

Screening for Glaucoma

A draft report for the
UK National Screening Committee

April 2015

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This work was undertaken by Solutions for Public Health (SPH) who received funding from the Department of Health via the National Screening Committee. Views expressed in this publication are those of the authors and not necessarily of the Department of Health.

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Introduction

1. This report reviews screening for glaucoma against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search first conducted by the National Screening Committee in June 2012 (Coles 2012) and updated in October 2014. Full details of the search strategy are set out in Appendix A.
2. Glaucoma is the term used for a group of eye diseases in which progressive damage to the optic nerve leads, if untreated, to impaired vision and blindness. There are two forms of primary glaucoma (i.e. glaucoma that does not result from another eye disease or systemic disease): open angle glaucoma (OAG) and angle closure glaucoma (Burr et al 2007). This review concerns screening for OAG.
3. The National Institute for Health and Care Excellence (NICE) has specified several assumptions that define chronic OAG (COAG) (NCCAC 2009):
 - Open drainage angles on gonioscopy¹
 - Visual field damage compatible with nerve fibre loss
 - One or more of:
 - Optic damage with glaucomatous cupping
 - Optic disc damage with loss of neuroretinal rim
 - Nerve fibre damage with nerve fibre layer defect
 - Included variants:
 - COAG with repeatedly elevated untreated or treated intraocular pressure (IOP) (above 21mmHg²) identified as Primary Open Angle Glaucoma
 - COAG with repeatedly normal untreated IOP (21 mmHg or less) identified as Normal Tension Glaucoma
 - COAG with pigment dispersion
 - COAG with pseudo-exfoliation
 - Absence of other secondary cause for IOP elevation (e.g. trauma, uveitis).
4. NICE has also specified several assumptions that define suspected COAG (NCCAC 2009):
 - Open drainage angles on gonioscopy
 - One or more of:
 - Possible optic disc damage with suspicion of glaucomatous cupping
 - Possible optic disc damage with suspicion of loss of neuroretinal rim
 - Possible nerve fibre damage with suspicion of nerve fibre layer defect
 - Normal or equivocal visual field
 - Included variants:
 - COAG suspect with pigment dispersion
 - COAG suspect with pseudo-exfoliation
 - COAG suspect with repeatedly elevated untreated IOP (above 21 mmHg) identified as Primary Open Angle Suspect
 - COAG suspect with repeatedly normal untreated IOP (21 mmHg or less) identified as Normal Tension Glaucoma Suspect
 - Absence of other secondary cause for IOP elevation (e.g. trauma, uveitis).
5. The current NSC policy is that screening for glaucoma should not be offered³. A 2007 Health Technology Assessment (HTA) (Burr et al 2007) evaluated the clinical and cost-

¹ Gonioscopy is the examination of the anterior chamber angle using a gonioscope to observe angle structures and estimate depth of angle (NICE 2009)

² mmHg (millimetre of mercury) is a unit of pressure

effectiveness of screening for open-angle glaucoma and concluded that population screening is not cost-effective, however targeted screening of high-risk groups may be.

6. The United States Preventative Services Task Force (USPSTF) considered the case for screening in 2013 and concluded that “the current evidence is insufficient to assess the balance of benefits and harms of screening for primary open-angle glaucoma (POAG) in adults” (Moyer et al 2013).
7. This current review examines new research published since the 2007 HTA, with particular focus on the following key questions:
 - **Have any studies identified a test with acceptable sensitivity and specificity for screening the general population, and with optimum cut-off levels?**
 - **Is there any high quality evidence demonstrating treatment of glaucoma to be more effective than no treatment?**
 - **Are there any data from RCTs assessing whether a screening programme for glaucoma would be effective in reducing morbidity?**

