertainty addressed by sensitivity analysis on the base case are then described. Further sensitivity analysis focused on situations where it is believed screening may possibly be cost-effective is next described. The following two subsections report the results of the base case and its associated sensitivity analysis, as well as the results of the further focused sensitivity analyses. Finally, the implications of these results are discussed.

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TABLE 37 *Incremental cost per case detected from screening model produced by Gooder*[281a]

Strategy	Total costs (1995 UK£)	Cases detected	Incremental costs (1995 UK£)	Relative difference in cost (%)	Incremental cases detected	Relative difference in effects (%)	ICER compared to	IC per case detected
Current practice	308,660[b]	330						
Tonometry	1,905,800	500	1,597,140	517	170	152	Current practice	9,395
NCT and fields	2,923,294	917	1,017,494	153	417	183	Tonometry	2,440

[a] All costs reported in 1995 UK pounds sterling.
[b] This assumes that opportunistic eye tests would not be displaced by the screening strategy as they are conducted for other reasons, but that costs of referral and subsequent treatment following opportunistic case finding are relevant for inclusion.

TABLE 38 *Incremental cost per case detected from the screening model produced by Tuck and Crick*[283a]

Strategy no.	Screening strategies	True positives	Incremental cases detected	Relative difference in effects (%)	Total costs ($)	Incremental costs ($)	Relative difference in cost (%)	ICER compared to strategy no.	IC per case detected
1	Tonometry and perimetry if IOP > 20 mmHg	40			30,400				
2	Tonometry and perimetry if IOP > 22 mmHg	47	7	118	35,908	5,508	118	1	787
3	Tonometry at thresholds of IOP > 22 mmHg	49	2	104	43,806	7,898	122	2	3,949
5	Perimetry	55	6	112	57,970	14,164	132	3	2,361
8	Ophthalmoscopy and tonometry followed by perimetry for 'referral' candidates (lx)	56	1	102	76,552	18,582	132	5	18,582
11	Ophthalmoscopy and tonometry followed by perimetry for 'high-risk' candidates (sv)	67	11	120	82,678	6,126	108	8	557
13	Ophthalmoscopy and tonometry followed by perimetry for 'high-risk' candidates (lx)	70	3	104	95,060	12,382	115	11	4,127
15	Ophthalmoscopy and tonometry and perimetry (sv)	73	3	104	103,514	8,454	109	13	2,817
16	Ophthalmoscopy and tonometry and perimetry (lx)	80	7	110	117,520	14,006	114	15	2,001

[a] All costs reported in 1995 US dollars.

Interventions considered within the model

Screening and diagnostic interventions

The screening and diagnostic interventions are described in detail elsewhere (see the section 'Economic model', p. 15). In brief, three strategies have been considered: one representing current practice and the two alternative screening strategies (see *Figures 5–7*, pp. 14–15). Current practice reflects current glaucoma detection by case finding by a community optometrist as part of a routine eye test. The two alternative screening strategies vary in how screening would be organised. In one strategy individuals are invited for a screening examination by a glaucoma-trained optometrist. In the second strategy individuals are invited for a simple test assessing either visual field loss or structural damage, together with a measurement of the IOP by a technician. Individuals identified as at risk or positive by these technician tests would then be seen by a glaucoma optometrist. In all three strategies any individual identified as positive at the end of screening or case finding would be referred to an ophthalmologist for definitive diagnosis and, if necessary, treatment.

With respect to the actual test used in the various strategies it was concluded that for the purposes of the economic evaluation the IOP test used by the technician is Goldmann applanation tonometry with disposable tips and a slit-lamp microscope. For the second assessment within the 'technician screening' strategy, there is a number of possible screening tests available; details of the tests and their performance are described in Chapters 3 and 6. The model included a range of sensitivity and specificity values, rather than modelling the performance of one test or combination of tests as none of the candidate tests, or combinations of tests was clearly superior (Chapter 6).

The glaucoma optometrist assessment was assumed to be the same test combination as ophthalmologist diagnosis. This diagnostic test is a combination of IOP measurement by GAT, slit-lamp examination, fundoscopy and a visual field test.

Management of glaucoma

Should the ophthalmologist diagnose OAG, it has been assumed that treatment would be initiated. The following treatment pathway has been assumed in the model. Initial medical treatment would be with a topical treatment β-blocker or prostaglandin analogue). If that failed, this would be followed by an additional drop of another class of medications. For those patients for whom this fails, argon laser trabeculoplasty (ALT) or surgery (trabeculectomy) is the next treatment step. In addition to medications, treatment would involve visits to the ophthalmologist every 6 weeks at the beginning of treatment and a full assessment every 6 months. After surgery the patient would be seen at an ophthalmology outpatient clinic at 1, 2, 4, 8, 12 and 26 weeks after surgery.

Parameter estimates used in the model

Parameter estimates required to populate the model were obtained from the systematic reviews of test accuracy, OAG epidemiology, treatment effectiveness and cost-effectiveness, as well as other systematic, focused searches of the literature. The following sections give details on the probabilities, costs and utility data used, as well as the probability distributions adopted within the model.

Probabilities

Table 39 shows data on prevalence, incidence and progression of glaucoma used in the model. Within the model, prevalence was not formally based on data from the literature, as there were many different subgroups for which screening could be determined. The model was run for a range of prevalence values, informed by the review, aiming to identify those prevalences where screening strategies might be considered worthwhile. Once these were determined they were related to relevant subgroups to which the results might apply.

The proportion of OAG subjects with each severity of disease was informed by the systematic review of epidemiology (see *Table 10*, p. 32, for details). However, data were limited, as the majority of studies reporting severity did not report severity status for newly detected cases, and for the majority of participants severity status was not reported. Estimation was therefore based on expert opinion from ophthalmologists (RW, AAB and JB), and the included studies informed the distribution around these estimates. Limited data were obtained for incidence and progression of glaucoma. Incidence data were obtained as described in Chapter 5. Progression data, as well as the relative rate of progression between treated and untreated individuals, were based on a review of randomised and non-randomised evidence reported in Chapter 7. For the probabilistic sensitivity analysis triangular distributions were chosen for incidence and progression, and a log-normal distribution for the relative risk of progression for treated compared with untreated individuals.

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TABLE 39 *Prevalence, incidence and progression of glaucoma*

Probability	Value	Source	Distribution (values used to define the distribution)
Cohort start age	40	Base-case assumption	60 and 75 years old
Prevalence of glaucoma	0 to 0.2		
Proportion of glaucoma mild	0.50	Expert opinion/Chapter 5	0.475 and 0.45 for 60 and 75 years old, respectively
Proportion of glaucoma moderate	0.30	Expert opinion/Chapter 5	
Proportion of glaucoma severe	0.15	Expert opinion/Chapter 5	
Proportion of visual impaired	0.05	Expert opinion/Chapter 5	0.075 and 0.10 for 60 and 75 years old, respectively
Incidence of glaucoma		Chapter 5	
40 years old	0.0003	Chapter 5	Triangular (min. = 0.0001, likeliest = 0.0003, max. = 0.0008)
50 years old	0.0003	Chapter 5	Triangular (min. = 0.0001, likeliest = 0.0003, max. = 0.0008)
60 years old	0.0008	Chapter 5	Triangular (min. = 0.0002, likeliest = 0.0008, max. = 0.0022)
70 years old	0.00181	Chapter 5	Triangular (min. = 0.00068, likeliest = 0.00181, max. = 0.0044)
80 years old	0.00141	Chapter 5	Triangular (min. = 0.00097, likeliest = 0.00141, max. = 0.01)
Progression to glaucoma moderate	0.25	'Probability of glaucoma deterioration from mild disease to visual impairment' (p. 89)	Triangular (min. = 0.125, likeliest = 0.25, max. = 0.75)
Progression to glaucoma severe	0.11	'Probability of glaucoma deterioration from mild disease to visual impairment' (p. 89)	Triangular (min. = 0.055, likeliest = 0.11, max. = 0.33)
Progression to visual impaired	0.1	'Probability of glaucoma deterioration from mild disease to visual impairment' (p. 89)	Triangular (min. = 0.05, likeliest = 0.1, max. = 0.30)
RR treated–non-treated	0.65	'Effectiveness of glaucoma treatment' (p. 87)	Log-normal, (mean = –0.43, SD = 0.148)
Mortality	Various	See Appendix 21 for interim life table	

The annual probabilities of having an eye test are presented in *Table 40*. Data on these were scarce. It is plausible, for instance, that the annual probabilities of having an eye test differ between a general population and an OAG population, or between the same population in a screening or non-screening strategy. Moreover, these probabilities might also depend on the period between screening waves. The model structure allowed the incorporation of such differences. Unfortunately, data were not available at the level of detail required. Data on eye test, gender and age were obtained from the British Household Panel Survey (BHPS).[286] The total sample size for the BHPS was approximately 10,000 households from across the UK. Individuals in the included households are interviewed yearly. A probit regression model was used to obtain the probabilities of having an eye test. Alternative data were retrieved from the Sight Test Volume and Workforce Survey 2003/04 (STV&WS) and other published studies.[47,113] The results of the regression analysis of the BHPS data, consistent with the STV&WS and published studies, were used in the model for the probability of having an eye test (by a community optometrist) in the current practice strategy. Normal probability distributions were attached to the mean values for probabilistic analysis. Screening acceptance data were obtained from the epidemiology review (Chapter 5). Triangular distribution was attached to this parameter with upper and lower limits obtained from Hollows and Graham[21] and Wolfs and colleagues,[169] respectively.

Table 41 shows data on test performances. Seven reports provided information on the accuracy of referrals by community-based optometrists for people with suspected glaucoma.[287–293] However, no studies were identified that reported the diagnostic accuracy of the test strategy of community optometrists or glaucoma-trained

TABLE 40 *Probabilities of having an eye test in current practice and screening acceptance for screening strategies*

Age group (years)	Value	Source	Distribution (values used to define the distribution)
40–59	0.248	Regression analysis on BHPS data	Normal, (mean 0.248, SE 0.0019142)
60–75	0.3769	Regression analysis on BHPS data	Normal (mean 0.3769, SE 0.0046524)
⩾75	0.42	Regression analysis on BHPS data	Normal (mean 0.42, SE 0.0051359)
Screening acceptance; all groups	0.78	Epidemiology review. Range: min. from Wolfs 1999[169] (Rotterdam Study); Max from Hollows 1966[21] (Rhondda Valley Study)	Triangular (min. = 0.66, likeliest = 0.78, max. = 0.918)

optometrists, or included sufficient data to produce a 2×2 table to calculate sensitivity and specificity. Sensitivity and specificity for optometrist testing were derived from Tuck.[293] This study reported a survey conducted on behalf of the IGA involving 241 optometrists in England and Wales who, mainly commencing between November 1988 and February 1989, carried out 275,600 sight tests over a 6-month period (equivalent to 5% of the national total). The optometrists referred 1505 patients for suspected OAG. A diagnosis was confirmed and known for 1048, of whom 436 (41.6%) had a diagnosis of OAG confirmed by a consultant ophthalmologist. This allowed the calculation of true positives ($n = 436$), false positives ($n = 612$), total testing positive ($n = 1048$) and total testing negative ($n = 274{,}552$). As those testing negative did not receive confirmation of this by way of examination by a consultant ophthalmologist, there was no information on those who tested negative but actually had glaucoma (false negatives) or indeed did not have OAG (true negatives). Of the three studies considered, this one was the most appropriate (in terms of geographical coverage, number of patients seen and number of

TABLE 41 *Data on tests and test performance*

Probability	Value	Source	Distribution (values used to define the distribution)
Optometrist test sensitivity	0.32	Tuck, 1991[293]	Beta ($n = 1378$, $r = 436$)
Optometrist test specificity	0.99	Tuck, 1991[293]	Beta ($n = 274{,}228$, $r = 273{,}614$)
Glaucoma optometrist test sensitivity	0.73	Grampian optometry study (Burr J: personal communication)	Beta ($n = 33$, $r = 24$)
Glaucoma optometrist test specificity	0.96	Grampian optometry study (Burr J: personal communication)	Beta ($n = 67$, $r = 64$)
Proportion of normal with IOP < 26	0.96	Sommer, 1991[23] (Baltimore Eye Survey, see Chapter 5)	Beta ($n = 5682$, $r = 5455$)
Proportion of glaucoma with IOP ⩾ 26	0.35	Sommer, 1991[23] (Baltimore Eye Survey, see Chapter 5)	Beta ($n = 20$, $r = 7$)
Technician further test indeterminacy	0.1	Systematic review data, diagnostic (Chapter 6)	Uniform (0.06–0.20)
Technician further test sensitivity	0.8	Assumption	Uniform (0.8–1)
Technician further test specificity	0.8	Assumption	Uniform (0.8–1)
Ophthalmologist test sensitivity	1	Assumption	None defined
Ophthalmologist test specificity	1	Assumption	None defined
Ophthalmologist proportion diagnosed as 'observation' state	0.43	Henson. Manchester Glaucoma Optometry scheme 2005 data (Henson D, Aberdeen: personal communication, 2006)	Uniform (0.39–0.47)

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participating optometrists) for estimating OAG prevalence and hence arriving at an approximation of sensitivity and specificity. A 0.5% prevalence of undetected glaucoma was assumed (1378 patients out of the total of 275,600 seen). This allowed the calculation of false negatives (n = 942) and true negatives (n = 273,610) to complete a 2 x 2 table and provide an estimated sensitivity and specificity for community-based optometrist referrals for OAG glaucoma of 31.6% and 99.8%, respectively.

To estimate the diagnostic accuracy of glaucoma-trained optometrists, data were used from a study in Grampian evaluating a pilot community optometry glaucoma service, the Grampian Optometrist Study. The purpose of this study was to assess the diagnostic accuracy of the management decision made by accredited glaucoma optometrists. The optometrist decision was compared with two reference standards: an ophthalmologist with a special interest in glaucoma, and management decision made in usual care in the hospital-based new patient clinic. The study was completed in January 2006 and a publication is in preparation (Burr JM, Azuara-Blanco A, Thomas R, McLennan G, University of Aberdeen: personal communication, 2006). For the purpose of this analysis, disease was classified as OAG or ocular hypertension requiring treatment. The categories normal and discharged, and suspect requiring optometric review were classified as no disease. The consultant ophthalmologist with a special interest in glaucoma was the reference standard. The sensitivity of the glaucoma optometrist was 0.73 (95% CI 0.56 to 0.85), with a specificity of 0.96 (95% CI 0.88 to 0.99).

Data from the Baltimore Eye Survey were used for the estimation of the proportion of normal or OAG patients with IOP of at least 26 mmHg.[23] Details of this study can be found in Chapter 5. Estimation of the proportion of people able to perform the test (rate of indeterminancy) as part of the 'technician' screening strategy was obtained from the systematic review of screening tests (see Chapter 6). In summary, for the tests the percentage of interpretable results ranged from 80% for RNFL photography to 99% for SAP (threshold) and GAT, with a median rate across all tests of 97%. The number of studies contributing data for each test was very small, although the rates were very similar across tests.

The model used sensitivity and specificity values for the technician tests equal to or greater than 0.8. For the ophthalmologist assessment an assumption was made that this was the gold standard and that the sensitivity and specificity were equal to 1.

Beta distributions were used in the probabilistic sensitivity analysis for the accuracy of the optometrist in the current practice case-finding strategy, and for the glaucoma optometrist test sensitivities and specificities. Beta distributions were also used for the proportion of OAG individuals with IOP of at least 26 mmHg and proportion of normal individuals with IOP below 26 mmHg. Uniform distributions were used for technician further test indeterminacy, and for sensitivity and specificity. Finally, a uniform distribution was assumed for the proportion of people classified as glaucoma suspects (observation state) following diagnostic assessment by an ophthalmologist.

Costs

Tables 42 and *43* show the cost estimates used in the model. All figures are reported in 2006 pounds sterling. Where costs had to be adjusted into a common price year, a 2% inflation rate was assumed where no inflation rate indices were available. *Table 42* shows the costs for the current optometrist case-finding strategy. The cost for the optometrist test was obtained from the NHS fee for an eye test paid to an optometrist.[294] A triangular distribution was assumed for this variable. No information on ranges was available, and as a consequence rates of 0.5 and 1.5 times the likeliest value were used as lower and upper limits. The cost for the ophthalmologist diagnosis was calculated using data from Scottish National Statistics for April 2004 to March 2005 (source: www.isdscotland.org). The average reported cost for an ophthalmologist outpatient visit was £65. This value was inflated by the assumed 2% inflation rate for 2005/06. It was also assumed, based on the likely need for visual field testing to be performed as an additional outpatient visit, that the ophthalmological diagnosis would be equivalent to the cost of two standard ophthalmology department outpatient consultations. A triangular distribution was assumed for this parameter. The minimum and maximum limits values were developed in the same way as the likeliest mean value, but with the Scottish NHS Board lowest and highest average cost for an ophthalmologist outpatient visit (i.e. £38 and £195, respectively). This cost was also used for cost of the observation state within the model where it was assumed that patients judged to be at risk would be seen yearly for a maximum of 5 years in this state or until OAG was diagnosed.

TABLE 42 *Current practice costs*

Costs	Value (£)	Source	Distribution (values used to define the distribution)
Optometrist test	18.39	Department of Health[294]	Triangular (min. = 9.20, likeliest = 18.39, max. = 27.59)
Ophthalmologist diagnosis tests	133	Scotland National Statistics[a]	Triangular (min. = 77, likeliest = 133, max. = 397)
Glaucoma mild treatment	420	Traverso, 2005[259]	Triangular (min. = 210, likeliest = 420, max. = 630)
Glaucoma moderate treatment	473	Traverso, 2005[259]	Triangular (min. = 236.5, likeliest = 473, max. = 709.5)
Glaucoma severe treatment	376	Traverso, 2005[259]	Triangular (min. = 188, likeliest = 376, max. = 564)
Visual impairment annual cost	669	Traverso, 2005[259]	Triangular (min. = 585.41, likeliest = 669, max. = 752.06)

[a] Source: ISD Scotland (www.isdscotland.org).

Costs of treatment were calculated from Traverso and colleagues.[259] This is a Europe-based study and includes data for the UK by severity of glaucoma. In this study, the authors obtained records for 194 patients. Unfortunately, the sample sizes per country were not reported and the figures might be subject to 'small numbers' bias. The study reported costs in euros. The price year used was not reported in the study so it was assumed to be 2004. Costs in the common price year were estimated using the average 2004 exchange rate from euros into pounds sterling (e.g. 0.6787; source: http://www.oanda.com/convert/fxhistory), and a 2% annual inflation rate was assumed. Triangular distributions were attached to treatment costs. No additional data were available to allow for construction of a range, so the assumption of 0.5 and 1.5 times the likeliest value was applied. The exception to this was the annual cost for visual impairment. The likeliest value for the cost of visual impairment used in this model was based on the mean value of the last two disease stages reported in Traverso and colleagues, as these corresponded to the visual impairment category used in this study. A triangular distribution was assumed for this cost, with the minimum value being equal to the mean value of the less costly of the last two disease stages from Traverso and the maximum being equal to the mean value of the more costly of these stages.

Table 43 shows costs used for the screening strategies. Screening invitation costs were obtained from Facey and colleagues.[295] This was a study on the organisation of the diabetic retinopathy screening programme for Scotland. These figures include the cost for national coordination, local health board coordination, screening offices and call and recall operation, development and maintenance of call and recall software, and development and maintenance of image capture software. It also assumed around 125,000 people are screened. New NHS fees for optometrists in

TABLE 43 *Screening strategy costs*

Costs	Value (£)	Source	Distribution (values used to define the distribution)
Screening invitation	10.45	NHS Quality Improvement Scotland[295]	Triangular (min. = 5.23, likeliest = 10.45, max. = 15.68)
Glaucoma optometrist test	46.50	Scottish Executive[296]	Triangular (min. = 23.25, likeliest = 46.50, max. = 69.75)
Technician IOP tests	10.63	NHS Quality Improvement Scotland[295]	Triangular (min. = 5.32, likeliest = 10.63, max. = 15.95)
Technician second test	10.63	NHS Quality Improvement Scotland[295] likeliest = 10.63, max. = 15.95)	Triangular (min. = 5.32,

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TABLE 44 *Estimated health state utilities for the different levels of severity*

Value	Mild severity (*n* = 37)	Moderate severity (*n* = 14)	Severe severity (*n* = 9)
Mean	0.8015	0.7471	0.7133
Median	0.7960	0.7435	0.7960
SD	0.1254	0.1881	0.2549
Minimum	0.29	0.20	0.09
Maximum	0.92	0.90	0.92

Scotland were used for glaucoma optometrist assessment.[296] The new Scottish eye examination would include a full examination of the eye, visual field and IOP (e.g. with NCT), and supplementary exams if clinically indicated (e.g. applanation pressures and threshold fields). For the technician screening strategy, the technician IOP test and second round test costs were obtained from the Scottish Diabetic Retinopathy Screening study.[295] The costs were based on the variable costs for non-mydriatic camera, hospital-based, one technical staff screening estimated by this study. Triangular distributions were attached to the costs in *Table 43* with the assumption of 0.5 and 1.5 times the likeliest value used to estimate minimum and maximum values.

Data for treatment costs and ophthalmologist diagnosis were the same as in the no-screening strategy.

Health state utilities

The primary purpose of the economic model was to inform decision making in a UK setting. Recent guidance suggests that estimates of QALYs should ideally be based on generic health state valuation methods using UK population values,[297] and therefore a focused search of the literature and other relevant sources such as the Harvard cost–utility database for relevant utility data was conducted. A number of studies reporting health state utilities was identified. These studies used a wide variety of health state valuation techniques and utilities were obtained from a variety of different settings and respondents. However, none of these studies reported utilities applicable to a UK decision-making setting.

For this reason the results of an ongoing study were used to provide relevant utility estimates. This study is attempting to develop a glaucoma-specific measure of quality of life suitable for use in economic evaluations. The study involved the administration of a participant self-completed questionnaire to people with glaucoma attending the ophthalmology outpatient departments of Aberdeen Royal Infirmary and the United Leeds Teaching Hospital Trust (Leeds General Infirmary, St James' Hospital and St George's Community Eye Centre). UK members of the IGA also participated. All participants were asked to complete a questionnaire that included information on self-rating of glaucoma severity (mild, moderate or severe), a discrete choice experiment and the EuroQol 5 Dimensions (EQ-5D). A subsample of patients from Aberdeen underwent an objective assessment of glaucoma severity. This was by a grading of the binocular visual field using the integrated visual field method as described by Crabb and colleagues (see *Table 1*, p. 17).[89] The responses to the EQ-5D were converted to health state utilities using UK population tariffs and analysed according to the objective and subjective assessment of glaucoma severity (Kilonzo M, University of Aberdeen: personal communication, 2006). *Table 44* shows the estimates of utility for those people with an objective assessment of their glaucoma severity. Although these data are based on a subsample they were chosen from the larger sample available from the two hospitals and the IGA owing to the relatively poor concordance between objective and subjective assessments of glaucoma severity (Appendix 22). Nevertheless, due to the uncertainty surrounding which data to use, the estimates provided by the whole data set (reported in Appendix 22) have been used as part of a sensitivity analysis.

The estimates used in the model, using these data, are detailed in *Table 45*. A value of 1 was assumed for normal and observation states, while the corresponding mean values of *Table 44* were used as utility weights for OAG states mild, moderate and severe. The visual impaired utility state was developed using data from *Table 44* and from Gupta and colleagues.[298] This study presented utility values for categories that matched glaucoma severe and visual impaired states in the present study. Then, the relative difference between these

TABLE 45 *Health state utility estimates used in the model*

Quality of life	Utility weight	Source	Distribution (values used to define the distribution)
Normal	1	Assumption	None
Glaucoma mild	0.8015	(Kilonzo M, University of Aberdeen: personal communication, 2006)	Beta (alpha = 8.2, beta = 2)
Glaucoma moderate	0.7471	(Kilonzo M, University of Aberdeen: personal communication, 2006)	Beta (alpha = 11.4, beta = 3.5)
Glaucoma severe	0.7133	(Kilonzo M, University of Aberdeen: personal communication, 2006)	Beta (alpha = 1.2, beta = 0.4)
Visually impaired	0.5350	Developed using data from Gupta, 2005[298]	Log-normal (u = –0.31029, sigma = 0.16631)

two glaucoma states from Gupta and colleagues was used to obtain the utility score for visual impaired in *Table 45*. Beta distributions were attached to these glaucoma utility weight parameters (*Table 45*). It was assumed that there were no differences in the utility between undiagnosed OAG and treated OAG at each level of severity.

Base-case and sensitivity analysis

Base-case analysis

The base-case analysis was run for a cohort of 40-, 60- and 75-year-old males with screening occurring every 3 years. The choice of these ages and a 3-year screening interval was arbitrary. It was felt that the age groups covered the range over which screening might be considered and a 3-year screening interval was considered a plausible starting point for the analysis (the impact of using other screening intervals was considered). Gender-specific variables were not available for any of the model parameters except for mortality, and a decision was made to use male mortality rates in the base-case analysis, consistent with good modelling practice, as they are a conservative assumption for screening.

The model was run for a range of possible OAG prevalence values and for a lifetime horizon. Cycles length was set at 1 year. Costs are presented in 2006 pounds sterling and effectiveness in QALYs. A discount rate of 3.5% for costs and benefits was used following guidelines for technology assessment by the National Institute for Health and Clinical Excellence (NICE).[297] Results are presented in ICERs. This measure is a ratio of the difference in costs divided by the difference in the effectiveness between two alternative strategies. These data can be interpreted as how much society would have to pay for an extra unit of effectiveness. Probabilistic analysis results are presented for society's willingness to pay values of £10,000, £20,000, £30,000 and £50,000. Cost-effectiveness acceptability curves (CEACs) for these analyses are presented in Appendix 23. These plot the probability of each strategy being the optimal decision against a range of values for society's willingness to pay for an extra unit of effectiveness. Central to the assessment of cost-effectiveness is the value that society would put on gaining an additional QALY. NICE states that "Below a most plausible ICER of £20,000 per QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate. Above a most plausible ICER of £20,000 per QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:

- the degree of uncertainty surrounding the calculation of ICERs;
- the innovative nature of the technology;
- the particular features of the condition and population receiving the technology; and
- where appropriate, the wider societal costs and benefits.

Above an ICER of £30,000 per QALY, the case for supporting the technology on these factors has to be increasingly strong."[297](p. 33). In the absence of a more definitive statement this report focuses on a willingness to pay of £30,000 for a QALY.

The main results of the base-case analysis are presented in the section 'Results of base-case

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analysis and sensitivity analysis on the base-case' (p. 115). Full probabilistic analyses were carried out for the three cohort groups and rates of OAG prevalence from 0.1% and 20%.

Sensitivity analysis

Sensitivity analysis was carried out to explore uncertainties within the model. As described below, deterministic (one-way, two-way and multiway) sensitivity analyses were carried out for the main parameters within the model. Probabilistic sensitivity analyses were developed to address further parameter uncertainty in the model.

Changes to the screening interval

The effects of longer screening intervals (e.g. 5 and 10 years) were explored using one-way sensitivity analysis, as well as part of the probabilistic sensitivity analysis.

Changes to the probability of having an eye test

Deterministic analyses were conducted for the probability of having an eye test with a community optometrist assuming low, medium and high uptake rates. These were defined as an annual probability of an eye test of 2%, 13% and 37%. The rationale for these figures was based on discussion among the members of the study steering group. It was agreed that it was likely that a part of the population would have lower utilisation (caused by either lower access or the exercise of choice) to a community optometrist test. Moreover, some people may have almost no access to these services. The values adopted would give approximately 10%, 50% and 90% of the cohort receiving an eye test in the community setting over a 5-year period.

Changes to the sensitivity and specificity of the technician tests

In the base-case analysis it was assumed that the sensitivity and specificity of this test was 0.8 and 0.8. In this sensitivity analysis the sensitivity and specificity were varied between plausible ranges of 0.5 to 1.0 for sensitivity and 0.8 to 1.0 for specificity.

Further targeted sensitivity analyses for potentially cost-effective scenarios

Further sensitivity analyses were carried out for the combinations of the cohort, prevalence rate and screening interval that seemed to be most likely to be cost-effective. Specifically, the following sensitivity analyses were conducted for the 40-year-old cohort, at a 5% (except where otherwise stated) OAG prevalence rate and a 10-year screening interval.

Changes to the uptake of the community optometrist

It is likely that the cohort of individuals with higher OAG prevalence rates would have a higher probability of going for an eye test, for example people with a family history of OAG or people with myopia. Conversely, ethnic minority groups may have a lower probability of attending for an eye test. Additional sensitivity analysis was completed assuming 1.5 times and twice the probability of having an eye test for the no-screening strategy.

Changes to incidence and progression of glaucoma

Although considerable efforts were made to identify the estimates for incidence and progression, few data were available. Within the base-case analysis distributions were defined to reflect the variability surrounding these estimates. Despite this it was felt possible that the values used might have been substantially lower or higher than those used in the base case. In the first of these sensitivity analyses the incidence of OAG was assumed to be equal to the maximum for incidence reported in *Table 39*. A triangular distribution was attached, where the maximum was assumed to be twice the maximum used in the base case (truncated if necessary at 1) and the minimum value was assumed to be equal to the likeliest value from the base case.

For the second of these analyses the incidence of OAG was assumed to be equal to the minimum for incidence reported in *Table 39*. A triangular distribution was attached, where the maximum was assumed to be the likeliest value from the base case (truncated if necessary at 1) and the minimum value was assumed to be equal to zero.

With respect to progression in the 'high' analyses, the maximum values for the rates of progression were used. Likewise, in the 'low' analyses, the minimum values for the rates of progression were used. A triangular distribution around the likeliest values used in the analyses was defined using the same methods as described above.

Further sensitivity analysis was carried out based on time to progression, rather than average risk of progression (Chapter 7), for untreated patients for each corresponding glaucoma state by applying the treatment effect of 0.65 to the number of years until progression occurred. Using

this method the progression rates for the untreated were 0.31 for progression to glaucoma moderate, 0.11 for progression to glaucoma severe and 0.09 for progression to visually impaired. Triangular distributions were attached to these parameters' mean values using the same methodology described above.

Changes to the sensitivity and specificity of the technician tests

In this sensitivity analysis the same methods as described in the section 'Base-case and sensitivity analysis' (p. 113) were used to explore how the results changed as the sensitivity and specificity of the second test performed by the technician in the 'technician screening' strategy were changed.

Sensitivity analysis on health state utilities

In previous analyses health state utilities were based on objective assessment of the severity of OAG. In this sensitivity analysis a larger data set where the severity of OAG was based on the subjective assessment of severity was used. The data used in this analysis were described in Appendix 22. As noted in Appendix 22, objective and subjective assessments did not always agree. The main difference between the utility values based on subjective and objective assessments was the difference in utility weights between states. For example, in the base-case analysis, a loss of around 7% and 5% in quality of life would occur when moving from glaucoma mild to glaucoma moderate and from glaucoma moderate to glaucoma severe, respectively. These changes are approximately 2.5% and 10%, respectively, for this analysis.

Sensitivity analysis on costs

Costs of screening, diagnosis and treatment

As described in 'Parameter estimates used in the model' (p. 107), the data available on costs were limited and consideration was given to variations in the costs used in the model. In this sensitivity analysis low and high estimates were derived. For the cost of diagnosis by the ophthalmologist low and high values were developed using data from Scotland National Statistics (see *Table 42*). For example, in this situation, the high value was almost three times the base-case value used.

The treatment costs of the different disease states were also varied in a further treatment cost scenario. In this scenario the costs for each disease state were assumed to be either half or twice the costs used in the base-case analysis (*Table 42*).

A third scenario was also considered for sensitivity analysis around cost estimates. In this scenario the costs of the screening invitation and the tests performed during screening were varied. Each cost was assumed to be either half or twice the values used in the base-case analysis (*Table 43*).

Changes to the cost of visual impairment

The perspective taken for the estimate of costs was that of the NHS. In this sensitivity analysis the effect of widening the perspective to include other sectors of the economy such as Personal Social Services and the patient was explored. The effect of this wider perspective was assumed to affect the costs of visual impairment alone. This analysis was conducted for a 40-year-old cohort undergoing screening every 10 years, but with a prevalence of OAG of either 1% or 5%. For both prevalence rates one-way sensitivity analysis was used to identify threshold values for the annual cost of visual impairment. To interpret these thresholds it should be borne in mind that, based on the data reported by Meads and Hyde,[299] the annual cost of a year of visual impairment can be calculated as £7851 for the first year of visual impairment and £7657 for subsequent years (details as to how these estimates were derived are described in Appendix 24).

Results of base-case analysis and sensitivity analysis on the base case

Estimates of costs and QALYs for the base case

Tables 46–48 report the estimated relative cost-effectiveness by screening strategy at different levels of prevalence of OAG for cohorts aged 40, 60 and 75 years, respectively. These results are based on a screening interval of 3 years.

In each of these analyses, as prevalence increases cost also increases and QALYs fall for all three strategies and all age cohorts. Costs increase as prevalence increases because a larger proportion of individuals in the cohort incurs the costs of diagnosis and the continuing costs of treating the OAG. The mean cost per person is higher for the 40-year-old cohort than the older cohorts because they are less likely to die during the time-horizon of the model and thus have more opportunity to incur costs. Estimated mean QALYs fall as prevalence increases. This is because a greater proportion of the cohort experience the adverse health effects of OAG. Estimated mean QALYs are greater for the younger age group than the older age groups at each prevalence level, primarily because members of the younger age group are less likely to die during the time-horizon of the model.

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TABLE 46 *Incremental cost-effectiveness for the 40-year-old cohort by different prevalence rates*

Prevalence	Strategy	Cost (£)	QALYs	ICER
1%	No screening	257.40	19.231	
	Technician	520.36	19.233	107,938
	GO	617.34	19.234	398,881
2%	No screening	333.89	19.166	
	Technician	608.76	19.170	65,924
	GO	705.86	19.171	240,717
4%	No screening	486.85	19.036	
	Technician	785.57	19.044	39,118
	GO	882.89	19.045	134,460
6%	No screening	639.82	18.906	
	Technician	962.38	18.918	29,051
	GO	1,059.93	18.919	93,416
8%	No screening	792.79	18.777	
	Technician	1,139.19	18.791	23,775
	GO	1,236.97	18.793	71,648
10%	No screening	945.76	18.647	
	Technician	1,316.00	18.665	20,527
	GO	1,414.00	18.667	58,158
12%	No screening	1,098.72	18.517	
	Technician	1,492.80	18.539	18,326
	GO	1,591.04	18.541	48,979
14%	No screening	1,251.69	18.387	
	Technician	1,669.61	18.412	16,737
	GO	1,768.07	18.415	42,330
16%	No screening	1,404.66	18.258	
	Technician	1,846.42	18.286	15,535
	GO	1,945.11	18.289	37,290
18%	No screening	1,557.63	18.128	
	Technician	2,023.23	18.160	14,594
	GO	2,122.15	18.163	33,339
20%	No screening	1,710.59	17.998	
	Technician	2,200.04	18.033	13,838
	GO	2,299.18	18.037	30,159

GO, 'glaucoma optometrist' strategy.

In each analysis at each prevalence level and age group considered, 'no screening' (i.e. the current strategy of opportunistic case finding by the community optometrist) is the least costly but also the least effective of the three strategies considered. Adopting a strategy where a technician performs the initial screening tests is more effective but more costly than a no-screening strategy, and a strategy of screening by a glaucoma optometrist is more effective but more costly than the 'technician' screening strategy.

Estimated cost-effectiveness

For each age group considered the incremental cost per QALY gained from adopting 'technician' screening compared with 'no screening' falls as prevalence increases. The incremental cost per QALY gained indicates how well the extra costs of a more expensive but more effective treatment are converted into additional benefits. As the incremental cost per QALY gained falls the more likely it becomes that technician screening will be considered cost-effective compared with no screening. Similarly, for each age group considered, the incremental cost per QALY gained from adopting glaucoma optometrist screening compared with technician screening falls as prevalence increases. This indicates that as prevalence increases it is more likely that technician screening will be considered cost-effective compared with no screening.

TABLE 47 *Incremental cost-effectiveness for the 60-year-old cohort by different prevalence rates*

Prevalence	Strategy	Cost (£)	QALYs	ICER
1%	No screening	187.10	12.477	
	Technician	364.37	12.479	134,060
	GO	430.42	12.479	409,416
2%	No screening	232.42	12.438	
	Technician	418.47	12.440	88,094
	GO	484.79	12.440	264,869
4%	No screening	323.06	12.360	
	Technician	526.67	12.363	55,160
	GO	593.52	12.364	156,016
6%	No screening	413.71	12.281	
	Technician	634.87	12.286	41,963
	GO	702.25	12.287	111,083
8%	No screening	504.35	12.203	
	Technician	743.07	12.209	34,851
	GO	810.98	12.210	86,547
10%	No screening	594.99	12.124	
	Technician	851.27	12.132	30,405
	GO	919.71	12.133	71,088
12%	No screening	685.64	12.045	
	Technician	959.47	12.055	27,361
	GO	1,028.44	12.057	60,456
14%	No screening	776.28	11.967	
	Technician	1,067.67	11.979	25,147
	GO	1,137.17	11.980	52,695
16%	No screening	866.92	11.888	
	Technician	1,175.87	11.902	23,464
	GO	1,245.90	11.903	46,781
18%	No screening	957.57	11.810	
	Technician	1,284.07	11.825	22,142
	GO	1,354.63	11.826	42,124
20%	No screening	1,048.21	11.731	
	Technician	1,392.27	11.748	21,076
	GO	1,463.36	11.750	38,362

The base-case model suggests that for a 40-year-old cohort a technician screening strategy compared with a no-screening strategy is associated with an incremental cost per QALY that society might be willing to pay at a prevalence somewhere between approximately 6 and 10% (*Table 46*). For a 60-year-old cohort a technician screening strategy compared with a no-screening strategy might be considered cost-effective at a prevalence between approximately 12 and 20% (*Table 47*). For a 75-year-old cohort, a no-screening strategy has an incremental cost per QALY gained at any of the prevalence levels considered (*Table 48*). Furthermore, for no age cohort and no prevalence level is screening by the glaucoma optometrist instead of screening by the technician associated with an incremental cost per QALY gained that society might typically be willing to pay.

Tables 46–48 present mean costs, QALYs and incremental costs per QALY gained. Such data do not represent the imprecision surrounding the parameter estimates used in the model. This uncertainty was addressed by the probabilistic sensitivity analyses conducted. These show the likelihood that each screening strategy would be considered cost-effective at different threshold values for society's willingness to pay for a QALY (*Tables 49–51*).

Tables 49 indicates for a 40-year-old cohort that at prevalence levels of 1% or less there is very little likelihood that any screening strategy would be

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TABLE 48 *Incremental cost-effectiveness for the 75-year-old cohort by different prevalence rates*

Prevalence	Strategy	Cost (£)	QALYs	ICER
1%	No Screening	103.47	6.905	
	Technician	210.76	6.905	200,028
	GO	250.74	6.905	521,062
2%	No screening	125.01	6.884	
	Technician	238.87	6.885	137,032
	GO	279.22	6.885	350,449
4%	No screening	168.11	6.843	
	Technician	295.11	6.845	89,440
	GO	336.17	6.845	213,985
6%	No screening	211.20	6.802	
	Technician	351.35	6.804	69,757
	GO	393.12	6.804	155,507
8%	No screening	254.30	6.761	
	Technician	407.58	6.764	58,999
	GO	450.08	6.764	123,022
10%	No screening	297.39	6.720	
	Technician	463.82	6.723	52,218
	GO	507.03	6.723	102,350
12%	No screening	340.49	6.679	
	Technician	520.06	6.683	47,552
	GO	563.98	6.683	88,039
14%	No screening	383.59	6.638	
	Technician	576.30	6.642	44,146
	GO	620.94	6.643	77,544
16%	No screening	426.68	6.597	
	Technician	632.53	6.601	41,550
	GO	677.89	6.602	69,519
18%	No screening	469.78	6.555	
	Technician	688.77	6.561	39,505
	GO	734.84	6.562	63,183
20%	No screening	512.87	6.514	
	Technician	745.01	6.520	37,853
	GO	791.80	6.521	58,055

more cost-effective than no screening. At a 5% prevalence level there is just over 40% likelihood that technician screening would be considered cost-effective if society's willingness to pay for a QALY was £30,000. This climbs to 56% when the prevalence is 10%. Screening by a glaucoma optometrist is unlikely to be considered cost-effective at any of the prevalence levels or cost per QALY thresholds considered.

For a 60-year-old cohort there is less than a 50% chance that technician screening would be considered cost-effective when society's willingness to pay for a QALY is £30,000 (*Tables 50*) for all prevalences up to 20%. Again, screening by a glaucoma optometrist is unlikely to be considered cost-effective at any of the prevalence levels or cost per QALY thresholds considered.

There is only a low likelihood that any strategy other than no screening would be considered cost-effective for the 75-year-old cohort at any of the prevalence levels considered if society's maximum willingness to pay for a QALY is £30,000. Should society's willingness to pay for a QALY be higher than £30,000 then the likelihood that the technician or glaucoma optometrist screening strategy would be considered cost-effective increases. Nevertheless, even at a willingness to pay for a QALY of £50,000, no screening is most likely to be the most cost-effective strategy.

Sensitivity analysis performed around the base case

Changes to the screening interval

The base-case analysis has assumed that screening will take place every 3 years. In this analysis the

TABLE 49 *Probabilistic sensitivity analysis for 40-year-old cohort: probability of being the optimal strategy at different threshold levels for society's willingness to pay for a QALY*

Prevalence	Strategy	Cost (£)	QALYs	ICER	Probability that intervention is cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
1%	No Screening	257.40	19.231		100.0	98.8	93.9	78.5
	Technician	520.36	19.233	107,938	0.0	1.20	5.9	21.0
	GO	617.34	19.234	398,881	0.0	0.0	0.2	0.5
5%	No screening	563.34	18.971		94.4	71.5	50.8	34.9
	Technician	873.97	18.981	33,153	5.4	27.9	48.0	61.3
	GO	971.41	18.982	110,218	0.2	0.6	1.2	3.8
10%	No screening	945.76	18.647		79.6	48.6	35.0	24.2
	Technician	1,316.00	18.665	20,527	19.9	49.6	60.0	62.3
	GO	1,414.00	18.667	58,158	0.5	1.8	5.0	13.5
15%	No screening	1,328.17	18.323		68.9	39.6	29.2	20.6
	Technician	1,758.02	18.349	16,097	30.1	55.3	59.4	56.7
	GO	1,856.59	18.352	39,648	1.0	5.1	11.4	22.7
20%	No screening	1,710.59	17.998		59.9	34.9	26.8	18.9
	Technician	2,200.04	18.033	13,838	38.5	55.9	54.3	48.0
	GO	2,299.18	18.037	30,159	1.6	9.2	18.9	33.1

See Appendix 23, *Figures 53–57*, for CEACs.

TABLE 50 *Probabilistic sensitivity analysis for 60-year-old cohort: probability of being the optimal strategy at different threshold levels for society's willingness to pay for a QALY*

Prevalence	Strategy	Cost (£)	QALYs	ICER	Probability that intervention is cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
1%	No screening	187.10	12.477		100.0	98.4	92.9	79.2
	Technician	364.37	12.479	134,060	0.0	1.5	6.9	20.2
	GO	430.42	12.479	409,416	0.0	0.1	0.2	0.6
5%	No screening	368.38	12.320		96.4	79.3	64.0	46.1
	Technician	580.77	12.325	47,399	3.5	20.1	34.7	50.5
	GO	647.88	12.325	129,684	0.1	0.6	1.3	3.4
10%	No screening	594.99	12.124		87.6	63.0	48.4	34.3
	Technician	851.27	12.132	30,405	12.0	35.3	46.7	53.0
	GO	919.71	12.133	71,088	0.4	1.7	4.9	12.7
15%	No screening	821.60	11.928		81.3	53.2	41.2	30.3
	Technician	1,121.77	11.940	24,252	17.8	42.3	49.0	49.1
	GO	1,191.54	11.941	49,551	0.9	4.5	9.8	20.6
20%	No screening	1,048.21	11.731		76.7	49.4	36.2	27.8
	Technician	1,392.27	11.748	21,076	22.0	42.4	47.5	43.5
	GO	1,463.36	11.750	38,362	1.3	8.2	16.3	28.7

See Appendix 23, *Figures 58–62*, for CEACs.

impact of changing the screening interval to 5 or 10 years has been explored (*Figures 40–42*). These data indicate that as the screening interval increases the incremental cost per QALY gained reduces. This is because it has been assumed that OAG progresses relatively slowly and any reduction in total QALYs is more than compensated for by a reduction in costs.

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TABLE 51 *Probabilistic sensitivity analysis for 75-year-old cohort: probability of being the optimal strategy at different threshold levels for society's willingness to pay for a QALY*

Prevalence	Strategy	Cost (£)	QALYs	ICER	Probability that intervention is cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
1%	No screening	103.47	6.905		100.0	99.6	96.1	88.1
	Technician	210.76	6.905	200,028	0.0	0.4	3.7	11.5
	GO	250.74	6.905	521,062	0.0	0.0	0.2	0.4
5%	No screening	189.66	6.823		99.1	89.8	78.7	64.0
	Technician	323.23	6.824	77,908	0.9	9.9	20.4	33.8
	GO	364.65	6.825	179,873	0.0	0.3	0.9	2.2
10%	No screening	297.39	6.720		95.5	79.3	67.5	50.7
	Technician	463.82	6.723	52,218	4.3	19.6	30.0	40.0
	GO	507.03	6.723	102,350	0.2	1.1	2.5	9.3
15%	No screening	405.13	6.617		91.7	74.3	62.1	46.2
	Technician	604.41	6.622	42,766	7.9	23.5	31.1	38.9
	GO	649.41	6.622	73,281	0.4	2.2	6.8	14.9
20%	No screening	512.87	6.514		89.7	70.0	57.0	43.6
	Technician	745.01	6.520	37,853	9.5	25.2	31.9	35.8
	GO	791.80	6.521	58,055	0.8	4.8	11.1	20.6

See Appendix 23, *Figures 63–67* for CEACs.

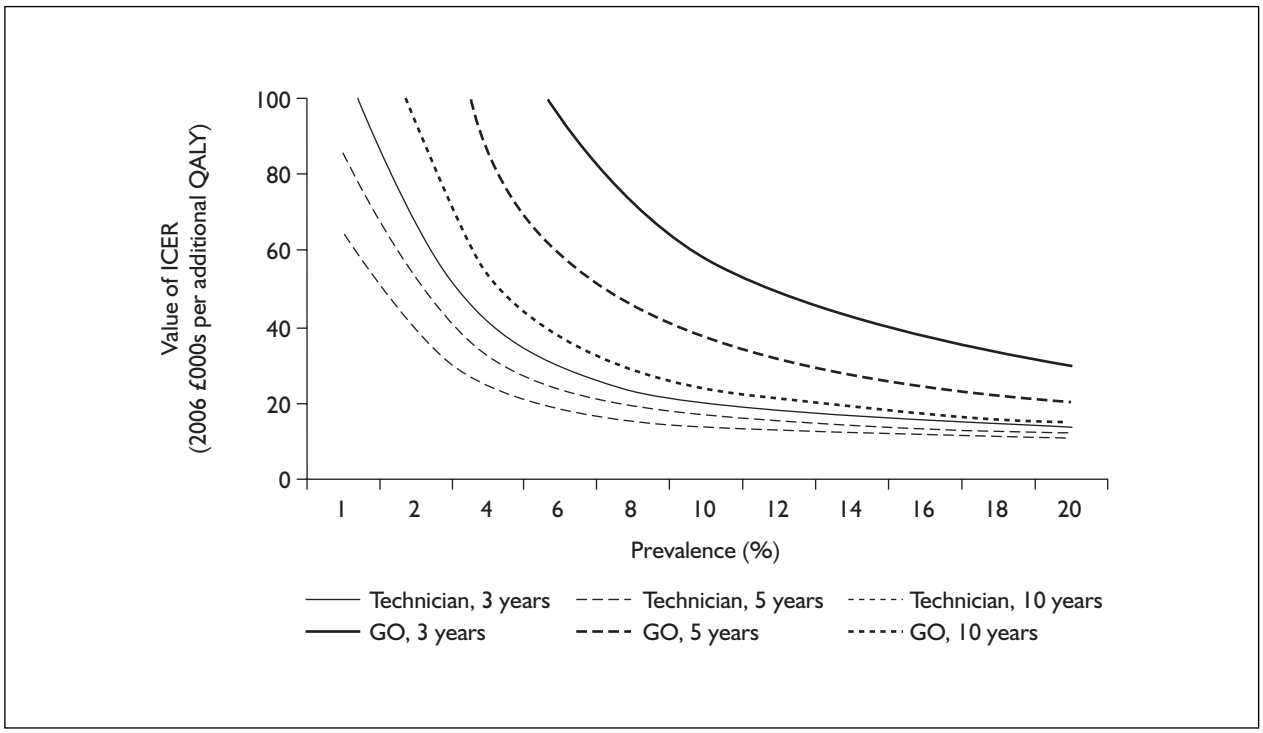

FIGURE 40 *Incremental cost per QALY gained by prevalence rate and at 3-, 5- and 10-year screening intervals for the 40-year-old cohort. Incremental cost per QALY for 'technician' strategy is for the comparison of 'technician' strategy with 'no screening' strategy. Incremental cost per QALY for 'glaucoma optometrist' strategy (GO) is for the comparison of 'glaucoma optometrist' strategy with 'technician' strategy.*

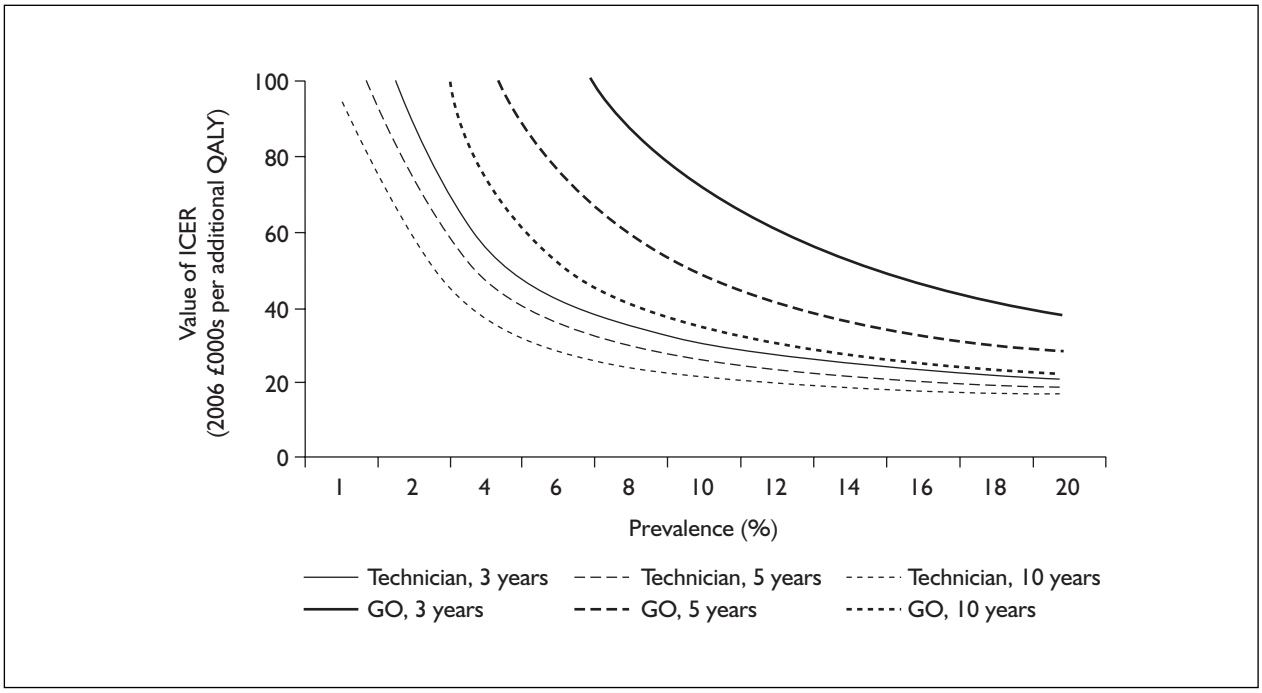

FIGURE 41 *Incremental cost per QALY gained by prevalence rate and at 3-, 5- and 10-year screening intervals for the 60-year-old cohort. Incremental cost per QALY for 'technician' strategy is for the comparison of 'technician' strategy with 'no screening' strategy. Incremental cost per QALY for 'glaucoma optometrist' strategy (GO) is for the comparison of 'glaucoma optometrist' strategy with 'technician' strategy.*

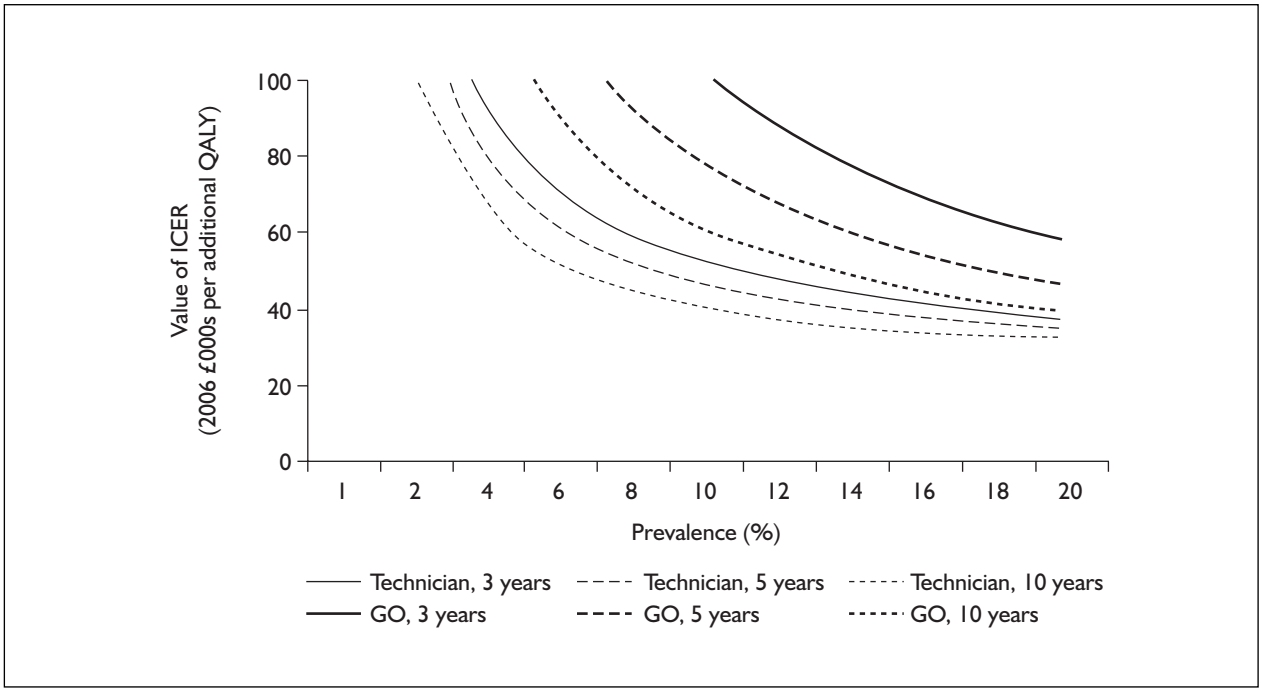

FIGURE 42 *Incremental cost per QALY gained by prevalence rate and at 3-, 5- and 10-year screening intervals for the 75-year-old cohort. Incremental cost per QALY for 'technician' strategy is for the comparison of 'technician' strategy with 'no screening' strategy. Incremental cost per QALY for 'glaucoma optometrist' strategy (GO) is for the comparison of 'glaucoma optometrist' strategy with 'technician' strategy.*

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TABLE 52 *Likelihood of a strategy being cost-effective for different age cohorts and screening intervals: 1% prevalence of OAG*

Cohort	Screening interval	Strategy	Probabilistic cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
			£10,000	£20,000	£30,000	£50,000
40 years old	3 years (base case)	No screening	100.0	98.8	93.9	78.5
		Technician	0.0	1.2	5.9	21.0
		GO	0.0	0.0	0.2	0.5
	5 years	No screening	100.0	97.1	88.2	69.2
		Technician	0.0	2.7	11.5	30.1
		GO	0.0	0.2	0.3	0.7
	10 years	No screening	99.8	92.1	79.1	56.2
		Technician	0.2	7.7	20.3	42.5
		GO	0.0	0.2	0.6	1.3
60 years old	3 years (base case)	No screening	100.0	98.4	92.9	79.2
		Technician	0.0	1.5	6.9	20.2
		GO	0.0	0.1	0.2	0.6
	5 years	No screening	100.0	97.2	90.0	74.4
		Technician	0.0	2.7	9.6	24.7
		GO	0.0	0.1	0.4	0.9
	10 years	No screening	100.0	95.1	86.9	69.3
		Technician	0.0	4.8	12.7	29.5
		GO	0.0	0.1	0.4	1.2
75 years old	3 years (base case)	No screening	100.0	99.6	96.1	88.1
		Technician	0.0	0.4	3.7	11.5
		GO	0.0	0.0	0.2	0.4
	5 years	No screening	100.0	99.6	96.5	88.1
		Technician	0.0	0.4	3.5	11.9
		GO	0.0	0.0	0.0	0.0
	10 years	No screening	100.0	99.1	94.6	84.3
		Technician	0.0	0.9	5.2	15.1
		GO	0.0	0.0	0.2	0.6

See Appendix 23, *Figures 68–73*, for CEACs.