The Condition

The condition should be an important health problem

8. Glaucoma is the leading cause of irreversible blindness in the world and is the second most common cause of blindness in UK adults, after age-related macular degeneration (Burr et al 2007). An analysis of the main causes of blindness for England and Wales in the year 1999-2000 found that OAG was the main cause in 11% of incident blind registrations and 10% of partial sight registrations. However these numbers may underestimate the true proportion of cases as not all individuals who are eligible to register as blind or partially sighted do so (Burr et al 2007).
9. Glaucoma can impair navigational vision which can lead to restricted mobility and negatively impact the ability to self-care. Impaired vision caused by glaucoma can also impact quality of life, for example in the deterioration of vision to a level below that which is necessary for a driving licence (Burr et al 2007).
10. In the absence of screening, suspected glaucoma cases are identified by community optometrists and referred to secondary care for diagnosis by an ophthalmologist. It is estimated from population surveys that, in developed countries, more than 50% of prevalent OAG is undetected (Burr et al 2007).
11. This condition is met.

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

12. OAG is asymptomatic before the development of visual field loss (Hatt et al 2006) and an estimated 40-50% of nerve fibres may be lost before functional visual loss occurs (Andreou et al 2007). People may be unaware that they have a problem with their eyes until after severe visual damage has occurred (NICE 2009).

³ <http://www.screening.nhs.uk/glaucoma>

13. Damage resulting from glaucoma typically occurs slowly over a long period of time and many people who are diagnosed with glaucoma will never develop significant visual impairment during their lifetime (Burr et al 2007). Burr et al estimated that it would take 35 years for a treated population with OAG to progress to unilateral blindness. This time period was broken down into five years for progression from mild (Mean Defect⁴ score of ≤ -6 dB) to moderate (≥ -6 dB to -12 dB) disease, 14 years with moderate OAG and 16 years with severe disease (≥ -12 dB to -20 dB). Severe disease would involve visual loss that is sufficient to prevent someone from being able to drive. A mean defect of > -20 dB would represent blindness (Burr et al 2007).
14. OAG usually affects both eyes, but there may be some asymmetry with more advanced disease in one eye (Hatt et al 2006). Structural changes at the optic nerve may precede functional visual loss and could therefore represent a disease marker that is detectable before visual field loss has a negative impact on health related quality of life (Burr et al 2007). The proportion of people who present early with OAG and progress to severe visual loss is not known (Hatt et al 2006).
15. The UK prevalence of OAG is estimated to be 2.1%, (2,100 per 100,000). Prevalence varies with age, ranging from 0.3% (300 per 100,000) in people aged 40 years to 3.3% (3,300 per 100,000) in people aged 70 years. The incidence of OAG ranges from 0.03% (30 per 100,000) for people aged 40 years to 0.181% (181 per 100,000) for people aged 70 years (Burr et al 2007).
16. An estimated 67% of OAG cases are undetected. It has been estimated that the prevalence of undetected OAG ranges from 0.2% (200 per 100,000) in people aged 40 years to 2.1% (2,100 per 100,000) in people aged 70 years (Burr et al 2007).
17. A number of risk factors for OAG have been identified including increasing age, family history in a first-degree relative (accounting for an estimated 6.7% of cases in people aged 40 to 75 years), diabetes (3.3%) and myopia (2.7%) (Burr et al 2007). The risk of OAG is also four to five times higher in people of African ethnicity compared to people of European or Asian ethnicity (Hatt et al 2006).
18. Raised IOP is often associated with OAG but is now not thought to be a specific indicator for OAG (Hatt et al 2006). It is recognised that whilst people with an IOP below 21 mmHg may have OAG, the risk of developing glaucoma and the risk of worsening glaucoma does increase with increasing IOP (Burr et al 2007). People with an IOP of 26 mmHg or greater are estimated to have a risk of glaucoma 13 times higher than people with a lower IOP (Burr et al 2007).
19. The natural progression of IOP in patients with early OAG was assessed in a group of patients who formed the untreated (control) group of the Early Manifest Glaucoma Trial. Patients (n=118) were followed up for six years or until disease progression occurred⁵. For the 80 patients who showed disease progression, the median time to progression was 48.2 months (Hyman et al 2010). The authors found that 'the vast majority of control patients experienced minimal annual IOP changes during 6 years [without treatment], with IOP changes limited to within ± 1.1 mmHg/year for about two-thirds of controls'. The baseline median IOP of this cohort was 20.8 mmHg. However, further analysis showed that the 15 patients with exfoliation glaucoma had a statistically significant larger change in median IOP of +1 mmHg/year (range -16.22 to 23.32 mmHg/year, $p=0.004$). The

⁴ The Mean Defect (MD) refers to the average deviation in decibels of the measured threshold values from the age-corrected normal value

⁵ The disease progression criteria were based on significant worsening in visual fields, as detected by computerized analysis in glaucoma probability maps, and optic disc cupping, as detected by an independent disc photograph reading centre (Hyman et al 2010)

median baseline IOP for this subgroup was also higher at 24.0 mmHg (Hyman et al 2010).

20. A study assessing the performance of a prediction equation for estimating the five-year risk of OAG for people with ocular hypertension (Takwoingi et al 2014) provided data on the number of people who progressed to OAG from four cohorts of patients. These data were drawn from the two randomised controlled trials from Moorfields Eye Hospital in London (n=298) and Rotterdam Eye Hospital in The Netherlands (n=393), and two cohort studies from Dunfermline Hospital in Scotland (n=188) and Queens Medical Centre in Nottingham (n=159). The median follow-up ranged from 2.7 years to 9.3 years. The proportion of patients who developed OAG was 15%, 7%, 15% and 3% respectively.
21. The main risk factor for glaucoma blindness is late presentation with advanced disease (Burr et al 2007).
22. This condition is met.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

23. Very few of the risk factors associated with glaucoma are preventable. The exception is diabetes, however this is thought to only account for a relatively small number of cases (about 3%) (Burr et al 2007).

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

24. In 2007 Burr et al concluded that genetic screening for glaucoma is not indicated as only a small number of cases have an identifiable gene mutation.

The Test

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

25. Testing for glaucoma involves assessment of structural changes at the optic nerve head, functional visual loss by visual field testing and measurement of intraocular pressure (IOP). Since most of the visual disability in glaucoma is related to visual field loss, it is reasonable to test for early visual field loss (i.e. perimetric glaucoma) in OAG screening. However, this does not rule out structural tests from glaucoma screening. A structural test may have a better diagnostic performance than a functional test in the perimetric stage of glaucoma (when only minimal visual field loss has occurred) because, in this stage, the disc damage would have progressed beyond early stage and would therefore be easier to detect (Burr et al 2007).
26. OAG is a clinical diagnosis and there is no optimal reference standard or classification for severity (Burr et al 2007). The lack of an established gold standard against which individual screening tests can be compared was identified as a limitation within the USPSTF review of screening for glaucoma (Moyer et al 2013). Moyer et al stated that “instead of an established gold standard, many investigators used confirmation of POAG at follow-up examination, diagnosis of POAG requiring treatment, and other individual tests or combinations of tests as the reference against which to evaluate accuracy.”
27. The key question relating to testing for glaucoma to be addressed in this review is:
 - **Have any studies identified a test with acceptable sensitivity and specificity for screening the general population, and with optimum cut-off levels?**
28. Burr et al (2007) reviewed screening tests for glaucoma and identified a number of tests that were considered potentially feasible for use in an OAG screening programme, namely:
 - Optic disc photography (*assesses structure*)
 - Heidelberg retina tomography (HRT) II (*assesses structure*)
 - Frequency doubling technology (FDT) (*assesses visual function*)
 - Standard automated perimetry (SAP) (*assesses visual field loss*)
 - Goldmann applanation tonometry (GAT) (*measures IOP*)
29. Pooled meta-analyses on the diagnostic performance of each test were performed by Burr et al. However, it was not possible to identify a single test or group of tests as the most accurate because of heterogeneity between the individual studies and imprecision in the estimates from the meta-analysis. Burr et al also concluded that appropriate cut-off levels were available for standard tests but that more research was needed to determine suitable cut-offs and test accuracy in a screening setting.
30. Burr et al (2007) made the following research recommendations regarding screening tests for OAG, which highlight the deficiencies of research on testing for glaucoma up to 2005:
 - 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.