For the 40-year-old cohort, adopting the technician strategy in preference to a no-screening strategy would be associated with an incremental cost per QALY that society might consider acceptable at a prevalence of approximately 4% (5-year screening interval) and just less than 4% (10-year screening interval). Furthermore, at a prevalence of approximately 12% adopting the screening by a glaucoma optometrist would be associated with an incremental cost per QALY that society might consider acceptable. For the 60-year-old age group similar prevalences for the cost-effectiveness of technician screening are 8% (5-year screening interval) and 6% (10-year screening interval). Screening by a glaucoma optometrist would be associated with an incremental cost per QALY that society might consider acceptable at approximately 20% prevalence. At none of the screening intervals or prevalences considered for 75 year olds would either technician screening or the screening by the glaucoma optometrist be considered cost-effective.

Figures 40–42 do not reflect the statistical imprecision surrounding the parameter estimates used in the calculation of the estimates of the incremental cost per QALY gained. The probabilistic sensitivity analyses reported in *Tables 52–54* show the likelihood that each of the strategies might be considered cost-effective at different threshold values for willingness to pay for a QALY at 3-, 5- and 10-year screening intervals. *Table 52* shows these data when the prevalence is 1%, *Table 53* shows the results for a 5% prevalence level and *Table 54* shows the results for a 10% prevalence level. As these tables show, the

TABLE 53 *Likelihood of a strategy being cost-effective for different age cohorts and screening intervals: 5% prevalence of OAG*

Cohort	Screening interval	Strategy	Probabilistic cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
			£10,000	£20,000	£30,000	£50,000
40 years old	3 years (base case)	No screening	94.4	71.5	50.8	34.9
		Technician	5.4	27.9	48.0	61.3
		GO	0.2	0.6	1.2	3.8
	5 years	No screening	87.6	58.6	43.2	29.2
		Technician	12.2	40.2	53.3	60.4
		GO	0.2	1.2	3.5	10.4
	10 years	No screening	82.5	54.3	40.2	29.6
		Technician	16.7	42.3	51.4	51.1
		GO	0.8	3.4	8.4	19.3
60 years old	3 years (base case)	No screening	96.4	79.3	64.0	46.1
		Technician	3.5	20.1	34.7	50.5
		GO	0.1	0.6	1.3	3.4
	5 years	No screening	93.1	73.3	56.7	40.3
		Technician	6.7	25.7	40.5	50.8
		GO	0.2	1.0	2.8	8.9
	10 years	No screening	88.1	63.9	49.3	34.9
		Technician	11.5	33.6	44.0	48.4
		GO	0.4	2.5	6.7	16.7
75 years old	3 years (base case)	No screening	99.1	89.8	78.7	64.0
		Technician	0.9	9.9	20.4	33.8
		GO	0.0	0.3	0.9	2.2
	5 years	No screening	98.2	86.9	74.5	59.9
		Technician	1.7	12.4	24.2	34.9
		GO	0.1	0.7	1.3	5.2
	10 years	No screening	96.1	82.2	69.7	53.8
		Technician	3.8	16.9	27.9	37.5
		GO	0.1	0.9	2.4	8.7

See Appendix 23, *Figures 74–79* for CEACs.

likelihood that either the technician or the glaucoma optometrist strategy would be considered cost-effective increases as prevalence and screening interval increase for all three age cohorts. Again, the likelihood of the glaucoma optometrist strategy being cost-effective is rarely greater than 20%.

Changes in the probability of having an eye test with a community optometrist

It was discussed and agreed in the steering group meeting that part of the population would have a lower attendance for a sight test by a community optometrist. In this analysis 2%, 13% and 37% community optometrist test uptake rates were assumed. The rationale for these figures was that they would result in about 10%, 50% and 90% of the cohort having an eye test in 5 years' time.

Tables 55–57 show the results for the 40-, 60- and 75-year-old cohorts, respectively. As expected, the cost and QALY rise when uptake rates for attendance at a community optometrist are higher. The higher the uptake rate, the better the no-screening strategy performs. For instance, the incremental cost per QALY for a 1% prevalence rate of OAG for the comparison of the technician with the no-screening strategy was £107,938 (*Table 46*), whereas the incremental cost per QALY when there was a low uptake rate of the community optometrist was £59,191 (*Table 55*). Moreover, if there is a group of individuals within the cohort that do not access a community optometrist service, the screening strategies become more cost-effective the bigger the deprived group is. The assumption within the model is that this group will attend screening.

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TABLE 54 *Likelihood of a strategy being cost-effective for different age cohorts and screening intervals: 10% prevalence of OAG*

Cohort	Screening interval	Strategy	Probabilistic cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
			£10,000	£20,000	£30,000	£50,000
40 years old	3 years (base case)	No screening	79.6	48.6	35.0	24.2
		Technician	19.9	49.6	60.0	62.3
		GO	0.5	1.8	5.0	13.5
	5 years	No screening	72.9	42.7	30.1	22.0
		Technician	26.1	51.4	57.1	53.3
		GO	1.0	5.9	12.8	24.7
	10 years	No screening	61.2	36.3	27.7	19.6
		Technician	36.1	49.8	48.2	39.5
		GO	2.7	13.9	24.1	40.9
60 years old	3 years (base case)	No screening	87.6	63.0	48.4	34.3
		Technician	12.0	35.3	46.7	53.0
		GO	0.4	1.7	4.9	12.7
	5 years	No screening	83.0	56.3	43.3	31.7
		Technician	16.1	39.4	46.7	47.9
		GO	0.9	4.3	10.0	20.4
	10 years	No screening	77.5	50.9	38.7	29.1
		Technician	21.1	39.3	43.1	39.1
		GO	1.4	9.8	18.2	31.8
75 years old	3 years (base case)	No screening	95.5	79.3	67.5	50.7
		Technician	4.3	19.6	30.0	40.0
		GO	0.2	1.1	2.5	9.3
	5 years	No screening	93.3	76.0	64.2	48.5
		Technician	6.4	22.3	30.1	37.6
		GO	0.3	1.7	5.7	13.9
	10 years	No screening	90.7	72.0	60.7	45.3
		Technician	8.7	24.0	29.8	35.6
		GO	0.6	4.0	9.5	19.1

See Appendix 23, *Figures 80–85* for CEACs.

Changes to the sensitivity and specificity of the test following the measurement of IOP in the 'technician' strategy

Overall, the results of the analysis indicate that the incremental cost per QALY is relatively insensitive to changes to either the specificity or sensitivity of this test. *Figures 43–45* illustrate this. These figures show that as specificity increases the incremental cost per QALY of the technician testing strategy falls. Likewise, as sensitivity increases the incremental cost also falls. The figures also illustrate that changes in specificity are more important than changes in sensitivity and that the importance of changes in specificity and sensitivity declines as prevalence increases. The impact of changes in sensitivity and specificity does not appear to be greatly influenced by the age of the cohort screened.

As would be expected, as the sensitivity and the specificity of tests in the glaucoma optometrist strategy were not changed, any increase in the performance of tests performed as part of the technician strategy would make the glaucoma optometrist strategy less cost-effective compared with the technician strategy.

Results of further targeted sensitivity analysis

As indicated above, the results of the base-case analysis and its associated sensitivity analysis have indicated that the following are likely to increase the cost-effectiveness of screening:

- starting to screen at a younger age rather than an older age (e.g. screening at 40 is more likely

TABLE 55 *ICERs for different annual community optometrist test uptake rates: 40-year-old cohort*

		Low			Medium			High		
Prevalence	**Strategy**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**
1%	No screening	85.30	19.227		148.80	19.229		268.80	19.231	
	Technician	419.90	19.233	59,191	453.90	19.233	75,830	527.10	19.233	121,443
	GO	518.60	19.233	292,714	551.90	19.233	331,257	623.90	19.234	424,490
2%	No screening	144.24	19.160		217.54	19.163		348.36	19.167	
	Technician	507.76	19.169	38,559	542.18	19.170	48,474	616.03	19.170	75,528
	GO	606.92	19.170	181,346	640.49	19.170	204,316	712.82	19.171	259,384
4%	No screening	262.11	19.026		354.96	19.031		507.51	19.038	
	Technician	683.39	19.043	24,817	718.72	19.043	30,200	793.88	19.044	44,903
	GO	783.51	19.044	103,626	817.62	19.044	116,122	890.68	19.045	145,898
6%	No screening	379.97	18.892		492.37	18.899		666.65	18.909	
	Technician	859.02	18.916	19,534	895.25	18.917	23,163	971.74	18.918	33,121
	GO	960.09	18.917	72,953	994.75	18.918	81,404	1,068.54	18.919	101,495
8%	No screening	497.83	18.757		629.78	18.768		825.80	18.780	
	Technician	1,034.65	18.789	16,738	1,071.79	18.790	19,436	1,149.60	18.792	26,882
	GO	1,136.68	18.791	56,533	1,171.88	18.792	62,840	1,246.40	18.793	77,815
10%	No screening	615.70	18.623		767.20	18.636		984.94	18.651	
	Technician	1,210.28	18.663	15,007	1,248.32	18.664	17,129	1,327.46	18.666	23,020
	GO	1,313.27	18.665	46,305	1,349.01	18.666	51,283	1,424.26	18.667	63,096

Low = 2%, medium = 13%, high = 37%.

TABLE 56 *ICERs for different annual community optometrist test uptake rates: 60-year-old cohort*

		Low			Medium			High		
Prevalence	**Strategy**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**
1%	No screening	45.60	12.475		90.99	12.476		176.50	12.477	
	Technician	285.90	12.478	75,671	308.85	12.478	90,207	357.90	12.479	129,517
	GO	353.90	12.479	288,783	376.15	12.479	321,553	424.00	12.479	400,583
2%	No screening	74.61	12.435		127.08	12.436		221.48	12.438	
	Technician	338.74	12.440	52,500	362.15	12.440	61,530	411.99	12.440	85,921
	GO	407.36	12.440	190,446	429.99	12.440	211,082	478.44	12.440	260,427
4%	No screening	132.70	12.354		199.24	12.356		311.43	12.359	
	Technician	444.34	12.362	35,656	468.76	12.363	40,642	520.23	12.363	54,217
	GO	514.36	12.363	114,688	537.68	12.363	126,330	587.23	12.364	153,998
6%	No screening	190.80	12.273		271.40	12.276		401.38	12.281	
	Technician	549.93	12.285	28,849	575.36	12.286	32,191	628.47	12.286	41,401
	GO	621.36	12.286	82,979	645.37	12.286	90,946	696.02	12.287	109,843
8%	No screening	248.90	12.192		343.57	12.196		491.32	12.202	
	Technician	655.53	12.208	25,166	681.97	12.208	27,617	736.70	12.209	34,468
	GO	728.36	12.209	65,553	753.06	12.209	71,524	804.81	12.210	85,676
10%	No screening	306.99	12.111		415.73	12.116		581.27	12.124	
	Technician	761.13	12.131	22,859	788.57	12.131	24,750	844.94	12.132	30,123
	GO	835.37	12.132	54,535	860.76	12.132	59,251	913.60	12.133	70,430

Low = 2%, medium = 13%, high = 37%.

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TABLE 57 *ICERs for different annual community optometrist test uptake rates: 75-year-old cohort*

		Low			Medium			High		
Prevalence	**Strategy**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**	**Cost (£)**	**QALYs**	**ICER**
1%	No screening	18.80	6.904		44.20	6.904		93.90	6.905	
	Technician	163.90	6.905	131,756	177.00	6.905	147,916	205.00	6.905	189,980
	GO	205.30	6.905	391,271	218.00	6.905	424,562	245.20	6.905	503,522
2%	No screening	30.66	6.883		59.65	6.883		114.60	6.884	
	Technician	190.75	6.885	94,169	204.30	6.885	104,328	233.01	6.885	130,740
	GO	232.76	6.885	267,262	245.78	6.885	288,725	273.53	6.885	339,283
4%	No screening	54.46	6.841		90.56	6.842		156.08	6.843	
	Technician	244.40	6.844	65,574	258.79	6.844	71,193	288.99	6.845	85,921
	GO	287.76	6.844	166,618	301.42	6.845	178,888	330.29	6.845	207,657
6%	No screening	78.25	6.799		121.47	6.800		197.57	6.802	
	Technician	298.04	6.803	53,697	313.28	6.804	57,436	344.97	6.804	67,367
	GO	342.77	6.804	123,087	357.06	6.804	131,494	387.05	6.804	151,182
8%	No screening	102.05	6.758		152.38	6.759		239.06	6.761	
	Technician	351.69	6.763	47,193	367.77	6.763	49,905	400.95	6.763	57,223
	GO	397.77	6.763	98,799	412.71	6.763	105,080	443.81	6.764	119,790
10%	No screening	125.85	6.716		183.29	6.717		280.54	6.719	
	Technician	405.33	6.722	43,089	422.27	6.722	45,153	456.93	6.723	50,827
	GO	452.78	6.723	83,303	468.35	6.723	88,239	500.57	6.723	99,808

Low = 2%, medium = 13%, high = 37%.

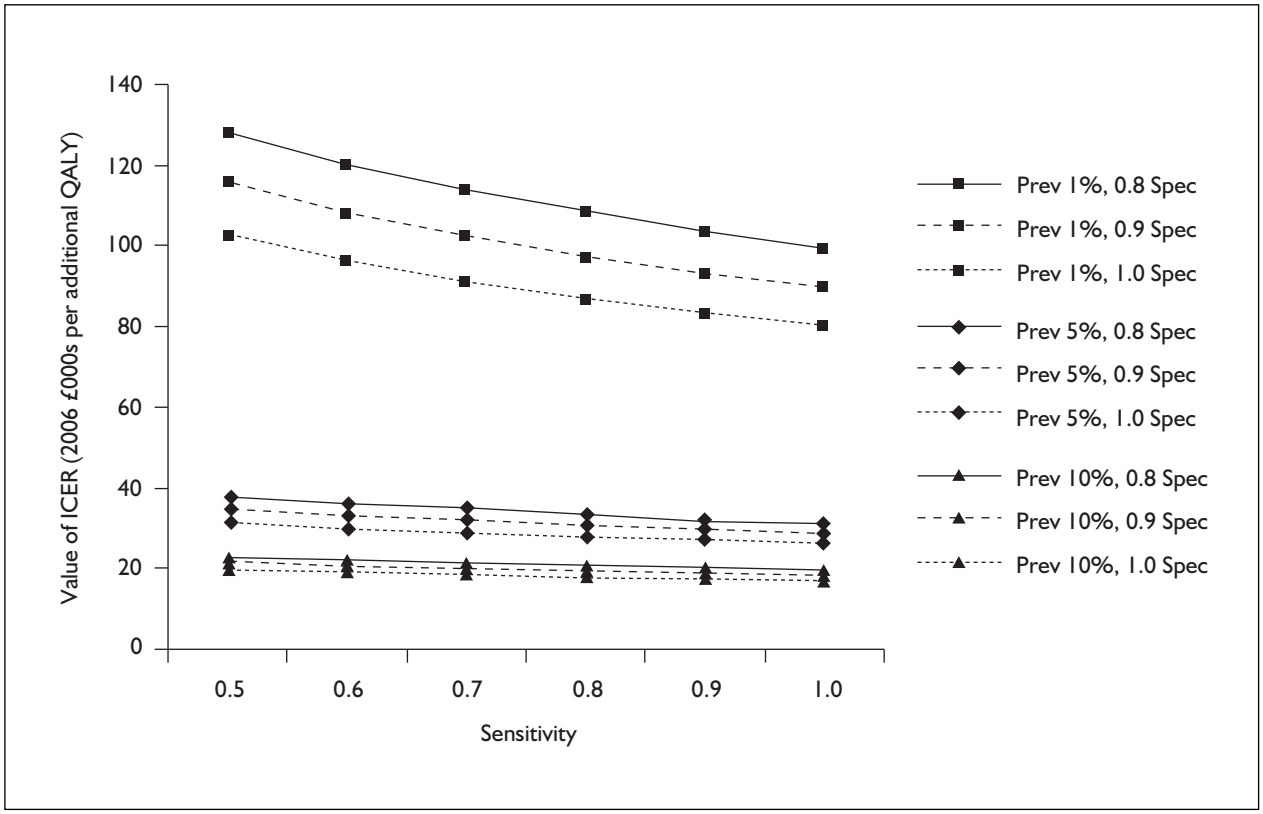

FIGURE 43 *Influence of changes in sensitivity and specificity (Spec) of the second test in the technician strategy in a 40-year-old cohort by prevalence level (Prev)*

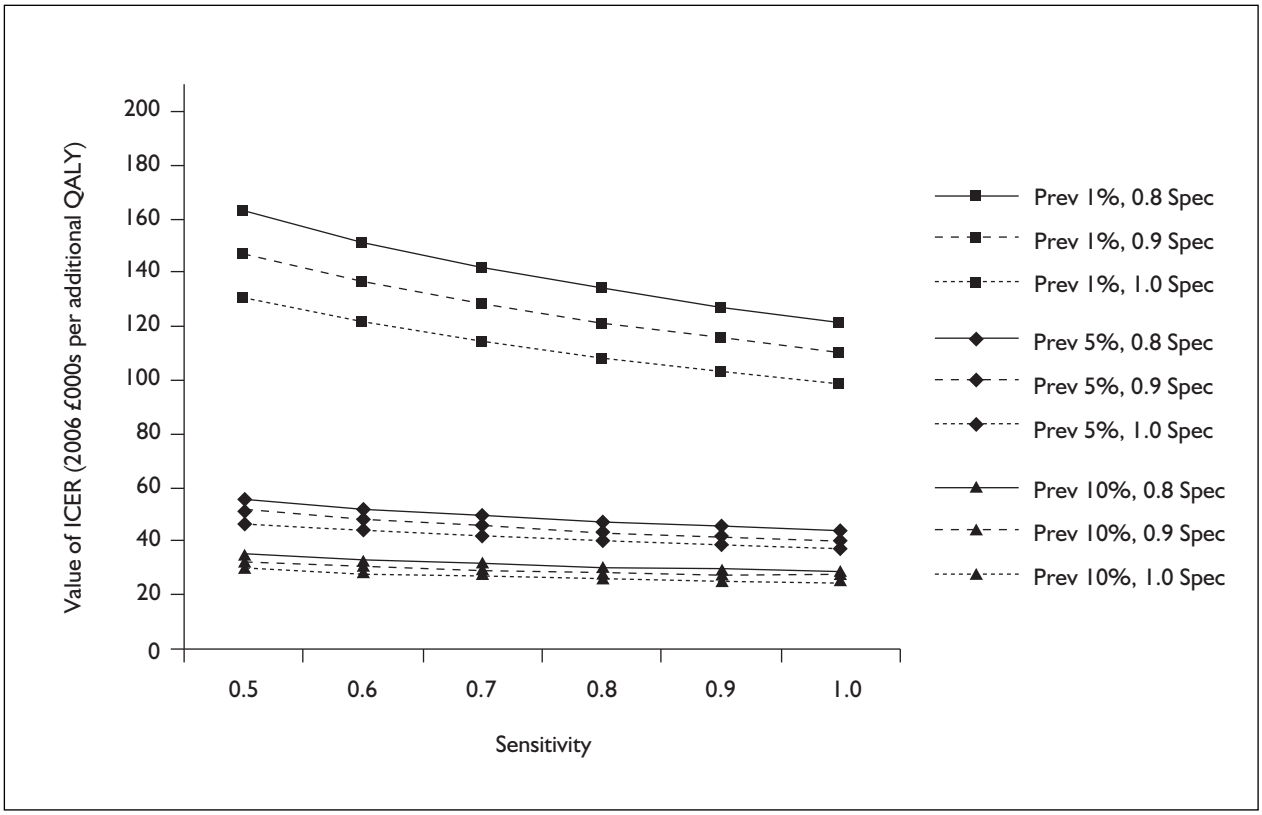

FIGURE 44 *Influence of changes in sensitivity and specificity of the second test in the technician strategy in a 60-year-old cohort by prevalence level*

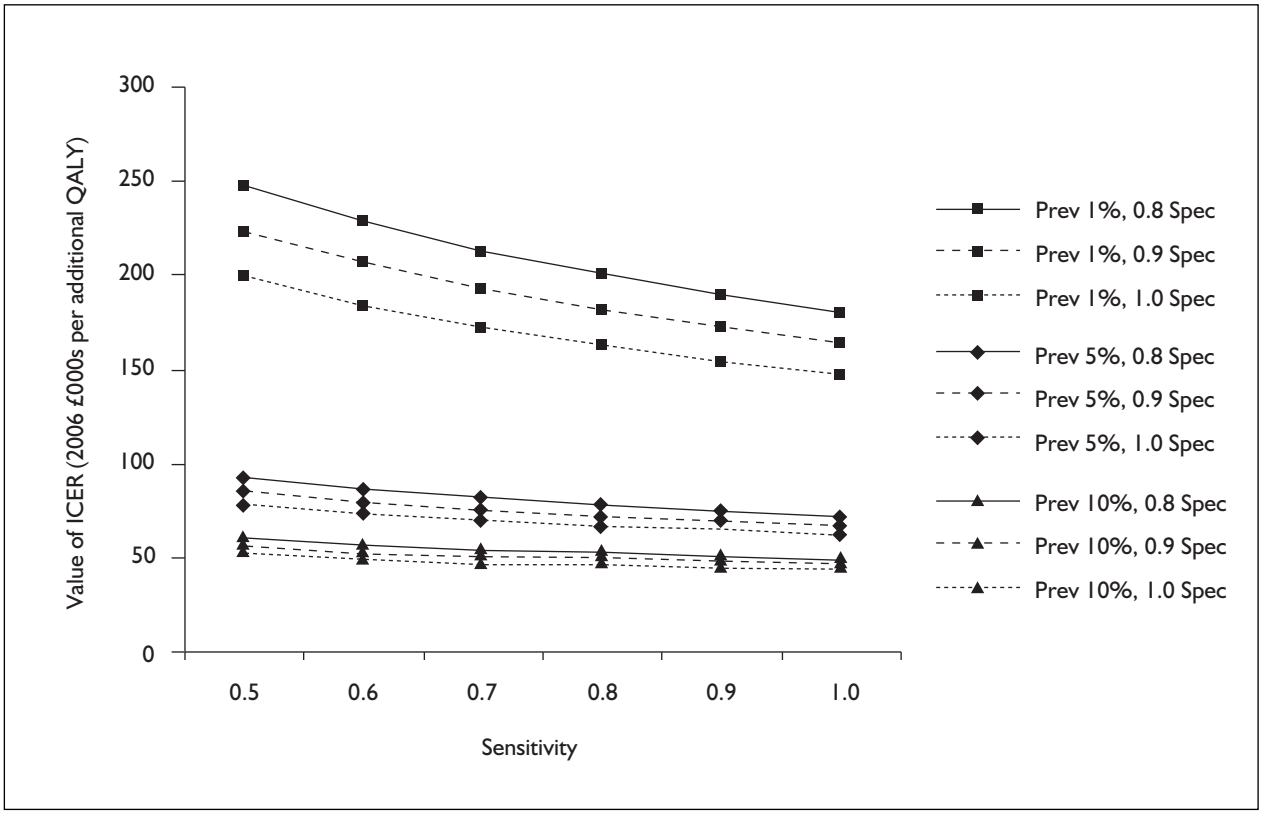

FIGURE 45 *Influence of changes in sensitivity and specificity of the second test in the technician strategy in a 75-year-old cohort by prevalence level*

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TABLE 58 *Deterministic and probabilistic analysis results: base case 40-year-old cohort, 10-year screening interval, 5% OAG prevalence rate*

Strategy	Cost (£)	QALYs	ICER	£10,000	£20,000	£30,000	£50,000
No screening	563.34	18.971		82.5%	54.3%	40.2%	29.6%
Technician	703.24	18.978	20,571	16.7%	42.3%	51.4%	51.1%
GO	744.38	18.979	42,188	0.8%	3.4%	8.4%	19.3%

TABLE 59 *Changes to the chance of receiving an eye test in the community for a 40-year-old cohort and a 10-year screening interval for various prevalence levels*

Prevalence	Strategy	1.5 times the rate in base case			2 times the rate in base case		
		Cost (£)	QALYs	Incremental cost per QALY	Cost (£)	QALYs	Incremental cost per QALY
2.0%	No screening	417.15	19.167		495.70	19.168	
	Technician	513.60	19.170	46,307	581.28	19.170	53,889
	GO	550.88	19.170	111,051	617.93	19.170	130,021
2.6%	No screening	465.33	19.129		545.29	19.130	
	Technician	566.13	19.132	37,781	634.19	19.132	43,550
	GO	603.85	19.132	88,125	671.17	19.132	102,582
3.2%	No screening	513.50	19.090		594.88	19.092	
	Technician	618.65	19.094	32,322	687.10	19.094	36,968
	GO	656.82	19.094	73,337	724.42	19.095	84,972
3.8%	No screening	561.67	19.052		644.46	19.053	
	Technician	671.18	19.055	28,528	740.01	19.056	32,410
	GO	709.79	19.056	63,006	777.67	19.057	72,712
4.4%	No screening	609.84	19.013		694.05	19.015	
	Technician	723.71	19.017	25,738	792.92	19.018	29,068
	GO	762.76	19.018	55,382	830.91	19.019	63,685
5.0%	No screening	658.01	18.974		743.64	18.977	
	Technician	776.23	18.979	23,600	845.83	18.980	26,511
	GO	815.72	18.980	49,523	884.16	18.981	56,761

to be cost-effective than screening at 60 years of age)
- increasing the screening interval from 3 to 10 years
- screening cohorts with a higher expected prevalence of OAG.

In this section further sensitivity analyses were undertaken for a specific cohort which reflected the above factors. In these sensitivity analyses it has been assumed that screening will be performed in a 40-year-old cohort with a 10-year screening interval and a 5% OAG prevalence rate, except where specifically stated otherwise.

The results of the comparison between the alternative screening strategies are shown in *Table 58*. The deterministic results indicate that screening with the technician strategy might be considered worthwhile. The probabilistic sensitivity analysis shows that the considerable uncertainty around the parameter estimates which are used within the model is important. For example, even though the point estimate of incremental cost-effectiveness for the comparison of the technician with the no-screening strategy is £20,571, there is only a 42% likelihood that the cost per QALY would be less than £20,000 (*Figure 75* in Appendix 23 shows the cost-effectiveness acceptability curves for this analysis).