31. In their review of the comparative effectiveness of screening for glaucoma, Ervin et al (2012) considered the predictive value of screening tests for OAG. Ervin et al considered studies published up to October 2011 and included randomised controlled trials (RCT), quasi-RCTs, and observational study designs including cohort studies, case-control studies, cross-sectional studies and case series with more than 100 participants. The population of interest was adult asymptomatic patients in general or high-risk populations. Studies of participants who had been previously tested or diagnosed with glaucoma, or who presented with symptoms associated with a diagnosis of glaucoma were excluded. Studies including participants suspected of having glaucoma (with an unconfirmed diagnosis) were included. In presenting their results, Ervin et al started by summarising the findings of Burr et al's 2007 HTA and then considered additional studies published since the HTA.

32. Ervin et al (2012) identified additional studies (published since Burr et al 2007) on the following tests of structure: Heidelberg retina tomograph (HRT) II, HRT III, optical coherence tomography (OCT), optic disc photography, retinal nerve fibre layer (RNFL) photography and scanning laser polarimetry. Tests of optic nerve function assessed included FDT perimetry (C-20-1; C-20-5 and 30-2) and FDT N-30 perimetry. Additional tests assessed included Goldmann applanation tonometry, Humphrey visual field analyser, noncontact tonometry and tendency-orientated perimetry.

33. Ervin et al (2012) concluded:

“We identified several additional studies assessing the performance of glaucoma screening tests not included in the Burr et al. review. The studies included newer imaging (scanning laser polarimetry (GDx), HRT III, OCT) and functional (short wave automated perimetry, new FDT patterns) technologies. However, despite improvements in the technology it is still not clear that there is any one test or combination of tests suitable for use in glaucoma screening in the general population. Significant barriers to identifying and characterising potential glaucoma screening tests remain. These barriers include the lack of a definitive diagnostic reference standard for glaucoma and heterogeneity in the design and conduct of the studies. Because of these barriers, the ranges of sensitivities, specificities and areas under the curve are large and prevent a coherent synthesis.”

34. A study by The Glaucoma Screening Platform Study Group (GSPSG) combined interviews with 46 UK eye-care providers, policy makers and health service commissioners with economic modelling of potential test strategies to explore the feasibility and acceptability of a glaucoma screening trial. The authors concluded that whilst there are many sophisticated tests for diagnosing glaucoma, these are not affordable for a public health intervention such as screening (GSPSG 2011).

35. The authors integrated the findings from the interviews and modelling to identify the components of a screening test intervention that could be implemented from a service perspective. These were (GSPSG 2011):

“General population screening for a cohort at age forty (based on findings of the qualitative interviews of the need to balance feasibility and equity with cost-effectiveness criteria) in a primary health care setting. Screening would be conducted by ophthalmic trained technical assistants, undertaking optic nerve

photography or screening mode perimetry (a measure of visual field sensitivity) with or without tonometry.”

36. This finding suggests four possible screening protocols:

- a. Optic nerve photography with tonometry (*assessing structure and IOP*)
- b. Optic nerve photography without tonometry (*assessing structure only*)
- c. Screening mode perimetry with tonometry (*assessing visual function and IOP*)
- d. Screening mode perimetry without tonometry (*assessing visual function only*)

37. For the current review we retrieved the full text of primary studies in which a glaucoma test had been evaluated as a potential test for a population screening programme and that were published after the December 2005 search date used by Burr et al (2007). These studies were classified according to the four possible screening protocols set out above. Papers that did not fit into one of the four possible screening protocols, for example those assessing a combination of structural and function tests, were not included.