Changes to the uptake rates of the community optometrist

In this sensitivity analysis the probability of receiving an eye test in the community varied (*Table 59*). As the probability of receiving an eye test in the community increased, both the costs and outcomes associated with the no-screening

TABLE 60 *Likelihood of a strategy being cost-effective for different incidence and progression parameters: analysis for a 40-year-old cohort with a 10-year screening interval and 5% prevalence of OAG*

Cohort	Probability distribution parameters	Strategy	Probabilistic cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
			£10,000	£20,000	£30,000	£50,000
Base case		No screening	82.5	54.3	40.2	29.6
		Technician	16.7	42.3	51.4	51.1
		GO	0.8	3.4	8.4	19.3
Incidence	High	No screening	82.0	53.9	40.0	29.6
		Technician	17.0	42.4	50.7	50.0
		GO	1.0	3.7	9.3	20.4
	Low	No screening	83.6	55.7	42.6	30.6
		Technician	15.5	40.6	48.2	49.3
		GO	0.9	3.7	9.2	20.1
Progression mild	High	No screening	78.8	48.0	35.2	23.8
		Technician	20.5	48.3	55.3	54.8
		GO	0.7	3.7	9.5	21.4
	Low	No screening	82.2	54.6	39.2	27.8
		Technician	16.9	42.4	51.3	53.2
		GO	0.9	3.0	9.5	19.0
Progression moderate	High	No screening	77.4	41.2	28.2	18.1
		Technician	21.9	55.2	62.2	59.2
		GO	0.7	3.6	9.6	22.7
	Low	No screening	89.6	68.2	52.3	36.2
		Technician	10.1	30.2	42.0	50.8
		GO	0.3	1.6	5.7	13.0
Progression severe	High	No screening	75.8	46.2	32.8	22.3
		Technician	23.2	49.8	57.4	55.4
		GO	1.0	4.0	9.8	22.3
	Low	No screening	86.9	66.2	53.1	41.6
		Technician	12.5	31.4	39.9	42.6
		GO	0.6	2.4	7.0	15.8
Alternative analysis: time to progression mean values		No screening	79.9	49.5	35.8	25.3
		Technician	19.3	46.8	54.9	53.7
		GO	0.8	3.7	9.3	21.0

strategy increased. The gain in QALYs for the no-screening strategy more than compensates for the increase in cost of this strategy. As a consequence, the incremental cost per QALY of the technician strategy compared with no screening increased (for comparison, for a 40-year-old cohort screened at 10-year intervals the incremental cost per QALY was £38,456 at a 2% prevalence level and £15,808 at an 8% prevalence level; *Figure 40*). The incremental cost per QALY for the comparison of the glaucoma optometrist strategy compared with the technician strategy also increased (the incremental cost per QALY was £91,906 at a 2% prevalence level and £28,749 at an 8% prevalence level; *Figure 40*).

Changes to incidence and progression of glaucoma

Table 60 describes the results of the sensitivity analyses for changes in the incidence and progression of OAG. The likelihood of either of the two screening strategies being considered cost-effective did not greatly alter when either lower or higher rates of incidence of OAG were used in the analysis.

Sensitivity analysis was also conducted around changes to the rate of progression. As the rate of progression increases (i.e. the 'high' analyses), the likelihood that either the technician or glaucoma optometrist strategy would be considered cost-

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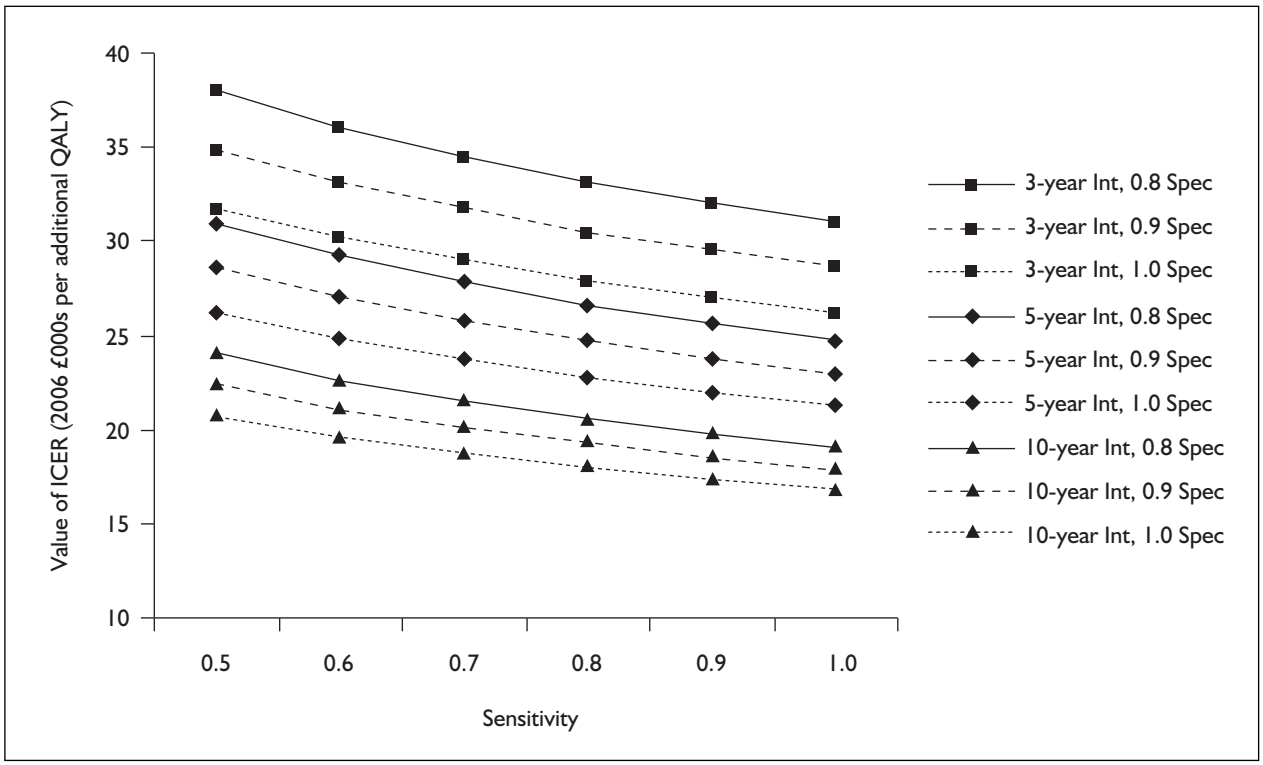

FIGURE 46 *Influence of changes in sensitivity and specificity of the second test in the technician strategy in a 40-year-old cohort by screening interval (Int)*

TABLE 61 *Sensitivity analyses around utilities: 40-year-old cohort, 10-year screening interval, 5% OAG prevalence rate*

Strategy	Cost (£)	QALYs	ICER	£10,000	£20,000	£30,000	£50,000
No screening	563.34	19.007		74.1%	38.2%	23.8%	14.5%
Technician	703.24	19.015	17,762	24.7%	55.0%	63.9%	58.2%
GO	744.38	19.016	36,403	1.2%	6.8%	12.3%	27.3%

effective increases. This is as would be expected, as screening is likely to detect more cases and hence delay progression. In this situation the gain in QALYs resulting from earlier detection and treatment more than offsets any increase in cost.

Changing the rate of progression from moderate to severe disease appears to have a greater impact than changing the risk of progression from mild to moderate or severe state to visually impaired. This is caused by the interplay of the effect on QALYs, cost and the number of people in the state. Using alternative mean progression values, based on applying the relative risk of progression following treatment to estimates of the time to progression, rather than to the annual risk of progression as adopted for the rest of the analysis, results in a slightly better case for screening. The CEACs are presented in Appendix 23 (*Figures 86–94*).

Sensitivity and specificity of the second test performed by the technician

In this sensitivity analysis the sensitivity and specificity of the second test performed by the technician and the screening interval were varied (*Figure 46*). As the screening interval increases, the 'technician' strategy is more likely to be considered cost-effective. The effects of changes in sensitivity and specificity are relatively modest in comparison to the changes in the screening interval.

Changes in the sources of health state utilities

In this sensitivity analysis the results of the economic evaluation were revised using the health state valuations based on the subjective assessment of disease severity rather than the objective assessment of disease severity used in the base-case analysis. Using these valuations both the technician and the glaucoma optometrist

TABLE 62 *Sensitivity analyses around costs: 40-year-old cohort, 10-year screening interval, 5% OAG prevalence rate*

		Low			High		
	Strategy	**Cost (£)**	**QALY**	**ICER**	**Cost (£)**	**QALY**	**ICER**
Ophthalmologist diagnosis	No screening	555.89	18.971		598.98	18.971	
	Technician	693.27	18.978	20,200	750.96	18.978	23,172
	GO	728.73	18.979	36,369	819.25	18.979	117,457
Treatment costs	No screening	478.85	18.971		732.31	18.971	
	Technician	581.82	18.978	15,140	946.08	18.978	31,432
	GO	617.66	18.979	36,761	997.80	18.979	53,041
Tests and screening invitation	No screening	501.88	18.971		686.33	18.971	
	Technician	601.93	18.978	14,712	905.98	18.978	32,297
	GO	633.17	18.979	32,044	966.86	18.979	62,438

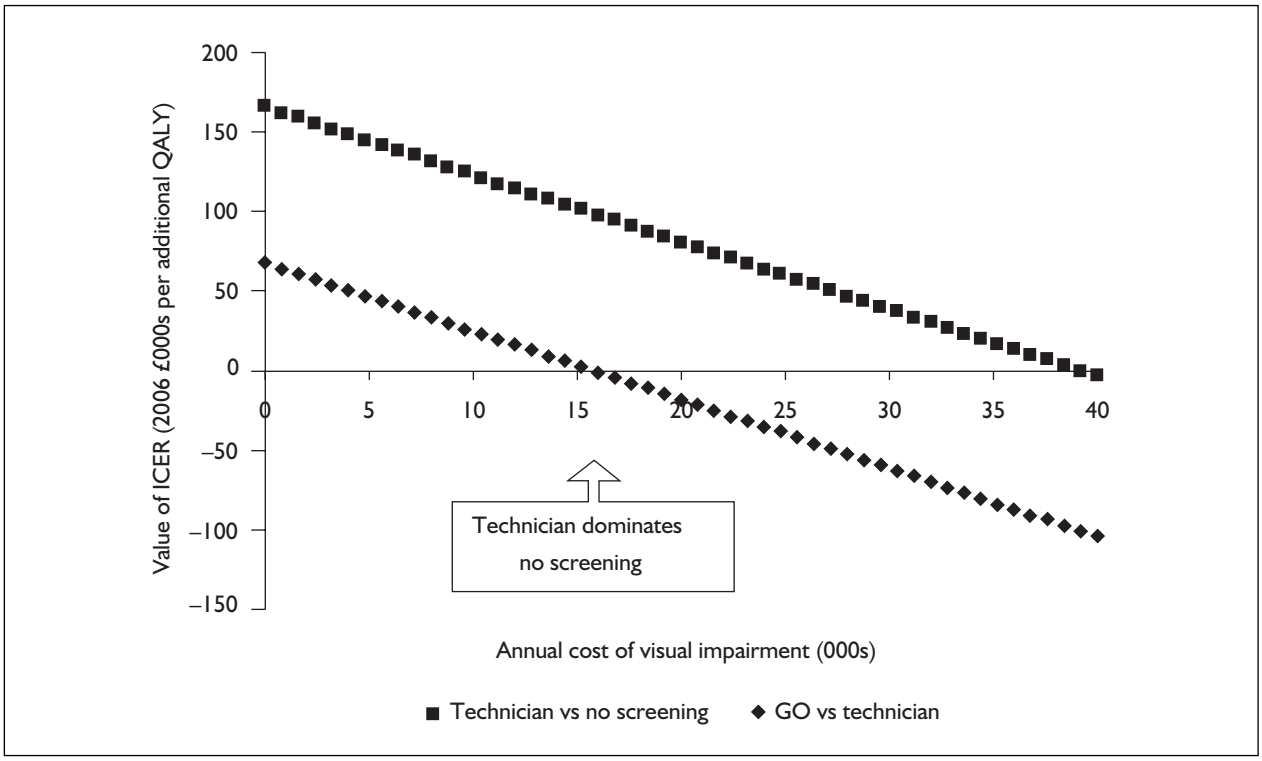

FIGURE 47 *Value of ICERs for alternative visually impaired annual costs: 40-year-old cohort, 10-year screening interval, 1% OAG prevalence rate*

strategies are more likely to be considered cost-effective. For example, the likelihood for the technician strategy of being considered optimal rose from less than 50% (*Table 58*) to about 55% and over 60% for society's willingness to pay for an extra QALY of £20,000 and £30,000, respectively (*Table 61*). The CEACs that illustrate this more fully are presented in Appendix 23 (*Figure 75–95*).

Sensitivity analysis on costs

Table 62 shows the results for sensitivity analysis performed on the cost estimates used within the model. Varying the cost of diagnosis by the ophthalmologist did not have a great impact on the cost-effectiveness of the technician strategy. There was rather more effect on the cost-effectiveness of the glaucoma optometrist strategy, but this was not of sufficient magnitude to change conclusions about the cost-effectiveness of this strategy. The cost-effectiveness of the technician strategy compared with no screening was more sensitive to changes in the costs of treatment or the costs of inviting people to be screened or their subsequent tests. Changes to these costs had less effect on the cost-effectiveness of the glaucoma

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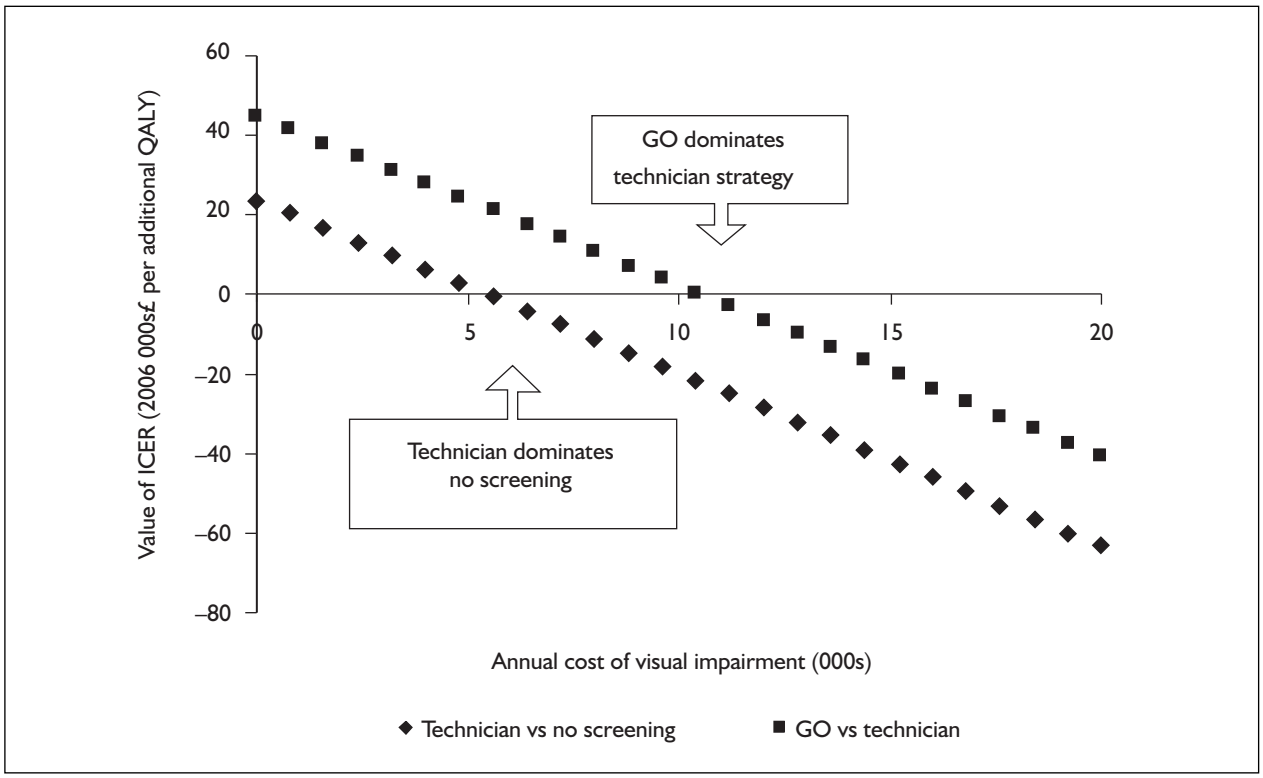

FIGURE 48 *Value of ICERs for alternative visually impaired annual costs: 40-year-old cohort, 10-year screening interval, 5% OAG prevalence rate*

optometrist strategy compared with the technician strategy for the usual values of society's willingness to pay for an extra QALY.

Changes to the cost of visual impairment

Figure 47 shows the results of this threshold analysis for the cost of visual impairment when the prevalence of OAG was 1%. In this case, the technician strategy dominates the no-screening strategy when the annual cost for visual impairment is around £16,000. The cost of visual impairment would need to be £8800 for the incremental cost per QALY for the technician compared with the no-screening strategy to be £30,000. The glaucoma optometrist strategy would dominate the technician strategy at high values of annual cost for visual impairment (e.g. over £59,000; not shown) and it needs the annual cost of visual impairment to be greater than £40,000 for the incremental cost per QALY to be £30,000 or less.

When the prevalence of OAG is changed to 5% and the annual costs of visual impairment are approximately £5700 and £15,000, the technician strategy dominates the no-screening strategy, and glaucoma optometrist dominates the technician strategy, respectively (*Figure 48*).

Discussion

At the beginning of this chapter, the paucity and limitations of existing evidence on the cost-effectiveness of screening for OAG were highlighted. Only one previous study was identified that attempted to compare an active screening strategy with current practice.[281] This study concluded that screening for OAG was not cost-effective. In the economic evaluation reported in this section some evidence has been provided that screening might be cost-effective for selected at-risk subgroups. It is, however, supportive of the earlier study in that screening at prevalence levels likely to be seen in the general population is unlikely to be cost-effective. The results presented in the analysis do not address precisely for which specific cohorts of individuals screening might be considered as cost-effective; this will be considered later.

The evidence on cost-effectiveness should be treated cautiously. In part, this is due to the inherent problems in combining data, even when they have been systematically assembled, from multiple sources. Caution must also be exercised as it is currently unknown whether any of the parameter estimates (e.g. uptake of screening, diagnostic performance, disease progression,

treatment effectiveness, costs or utilities) would be applicable to any of the groups for which the model provides some evidence that screening might possibly be cost-effective. Nevertheless, despite the limitations of the analysis, the results indicate some patient groups where the organisation of a screening service might be given further consideration. In situations where it may be feasible to organise a service for the target patient group, further primary research on the effectiveness and cost-effectiveness of screening for OAG would be required.

As described in the section 'Results of further targeted sensitivity analysis' (p. 124), a probabilistic sensitivity analysis has been conducted to address the statistical imprecision surrounding the point estimates used within the model. In this analysis each parameter estimate has an associated statistical distribution which provides information on the likelihood of the parameter estimate taking any particular value. The type of distribution for each parameter is itself a cause of some uncertainty for any economic evaluation. In this study the type of distribution varied by parameter, but was consistent with prior experience about which type of distribution would be appropriate for the type and nature of the data available.[91,300] Despite these efforts, the precise definition of parameter distributions for some variables was limited, as in some cases it was difficult to fit a distribution to the few data available.

Further strengths and limitations of many of the parameter estimates have been expanded upon in the preceding chapters. These issues do not need to be reiterated, except to emphasise that any limitations identified in earlier chapters are equally applicable when these data are used for the economic model. An assumption of the model is that no one in the cohorts is receiving treatment prior to screening or opportunistic case detection. Relaxing this assumption would result in screening being less likely to be considered cost-effective. This is because the number of cases of OAG who could potentially benefit from screening would be reduced. It is also possible that screening might identify people for whom it is recommended that treatment should be stopped, but who subsequently go on to develop glaucoma; the net effect is unclear. Two sets of variables that were not the focus of previous chapters are costs and utilities. Only very limited data on the costs of diagnosis and treatment were available, and although efforts were made to identify the best data applicable to the UK these are sparse. The model estimates would be more robust if further data were to become available and consideration should be given as to whether further primary research is needed. The model also proved to be very sensitive to the costs assumed for visual impairment. In the base-case analysis the perspective taken for the assessment of costs was the NHS. In a threshold analysis the effect of considering those costs that fall on other groups was also considered. The inclusion of these costs improves the cost-effectiveness of the screening strategies and the thresholds identified are not dissimilar to the annual costs of visual impairment estimated by Meads and Hyde,[299] whose data suggest an annual cost of visual impairment of approximately £7900 for the first year of visual impairment and £7700 for subsequent years (see Appendix 24 for details).

Data with respect to health state utilities were also very sparse. Few data reporting utilities were available from the literature and none was available for a UK population. This problem was anticipated at the outset of the study and data were collected using the EQ-5D questionnaire from a sample of people with glaucoma as part of another ongoing study (Kilonzo M, University of Aberdeen: personal communication, 2006). These data, however, were not specific to people with OAG and the sample included some people with other forms of glaucoma. Nevertheless, these data were used as it was felt that the impact on quality of life of the different types of glaucoma would be similar. The data used to provide utilities data were collected from respondents with a mean age between 69 and 70 years. It is unclear how these utilities might vary for lower age groups. As a consequence, it is not clear whether the results of the model would be influenced by utility data from a younger age group. It should also be noted that for the purposes of decision-making it has been argued that utilities reflecting the preferences of the general population rather than a specific subgroup (e.g. by age or presence of OAG) should be used.

Of greater concern is that these utilities are based on people receiving treatment. Utility data are not available for untreated glaucoma cases. In the analysis it has been assumed that the utility associated with treated and untreated glaucoma is the same. This is justifiable in the sense that treatment does not remove the symptoms of glaucoma. However, this approach fails to reflect any loss of utility associated with the side-effects of treatment. Ideally, further data should be collected in people whose glaucoma has not progressed, both before and after treatment has started. This

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would allow the impact and importance of side-effects of treatment to be determined.

The quality and usefulness of the economic model is dependent not only on the quality of the data, but also on the way in which the data are used. The data requirements and the use of the data were determined by the structure adopted for the model. The development of the economic model was, as described in Chapter 4, based on discussions with a number of key stakeholders. It then underwent a prolonged period of refinement during which the care pathways were critically examined and refined. The model structure applies to a UK context, and may not be relevant to other country settings, although other strategies could be developed and readily added to the model. As described in Chapter 4, the model structure was developed so that the assumptions made in the base-case analysis could be explored in future work. For example, in the base-case analysis it was assumed that the ophthalmologist would make a perfect diagnosis. The model structure has allowed for the possibility that this will not be the case and that the ophthalmologist might possibly initiate treatment when it is not required (a false positive) and fail to diagnose some cases of OAG (a false negative). Nonetheless, since the test characteristics of the diagnostic tests were all based on the assumption that ophthalmologist assessment is the gold standard, the sensitivity and specificity of those tests should be adjusted for the fact that they are based on an imperfect gold standard. It should be mentioned that it is not possible to do this unless there is another gold standard to get all tests' sensitivity and specificity (and ophthalmologist assessment) adjusted for. The model is a simplification of the care pathways that may follow. For example, the diagnostic performance of the tests performed by the glaucoma optometrist has been represented by a single value for sensitivity and specificity of a test. In reality, a battery of tests would be performed, each with its own values for sensitivity and specificity. This simplification was made as there is a plethora of tests that may be used and the values for sensitivity and specificity used in the model appeared to be consistent with the estimates from the literature. A second simplification made in the model was the relatively small number of stages used to reflect the progression of this chronic condition. This assumption may fail to represent the subtleties of disease progression. Owing to limitations of the primary data, estimates of the risk of progression between health states are based on data from one eye, and do not necessarily represent the definition of the heath states in the model, which is based on binocular visual field loss. This is a limitation as the second eye may not have such advanced disease as the study eye so may be overestimated, but equally studies may have used the better eye for analysis and may underestimate the risk of progressive binocular visual field loss. Furthermore, there were insufficient data to determine whether many of the parameter values varied between the stages of disease, for example whether diagnostic performance of the tests or rate of progression would vary by severity of disease. The model was, however, structured in such a way that should such data become available in the future they could be readily incorporated.

A further simplification in the model structure is that rather than modelling the full variety of treatments available for OAG it has been assumed that the effect of treatment can be represented by a single relative effect size for treatment compared with no treatment.

Finally, when interpreting the results of the economic evaluation it should be borne in mind that the estimates of cost-effectiveness relate to a male cohort. Gender-specific data were not available for any of the parameter estimates except for annual all-cause mortality. Had the analysis been repeated with estimates of female all-cause mortality it might be expected that, so long as the other parameters are unchanged, screening would be more likely to be considered cost-effective. This is because, on average, females have a longer life expectancy and are therefore more likely to gain the benefits from earlier detection of OAG.

Conclusion

Screening for OAG is associated with an ICER that society might be willing to pay for particular cohorts of patients. A particular cohort of interest was 40 year olds who might be expected to have a prevalence of OAG of between 6 and 10% (depending on society's threshold willingness to pay for a QALY) when screening is conducted at a 3-year interval. As the screening interval increases the cost-effectiveness of the screening strategies improves.

The results should be treated with some caution and further data are required to confirm the findings. Such data relate to both improving the estimates available for some of the parameters in the model, and also from a well-designed controlled study comparing viable screening strategies in the cohorts of patients for whom this research has indicated that screening may be cost-effective.

Chapter 9

Factors relevant to the NHS, other sectors of the economy and patients

Potentially relevant target groups for screening

The results of the economic evaluation reported in Chapter 8 suggest that screening is most likely to be cost-effective for people who have a family history of OAG and people of black ethnicity, with a 10-year screening interval. Assuming that screening might commence at 40, 50 or 60 years of age, *Table 63* shows the percentage of people from the UK population who would be in the target age, the prevalence of OAG and the percentage of these who might be described by the target risk factors. Although people with myopia or diabetes who fall within a similar age range are less likely to be considered cost-effective because of their lower prevalence of OAG, extending the invitation to screening to them might also be considered. *Table 63* also shows the estimated proportions of the population with each of these risk factors.

Estimating the numbers eligible for screening

The numbers of people eligible for screening and the proportions of cases of OAG that might be expected to be included or excluded from the screened populations can be estimated from the data reported in *Table 63* (details of how these estimates were derived are provided in Appendix 25). It could be decided that people of black race and/or with a family history of OAG are the only groups where the prevalence of OAG is sufficiently high to warrant screening. However, when considering just the first cycle of screening, these groups represent only an estimated 6% of the age cohort for screening starting at 40, 50 or 60 years of age. Therefore, the majority of the age cohort would not be eligible for screening. As a consequence, this strategy would have the chance to detect only 21% of all the expected cases in these age cohorts (although this could be as high as 29% when the extremes of confidence intervals for prevalence of risk factors and relative risks of OAG reported in *Table 63* are considered). If the eligibility criteria were extended to include other at-risk groups (e.g. people with myopia or diabetes) then, as myopia is common, screening would cover at most approximately 40% of the 40-year-old cohort (and 44% and 28% of the 50- or 60-year-old cohorts) and would have the chance of detecting 58% (although it might be as high as 85%) of all the expected cases in the 40-year-old cohort (similar percentages are 66% and 36% for screening at 50 and 60 years, respectively).

Although the precise way in which a screening programme might be implemented is unclear, over time it might be expected that all those people with the target risk factors would be eligible for screening. In *Table 64* estimates are provided on the basis that screening is limited to

TABLE 63 *Characteristics of the groups for whom screening for OAG may be cost-effective*

Age (years)	% of total population[a]	Prevalence of OAG (95% CI)	% of target population with risk factor			
			Myopia[301]	Diabetes[302]	Black[303]	Family history[b]
40	3.24	0.3 (0.1 to 0.5)	31	3	2	4
50	2.64	0.9 (0.6 to 1.3)	35	3	2	4
60	2.05	1.4 (0.9 to 1.8)	19	3	2	4
RR (95% CI)			1.88 (1.5 to 2.3)	2.08 (1.4 to 2.99)	3.8 (2.5 to 5.64)	3.14 (2.32 to 4.25)

[a] Based on a UK population aged 40 and above of 27,116,127 and the number of people of this age as reported in *Table 8* (p. 31).
[b] Assuming that each case of OAG has two blood relations in the target age group.

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TABLE 64 *Estimate of the number of people eligible for screening as well as the estimated number of cases in the eligible and ineligible population*

Overall population figures	Mean	High
Total cohort	100,000	100,000
Eligible cohort (with a risk factor)	6,200	6,200
Number eligible with glaucoma	437	437
Number with glaucoma in total cohort	2,100	2,500
Cases not called for screening, but may be picked up by case finding	1,663	1,772

TABLE 65 *Performance of the tests in a 100,000 cohort at 5% prevalence of OAG*[a]

	Technician	No screening
(1) Number of people referred to the ophthalmologist	3,535	611
(2) Number of cases identified by the ophthalmologist as positive	2,456	376
(3) Number of cases identified by the ophthalmologist as negative (i.e. false positives of screening)	1,079	235
(4) Of those judged as negative by the ophthalmologist in (3) above this number will be kept under observation by the ophthalmologist	464	101
(5) Number of true negatives[b]	93,698	94,542
(6) Number of false negatives after the first year[b]	2,283	4,363

[a] Numbers presented do not include the 485 people with each strategy who would be expected to die of natural causes within the first year.
[b] Includes people not presenting for screening or to the community optometrist.

those aged 40 years and above of black race and/or with a family history of OAG. Two sets of estimates are provided in this table. The mean estimates were derived using the point estimates of prevalence and relative risk of OAG along with the information of the percentage of people in the population with the target risk factors. The high estimates combined the upper values from the 95% confidence intervals for relative risks and prevalence of OAG with information on the percentage of people in the population with the target risk factors.

If the criteria for screening were extended to include those with myopia or diabetes then approximately 37% of the 100,000 total cohort would be eligible for screening. The screening strategy would also have the chance to detect approximately 80% of all the expected cases in the total cohort.

When considering the data presented in this section it is essential to remember that all the estimates presented are associated with considerable uncertainty. Although they have been calculated using the best available data their calculation has required some very strong assumptions to be made. Furthermore, it should also be borne in mind that although a considerable number of cases of OAG will be missed because they occur in people who are not part of the eligible cohort it is still possible that at least some of these cases will be detected within the community by case finding.

Consideration of screening performance

Performance of the strategies in terms of diagnosis

The relative performance of the screening programmes considered has been estimated from the economic model reported in the section 'Economic evaluation of screening for OAG' (p. 106). These estimates have been provided for the comparison of a technician strategy with current practice (no-screening strategy) for 100,000 people with a prevalence of OAG of 5% at the start of screening (*Table 65*).

In the first year in which a screening programme would be initiated, approximately 0.6% and 3.5% of the whole cohort would be referred to the ophthalmologist with the no-screening strategy and technician strategy, respectively. This would enable approximately 49% of the total cases of OAG within the 100,000 cohort of 40 year olds to

be detected by the technician strategy compared with approximately 8% with the no-screening strategy (*Table 65*). It has been assumed within the model that treatment will be initiated in all these individuals identified by the ophthalmologist as having OAG and that treatment would slow the progression of the disease (treated cases of OAG have a relative risk of progression of 0.65 compared with untreated OAG).

In screening strategies not all those referred to the ophthalmologist would have OAG. Of those referred to the ophthalmologist approximately 38% and 30% of people would have been incorrectly identified as positive for OAG (false positives) with the no-screening strategy and technician strategy, respectively (*Table 65*). This is equivalent to approximately 800 more false positives following technician screening. Within the economic evaluation the extra cost of investigating the false positives by the ophthalmologist has been considered. What has not been considered is the anxiety that this may cause to someone who is incorrectly identified as having OAG. The magnitude of this effect is uncertain, but in total it will be greater for the technician strategy than for the no-screening strategy.

Of the people referred to the ophthalmologist as positive for OAG but for whom the ophthalmologist does not make a diagnosis of OAG (i.e. false positives), a proportion will still be considered as at risk and kept under further observation. In the model it has been assumed that these people will be followed up annually for a maximum of 5 years or until OAG is diagnosed (at which point treatment is commenced). Given the assumptions used within the model, in particular the assumption of perfect diagnosis, none of the suspect cases actually has OAG when they start observation. They would, however, have a chance of developing OAG during the period of observation. Should this happen, the model assumptions mean that any new cases of OAG that develop will be identified (and treated). In the first year of screening approximately 0.4% of people in the technician strategy arm and 0.1% of people in the no-screening strategy arm would go into an observation state (*Table 65*).

Even with the unrealistic assumption that the diagnostic performance of the ophthalmologist is perfect, these estimates illustrate the number of people who would be held under observation by the ophthalmologist with the technician strategy (further details of the numbers of people held in an observation state are reported in Appendix 26, and further implications to both the NHS and those people considered as suspect are considered below).

The data presented above represent estimates for the first year of screening. In the model used to derive these estimates it has been assumed that screening will be repeated every 10 years and that people in both the technician and the no-screening strategy can be identified as having OAG by case finding. Given that a high proportion of the cases of OAG is detected in the first year of screening with the technician strategy, the performance of the technician strategy would compare less favourably with the no-screening strategy in subsequent years because there would be fewer cases of OAG to detect. Further details of the performance of the alternative strategies over the duration of follow-up considered by the economic model reported in the section 'Economic evaluation of screening for OAG' (p. 106) are shown in Appendix 27. This appendix reports the number of people referred to the ophthalmologist, the number of these who are either true or false positives and the number of true and false negatives. From these data it is possible to calculate the positive predictive value, the negative predictive value and the sensitivity and specificity of the strategies for each year of follow-up (reported in Appendix 27). Consideration of these data may also help to inform a decision about the maximum age at which screening once initiated should continue (something that the evaluation has not otherwise explicitly considered, but is worthy of further consideration).

Information on the diagnostic performance predicted by the model can also be used to provide estimates of the cost-effectiveness of the different strategies in terms of incremental cost per case detected. *Table 66* reports the average cost of diagnosis and probability of correctly detecting OAG over the lifetime of a cohort of 40-year-old individuals for whom there is a 5% prevalence of OAG and for whom screening is repeated every 10 years. Further details of the number of cases detected for both the technician and the no-screening strategy are supplied in Appendix 28.

In the calculations that form the basis of the data presented in *Table 66* the cost of ophthalmologists had been omitted. It should be noted that over the remaining lifetime of a 40 year old there is approximately a 17.6% chance of seeing an ophthalmologist with the no-screening strategy and a 21.5% chance with the technician strategy.

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TABLE 66 *Incremental cost per case detected for a 40 year old with a 5% chance of having OAG and assuming a 10-year screening interval*

Strategy	Cost (£)	Incremental cost (£)	Average cases detected	Incremental cases detected	Incremental cost per case detected (£)
No screening	123		0.05351		
Technician	203	80	0.06255	0.0090	8823

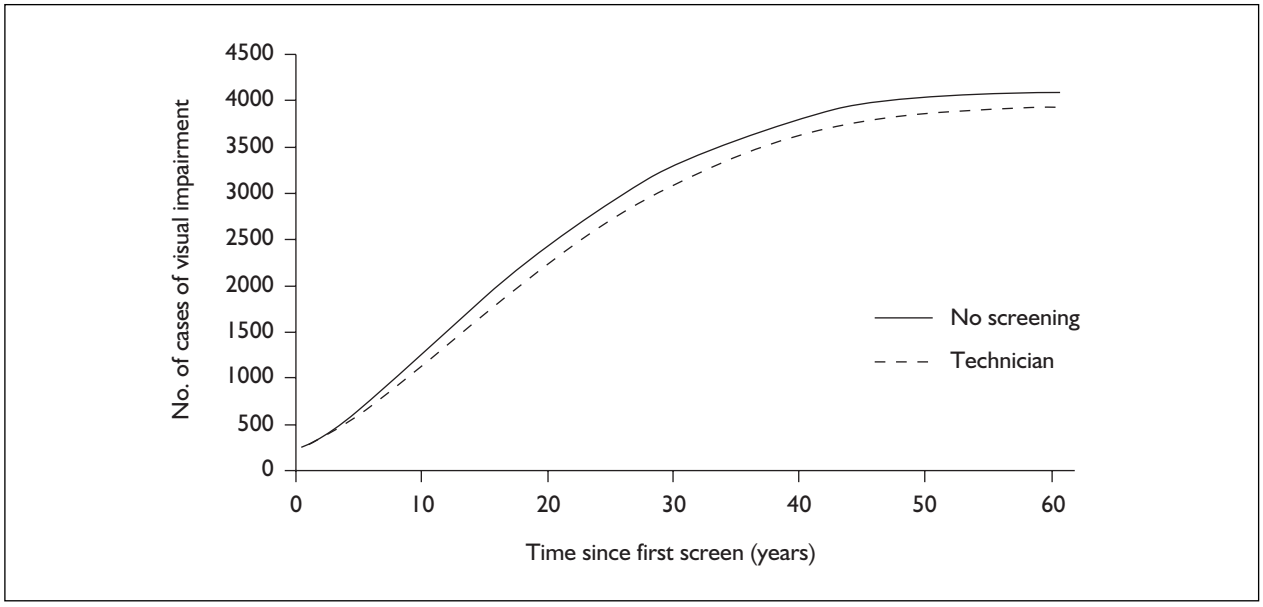

FIGURE 49 *Cumulative number of cases of visual impairment occurring over time for the initial cohort of 100,000*

The estimates provided in *Table 66* also do not include cases of OAG that occur among people who are held by the ophthalmologist in observation. Given the assumptions within the model of perfect diagnosis of OAG by ophthalmologists, there is only a 6% and an 8% chance of a 40-year-old person entering an observation state over their lifetime for the no-screening and technician strategy, respectively. The likelihood of OAG being detected in this state is equal to the likelihood of a new case of OAG developing.

Performance of the strategies in terms of visual impairment

One indication of the importance of detecting cases of OAG is to consider both the number of people who enter the state of severe OAG (i.e. losing vision to below the standard required for driving) or visual impairment and the mean time spent in these states. *Figure 49* describes the cumulative number of cases of visual impairment that are predicted by the model to occur over time for both the technician and the no-screening strategy. These estimates are based on a 40-year-old cohort which has a 5% prevalence of disease and is invited for screening every 10 years. It should be noted that it has been assumed that out of a total cohort of 100,000 a small number of people will already be visually impaired. Hence, in the figure the two curves for the number of people with visual impairment cross the *x*-axis at approximately 250 cases.

In addition to the estimates of the cumulative number of people with visual impairment it may be important to consider how long people who have visual impairment spend in this state (*Table 67*). In this table data have also been added on the number of people with severe OAG, as this is the stage where the OAG greatly affects activities of daily living (e.g. people may have to give up driving).

Fewer people develop severe OAG with the technician strategy, but they spend longer in this state compared with the no-screening strategy. This is because cases of severe OAG progress more

TABLE 67 *Estimated time spent with severe OAG or visually impaired*

	Technician	No screening	Difference
Total individuals visually impaired	3,981	4,154	–173
Total individuals with severe OAG	6,477	6,777	–300
Total number of years visually impaired	81,690	87,652	–5,963
Total number of years with severe OAG	52,043	50,780	1,263
For people who are visually impaired the average years spent as visually impaired	20.5	21.1	–0.6
For people who have severe OAG the average years spent with severe OAG	8.0	7.5	0.5

rapidly to becoming visually impaired, as is indicated by the greater number of people becoming visually impaired with the no-screening strategy (*Table 67*).

A consequence of fewer and later cases of visual impairment is that the estimated number of total years spent visually impaired on average is less for the technician strategy than for the no-screening strategy. The average time spent visually impaired is on average also less with the technician strategy.

Implications for service provision

Screening, at least in the way in which the screening strategies have been defined, is likely to result in significant increases in the workload of ophthalmology departments. In part, this will be because more people will be correctly identified as having OAG. However, ophthalmologists may also have to deal with more people who have been referred to them as being potentially positive. Ophthalmologist departments may also have an increase in their workload due to the increased number of people considered as suspect.

One aspect of service provision not included in the economic model, which may also be affected by a screening strategy, is the provision of services to those people who are visually impaired. Although the costs of these services may fall outside the health service (notably local authorities and the voluntary sector) they may be of sufficient magnitude to change a decision about the cost-effectiveness of screening. Updating the estimates from Meades and Hyde to 2006 UK pounds gives a cost of the first year of blindness of £7851 and a cost for subsequent years of £7657 (the cost of vision aids and rehabilitation were only incurred in the first year).[299] As illustrated by *Figure 48* (p. 132), this is sufficient for the technician strategy to be considered both less costly and more effective (i.e. dominant) compared with no screening for a cohort of 40 year olds with a 5% prevalence of OAG. It is not, however, large enough for the glaucoma optometrist strategy to be associated with an incremental cost per QALY of less than £30,000 when compared with the technician strategy. It is clear that expanding the perspective of costs beyond the NHS will increase the cost associated with visual impairment and hence improve the cost-effectiveness of screening. However, it is unclear whether improvement in cost-effectiveness will be of sufficient magnitude for society to consider screening to be worthwhile for older age groups at risk of OAG.

A further implication for the provision of services not considered by the economic model is the capacity of screening to detect other significant eye disease. Such disease may be identified either by the community or glaucoma optometrists, or by the ophthalmologist. Given the potentially larger numbers of people seen by these groups of healthcare professionals within the technician strategy, it might be expected that more cases of other significant eye disease will be detected compared with the no-screening strategy. Should this occur there would be a consequent increase in workload and healthcare costs in order to manage these conditions (as well as, hopefully, an improvement in health).

Implications for patients and their families

The economic model has not taken into account a number of intangible benefits and disbenefits associated with the process of diagnosing OAG. These benefits and disbenefits may include anxiety following either a true or a false positive, reassurance following a true negative and the

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anger and despair following a false negative. With respect to anxiety following a true positive, some of this may be considered worthwhile if detection prevents or delays the onset of visual impairment. However, for some people correctly diagnosed as having OAG the anxiety may not be worthwhile. This may be because of the importance they attach to the health consequences of OAG or because the diagnosis of OAG will not result in any health benefits in that person's lifetime.

In addition to the intangible benefits relating to diagnosis, earlier diagnosis may help to alleviate the fear of becoming blind, which may be especially acute for people with experience of someone close to them becoming blind, such as those with a family history of OAG.

There may also be an intangible effect on those excluded from the screening programme. For example, people excluded from the target population for an active screening strategy may

TABLE 68 *Balance sheet comparing the factors favouring screening or no screening (current practice)*

For screening	Comment	Against screening
More cases of OAG detected resulting in: • *Better health on average* • *Fewer cases of severe OAG and VI* • *Delay in onset of severe OAG and VI on average* • *Fewer years of life spent with severe OAG and VI on average* • *Lower costs to other sectors of the economy of managing VI* • *Lower costs to patients and their families of managing VI*	Unclear; probably, on balance, favours screening	More cases of OAG detected and treated, resulting in: • *More suffering from the side-effects of treatment* • *More people experiencing the dislike of continuing treatment* • *Increased costs of monit*oring of cases • Inc*reased costs of treatment* • *Increased anxiety due to a diagnosis of OAG*
Avoiding the false positives caused by no-screening, resulting in: • *Reduction in anxiety caused* • *Reduction in the costs of diagnosis to the NHS* • *Reduction in the costs of diagnosis to the patient*	Favours no screening as there are more false positives with screening	Large number of false positives identified at every screen, resulting in: • *Increase in anxiety among those incorrectly diagnosed as positive* • *Increase in the costs of diagnosis* • *Increase in the costs of diagnosis to the patient*
Avoidance of false negatives, resulting in: • *Less loss of health due to untreated OAG* • *Less regret and despair caused by late diagnosis*	On balance, favours screening	Avoidance of false negatives, resulting in: • *More anxiety as previously unaware of diagnosis* • *More side-effects of treatment*
Screening involves the selection of at-risk groups, resulting in: • *Reassurance gained from knowing they have access to screening*	Unclear; probably, on balance, favours no screening	Screening involves the selection of at-risk groups, resulting in: • *Anxiety among at-risk groups on being informed they are at risk* • *Feelings of exclusion in those not eligible for screening* • *Adverse health consequences and costs for those not eligible for screening*
More cases of other significant eye disease detected and treated, resulting in: • *Better health on average* • *Fewer cases of VI* • *Delay in onset of VI on average* • *Fewer years of life spent with VI on average* • *Lower costs to other sectors of the economy of managing VI* • *Lower costs to patients and their families of managing VI*	Unclear; probably, on balance, favours screening	More cases of other significant eye disease detected and treated, resulting in: • *More suffering from the side-effects of treatment* • *More people experiencing the dislike of continuing treatment* • *Increased costs of monitoring of cases* • *Increased costs of treatment* • *Increased anxiety due to a diagnosis of OAG*

VI, visual impairment.

have strong feelings about the fact that they are excluded.

Further implications to patients and their families not otherwise included in the analyses relate to the costs and worries (both to the individual and to the people providing informal care) of visual impairment. Although not measured or valued, it would be expected that as the number of cases of visual impairment falls, the total costs and disbenefits associated with visual impairment would fall. Furthermore, as the number of years spent with visual impairment falls, the costs and disbenefits of suffering visual impairment to the individual and carer would also fall.

As indicated in the section 'Implications for service provision' (p. 139), screening may lead to the identification and treatment of other significant eye disease. Treatment of such conditions may improve the health of the individual (at extra cost to the health service), but it may also result in similar sorts of intangible benefits and disbenefits as described above. Furthermore, it may also reduce the costs and worries to both the individual and any carers for those who may otherwise have gone on to develop some degree of visual impairment caused by other significant eye disease that affects the activities of daily living.

Summary

In this chapter an attempt has been made to highlight the consequences of alternative screening strategies based on selected groups. An attempt has also been made to consider the implications for the health service, other sectors of the economy and the individuals who may be considered eligible or ineligible for screening. Within the evaluation conducted as part of this study not all of these implications have been explicitly measured and valued. This does not necessarily mean that such potential effects should be ignored. *Table 68* summarises the implications for the NHS, other sectors of the economy and the potential recipients of screening. This has been presented as a balance sheet where an attempt has been made to consider the likely direction of effect, even if the magnitude of the effect has not been measured and valued. In this balance sheet those factors not explicitly measured or valued are shown in italic. It is a matter for decision-makers to consider whether any or all of these issues are pertinent to the decisions they have to make.

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Chapter 10

Does screening for open angle glaucoma meet the National Screening Committee criteria?

The UK NSC assesses proposed new screening programmes against a set of internationally agreed criteria covering the condition, the test, the treatment options, and effectiveness and acceptability of the screening programme. Assessing programmes in this way is intended to ensure that they do more good than harm at a reasonable cost. This chapter assesses whether screening for OAG in the UK would meet the NSC criteria based on the evidence presented in the previous chapters.

The authors' views on the extent to which each criterion is satisfied is appended after each criterion.

The condition

The condition should be an important health problem

Glaucoma is second to age-related macular degeneration as the most common cause of blindness in adults in the UK. Glaucoma blindness is particularly disabling as navigational vision is impaired and severely restricts independent mobility and the ability to self-care.

The major risk factor for developing glaucoma blindness is late presentation with advanced disease. Currently, an estimated 67% of cases of OAG are undetected by the current practice of opportunistic case finding. Thus, it is likely that improving detection strategies for population groups at risk of sight-threatening OAG would reduce the incidence of visual impairment due to OAG. This review has addressed whether a screening programme for OAG is effective and cost-effective in preventing severe disease and visual impairment. Severe disease refers to sufficient visual loss such that one is not able to drive, and visual impairment means being blind or partially sighted.

Best estimates suggest that 3108–3138 people aged over 50 years were newly registered with visual impairment (blind and partial sight) due to glaucoma in England and Scotland in 2002/03. Of these, at least 1192 new registrations were due to OAG as the main cause, but the true number may be higher than this, as some OAG cases would have been registered as glaucoma non-specified.

Criterion met? Yes.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

The systematic review of the epidemiology identified risk factors for developing OAG. These are: increasing age, higher levels of IOP, African ethnicity, diabetes, myopia and family history in a first-degree relative. Insufficient data were available to estimate the prevalence of OAG in other ethnic minority groups in the UK. Further research is required to quantify these risks at different ages.

In early glaucoma, structural changes at the optic nerve may precede functional visual loss and this potentially identifies a latent period before glaucomatous visual field loss. The visual loss in early glaucoma is in the mid-peripheral field of vision and individuals may not perceive a visual difficulty or incorrectly attribute symptoms to a normal ageing process. In the late stages of disease the visual field loss impacts on central vision and reduces HRQoL. Treatment at an early stage can prevent serious visual impairment, as presenting late with already advanced disease is a major risk factor for blindness.

Criterion met? Yes.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

OAG is not amenable to primary prevention. The only potentially modifiable risk factor is diabetes mellitus, but this is unlikely to have an impact as

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the proportion of cases in the population that are attributable to diabetes is low.

Criterion met? Yes.

If the carriers of a mutation are identified as a result of the screening, the natural history of people with this status should be understood, including the psychological implications

Genetic screening is not indicated, as only a small number of cases have an identifiable gene mutation. Research is ongoing looking for causative gene mutations that may be implicated in adult-onset OAG, and also for mutations that are a determinant of raised IOP. If a gene mutation is identified that is a major determinant of adult OAG, a case for genetic screening could be considered.

Criterion met? Not currently relevant.

The test

There should be a simple, safe, precise and validated screening test

There are numerous potentially suitable screening tests for OAG. The systematic review of screening tests found that all tests perform reasonably well and no single test (or strategy) is clearly better than the others. Furthermore, within the range observed, the performance of the screening programme (as judged by its cost-effectiveness) was not particularly sensitive to test accuracy. However, data were of limited quality and it remains unclear what the optimal testing strategy should be.

Criterion met? No.

The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Appropriate cut-offs are available for standard optic disc photography and visual field testing. There are widely used cut-offs for IOP and the appropriate choice depends on how IOP testing is combined with other screening tests. More recent technologies (e.g. HRT, SLP, OCT and FDT) have the advantage over subjective assessments in that 'machine classifiers' have been developed to define abnormal results, but these cut-offs may not be appropriate for a screening situation. Further research is required to determine suitable cut-offs and test accuracy in a screening setting.

Criterion met? Partially met.

The test should be acceptable to the population

Overall, the tests are safe. There are potential minor risks with some of the tests. IOP testing using applanation may have a potential for cross-infection, but disposable tips can be used to eliminate the risk. Rarely, incorrect applanation tonometry may result in a corneal abrasion. This would be unacceptable and painful, although it usually heals in 24 hours. NCT avoids these risks. Ophthalmoscopy and photography require dilation of the pupil, which is associated with some short-term discomfort (1–2 hours) such as light sensitivity and glare. Rarely, pupil dilation can precipitate angle closure glaucoma, but if appropriately warned of the symptoms the condition is easily treated. Objective tests of structural damage and functional tests do not require pupil dilation.

These potential concerns were discussed with representatives from a patient organisation (the IGA). In the opinion of all five participants, these were potential risks and discomfort that if explained at the time of screening were acceptable.

Criterion met? Yes.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

Diagnostic investigation of the positives on screening would be best placed in a community optometric setting. The evaluation has evaluated the costs and benefits of using a care pathway whereby optometrists, who have received additional training in glaucoma assessment, examine screen positives, with positives from the optometrist assessment referred to an ophthalmologist. This pathway fits with current initiatives by the Department of Health, the Scottish Executive and the Wales Eye Care Initiative in their reviews of general ophthalmic services.[51–55,296]

Criterion met? Partially met.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Criterion met? Not relevant.

The treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Evidence from two RCTs of treatment compared with no treatment suggests that treatment in early disease slows the rate of progression. Extrapolating from this, and assuming accelerated progression with advancing disease severity, it can be estimated that, without treatment, the mean time to blindness in at least one eye is 23 years, and with treatment this is approximately 35 years. The extrapolation from medium- to long-term outcome is supported by evidence from retrospective, observational studies of the risk of blindness from glaucoma, although results from these studies should be interpreted with caution, as selection bias is likely. Data from prospective, long-term cohort studies are required to confirm these findings.

From the limited data available, a patient's valuation of their health status (utility value) decreases, as expected, as glaucoma becomes more severe. The modelling of a screening strategy and treatment effectiveness to long-term outcome suggests that earlier detection and treatment improves health status compared with no screening. Further research is required to develop valid and reliable measures of visual disability and quality of life in glaucoma, and to determine how early detection and treatment impact on patient-reported health outcomes.

Criterion met? Yes.

There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Clinical guidelines for the treatment of OAG exist.[3,5,7,304] Evidence-based guidelines for the management of OAG are in development as part of the clinical guidelines programme of NICE.[305]

Criterion met? Yes.

Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme

In the UK, various healthcare practitioners are involved in the detection and management of glaucoma: optometrists, nurse practitioners and ophthalmologists. Overall responsibility rests with the consultant ophthalmologist. There are concerns that, with an ageing population and improved detection of OAG, the current hospital eye service for managing detected cases will become overloaded. Initiatives to define and develop a glaucoma clinical care pathway are underway. These, together with a review of general ophthalmic services and a connected information technology system in the NHS, provide the basis for a standardised diagnostic and treatment service for glaucoma.

Criterion met? Yes, in principle.

The screening programme

There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity

No RCTs of the effectiveness of screening for OAG were identified.

Criterion met? No.

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public

No studies on the social and ethical acceptability of screening were identified, but in view of the safety and non-invasive nature of the tests, major concerns on acceptability would not be anticipated. It is likely that if screening were to be considered it would be targeted at higher risk groups, such as people with a family history of glaucoma or of African ethnicity, covering about 6% of the UK population. This might be considered unacceptable for the majority of the population not called for screening.

Currently, the only identifiable risk factor for identifying people to attend for screening is age. It is feasible that specific age cohorts could be identified and invited to complete a questionnaire of risk factors, and then those at risk could be invited for screening. However, self-reporting of risk factors other than ethnicity is likely to be unreliable. Ethnic minority groups may be less likely to attend for screening, and campaigns to improve communication and awareness of

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glaucoma, its effect on vision and the importance of attending for testing would be needed.

Discussion with representatives from a patient group (the IGA) highlighted the fact that a screening programme would be very welcome, and no concerns were raised about harms of screening. However, this was a very small sample and the views of this select group are likely to be in favour of screening.

Further research is required on patient preferences for screening compared with no screening, and a patient-based valuation on the benefits and harms of screening.

Criterion met? No.

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

Potential harms of screening include concerns regarding overdetection (i.e. identifying OAG at a stage that is not likely to cause significant impairment in a person's lifetime), anxiety and inconvenience associated with being falsely identified as positive, being a missed case, and adverse effects that may be associated with treatment of a condition that is asymptomatic at detection.

Even in higher risk groups, the prevalence of OAG is low, and this evaluation suggests that 30% of the test positives would be falsely identified as OAG (although 43% of these would be suspect and require observation), and thus have the consequent anxiety and inconvenience associated with this. However, the balance of this is that screening detects more cases, but this may also be associated with more anxiety and side-effects of treatment.

No adverse effects of screening tests were reported in the systematic review. The potential psychological harms of screening, being a false positive or a false negative, were not reported. Medical treatments for OAG can have adverse effects; these may be local eye discomfort, or systemic, particularly with topical β-blocker agents. Alternative medications, for example with prostaglandin analogues, have better safety and effectiveness profiles.

Any harmful effects of screening should be considered as important outcomes in an RCT of screening for OAG compared with no screening.

Criterion met? Partially met.

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should economically balance in relation to expenditure on medical care as a whole (i.e. value for money)

The economic evaluation suggests that screening is cost-effective in a cohort of people aged 40, and possibly aged 50, if OAG prevalence is 4% with a screening interval of 10 years. At 60 years the prevalence would need to be 6% to be considered cost-effective. The evaluation has identified certain target groups (black ethnicity, family history of OAG in a first-degree relative) where screening may be cost-effective. Other groups at risk are people with myopia and diabetes, but the prevalence is lower and it is unlikely to be cost-effective to screen these groups.

The economic evaluation has identified how a screening service might be organised in that a technology-based screening test for OAG is more cost-effective than a full ophthalmic assessment by a specialist optometrist. The evidence on cost-effectiveness should be treated cautiously, as the estimates used in the model are associated with considerable uncertainty.

Criterion met? No.

There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

This would need to be instituted.

Criterion met? Not yet.

Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

This is potentially feasible, but additional technical staff would need to be trained, and testing sites in primary care equipped and established. It is possible that a screening programme for OAG could use the same infrastructure as the National Screening Programme for sight-threatening diabetic retinopathy.

Criterion met? Not yet.

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available

In the absence of screening, an improved attendance rate for a sight test and an improved performance of the community optometrist at detecting glaucoma would improve the effectiveness of current case detection. However, if this improved performance of the community optometrist involved an increased cost of providing this eye examination, at levels approaching the cost of an assessment by a specialised optometrist, then improving the performance of current practice might not be a cost-effective approach to improved case detection. The economic modelling suggests that, although screening by a glaucoma optometrist is more effective, it is more costly than a technician strategy.

Awareness campaigns, aimed at improving the uptake of sight testing and earlier detection, might be effective at preventing late presentation with severe disease and improve health outcome. Further research is required on the effectiveness and cost-effectiveness of such an approach.

Criterion met? No.

Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

This evaluation provides evidence-based information on the consequences of testing, investigation and treatment such that guidelines could be produced, although more robust evidence is required on the long-term health outcomes and any potential harmful effects of screening to inform patients fully of the consequences of screening.

Criterion met? Partially met.

Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

The economic model provides scientifically justifiable evidence for the optimal screening interval and the performance of the screening programme. However, there are uncertainties in the parameter estimates in the model, in particular regarding the uptake of screening, disease progression, utility and costs associated with screening particular patient groups where screening may be most relevant. Further research to improve these parameter estimates is required.

Criterion met? Yes.

If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Criterion met? Not relevant.

Summary

Screening for OAG meets the UK NSC criteria regarding the condition and treatment, but does not meet most of the criteria for the test or a screening programme. Population screening appears not to be cost-effective, but targeted screening of high-risk groups may be. However, if a societal perspective on the costs of visual impairment is taken screening is more likely to be considered cost-effective. Measures to identify systematically those at risk and quality assure the programme would be required. Adequate service provision for the screen positives would need to be established.

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Chapter 11
Discussion

Main results

The purpose of this evaluation was to assess whether screening for OAG met the UK NSC criteria for a screening programme. In the absence of any evidence from RCTs of screening, a Markov modelling approach was used, informed by a series of systematic reviews, which compared the clinical and cost-effectiveness of screening for OAG with the current practice of case finding. Given the perspective of the analysis, the data on the effectiveness and more especially the cost-effectiveness may be of limited transferability to other countries.

An evaluation against the NSC criteria was a valuable tool to identify areas where the evidence was inadequate to make a judgement on whether a screening programme should be initiated. Screening for OAG met the criteria regarding the condition and the treatment, but did not meet most of the criteria for the test or a screening programme.

Screening using a strategy of inviting the at-risk cohort to a primary care setting for a measure of IOP, and a second test for people with IOP below 26 mmHg (the technician strategy), was more effective but more costly than a no-screening strategy. Screening by invitation to attend a highly trained optometrist for an ophthalmic assessment was more effective but more costly than the technician screening strategy. The main determinant of cost-effectiveness was the prevalence of disease: the higher the prevalence the more likely screening would be cost-effective. With screening, fewer people become visually impaired (defined as partial sight and blind) and spend less time with visual impairment. Likewise, fewer people lose vision to below driving standard, although with screening, time spent in this severe state is longer, as progression to the state of visual impairment is less likely to occur.

Taken at face value, the economic evaluation suggests that general population screening for OAG is not cost-effective at any age. The prevalence level would have to be in the region of 3–4% in 40 year olds with a screening interval of 10 years to approach what might be considered cost-effective. The prevalence of OAG in a 40-year-old cohort is around 0.3%; at this prevalence level there is very little likelihood that any screening strategy would be considered cost-effective compared with current practice. Similarly, in a 60-year-old cohort the prevalence of OAG would have to be about 6% to be considered cost-effective at screening intervals of 5 or 10 years: the prevalence of OAG in this age group is about 1.4%.

An important factor in assessing cost-effectiveness was the cost of visual impairment. The costs of visual impairment in the model were based on treatment costs, from an NHS perspective. If a wider societal perspective of costs is taken, then it is likely that the NHS cost of visual impairment used within the model is an underestimate. This is because it does not include the costs falling on individuals, carers and society in terms of loss of independence, and the need for social support. The threshold analysis conducted as part of the economic model suggests that, for a 40-year-old cohort with a 1% prevalence of OAG, the technician strategy would be associated with an incremental cost per QALY of £30,000 compared with current practice should the annual costs of visual impairment be £8800. This is approximately £1000 per year higher than the annual cost estimated by Meads and Hyde.[299] Should the prevalence of OAG be 5%, then the technician strategy would be more effective and less costly than current practice if the annual cost of visual impairment was £5700 per year. Recognising higher personal and societal costs of visual impairment makes screening considerably more likely to be cost-effective even at lower prevalence levels.

The results of the model indicate that even though the prevalence is lower, screening younger people appears to be the more cost-effective option. This is because the risk of developing visual disability and reduced quality of life is more likely over a longer lifetime. Screening high-risk groups (black ethnicity and family history) might be worthwhile, but for these groups at 40 years the prevalence of OAG is in the region of 1–2% and therefore not high enough to consider screening. At 50 years, the prevalence is higher, estimated as between

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2 and 5%, and approaches levels where screening might be considered. The model has not explicitly considered screening a 50-year-old cohort. Interpolating from the results of the model on 40-year-old and 60-year-old cohorts, one would predict that screening every 10 years might be cost-effective in a 50-year-old cohort at a prevalence of 4%. Targeted screening of those groups with the highest risk of having OAG would, however, only cover a small proportion (6%) of the population and this might be considered unacceptable. Extending the target population to include other higher risk groups (myopia and diabetes) would give greater population coverage (37%), but the prevalence estimates in 40–60 year olds are most likely to be 0.6–3.6% and, as such, not sufficiently high to be considered cost-effective.

At the first screen for a cohort with a 5% prevalence of OAG, using a technician strategy gave a positive predictive value of screening of 52% compared with 62% for case finding. The negative predictive value was 98% and 96%, respectively. Screening detects more cases, but with a consequent increase in false-positive referrals, which has considerable implications for service provision. Initiatives to develop glaucoma care pathways are underway in the UK,[51–55,296] and the implications of screening, if it is to be considered, would need to be incorporated into any future reconfiguration of eye care services.

The only readily identifiable risk factor currently available for inviting people to screening is age. It is feasible that specific age cohorts could be identified and invited to complete a questionnaire of risk factors, and then at-risk people invited for screening tests. However, self-reporting of risk factors other than ethnicity is likely to be unreliable. Inviting people with a family history of OAG for screening also poses considerable problems. A national register of all newly diagnosed cases of OAG would be required. This should be possible, but the initial costs of setting up this surveillance have not been incorporated into the economic model. The review has identified that people of black ethnicity have a higher risk of OAG. There were insufficient data to estimate the risk of OAG in other ethnic minority groups in the UK. Restricting screening to select minority groups is likely to be socially unacceptable. Future research should examine prevalence according to ethnicity and the acceptability of offering glaucoma testing to only selected at-risk groups.

In the absence of screening, an improved attendance rate for an eye test among at-risk groups and an improved performance of the community optometrist at detecting OAG would improve the effectiveness of current case detection. However, if the improved performance of the community optometrist involved an increased cost of providing the eye examination, at levels approaching the cost of a glaucoma optometrist test, then improving the performance of current practice might not be a cost-effective approach to improve case detection. The results of the economic modelling indicate that a technology-based screening test, rather than screening by a full optometric examination, is more likely to be cost-effective; as only those with suspect pathology go on to a more costly but effective full assessment, the feasibility of introducing automated testing into a primary care setting merits consideration. One high-risk group, namely people with diabetes, is already included in a screening programme for diabetic retinopathy, and this programme could be modified to include testing for glaucoma. Similarly, myopes, another higher risk group, are likely to be attending for eye tests and consideration should be given to improved awareness and case detection in these individuals.

When considering interventions to improve uptake current eye care services an understanding of the barriers to attendance for eye testing is required. Improved communication and awareness campaigns on the importance of attending for regular eye examinations would be required to improve uptake. An ongoing study in Birmingham, UK,[306] is assessing attitudes and beliefs related to eye disease and factors associated with presenting late to the eye-care services. This study will provide insight and estimates of how likely it is that high-risk groups would attend for screening.

Assumptions, limitations and uncertainties

A series of systematic reviews was undertaken and a language restriction was applied (except for the reports on effectiveness of screening). This restriction is a potential source of bias; however it was felt that studies reported in English were most likely to be relevant to the UK context. Despite a systematic search of the literature, data on the sensitivity and specificity of current optometric practice were not identified and assumptions had to be made. Data were available on the positive predictive value of testing, but details on the number of false negatives were not reported or,

more likely, the negatives on optometric examination were not assessed by a reference standard to ascertain whether they were true or false negatives.

The decision to use a cut-off of IOP of 26 mmHg was based on expert opinion. Although the IOP distribution in the population is known, the systematic review found only two studies that reported the risk of OAG according to IOP in newly detected cases. Although IOP does not define OAG, a higher risk of progressive disease at higher levels of IOP is reported,[25,27] and more severe disease at presentation is associated with higher levels of IOP.[28] In the systematic review of screening tests (Chapter 6), there were insufficient data to determine what IOP cut-off would give the best balance between sensitivity and specificity. Most studies reported a cut-off of above 21 mmHg. In the economic model, results from one population-based study in the USA were used to estimate the proportion of people with an IOP of 26 mmHg or above who did or did not have glaucoma, and similarly for people with an IOP below 26 mmHg. Data from this study were used to create a beta distribution around this estimate to reflect its considerable imprecision, but there are concerns that these data may not be applicable to the UK. The model only looked at two out of many possible screening strategies; in particular IOP measurement was used and GAT specified as part of the technician-based screening pathway. The model structure is such that other tests of IOP, such as NCT, could be considered, and based on the results of the sensitivity analyses on costs and test performance the decision regarding cost-effectiveness would not be expected to change. Within the whole economic model-based analyses it was assumed that the ophthalmologist assessment was the gold standard. In terms of the model this means that ophthalmologist assessment sensitivity and specificity are equal to 1. In other words, these professionals have perfect information and do not make mistakes in their patient management decisions. While this might not be the case, all test characteristics were calculated against ophthalmologist assessment. Should this perfect information assumption be relaxed, another reference standard should be chosen against which every test sensitivity and specificity within the model, as well as ophthalmologist assessment, should be tested.

The results of the deterministic economic analysis presented do not take into account the imprecision around the data used to derive estimates of cost-effectiveness. This imprecision was reflected in the probabilistic sensitivity analysis in the model; it was shown that the prevalence of OAG would have to be 5% in a 40-year-old cohort for technician-based screening to have a 55% chance of being considered cost-effective. For a 60-year-old cohort and at this prevalence level the model suggests that screening is unlikely to be cost-effective.

Extensive sensitivity analyses explored the effects of changing the parameter estimates used in the model. The important drivers of estimates of cost-effectiveness were considered to be the attendance for sight tests in current case finding, the rate of glaucoma progression, the utility estimates associated with each stage of glaucoma and the costs of visual impairment.

One of the findings of the economic model was that more frequent attendance for eye testing in a no-screening strategy may affect the cost-effectiveness results; this higher rate of attendance for sight testing is likely to apply to people with myopia or diabetes and those aged 50–60 years, prompted by the need for reading glasses. This may also apply to family members of known cases of OAG, as they are more likely to be aware of the significance of OAG and the risk to vision. Other high-risk groups may attend less frequently for sight testing, making screening more cost-effective, although it might be expected that such groups would also have a lower uptake of screening. In the UK, if an African-derived population were to be invited for screening the attendance could be expected to be as low as 40%.[120] In the economic model an uptake of screening of 78% has been assumed, with a minimum of 66% and a maximum of 92%. The net effect of lower uptake rates in ethnic minority groups on the cost-effectiveness of screening is uncertain.

A sensitivity analysis around screening a 40-year-old cohort, using a technician-based strategy, at an OAG prevalence of 5% with a rescreen every 10 years, found that, as expected, cost-effectiveness increased as the sensitivity and specificity of the screening test used in the technician-based strategy increased. However, the sensitivity analysis found that the sensitivity and specificity of the screening test over the ranges considered did not greatly alter the estimates of cost-effectiveness. The specificity of the test does affect the impact that screening would have on diagnostic services; a highly specific test is required to reduce the large numbers of false-positive referrals from any of the screening strategies.

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The systematic review of the accuracy of potential screening tests found that no test, or combination of tests, was clearly superior as a screening test. For the potential tests on which data were available, the sensitivity was at least 50%, apart from IOP measurement, and all tests had specificity above 80%, apart from one test, FDT C-20-5, which had a specificity of 75%. There is uncertainty around all the estimates as the results are based on indirect comparisons and, as such, are prone to bias due to differences in the populations studied. In a screening situation it is important that the majority of people to be screened are able to perform the test and have results that can be read. In general, across all the tests 80–99% of the people tested were able to perform the test adequately. For some tests that were considered as potential candidate tests for OAG screening, no studies met the inclusion criteria for the accuracy review. As a result, this research has not been able to provide estimates for the test accuracy of SLP (the GDx VCC), OCT or the RTA.

The review of treatment effectiveness suggests that with treatment at an early stage of disease, the risk of progressive visual loss is reduced by approximately 35%, delaying time to blindness on average by 12 years. The treatment effect on long-term outcomes may be better or worse than this average effect. There was insufficient evidence to determine the rate of progression for different stages of OAG severity or different at-risk groups, and thus the rate of progression in higher risk disease is uncertain. A higher rate of progression would make screening more likely to be considered cost-effective.

There were limited published data for estimating the utility loss associated with different severities of OAG.[298,307] The populations used in these studies were not necessarily representative of a UK population, and as a result this evaluation used utility estimates as measured by the EQ-5D, in 264 people with glaucoma in whom severity was self-reported, apart from a subset (63 people) in whom disease severity was validated based on binocular visual field loss. This generic measure of health status may not adequately capture the utility loss due to glaucoma. However, the generic health state utilities were estimated using the EQ-5D based on UK population tariffs and such an approach has recently been advocated as being a necessary part of the reference case for health technology assessments conducted on behalf of NICE.[297]

The utility estimates used in the base case may also be imprecise as they were based on a small sample of glaucoma patients with validated disease severity. Using estimates based on the subjective assessment of disease severity led to both the technician and the glaucoma optometrist strategies being more likely to be considered cost-effective. For example, the likelihood for the technician strategy being considered optimal rose from less than 50% to about 61% and over 70% when society's willingness to pay for a QALY was £20,000 and £30,000, respectively.

The costs of visual impairment in the model were based on treatment costs, from an NHS perspective. If a wider perspective of costs is taken, then it is likely that the cost of visual impairment is an underestimate, and does not recognise the cost on individuals, carers and society in terms of loss of independence, and the need for social support. Recognising higher personal and societal costs of visual impairment makes screening considerably more likely to be cost-effective.

The model has not taken into account other potential benefits of screening for OAG, mainly the possibility of detecting other treatable eye disease. Both screening strategies are likely to detect other eye pathology. This is an additional benefit, but may be a negative consequence of screening in that referrals to ophthalmology services will be increased, and some of these will be false-positive referrals. It is unclear what effect the inclusion of costs and other effects of detecting other eye disease would have on the relative cost-effectiveness of screening. It might be expected that a glaucoma optometrist strategy would detect more cases of other significant eye disease, but would result in increased costs of diagnosis and treatment. How this might affect the relative cost-effectiveness of the 'glaucoma optometrist' strategy compared with the 'technician' strategy is also uncertain.

Chapter 12
Conclusions

Implications for healthcare

Based on the available evidence derived from the economic model, population screening of age cohorts between 40 and 75 years is not considered to be cost-effective. The model was particularly sensitive to estimates of prevalence and costs of visual impairment. Selective screening of groups with higher prevalence, such as those aged between 50 and 60 years with a family history of OAG, or of people of black ethnic origin may be worthwhile. Selective screening of these groups covers 6% of the population cohort and therefore would only have the chance to detect 20–30% of all the expected cases in the 50- or 60-year-old cohorts. Moreover, systematically identifying those at risk is not currently feasible in the UK.

The positive predictive value of the more cost-effective screening strategy, based on a screening test that does not require skilled interpretation, is about 52%, with a negative predictive value of 98%, and as such detects more cases but also results in a large number of false-positive referrals. This has implications for the ophthalmology services.

Based on the results of the model there are two strategies that will improve current case detection, namely improving the attendance rate for eye examination generally, particularly in high-risk groups, and improving the performance of current optometric assessment, either by refining optometric practice or by adding in a technology-based first assessment, the latter being the more cost-effective option. This has implications for any future organisational changes in community eye-care services in that if, in the absence of screening, recommendations are made to improve case finding, then recommendations that at-risk people require a full assessment by a specialised optometrist may not be the best use of healthcare resources, and the feasibility of improving case detection by an initial automated test strategy in a community setting should be explored. The economic evaluation suggests that the diagnostic skills of the optometrist are best utilised for people testing positive on an initial technology-based examination for OAG.

These recommendations that population screening is unlikely to be cost-effective are based on the results of an economic model; the parameter estimates are associated with considerable uncertainty and should be interpreted with caution. In particular, if the rate of progression and the costs of visual impairment are higher than estimated then screening is more likely to be cost-effective. For example, the annual cost of visual impairment would need to be £8800 for the technician strategy to have an incremental cost per QALY of £30,000 for a 40-year-old cohort with a 1% prevalence of OAG. At a 5% prevalence level of OAG, technician screening would be dominant (more effective and less costly) when the annual cost of visual impairment is £5700 or greater.

Priorities for further research

An RCT of screening is considered to be the optimal design to determine the benefits of screening. However, before initiating a trial, further research should aim to develop and provide quality data to populate the economic model. The model only considered a limited set of screening and case-finding strategies, and further research is required to determine what an optimal screening or case-finding strategy could be.

Priority 1: feasibility of screening strategies

This research has several components and would involve input from qualitative researchers, health psychologists, health economists and trialists. The main requirements are:

- to establish how the risk groups could be identified; multiple identification strategies would be required according to risk factor
- to determine the optimal test strategy in a community setting; this study should explore how a technician strategy might be incorporated into existing visual assessments, for example, as part of the diabetic retinopathy screening programmes
- to explore the acceptability of interventions to improve attendance for glaucoma testing and the acceptability of subsequent testing using established models of behaviour change from health psychology
- to value any potential harms and benefits associated with screening (or targeted case

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detection) by exploring the strength of preferences of potential users of the service using established health economics methodology.

Priority 2: identifying weaknesses in the model, and improving parameter estimates

There is considerable uncertainty regarding parameter estimates used in the model as the available data were considered to be too limited and of too poor quality to provide reliable estimates. Prospective data collection on the costs of detection, management and costs of visual impairment could be collected in the context of current service provision. Improved monitoring of health outcomes in large populations using registers of blindness by cause would provide surveillance for the estimation of the impact of prevention strategies over time. Surveillance systems should explicitly consider how to ensure completeness of ascertainment. Improved estimates of health status, both patient reported and estimates of the risk of progressive loss of visual function, are required. As further data, including new information as to how a screening strategy might be organised, become available these should be used to refine the model.
A value for information analysis is indicated to determine which data have most impact on the model results and hence where future primary research should be directed to inform decision-making.

Priority 3: improving uptake of glaucoma testing

An RCT of interventions to improve the uptake of screening, or enhanced case detection, informed by the results of the prior feasibility studies is indicated.

Acknowledgements

We thank members of the steering committee (Augusto Azuara-Blanco, John Cairns, Jon Deeks, Adrian Grant, Stephen McPherson, Richard Wormald, and David Wright) for advice and support and Bronwyn Davidson for secretarial assistance. We thank Rod Taylor and Norman Waugh for advising on the development of the protocol and commenting on drafts of the review. We thank the patient representatives from the International Glaucoma Association, and David Garway-Heath, David Henson, Anja Tuulonen and Stephen Vernon for their clinical expert input into the development of the screening pathways and economic model. We thank Sarah Hatt (Editor, Cochrane Eyes and Vision Group) and an author of the Cochrane review on screening for prevention of optic nerve damage due to OAG, a summary of which is provided in Chapter 7.

This report was commissioned by the NHS R&D Health Technology Assessment Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

The Health Services Research Unit and the Health Economics Research Unit are both core funded by the Chief Scientist Office of the Scottish Executive Health Department. The views expressed in this report are those of the authors and not necessarily those of the funders.

Contribution of authors

Jennifer Burr (Clinical Epidemiologist) led and coordinated all aspects of the project, and wrote the Executive Summary, Introduction, Background, Screening tests for glaucoma, Does screening for open angle glaucoma (OAG) meet the National Screening Committee criteria?, Discussion and Conclusions chapters. Jennifer Burr, Rodolfo Hernández (Research Fellow), Luke Vale (Senior Research Fellow) and Cynthia Fraser (Information Officer) wrote the Methods chapter. Tania Lourenco (Research Fellow), with the assistance of Jennifer Burr, Jonathan Cook (Statistician) and Craig Ramsay (Senior Statistician) conducted the epidemiology review. Graham Mowatt (Research Fellow) and Rehman Siddiqui (Clinical Research Fellow), with the assistance of Jennifer Burr, conducted the review of the accuracy of screening and diagnostic tests. The Cochrane Eyes and Vision Group, led by Richard Wormald (coordinating editor of the Cochrane Eyes and Vision Group), assisted by Jennifer Burr, conducted the review of screening for prevention of optic nerve damage due to OAG. Jennifer Burr updated systematic reviews on the effectiveness of glaucoma treatment. Craig Ramsay (Senior Statistician) conducted the review of probability of progressive visual field loss. Kannaiyan Rabindranath (Clinical Research Fellow), Rodolfo Hernández and Luke Vale conducted the review of economic evaluations of screening for glaucoma. Rodolfo Hernández conducted the economic evaluation with the assistance of Luke Vale. Luke Vale wrote the section on factors relevant to the NHS and other sectors, and the discussion on the economic evaluation. The tasks involved in conducting the various reviews included screening search results, assessing full-text studies for inclusion, undertaking data extraction and quality assessment, and writing the review. Jonathan Cook provided statistical support across the reviews and undertook the meta-analyses. Cynthia Fraser developed and ran the search strategies, obtained papers and formatted the references.

Augusto Azuara-Blanco (Consultant Ophthalmologist) and Richard Wormald (Consultant Ophthalmologist) provided clinical expert opinion on all aspects of the project. Jon Deeks (Professor of Health Statistics) provided methodological support for the screening and diagnostic accuracy review, and John Cairns (Professor of Health Economics) provided methodological support for the economic evaluation. Stephen McPherson (Optometrist) provided information and advice, representing optometry. Adrian Grant (Professor of Health Services Research) advised on the design of the project and commented on drafts of the report.

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References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;**90**:262–7.
2. Congdon N, Wang F, Tielsch JM. Issues in the epidemiology and population-based screening of primary angle-closure glaucoma. *Surv Ophthalmol* 1992;**36**:411–23.
3. AAOG Glaucoma Panel. Primary open-angle glaucoma: preferred practice pattern. American Academy of Ophthalmology; 2005. URL: http://www.aao.org/education/library/ppp/poag_new.cfm. Accessed April 2005.
4. Screening for glaucoma in the primary care setting. VHA clinical practice guideline. United States Department of Veterans Affairs; 2000. URL: http://www.oqp.med.va.gov/cpg/Glaucoma/GLA_CPG/navbar.htm#. Accessed April 2005.
5. Tuulonen A, Airaksinen PJ, Erola E, Forsman E, Friberg K, Kaila M, *et al.* The Finnish evidence-based guideline for open-angle glaucoma. *Acta Ophthalmol Scand* 2003;**81**:3–18.
6. Asia Pacific glaucoma guidelines. South East Asia Glaucoma Interest Group; 2003. URL: http://www.seagig.org/pdf/APGGuidelinesNMview.pdf. Accessed September 2005.
7. Terminology and guidelines for glaucoma. European Glaucoma Society; 2003. URL: http://www.eugs.org/preview.asp. Accessed September 2005.
8. World Health Organization. *Principles and practice of screening for disease*. Public Health Paper No. 34. Geneva: WHO; 1968.
9. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. UK National Screening Committee; 2003. URL: http://libraries.nelh.nhs.uk/screening/viewResource.asp?uri=http://libraries.nelh.nhs.uk/common/resources/?id=59772. Accessed September 2005.
10. Spry PG, Sparrow JM. An evaluation of open-angle glaucoma against the NSC criteria for screening viability, effectiveness and appropriateness. UK National Screening Committee; 2005. URL: http://rms.nelh.nhs.uk/screening/viewResource.asp?categoryID=1352&dg=107&uri=http://libraries.nelh.nhs.uk/common/resources/?id=61002. Accessed September 2005.
11. UK National Screening Committee's Policy Positions 2005. UK National Screening Committee; 2005. URL: http://rms.nelh.nhs.uk/screening/viewResource.asp?categoryID=7773&uri=http%3A//libraries.nelh.nhs.uk/common/resources/?id=61406. Accessed September 2005.
12. Fleming C, Whitlock E, Biel T, Smit B. Primary care screening for ocular hypertension and primary open-angle glaucoma: Evidence Synthesis No. 34. Agency for Healthcare Research & Quality, US Preventative Services Task Force; 2005. URL: http://www.ahrq.gov/clinic/uspstf05/glaucoma/glaucsyn.pdf. Accessed April 2005.
13. Retinal nerve fiber layer analysis for the diagnosis and management of glaucoma. TEC Assessment 18(7). Blue Cross Blue Shield Association; 2003. URL: http://www.bcbs.com/tec/Vol18/18_07.pdf. Accessed April 2005.
14. American Academy of Ophthalmology. Optic nerve head and retinal nerve fiber layer analysis. *Ophthalmology* 1999;**106**:1414–24.
15. Delgado MF, Nguyen NT, Cox TA, Singh K, Lee DA, Dueker DK, *et al*. Automated perimetry: a report by the American Academy of Ophthalmology. *Ophthalmology* 2002;**109**:2362–74.
16. Harasymowycz P, Kamdeu FA, Papamatheakis D. Screening for primary open-angle glaucoma in the developed world: are we there yet? *Can J Ophthalmol* 2005;**40**:477–86.
17. Scott, A. Optical coherence tomography for diagnosing retinal disease. Technote TN41. Alberta Heritage Foundation for Medical Research; 2003. URL: http://www.ahfmr.ab.ca/publications/?dept=&search=retinal&type=5&sort=date&dir=DESC. Accessed April 2005.
18. Sycha T, Vass C, Findl O, Bauer P, Groke I, Schmetterer L, *et al.* Interventions for normal tension glaucoma. *Cochrane Database Syst Rev* 2003 (Issue 1). Article No.: CD002222. DOI: 10.1002/14651858.CD002222.
19. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005;**331**:134–6.
20. Bonomi L, Marchini G, Marraffa M, Bernardi P, de Franco I, Perfetti S, *et al*. Prevalence of glaucoma and intraocular pressure distribution in a defined population: the Egna–Neumarkt study. *Ophthalmology* 1998;**105**:209–15.
21. Hollows FC, Graham PA. Intra-ocular pressure glaucoma and glaucoma suspects in a defined population. *Br J Ophthalmol* 1966;**50**:570–86.

© Queen's Printer and Controller of HMSO 2007. All rights reserved.

22. Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, *et al*. The Framingham Eye Study monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. *Surv Ophthalmol* 1980;**24**:335–610.

23. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, *et al*. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: the Baltimore Eye Survey. *Arch Ophthalmol* 1991;**109**:1090–5.

24. Wensor MD, McCarty CA, Stanislavsky YL, Livingston PM, Taylor HR. The prevalence of glaucoma in the Melbourne Visual Impairment Project. *Ophthalmology* 1998;**105**:733–9.

25. Kass MA, Gordon MO. Intraocular pressure and visual field progression in open-angle glaucoma. *Am J Ophthalmol* 2000;**130**:490–1.

26. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999;**106**:2144–53.

27. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, *et al*. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;**120**:1268–79.

28. Grodum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. *Acta Ophthalmol Scand* 2002;**80**:627–31.

29. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *Cochrane Database Syst Rev* 2004 (Issue 2). Article No.: CD004399. DOI: 10.1002/14651858.CD004399.pub2.

30. Vass C, Findl O, Sycha T, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension (Protocol). *Cochrane Database Syst Rev* 2004 (Issue 3). Article No.: CD003167. DOI:10.1002/14651858.CD003167.pub2.

31. de Rolim MC, Paranhos A. Laser trabeculoplasty for open angle glaucoma (Protocol). *Cochrane Database Syst Rev* 2002 (Issue 4). Article No.: CD003919. DOI: 10.1002/14651858.CD003919.

32. Bunce C, Wormald R. Leading causes of certification for blindness and partial sight in England & Wales. *BMC Public Health* 2006;**6**(8 March).

33. Kelliher C, Kenny D, O'Brien C. Trends in blind registration in the adult population of the Republic of Ireland 1996–2003. *Br J Ophthalmol* 2006;**90**:367–71.

34. Evans J. *Causes of blindness and partial sight in England and Wales 1990–1991*. London: Office of Population Censuses and Surveys; 1995.

35. Bamashmus MA, Matlhaga B, Dutton GN. Causes of blindness and visual impairment in the West of Scotland. *Eye* 2004;**18**:257–61.

36. *The National Assistance Act*. London: UK Ministry of National Insurance; 1948.

37. Registered blind and partially sighted persons, Scotland 2003. Scottish Executive; 2003. URL: http://www.scotland.gov.uk/stats/bulletins/00292-00.asp. Accessed February 2006.

38. Registered blind and partially sighted people: year ending 31 March 2003, England. Department of Health; 2003. URL: http://www.dh.gov.uk/PublicationsAndStatistics/Statistics/StatisticalWorkAreas/StatisticalSocialCare/StatisticalSocialCareArticle/fs/en?CONTENT_ID=4082697&chk=NrtmK1. Accessed February 2006.

39. Personal social services statistics, Wales 2002–03. Physical and sensory disability. Local Government Data Unit; Wales. URL: http://www.dataunitwales.gov.uk/eng/Project.asp?id=SXAEAE-A77F9255&Cat=23. Accessed February 2006.

40. King AJ, Reddy A, Thompson JR, Rosenthal AR. The rates of blindness and of partial sight registration in glaucoma patients. *Eye* 2000;**14**: 613–19.

41. Robinson R, Deutsch J, Jones HS, Youngson-Reilly S, Hamlin DM, Dhurjon L, *et al*. Unrecognised and unregistered visual impairment. *Br J Ophthalmol* 1994;**78**:726–40.

42. Sheldrick JH, Ng C, Austin DJ, Rosenthal AR. An analysis of referral routes and diagnostic accuracy in cases of suspected glaucoma. *Ophthalmic Epidemiol* 1994;**1**:31–9.

43. Harrison RJ, Wild JM, Hobley AJ. Referral patterns to an ophthalmic outpatient clinic by general practitioners and ophthalmic opticians and the role of these professionals in screening for ocular disease. *BMJ* 1988;**297**:1162–7.

44. Pooley JE, Frost EC. Optometrists' referrals to the Hospital Eye Service. *Ophthalmic Physiol Opt* 1999;**19**:S16–24.

45. College of Optometrists. *Members' handbook*. London: College of Optometrists; 2005.

46. Wormald RP, Rauf A. Glaucoma screening. *J Med Screen* 1995;**2**:109–14.

47. van der Pols JC, Thompson JR, Bates CJ, Prentice A, Finch S. Is the frequency of having an eye test associated with socioeconomic factors? A national cross sectional study in British elderly. *J Epidemiol Community Health* 1999;**53**:737–8.

48. Banes MJ, Culham LE, Crowston JG, Bunce C, Khaw PT. An optometrist's role of co-management in a hospital glaucoma clinic. *Ophthalmic Physiol Opt* 2000;**20**:351–9.

49. Gray SF, Spry PG, Brookes ST, Peters TJ, Spencer IC, Baker IA, *et al*. The Bristol shared care glaucoma study: outcome at follow up at 2 years. *Br J Ophthalmol* 2000;**84**:456–63.

50. Hume J, Abbott F. Setting up a shared care glaucoma clinic. *Nurs Stand* 1995;**10**:34–6.

51. Wales Eye Care Initiative. National Assembly for Wales. URL: http://new.wales.gov.uk/topics/health/healthservice/nhs/eye_care/?lang=en. Accessed April 2006.

52. *First report of the National Eye Care Services Steering Group*. London: UK Department of Health; 2004.

53. Review of eye care services in Scotland. Scottish Executive; 2005. URL: http://www.scotland.gov.uk/Publications/2005/10/21111455/14557. Accessed February 2006.

54. DOAS glaucoma: draft glaucoma clinical pathway and dataset. Do Once & Share Programme (DOAS). URL: http://www.doasglaucoma.org/draft.asp. Accessed April 2006.

55. Review of General Ophthalmic Services. UK Department of Health. URL: http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4118493&chk=66ZQro. Accessed February 2006.

56. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002;**86**:238–42.

57. Goldmann H. Un nouveau tome re d'applanation. *Bull Soc Ophthalmol Fr* 1955;**67**:474–8.

58. Bandyopadhyay M, Raychaudhuri A, Lahiri SK, Schwartz EC, Myatt M, Johnson GJ. Comparison of Goldmann applanation tonometry with the Tonopen for measuring intraocular pressure in a population-based glaucoma survey in rural West Bengal. *Ophthalmic Epidemiol* 2002;**9**:215–24.

59. Salvi SM, Sivakumar S, Sidiki SS. Use of disposable prism tonometry in routine clinical practice. *Eye* 2005;**19**:743–6.

60. Shields MB. The non-contact tonometer: its value and limitations. *Surv Ophthalmol* 1980;**24**:211–19.

61. Armaly MF. On the distribution of applanation pressure. *Arch Ophthalmol* 1965;**73**:11–18.

62. Davanger M, Ringvold A, Blika S, Elsas T. Frequency distribution of IOP. Analysis of a material using the gamma distribution. *Acta Ophthalmol (Copenh)* 1991;**69**:561–4.

63. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia: the Blue Mountains Eye Study. *Ophthalmology* 1996;**103**:1661–9.

64. Bankes JL, Perkins ES, Tsolakis S, Wright JE. Bedford Glaucoma Survey. *BMJ* 1968;**i**:791–6.

65. Klein BE, Klein R, Linton KL. Intraocular pressure in an American community – the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 1992;**33**:2224–8.

66. Leydecker W, Akiyama K, Neumann HG. The intraocular pressure of healthy eyes. *Klin Mbl Augenheilk* 1958;**133**:662–70.

67. Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2002;**30**:173–5.

68. Davanger M, Ringvold A, Blika S. The probability of having glaucoma at different IOP levels. *Acta Ophthalmol (Copenh)* 1991;**69**:565–8.

69. Morgan JE, Sheen NJ, North RV, Choong Y, Ansari E. Digital imaging of the optic nerve head: monoscopic and stereoscopic analysis. *Br J Ophthalmol* 2005;**89**:879–84.

70. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PT. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. *Ophthalmology* 1995;**102**:54–60.

71. Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 1994;**101**:1851–5.

72. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J, *et al*. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *Am J Epidemiol* 1991;**134**:1102–10.

73. Quigley HA. *Diagnosing early glaucoma with nerve fiber layer examination*. New York: Igaku-Shoin; 1996.

74. Wollstein G, Garway-Heath DF, Hitchings RA. Identification of early glaucoma cases with the scanning laser ophthalmoscope. *Ophthalmology* 1998;**105**:1557–63.

75. Vernon SA, Hawker MJ, Ainsworth G, Hillman JG, Macnab HK, Dua HS. Laser scanning tomography of the optic nerve head in a normal elderly population: the Bridlington eye assessment project. *Invest Ophthalmol Vis Sci* 2005;**46**:2823–8.

76. Iester M, Mikelberg FS, Drance SM. The effect of optic disc size on diagnostic precision with the Heidelberg retina tomograph. *Ophthalmology* 1997;**104**:545–8.

77. Medeiros FA, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Influence of disease severity and

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optic disc size on the diagnostic performance of imaging instruments in glaucoma. *Invest Ophthalmol Vis Sci* 2006;**110**:1145–50.

78. Hawker MJ, Vernon SA, Ainsworth G, Hillman JG, Macnab HK, Dua HS. Asymmetry in optic disc morphometry as measured by Heidelberg retina tomography in a normal elderly population: the Bridlington Eye Assessment Project. *Invest Ophthalmol Vis Sci* 2005;**46**:4153–8.

79. Scanning laser polarimetry. Primer excerpts – clinical guidance for using the GDx: the normative database. Carl Zeiss Medictec. URL: http://www.meditec.zeiss.com/C1256CAB00599F5D/Contents-Frame/55A2E554EFCFC5B98825726C0001A9A7. Accessed February 2007.

80. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, *et al*. Optical coherence tomography. *Science* 1991;**254**:1178–81.

81. Optical Coherence Tomography: Stratus OCT. Carl Zeiss Meditec. URL: http://www.meditec.zeiss.com/C125679E0051C774/search/47B36BB678C7F92188257070008 35AD5?OpenDocument. Accessed February 2006.

82. Adams CW, Bullimore MA, Wall M, Fingeret M, Johnson CA. Normal aging effects for frequency doubling technology perimetry. *Optom Vis Sci* 1999;**76**:582–7.

83. Sample PA, Bosworth CF, Blumenthal EZ, Girkin C, Weinreb RN. Visual function-specific perimetry for indirect comparison of different ganglion cell populations in glaucoma. *Invest Ophthalmol Vis Sci* 2000;**41**:1783–90.

84. Damato B, Groenewald C. Multifixation campimetry on line: a perimeter for the detection of visual field loss using the internet. *Br J Ophthalmol* 2003;**87**:1296–8.

85. Visual field test. Damato Multifixation Campimeter. URL: http://www.testvision.org/. Accessed February 2006.

86. Heijl A, Lindgren G, Olsson J. A package for the statistical analysis of visual fields. In: Greve EL, Heijl A, editors. *Documenta Opthalmologica Proceedings* Series 49, 7th International Visual Field Symposium. Dordrecht: W Junk Publishers; 1987. pp. 153–168.

87. Bengtsson B, Heijl A. Inter-subject variability and normal limits of the SITA Standard, SITA Fast, and the Humphrey Full Threshold computerized perimetry strategies, SITA STATPAC. *Acta Ophthalmol Scand* 1999;**77**:125–9.

88. Asman P, Heijl A. Glaucoma hemifield test. Automated visual field evaluation. *Arch Ophthalmol* 1992;**110**:812–9.

89. Crabb DP, Fitzke FW, Hitchings RA, Viswanathan AC. A practical approach to measuring the visual field component of fitness to drive. *Br J Ophthalmol* 2004;**88**:1191–6.

90. Crabb DP, Viswanathan AC. Integrated visual fields: a new approach to measuring the binocular field of view and visual disability. *Grafes Arch Clin Exp Ophthalmol* 2005;**243**:210–16.

91. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

92. Wirtz MK, Samples JR, Rust K, Lie J, Nordling L, Schilling K, *et al*. GLC1F, a new primary open-angle glaucoma locus, maps to 7q35-q36. *Arch Ophthalmol* 1999;**117**:237–41.

93. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, *et al*. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;**275**:668–70.

94. Stoilova D, Child A, Trifan OC, Crick RP, Coakes RL, Sarfarazi M. Localization of a locus (GLC1B) for adult-onset primary open angle glaucoma to the 2cen-q13 region. *Genomics* 1996;**36**:142–50.

95. Sheffield VC, Stone EM, Alward WL, Drack AV, Johnson AT, Streb LM, *et al*. Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. *Nat Genet* 1993;**4**:47–50.

96. Sarfarazi M, Child A, Stoilova D, Brice G, Desai T, Trifan OC, *et al*. Localization of the fourth locus (GLC1E) for adult-onset primary open-angle glaucoma to the 10p15-p14 region. *Am J Hum Genet* 1998;**62**:641–52.

97. Fingert JH, Heon E, Liebmann JM, Yamamoto T, Craig JE, Rait J, *et al*. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum Mol Genet* 1999;**8**:899–905.

98. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controll Clin Trial* 1986;**7**:177–88.

99. Anton A, Andrada MT, Mujica V, Calle MA, Portela J, Mayo A. Prevalence of primary open-angle glaucoma in a Spanish population: the Segovia Study. *J Glaucoma* 2004;**13**:371–6.

100. Bengtsson B. Findings associated with glaucomatous visual field defects. *Acta Ophthalmol (Copenh)* 1980;**58**:20–32.

101. Cooper RL, Grose GC, Constable IJ. Mass screening of the optic disc for glaucoma: a follow-up study. *Aust N Z J Ophthalmol* 1986;**14**:35–9.

102. Ellis JD, Evans JMM, Ruta DA, Baines PS, Leese G, MacDonald TM, *et al*. Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma? *Br J Ophthalmol* 2000;**84**:1218–24.

103. Gibson JM, Rosenthal AR, Lavery J. A study of the prevalence of eye disease in the elderly in an English community. *Trans Ophthalmol Soc UK* 1985;**104**:196–203.

104. Lee PP, Feldman ZW, Ostermann J, Brown DS, Sloan FA. Longitudinal prevalence of major eye diseases. *Arch Ophthalmol* 2003;**121**:1303–10.

105. Dielemans I, de Jong PT, Stolk R, Vingerling JR, Grobbee DE, Hofman A. Primary open-angle glaucoma, intraocular pressure, and diabetes mellitus in the general elderly population. The Rotterdam Study. *Ophthalmology* 1996;**103**:1271–5.

106. Bonomi L, Marchini G, Marraffa M, Morbio R. The relationship between intraocular pressure and glaucoma in a defined population. Data from the Egna–Neumarkt Glaucoma Study. *Ophthalmologica* 2001;**215**:34–8.

107. Cedrone C, Culasso F, Cesareo M, Zapelloni A, Cedrone P, Cerulli L. Prevalence of glaucoma in Ponza, Italy: a comparison with other studies. *Ophthalmic Epidemiol* 1997;**4**:59–72.

108. Coffey M, Reidy A, Wormald R, Xian WX, Wright L, Courtney P. Prevalence of glaucoma in the west of Ireland. *Br J Ophthalmol* 1993; **77**:17–21.

109. Ekstrom C. Prevalence of open-angle glaucoma in central Sweden. The Tierp Glaucoma Survey. *Acta Ophthalmol Scand* 1996;**74**:107–12.

110. Jonasson F, Damji KF, Arnarsson A, Sverrisson T, Wang L, Sasaki H, *et al*. Prevalence of open-angle glaucoma in Iceland: Reykjavik Eye Study. *Eye* 2003;**17**:747–53.

111. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, *et al*. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 1992;**99**:1499–504.

112. Kozobolis VP, Detorakis ET, Tsilimbaris M, Siganos DS, Vlachonikolis IG, Pallikaris IG. Crete, Greece glaucoma study. *J Glaucoma* 2000;**9**:143–9.

113. Reidy A, Minassian DC, Vafidis G, Joseph J, Farrow S, Wu J, *et al*. Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* 1998;**316**:1643–6.

114. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 1991;**266**:369–74.

115. Weih LM, Nanjan M, McCarty CA, Taylor HR. Prevalence and predictors of open-angle glaucoma: results from the Visual Impairment Project. *Ophthalmology* 2001;**108**:1966–72.

116. Wormald RPL, Wright LA, Courtney P, Beaumont B, Haines AP. Visual problems in the elderly population and implications for services. *BMJ* 1992;**304**:1226–9.

117. Jonasson F, Thordarson K. Prevalence of ocular disease and blindness in a rural area in the eastern region of Iceland during 1980 through 1984. *Acta Ophthalmol Suppl* 1987;**182**:40–3.

118. Ringvold A, Blika S, Elsas T, Guldahl J, Brevik T, Hesstvedt P, *et al*. The middle-Norway eye-screening study. II. Prevalence of simple and capsular glaucoma. *Acta Ophthalmol (Copenh)* 1991;**69**:273–80.

119. Schoff EO, Hattenhauer MG, Ing HH, Hodge DO, Kennedy RH, Herman DC. Estimated incidence of open-angle glaucoma in Olmsted County, Minnesota. *Ophthalmology* 2001;**108**:882–6.

120. Wormald RP, Basauri E, Wright LA, Evans JR. The African Caribbean Eye Survey: risk factors for glaucoma in a sample of African Caribbean people living in London. *Eye* 1994;**8**:315–20.

121. Hiller R, Podgor MJ, Sperduto RD, Wilson PWF, Chew EY, D'Agostino RB. High intraocular pressure and survival: the Framingham studies. *Am J Ophthalmol* 1999;**128**:440–5.

122. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. *Ophthalmology* 1997;**104**:712–8.

123. Podgor MJ, Leske MC, Ederer F. Incidence estimates for lens changes, macular changes, open-angle glaucoma and diabetic retinopathy. *Am J Epidemiol* 1983;**118**:206–12.

124. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. *Ophthalmology* 2005; **112**:1487–93.

125. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma: the visual impairment project. *Ophthalmology* 2002; **109**:1047–51.

126. Lee AJ, Wang JJ, Rochtchina E, Healey P, Chia EM, Mitchell P. Patterns of glaucomatous visual field defects in an older population: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2003; **31**:331–5.

127. Tielsch JM. A population-based perspective on low-tension and classic primary open-angle glaucoma: the Baltimore Eye Survey. *Chibret Int J Ophthalmol* 1994;**10**:1–5.

128. Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. *Acta Ophthalmol Scand* 2001; **79**:560–6.

129. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology* 1999; **106**:2010–15.

130. Weih LM, Mukesh BN, McCarty CA, Taylor HR. Association of demographic, familial, medical and

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ocular factors with intraocular pressure. *Arch Ophthalmol* 2001;**119**:875–80.

131. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors intraocular pressure and glaucoma in a white population. *Ophthalmology* 2003;**110**:211–17.

132. Klein BE, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes. The Beaver Dam Eye Study. *Ophthalmology* 1994;**101**:1173–7.

133. Mitchell P. Bias in self-reported family history and relationship to glaucoma. *Ophthalmic Epidemiol* 2002;**9**:333–45.

134. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma: the Baltimore Eye Survey. *Arch Ophthalmol* 1994;**112**:69–73.

135. Wolfs RC, Klaver CC, Ramrattan RS, Van Duijn CM, Hofman A, De Jong LA. Genetic risk of primary open-angle glaucoma: population based familial aggregation study. *Arch Ophthalmol* 1998;**116**:1640-5.

136. Beral V. 'The practice of meta-analysis': discussion. Meta-analysis of observational studies: a case study of work in progress. *J Clin Epidemiol* 1995; **48**:165–6.

137. Dickersin K. Systematic reviews in epidemiology: why are we so far behind? *Int J Epidemiol* 2002; **31**:6–12.

138. Weed DL. Interpreting epidemiological evidence: how meta-analysis and causal inference methods are related. *Int J Epidemiol* 2000;**29**:387–90.

139. Leske MC, Connell AM, Wu SY, Nemesure B, Li X, Schachat A, *et al*. The Barbados Eye Studies Group. Incidence of open-angle glaucoma: the Barbados Eye Studies. *Arch Ophthalmol* 2001; **119**:89–95.

140. Minassian DC, Reidy A, Coffey M, Minassian A. Utility of predictive equations for estimating the prevalence and incidence of primary open angle glaucoma in the UK. *Br J Ophthalmol* 2000; **84**:1159–61.

141. Kaimbo D, Buntinx F, Missotten L. Risk factors for open angle glaucoma: a study in two rural areas of the Democratic Republic of Congo. *Arch Public Health* 2002;**60**:101–14.

142. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. *Arch Ophthalmol* 1994;**112**:821–9.

143. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma. The Barbados Eye Study. *Arch Ophthalmol* 1995;**113**:918–24.

144. Murdoch IE, Cousens SN, Babalola OE, Yang YF, Abiose A, Jones BR. Glaucoma prevalence may not be uniformly high in all 'black' populations. *Afr J Med Med Sci* 2001;**30**:337–9.

145. Varma R, Ying-Lai M, Francis BA, Nguyen BBT, Deneen J, Wilson MR, *et al*. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology* 2004;**111**:1439–48.

146. Fong DS, Epstein DL, Allingham RR. Glaucoma and myopia: are they related? *Int Ophthalmol Clin* 1990;**30**:215–18.

147. Bonovas S, Peponis V, Filioussi K. Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. *Diabet Med* 2004;**21**:609–14.

148. Weinreb RN, Khaw KT. Primary open-angle glaucoma. *Lancet* 2004;**363**:1711–20.

149. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;**3**(10 November).

150. Leemis LM, Trivedi KS. A comparison of approximate interval estimators for the Bernoulli parameter. *Am Stat* 1996;**50**:63–8.

151. Zamora J, Muriel A. *Meta-DiSc for Windows: a software package for the meta-analysis of diagnostic tests*. Barcelona: XI Cochrane Colloquium. URL: www.hrc.es/investigacion/metadisc_en.htm

152. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;**20**:2865–84.

153. Spiegelhalter D, Thomas A, Best N. *WinBUGS: Bayesian inference using Gibbs sampling. User manual*, version 1.4. Cambridge: MRC Biostatistics Unit; 2003.

154. Christoffersen T, Fors T, Waage S, Holtedahl K. Glaucoma screening with oculokinetic perimetry in general practice: is its specificity acceptable? *Eye* 1995;**9**:36–9.

155. Detry-Morel M, Zeyen T, Kestelyn P, Collignon J, Goethals M, Belgian Glaucoma Society. Screening for glaucoma in a general population with the non-mydriatic fundus camera and the frequency doubling perimeter. *Eur J Ophthalmol* 2004;**14**:387–93.

156. Harasymowycz P, Papamatheakis D, Fansi AK, Gresset J, Lesk MR. Validity of screening for glaucomatous optic nerve damage using confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II) in high-risk populations: a pilot study. *Ophthalmology* 2005;**112**:2164–71.

157. Ivers RQ, Optom B, Macaskill P, Cumming RG, Mitchell P. Sensitivity and specificity of tests to detect eye disease in an older population. *Ophthalmology* 2001;**108**:968–75.

158. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. *Arch Ophthalmol* 1991;**109**:1684–9.

159. Katz J, Tielsch JM, Quigley HA, Javitt J, Witt K, Sommer A. Automated suprathreshold screening for glaucoma: the Baltimore Eye Survey. *Invest Ophthalmol Vis Sci* 1993;**34**:3271–7.

160. Katz J, Quigley HA, Sommer A. Repeatability of the Glaucoma Hemifield Test in automated perimetry. *Invest Ophthalmol Vis Sci* 1995; **36**:1658–64.

161 Mansberger SL, Johnson CA, Cioffi GA, Choi D, Krishnadas SR, Srinivasan M, *et al*. Predictive value of frequency doubling technology perimetry for detecting glaucoma in a developing country. *J Glaucoma* 2005;**14**:128–34.

162. Mundorf TK, Zimmerman TJ, Nardin GF, Kendall KS. Automated perimetry, tonometry, and questionnaire in glaucoma screening. *Am J Ophthalmol* 1989;**108**:505–8.

163. Robin TA, Muller A, Rait J, Keeffe JE, Taylor HR. Performance of community-based glaucoma screening using frequency doubling technology and Heidelberg retinal tomography. *Ophthalmic Epidemiol* 2005;**12**:167–78.

164. Vernon SA, Henry DJ, Cater L, Jones SJ. Screening for glaucoma in the community by non-ophthalmologically trained staff using semi automated equipment. *Eye* 1990;**4**:89–97.

165. Vernon SA, Jones SJ, Henry DJ. Maximising the sensitivity and specificity of non-contact tonometry in glaucoma screening. *Eye* 1991;**5**:491–3.

166. Vitale S, Smith TD, Quigley T, Kerrigan-Baumrind TA, Pease TE, Varma R, *et al*. Screening performance of functional and structural measurements of neural damage in open-angle glaucoma: a case–control study from the Baltimore Eye Survey. *J Glaucoma* 2000; **9**:346–56.

167. Wang F, Quigley HA, Tielsch JM. Screening for glaucoma in a medical clinic with photographs of the nerve fiber layer. *Arch Ophthalmol* 1994; **112**:796–800.

168. Wang F, Tielsch JM, Ford DE, Quigley HA, Whelton PK. Evaluation of screening schemes for eye disease in a primary care setting. *Ophthalmic Epidemiol* 1998;**5**:69–82.

169. Wolfs RC, Ramrattan RS, Hofman A, de Jong PT. Cup-to-disc ratio: ophthalmoscopy versus automated measurement in a general population: the Rotterdam Study. *Ophthalmology* 1999;**106**:1597–601.

170. Yamada N, Chen PP, Mills RP, Leen MM, Lieberman MF, Stamper RL, *et al*. Screening for glaucoma with frequency-doubling technology and Damato campimetry. *Arch Ophthalmol* 1999;**117**:1479–84.

171. Ekstrom C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open angle glaucoma – a population based 5 year follow up study. *Acta Ophthalmol (Copenh)* 1993;**71**:189–95.

172. Hammond EA, Begley PK. Screening for glaucoma: a comparison of ophthalmoscopy and tonometry. *Nurs Res* 1979;**28**:371–2.

173. Khong JJ, Dimitrov PN, Rait J, McCarty CA. Can the specificity of the FDT for glaucoma be improved by confirming abnormal results? *J Glaucoma* 2001;**10**:199–202.

174. Marraffa M, Marchini G, Albertini R, Bonomi L. Comparison of different screening methods for the detection of visual field defects in early glaucoma. *Int Ophthalmol* 1989;**13**:43–5.

175. Schultz RO, Radius RL, Hartz AJ, Brown DB, Eytan ON, Ogawa GSH, *et al*. Screening for glaucoma with stereo disc photography. *J Glaucoma* 1995;**4**:177–82.

176. Spry PGD, Hussin HM, Sparrow JM. Clinical evaluation of frequency doubling technology perimetry using the Humphrey Matrix 24-2 threshold strategy. *Br J Ophthalmol* 2005; **89**:1031–5.

177. Theodossiades J, Murdoch I. What optic disc parameters are most accurately assessed using the direct ophthalmoscope? *Eye* 2001;**15**:283–7.

178. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. *Am J Ophthalmol* 1984;**98**:566–71.

179. Anton A, Maquet JA, Mayo A, Tapia J, Pastor JC. Value of logistic discriminant analysis for interpreting initial visual field defects. *Ophthalmology* 1997;**104**:525–31.

180. Damato BE, Ahmed J, Allan D, McClure E, Jay JL. The detection of glaucomatous visual field defects by oculo-kinetic perimetry: which points are best for screening? *Eye* 1989;**3**:727–31.

181. Enger C, Sommer A. Recognizing glaucomatous field loss with the Humphrey STATPAC. *Arch Ophthalmol* 1987;**105**:1355–7.

182. Harper RA, Hill AR, Reeves BC. Effectiveness of unsupervised oculokinetic perimetry for detecting glaucomatous visual field defects. *Ophthalmic Physiol Opt* 1994;**14**:199–202.

183. Heeg GP, Blanksma LJ, Hardus PL, Jansonius NM. The Groningen Longitudinal Glaucoma Study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. *Acta Ophthalmol Scand* 2005;**83**:46–52.

© Queen's Printer and Controller of HMSO 2007. All rights reserved.

184. Heeg GP, Stoutenbeek R, Jansonius NM. Strategies for improving the diagnostic specificity of the frequency doubling perimeter. *Acta Ophthalmol Scand* 2005;**83**:53–6.

185. Stoutenbeek R, Heeg GP, Jansonius NM. Frequency doubling perimetry screening mode compared to the full-threshold mode. *Ophthalmic Physiol Opt* 2004;**24**:493–7.

186. Ieong A, Murdoch I, Cousens S, Healey P, Theodossiades J. Sensitivity and specificity of two glaucoma case-finding strategies for optometrists. *Ophthalmic Physiol Opt* 2003;**23**:341–6.

187. Johnson CA, Cioffi GA, Van Buskirk EM. Evaluation of two screening tests for frequency doubling technology perimetry. *13th International Perimetric Society Meeting*, Garda, Italy, September; 1999. p. 103.

188. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. *Arch Ophthalmol* 1980;**98**:1564–71.

189. Sommer A, Pollack I, Maumenee AE. Optic disc parameters and onset of glaucomatous field loss. II. Static screening criteria. *Arch Ophthalmol* 1979;**97**:1449–54.

190. Wollstein G, Garway-Heath DF, Fontana L, Hitchings RA. Identifying early glaucomatous changes. Comparison between expert clinical assessment of optic disc photographs and confocal scanning ophthalmoscopy. *Ophthalmology* 2000;**107**:2272–7.

191. Wood CM. Limitations of direct ophthalmoscopy in screening for glaucoma. *BMJ* 1987;**294**:1587–8.

192. Artes PH, Iwase A, Ohno Y, Kitazawa Y, Chauhan BC. Properties of perimetric threshold estimates from Full Threshold, SITA Standard, and SITA Fast strategies. *Invest Ophthalmol Vis Sci* 2002;**43**:2654–9.

193. Atanassov MA, Konareva MI. Reproducibility and agreement between three methods of intraocular pressure measurement. *Folia Medica (Plovdiv)* 2002;**44**:19–22.

194. Bengtsson B. Reliability of computerized perimetric threshold tests as assessed by reliability indices and threshold reproducibility in patients with suspect and manifest glaucoma. *Acta Ophthalmol Scand* 2000;**78**:519–22.

195. Bjerre A, Grigg JR, Parry NR, Henson DB. Test–retest variability of multifocal visual evoked potential and SITA standard perimetry in glaucoma. *Invest Ophthalmol Vis Sci* 2004; **45**:4035–40.

196. Bonomi L, Baravelli S, Cobbe C, Tomazzoli L. Evaluation of Keeler Pulsair non-contact tonometry: reliability and reproducibility. *Grafes Arch Clin Exp Ophthalmol* 1991;**229**:210–12.

197. Caprioli J, Klingbeil U, Sears M, Pope B. Reproducibility of optic disc measurements with computerized analysis of stereoscopic video images. *Arch Ophthalmol* 1986;**104**:1035–9.

198. Capris P, Corallo G, Gatti G, Zingirian M. SITA and full threshold strategies in the study of the perimetric defects in glaucoma. *Acta Ophthalmol Scand Suppl* 1999;**77**:18–19.

199. Dielemans I, Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. *Grafes Arch Clin Exp Ophthalmol* 1994;**232**:141–4.

200. Eiden SB, Cooper J, Olivares G, Horn D, London R. Interexaminer reliability of the optic cup to disc ratio assessment. *Am J Optom Physiol Opt* 1986;**63**:753–6.

201. Gillespie BW, Musch DC, Guire KE, Mills RP, Lichter PR, Janz NK, *et al*. The collaborative initial glaucoma treatment study: baseline visual field and test–retest variability. *Invest Ophthalmol Vis Sci* 2003;**44**:2613–20.

202. Harper R, Radi N, Reeves BC, Fenerty C, Spencer AF, Batterbury M. Agreement between ophthalmologists and optometrists in optic disc assessment: training implications for glaucoma co-management. *Grafes Arch Clin Exp Ophthalmol* 2001;**239**:342–50.

203. Kocak I, Orgul S, Saruhan A, Haefliger I, Hendrickson P, Flammer J. Measurement of intraocular pressure with a modern noncontact tonometer. *Ophthalmologica* 1998;**212**:81–7.

204. Lotti R, Frau B, Cerruti S, Trillo C, Traverso CE. Reliability of applanation tonometry readings obtained with a disposable latex cap. *Ophthalmologica* 1999;**213**:277–80.

205. Phelps CD, Phelps GK. Measurement of intraocular pressure: a study of its reproducibility. *Grafes Arch Clin Exp Ophthalmol* 1976;**198**:39–43.

206. Sekhar GC, Naduvilath TJ, Lakkai M, Jayakumar AJ, Pandi GT, Mandal AK, *et al*. Sensitivity of Swedish interactive threshold algorithm compared with standard full threshold algorithm in Humphrey visual field testing. *Ophthalmology* 2000;**107**:1303–8.

207. Shuttleworth GN, Khong CH, Diamond JP. A new digital optic disc stereo camera: intraobserver and interobserver repeatability of optic disc measurements. *Br J Ophthalmol* 2000;**84**:403–7.

208. Spry PG, Henson DB, Sparrow JM, North RV. Quantitative comparison of static perimetric strategies in early glaucoma: test–retest variability. *J Glaucoma* 2000;**9**:247–53.

209. Sturmer J, Poinoosawmy D, Broadway DC, Hitchings RA. Intra- and inter-observer variation

of optic nerve head measurements in glaucoma suspects using disc-data. *Int Ophthalmol* 1992; **16**:227–33.

210. Tatemichi M, Nakano T, Tanaka K, Hayashi T, Nawa T, Miyamoto T, *et al*. Performance of glaucoma mass screening with only a visual field test using frequency-doubling technology perimetry. *Am J Ophthalmol* 2002;**134**:529–37.

211. Tonnu PA, Ho T, Sharma K, White E, Bunce C, Garway-Heath D. A comparison of four methods of tonometry: method agreement and interobserver variability. *Br J Ophthalmol* 2005;**89**:847–50.

212. Westling AK, Newland HS. Interrater agreement in oculo-kinetic perimetry – a screening test for glaucoma. *Aust N Z J Ophthalmol* 1995;**23**:125–8.

213. Azuara-Blanco A, Katz LJ, Spaeth GL, Nicholl J, Lanzl IM. Detection of changes of the optic disc in glaucomatous eyes: clinical examination and image analysis with the Topcon Imagenet system. *Acta Ophthalmol Scand* 2000;**78**:647–50.

214. Brush MB, Chen PP. Test–retest variability in glaucoma patients tested with C-20-1 screening-mode frequency doubling technology perimetry. *J Glaucoma* 2004;**13**:273–7.

215. Carpineto P, Ciancaglini M, Zuppardi E, Falconio G, Doronzo E, Mastropasqua L. Reliability of nerve fiber layer thickness measurements using optical coherence tomography in normal and glaucomatous eyes. *Ophthalmology* 2003;**110**:190–5.

216. Ciancaglini M, Sebastiani A, Carpineto P, Costagliola C, Ciafre M, Parmegiani F, *et al*. Reproducibility of retinal thickness measurements with retinal thickness analyser in healthy and glaucomatous subjects. *Acta Ophthalmol Scand Suppl* 2002;**80**:43–4.

217. Eikelboom RH, Barry CJ, Jitskaia L, Voon AS, Yogesan K. Neuroretinal rim measurement error using PC-based stereo software. *Clin Exp Ophthalmol* 2000;**28**:178–80.

218. Frenkel S, Slonim E, Horani A, Molcho M, Barzel I, Blumenthal EZ. Operator learning effect and interoperator reproducibility of the scanning laser polarimeter with variable corneal compensation. *Ophthalmology* 2005;**112**:257–61.

219. Garway-Heath DF, Poinoosawmy D, Wollstein G, Viswanathan A, Kamal D, Fontana L, *et al*. Inter- and intraobserver variation in the analysis of optic disc images: comparison of the Heidelberg retina tomograph and computer assisted planimetry. *Br J Ophthalmol* 1999;**83**:664–9.

220. Harper R, Reeves B, Smith G. Observer variability in optic disc assessment: implications for glaucoma shared care. *Ophthalmic Physiol Opt* 2000; **20**:265–73.

221. Hatch WV, Trope GE, Buys YM, Macken P, Etchells EE, Flanagan JG. Agreement in assessing glaucomatous discs in a clinical teaching setting with stereoscopic disc photographs, planimetry, and laser scanning tomography. *J Glaucoma* 1999;**8**:99–104.

222. Heeg GP, Ponsioen TL, Jansonius NM. Learning effect, normal range, and test-retest variability of Frequency Doubling Perimetry as a function of age, perimetric experience, and the presence or absence of glaucoma. *Ophthalmic Physiol Opt* 2003;**23**:535–40.

223. Hollo G, Follmann P, Pap G. A clinical evaluation of XPERT NCT (Reichert) for glaucoma screening by optometrists. *Int Ophthalmol* 1992;**16**:291–3.

224. Hollo G, Suveges I, Nagymihaly A, Vargha P. Scanning laser polarimetry of the retinal nerve fibre layer in primary open angle and capsular glaucoma. *Br J Ophthalmol* 1997;**81**:857–61.

225. Liu X, Ling Y, Luo R, Ge J, Zheng X. Optical coherence tomography in measuring retinal nerve fiber layer thickness in normal subjects and patients with open-angle glaucoma. *Chin Med J (Engl)* 2001;**114**:524–9.

226. Mok KH, Lee VW, So KF. Increasing scans per examination improves the reproducibility on retinal nerve fiber layer measurements by optical coherence tomography. *Optom Vis Sci* 2004; **81**:268–71.

227. Sanchez-Galeana C, Bowd C, Blumenthal EZ, Gokhale PA, Zangwill LM, Weinreb RN. Using optical imaging summary data to detect glaucoma. *Ophthalmology* 2001;**108**:1812–18.

228. Sommer A, Quigley HA, Robin AL, Miller NR, Katz J, Arkell S. Evaluation of nerve fiber layer assessment. *Arch Ophthalmol* 1984;**102**:1766–71.

229. Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC, *et al*. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol* 1991;**109**:77–83.

230. Spalding JM, Litwak AB, Shufelt CL. Optic nerve evaluation among optometrists. *Optom Vis Sci* 2000;**77**:446–52.

231. Strouthidis NG, White ET, Owen VMF, Ho TA, Hammond CJ, Garway-Heath DF. Factors affecting the test–retest variability of Heidelberg retina tomograph and Heidelberg retina tomograph II measurements. *Br J Ophthalmol* 2005;**89**:1427–32.

232. Takamoto T, Schwartz B. Reproducibility of photogrammetric optic disc cup measurements. *Invest Ophthalmol Vis Sci* 1985;**26**:814–17.

233. Varma R, Steinmann WC, Scott IU. Expert agreement in evaluating the optic disc for glaucoma. *Ophthalmology* 1992;**99**:215–21.

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234. Watkins RJ, Broadway DC. Intraobserver and interobserver reliability indices for drawing scanning laser ophthalmoscope optic disc contour lines with and without the aid of optic disc photographs. *J Glaucoma* 2005;**14**:351–7.

235. Tielsch JM, Sommer A, Witt K, Katz J, Royall RM. Blindness and visual impairment in an American urban population. The Baltimore Eye Survey. *Arch Ophthalmol* 1990;**108**:286–90.

236. Medeiros FA, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am J Ophthalmol* 2005;**139**:1010–18.

237. Ellish NJ, Higginbotham EJ. Evaluating a visual field screening test for glaucoma: how the choice of the gold standard affects the validity of the test. *Ophthalmic Epidemiol* 2001;**8**:297–307.

238. Miglior S, Guareschi M, Romanazzi F, Albe E, Torri V, Orzalesi N. The impact of definition of primary open-angle glaucoma on the cross-sectional assessment of diagnostic validity of Heidelberg retinal tomography. *Am J Ophthalmol* 2005;**139**:878–87.

239. Streiner DL. Breaking up is hard to do: the heartbreak of dichotomizing continuous data. *Can J Psychiatry* 2002;**47**:262–6.

240. Caprioli J. Clinical evaluation of the optic nerve in glaucoma. *Trans Am Ophthalmol Soc* 1994; **92**:589–641.

241. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. *Arch Ophthalmol* 1982;**100**:135–46.

242. Garway-Heath D, Hitchings R. Sources of bias in studies of optic disc and retinal nerve fibre layer morphology. *Br J Ophthalmol* 1998;**82**:986.

243. Wild JM, Kim LS, Pacey IE, Cunliffe IA. Evidence for a learning effect in short-wavelength automated perimetry. *Ophthalmology* 2006; **113**:206–15.

244. Yenice O, Temel A. Evaluation of two Humphrey perimetry programs: full threshold and SITA standard testing strategy for learning effect. *Eur J Ophthalmol* 2005;**15**:209–12.

245. Matsuo H, Tomita G, Suzuki Y, Araie M. Learning effect and measurement variability in frequency-doubling technology perimetry in chronic open-angle glaucoma. *J Glaucoma* 2002;**11**:467–73.

246. Joson PJ, Kamantigue ME, Chen PP. Learning effects among perimetric novices in frequency doubling technology perimetry. *Ophthalmology* 2002;**109**:757–60.

247. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias and variation in diagnostic accuracy studies. *CMAJ* 2006;**174**:469–76.

248. Hatt S, Wormald R, Burr J. Screening for prevention of optic nerve damage due to chronic open angle glaucoma (Protocol). *Cochrane Database Syst Rev* 2006 (Issue 3). Article No.: CD006129. DOI: 10.1002/14651858.CD006129.

249. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. *Surv Ophthalmol* 1994;**39**:23–42.

250. Bateman DN, Clark R, Azuara-Blanco A, Bain M, Forrest J. The effects of new topical treatments on management of glaucoma in Scotland: an examination of ophthalmological health care. *Br J Ophthalmol* 2002;**86**:551–4.

251. Oxman AD. Checklists for review articles. *BMJ* 1994;**309**:648–51.

252. Oxman AD, Guyatt GH. The science of reviewing research. *Ann N Y Acad Sci* 1993;**703**:125–33.

253. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, *et al*. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005;**112**:366–75.

254. Schulzer M, Alward WL, Feldman F, Cashwell LF, Wilensky J, Geijssen HC, *et al*. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol* 1998;**126**:487–97.

255. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, *et al*. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;**108**:1943–53.

256. Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. *Ophthalmology* 1994;**101**:1445–55.

257. Katz J, Congdon N, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. *Arch Ophthalmol* 1999;**117**:1137–42.

258. Vesti E, Johnson CA, Chauhan BC. Comparison of different methods for detecting glaucomatous visual field progression. *Invest Ophthalmol Vis Sci* 2003;**44**:3873–9.

259. Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P, *et al*. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol* 2005;**89**:1245–9.

260. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, Budenz DL, *et al*. A multicenter, retrospective pilot

study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol* 2006;**124**:12–19.

261. Hodapp E, Parrish RK, Anderson DR. *Clinical decision in glaucoma*. St Louis, MO: Mosby; 1993.

262. Nouri-Mahdavi K, Caprioli J, Coleman AL, Hoffman D, Gaasterland D. Pointwise linear regression for evaluation of visual field outcomes and comparison with the advanced glaucoma intervention study methods. *Arch Ophthalmol* 2005;**123**:193–9.

263. Eid TM, Spaeth GL, Bitterman A, Steinmann WC. Rate and amount of visual loss in 102 patients with open-angle glaucoma followed up for at least 15 years. *Ophthalmology* 2003;**110**:900–7.

264. Hattenhauer MG, Johnson DH, Ing HH, Herman DC, Hodge DO, Yawn BP, *et al*. The probability of blindness from open-angle glaucoma. *Ophthalmology* 1998;**105**:2099–104.

265. Olivius E, Thorburn W. Prognosis of glaucoma simplex and glaucoma capsulare. A comparative study. *Acta Ophthalmol (Copenh)* 1978;**56**:921–34.

266. Quigley HA, Tielsch JM, Katz J, Sommer A. Rate of progression in open-angle glaucoma estimated from cross-sectional prevalence of visual field damage. *Am J Ophthalmol* 1996;**122**:355–63.

267. Sponsel WE. Frequency of sustained glaucomatous-type visual field loss and associated optic nerve cupping in Beaver Dam Wisconsin. *Clin Exp Ophthalmol* 2001;**29**:352–8.

268. Spry PG, Sparrow JM, Diamond JP, Harris HS. Risk factors for progressive visual field loss in primary open angle glaucoma. *Eye* 2005;**9**:643–51.

269. Jonas JB, Martus P, Budde WM, Junemann A, Hayler J. Small neuroretinal rim and large parapapillary atrophy as predictive factors for progression of glaucomatous optic neuropathy. *Ophthalmology* 2002;**109**:1561–7.

270. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, *et al*. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;**111**:1627–35.

271. Suzuki Y, Shirato S, Adachi M, Hamada C. Risk factors for the progression of treated primary open-angle glaucoma: a multivariate life-table analysis. *Grafes Arch Clin Exp Ophthalmol* 1999;**237**:463–7.

272. Tattersall CL, Vernon SA, Negi A. Is poor life expectancy a predictive factor in the progression of primary open angle glaucoma? *Eye* 2005; **19**:387–91.

273. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol* 2001;**131**:699–708.

274. Oliver JE, Hattenhauer MG, Herman D, Hodge DO, Kennedy R, Fang-Yen M, *et al*. Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. *Am J Ophthalmol* 2002;**133**:764–72.

275. Palmberg P. Risk factors for glaucoma progression: where does intraocular pressure fit in? *Arch Ophthalmol* 2001;**119**:897–8.

276. Garway-Heath T. Measurement of rate of progression. *Int Glaucoma Rev* 2006;**7**:9–11.

277. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.

278. *Improving access to cost-effectiveness information for health care decision making: the NHS Economic Evaluation Database*. CRD Report No. 6. York: NHS Centre for Reviews and Dissemination; 2001.

279. Boivin J, McGregor M. *The screening of primary open-angle glaucoma – systematic review*. Montreal: Conseil d'Evaluation des Technologies de la Sante du Quebec; 1995.

280. Boivin JF, McGregor M, Archer C. Cost effectiveness of screening for primary open angle glaucoma. *J Med Screen* 1996;**3**:154–63.

281. Gooder P. *Screening for glaucoma*. Development and Evaluation Committee (DEC) Report No. 38. Bristol: Research & Development Directorate South and West; 1995.

282. Gottlieb LK, Schwartz B, Pauker SG. Glaucoma screening. A cost-effectiveness analysis. *Surv Ophthalmol* 1983;**28**:206–26.

283. Tuck MW, Crick RP. The cost-effectiveness of various modes of screening for primary open angle glaucoma. *Ophthalmic Epidemiol* 1997;**4**:3–17.

284. Teagarden JR. Meta-analysis: whither narrative review? *Pharmacotherapy* 1989;**9**:274–81.

285. Demichelli V, Jefferson T, Vale L. Effectiveness estimates in economic evaluation. In: Donaldson C, Mugford M, Vale L, editors. *From effectiveness to efficiency – health economics and systematic review*. London: BMJ Books; 2002.

286. British Household Panel Survey (BHPS). Institute for Social & Economic Research, University of Essex. URL: http://www.iser.essex.ac.uk/ulsc/bhps/. Accessed April 2006.

287. Theodossiades J, Murdoch I. Positive predictive value of optometrist-initiated referrals for glaucoma. *Ophthalmic Physiol Opt* 1999;**19**:62–7.

288. Tuck M, Crick R. Glaucoma screening by optometrists: ten years on. *Health Trends* 1998;**30**:130–4.

289. Vernon SA, Ghosh G. Do locally agreed guidelines for optometrists concerning the referral of

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glaucoma suspects influence referral practice? *Eye* 2001;**15**:458–63.

290. Bowling B, Chen SD, Salmon JF. Outcomes of referrals by community optometrists to a hospital glaucoma service. *Br J Ophthalmol* 2005;**89**:1102–4.

291. Henson DB, Spencer AF, Harper R, Cadman EJ. Community refinement of glaucoma referrals. *Eye* 2003;**17**:21–6.

292. Brittain GPH, Austin DJ, Kelly SP. A prospective survey to determine sources and diagnostic accuracy of glaucoma referrals. *Health Trends* 1988;**20**:43–4.

293. Tuck MW. Referrals for suspected glaucoma: an International Glaucoma Association survey. *Ophthalmic Physiol Opt* 1991;**11**:22–6.

294. Busby, D. General ophthalmic services: increases to NHS sight test fee and NHS optical voucher values and tax credit limits from April 2005. Department of Health. URL: http://www.dh.gov.uk/assetRoot/04/10/70/47/04107047.pdf. Accessed April 2006.

295. Facey K, Cummins E, Macpherson K, Morris A, Reay L, Slattery J. *Organisation of services for diabetic retinopathy screening*. HTA Report 1. Glasgow: NHS Quality Improvement Scotland [Health Technology Board for Scotland (HTBS)]; 2002.

296. General ophthalmic services. Primary Care Circular PCA(O)(2005)03. Scottish Executive. URL: http://www.show.scot.nhs.uk/sehd/pca/PCA2005(O)03.pdf. Accessed February 2006.

297. Guide to the methods of technology appraisal. National Institute for Clinical Excellence. URL: http://www.nice.org.uk/page.aspx?o=201974. Accessed September 2005.

298. Gupta V, Srinivasan G, Mei SS, Gazzard G, Sihota R, Kapoor KS. Utility values among glaucoma patients: an impact on the quality of life. *Br J Ophthalmol* 2005;**89**:1241–4.

299. Meads C, Hyde C. How much is the cost of visual impairment: caveat emptor. *Pharmacoeconomics* 2006;**24**:207–9.

300. Iversen GR. *Bayesian statistical inference*. Thousand Oaks, CA: Sage; 1984.

301. Mutti DO, Zadnik K. Age-related decreases in the prevalence of myopia: longitudinal change or cohort effect? *Invest Ophthalmol Vis Sci* 2000;**41**:2103–7.

302. Diabetes population prevalence model. Diabetes UK. URL: http://www.diabetes.org.uk/infocentre/reports/prevalencemodel.doc. Accessed February 2006.

303. The UK population: by ethnic group. United Kingdom Census 2001. National Statistics. URL: http://www.statistics.gov.uk/CCI/nugget.asp?ID=273&Pos=4&ColRank=2&Rank=1000. Accessed February 2006.

304. Guidelines for the management of open angle glaucoma and ocular hypertension. Royal College of Ophthalmologists. URL: http://www.rcophth.ac.uk/docs/publications/glaucoma2004.pdf. Accessed February 2006.

305. Glaucoma. Clinical guideline in development. National Institute for Health and Clinical Excellence. URL: http://www.nice.org.uk/page.aspx?o=292041. Accessed February 2006.

306. Shah P, Cross V. ReGAE 1: using the Shah–Cross model as an orientating framework in African–Caribbean glaucoma research. *Eye* [serial on the Internet] 2006;doi: 10.1038/sj.eye.6702130.

307. Saw SM, Gazzard G, Eong KG, Oen F, Seah S. Utility values in Singapore Chinese adults with primary open-angle and primary angle-closure glaucoma. *J Glaucoma* 2005;**14**:455–62.

308. Perkins ES. The Bedford Glaucoma Survey. I. Long-term follow-up of borderline cases. *Br J Ophthalmol* 1973;**57**:179–85.

309. Bengtsson B. Manifest glaucoma in the aged. I: Occurrence nine years after a population survey. *Acta Ophthalmol (Copenh)* 1981;**59**:321–31.

310. Bengtsson BO. Incidence of manifest glaucoma. *Br J Ophthalmol* 1989;**73**:483–7.

311. Bonomi L, Marchine G, Marraffa M, Bernardi P, Morbio R, Varotto A, *et al*. Vascular risk factors for primary open-angle glaucoma. *Ophthalmology* 2001;**107**:1287–93.

312. Borger PH, van Leeuwen R, Hulsman CA, Wolfs RC, van der Kuip DA, Hofman A, *et al*. Is there a direct association between age-related eye diseases and mortality? The Rotterdam Study. *Ophthalmology* 2003;**110**:1292–6.

313. Ramrattan RS, Wolfs RC, Jonas JB, Hofman A, de Jong PT. Determinants of optic disc characteristics in a general population: The Rotterdam Study. *Ophthalmology* 1999;**106**:1588–96.

314. Ramrattan RS, Wolfs RCW, Panda-Jonas S, Jonas JB, Bakker D, Pols HA, *et al*. Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study. *Arch Ophthalmol* 2001;**119**:1788–94.

315. Grodum K. *Glaucoma characteristics and risk factors: results from Malmo Eye Survey*. Copenhagen: Blackwell Munksgaard; 2004.

316. Grodum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. *Ophthalmology* 2005;**112**:386–90.

317. Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, *et al*. The Framingham Eye Study. I. Outline and major prevalence findings. *Am J Epidemiol* 1977;**106**:17–32.

318. Kahn HA, Milton RC. Revised Framingham eye study prevalence of glaucoma and diabetic retinopathy. *Am J Epidemiol* 1980;**111**:769–76.

319. Kini MM, Leibowitz HM, Colton T, Nickerson RJ, Ganley J, Dawber TR. Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham eye study. *Am J Ophthalmol* 1978;**85**:28–34.

320. Graham PA. Prevalence of glaucoma. Population surveys. *Trans Ophthalmol Soc UK* 1978;**98**:288–9.

321. Duggal P, Klein AP, Lee KE, Iyengar SK, Klein R, Bailey-Wilson JE, *et al*. A genetic contribution to intraocular pressure: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 2005;**46**:555–60.

322. Klein BE, Klein R, Ritter LL. Relationship of drinking alcohol and smoking to prevalence of open-angle glaucoma: the Beaver Dam Eye Study. *Ophthalmology* 1993;**100**:1609–13.

323. Klein BE, Klein R, Lee KE. Heritability of risk factors for primary open-angle glaucoma: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 2004;**45**:59–62.

324. Klein BEK, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: The Beaver Dam Eye Study. *Br J Ophthalmol* 2005;**89**:284–7.

325. Klein R, Klein BEK, Moss SE. Age-related eye disease and survival: the Beaver Dam Eye Study. *Arch Ophthalmol* 1995;**113**:333–9.

326. Klein R, Klein BE, Tomany SC, Wong TY. The relation of retinal microvascular characteristics to age-related eye disease: the Beaver Dam Eye Study. *Am J Ophthalmol* 2004;**137**:435–44.

327. Viswanathan AC, Hitchings RA, Indar A, Mitchell P, Healey PR, McGuffin P, *et al*. Commingling analysis of intraocular pressure and glaucoma in an older Australian population. *Ann Hum Genet* 2004;**68**:489–97.

328. Lee AJ, Mitchell P, Rochtchina E, Healey PR, Blue Mountains Eye Study. Female reproductive factors and open angle glaucoma: the Blue Mountains Eye Study. *Br J Ophthalmol* 2003;**87**:1324–8.

329. Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history and risk of glaucoma. *Ophthalmology* 1999;**106**:2301–6.

330. Lee AJ, Rochtchina E, Mitchell P. Intraocular pressure asymmetry and undiagnosed open-angle glaucoma in an older population. *Am J Ophthalmol* 2004;**137**:380–2.

331. Wang JJ, Mitchell P, Smith W. Is there an association between migraine headache and open-angle glaucoma? Findings from the Blue Mountains Eye Study. *Ophthalmology* 1997; **104**:1714-19.

332. Younan C, Mitchell P, Cumming RG, Rochtchina E, Wang JJ. Myopia and incident cataract and cataract surgery: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* 2002; **43**:3625–32.

333. Lee AJ, Rochtchina E, Wang JJ, Healey PR, Mitchell P. Open-angle glaucoma and systemic thyroid disease in an older population: the Blue Mountains Eye Study. *Eye* 2004;**18**:600–8.

334. Mitchell P, Lee AJ, Rochtchina E, Wang JJ. Open-angle glaucoma and systemic hypertension: the Blue Mountains Eye Study. *J Glaucoma* 2004;**13**:319–26.

335. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population – the Blue Mountains Eye Study. *Ophthalmology* 1999;**106**:1066–72.

336. Mitchell P, Leung H, Wang JJ, Rochtchina E, Lee AJ, Wong TY. Retinal vessel diameter and open-angle glaucoma: the Blue Mountains Eye Study. *Ophthalmology* 2005;**112**:245–50.

337. Mitchell P, Wang JJ, Hourihan F. The relationship between glaucoma and pseudoexfoliation. *Arch Ophthalmol* 1999;**117**:1319–24.

338. Rahmani B, Tielsch JM, Katz J, Gottsch J, Quigley H, Javitt J, *et al*. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey. *Ophthalmology* 1996;**103**:1721–6.

339. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC, *et al*. Racial differences in the cause-specific prevalence of blindness in east Baltimore. *N Engl J Med* 1991;**325**:1412–17.

340. Sommer A. Glaucoma risk factors observed in the Baltimore Eye Survey. *Curr Opin Ophthalmol* 1996;**7**:93–8.

341. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma: a population-based assessment. *Arch Ophthalmol* 1995;**113**:216–21.

342. Tielsch JM, Katz J, Quigley HA, Javitt JC, Sommer A. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology* 1995;**102**:48–53.

343. Varma R, Hilton SC, Tielsch JM, Katz J, Quigley HA, Sommer A. Neural rim area declines with increased intraocular pressure in urban Americans. *Arch Ophthalmol* 1995;**113**:1001–5.

344. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the Visual Impairment Project. *Invest Ophthalmol Vis Sci* 2003;**44**:3783–9.

345. Van Newkirk MR, Weih L, McCarty CA, Taylor HR. Cause-specific prevalence of bilateral visual impairment in Victoria, Australia: the Visual Impairment Project. *Ophthalmology* 2001;**108**:960–7.

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346. Wensor M, McCarty C, Taylor H. Prevalence and risk factors of myopia in Victoria, Melbourne. *Arch Ophthalmol* 1999;**117**:658–63.

347. Wong EY, Keeffe JE, Rait JL, Vu HT, Le A, McCarty C, *et al*. Detection of undiagnosed glaucoma by eye health professionals. *Ophthalmology* 2004;**111**:1508–14.

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ISSN 1366-5278