38. These criteria yielded seven papers from the August 2012 NSC search and one further paper from the October 2014 NSC search. These studies were assessed using the same adapted quality assessment tool (QUADAS) that was used by Burr et al (2007). Six of these papers assessed structure using either optical coherence tomography (OCT), scanning laser tomography using the Heidelberg retina tomography (HRT II) or scanning laser polarimetry (GDx variable). The remaining two papers assessed function using frequency doubling technology perimetry (FDT). We did not identify any studies assessing a combination of a structural or functional test with a test of IOP.

Tests of structure

39. Summaries of the six studies assessing structural tests are presented in Table B2 in Appendix B. There was considerable heterogeneity between the studies in terms of the tests assessed. With the exception of Healy et al (2010) and Chan et al (2013), the studies had less than 200 participants overall, and small numbers of participants who were found to have glaucoma. This resulted in wide confidence intervals for the estimates of sensitivity and specificity.

40. The quality of the studies was assessed using the QUADAS checklist (Table B1, Appendix B). The scores ranged from 8/13 to 11/13, which compares with a mean score of 9/13 for the 20 population-based studies that were assessed by Burr et al (2007). Although all of the studies used confirmation of glaucoma at follow-up as their reference standard, three of the six studies only performed this for people identified as having possible glaucoma, rather than for all participants. It is therefore possible that some cases of glaucoma were missed in these studies, resulting in overestimates of the sensitivity and specificity of the screening tests. A further limitation is that in most of the studies it was not clear whether the definition of a positive index test was determined before the study was carried out, and all but one of the studies (Andreou et al 2007) explored sensitivity and specificity scores for a variety of potential cut-off values. This led to a wide range of potential sensitivity and specificity scores, depending on the cut-off value used.

Tests of function

41. Summaries of the two studies assessing functional tests are presented in Table B3 in Appendix B. Although both studies assessed FDT, the test screening protocols used differed. Both studies involved a large number of participants (550 and 3,021 respectively), however in both studies less than 100 participants were found to have glaucoma.

42. The QUADAS checklist was used to assess the quality of the studies (Table B1, Appendix B). The scores were 9/13 and 12/13, which compares with a mean score of 9/13 for the 20 population-based studies that were assessed by Burr et al (2007). In both studies the reference standard was follow-up confirmation of glaucoma. In Kamdeu Fansi et al (2011) all participants received verification using the reference standard. Various cut-off values were considered, resulting in sensitivity scores ranging from 40.7% to 78.9% and specificity scores ranging from 66.0% to 70.0%. The 95% confidence intervals for all these estimates were very wide. In Iwase et al (2007) only one cut-off value was assessed (at least one abnormal point on the C-20-1 screening protocol for FDT perimetry) resulting in a sensitivity of 55.6% and a specificity of 92.7%, however verification of the screening result was only performed for patients identified as having possible glaucoma.

Summary

43. None of the four studies with a large sample size (Iwase et al 2007; Healy et al 2010; Kamdeu Fansi et al 2011; Chan et al 2013) concluded that the test they assessed was adequate for population screening. In the four smaller studies, the numbers of cases of glaucoma detected were too small to produce reasonably precise estimates of sensitivity or specificity. It therefore remains unclear which, if any, of these structural or functional tests would be the most suitable for a population screening programme.
44. The October 2014 NSC search identified 12 case-control studies assessing newer tests for glaucoma. These studies examined the ability of the tests to detect glaucoma but did not consider performance in a screening population and are therefore not assessed in this review. Eight of these studies considered a single test of structure, namely spectral domain optical coherence tomography (SD-OCT) (five studies) and Cirrus high-definition OCT (three studies). Three studies considered combinations of structural tests (SD-OCT and scanning laser polarimeter (GDx); SD-OCT and HRT III; Cirrus OCT, HRT and GDx). Only one study assessed function (FDT).

Alternative approaches

45. In addition to the testing approaches discussed above, the updated NSC search (October 2014) identified two large studies that considered two alternative tests, both based on asymmetry between a participant's two eyes (Chang et al 2013; Choudhari et al 2013), and a third study that assessed a strategy in which a computer programme combined patient personal data with information from their medical retinal fundus image and their genome to estimate individuals' risk of glaucoma (Liu et al 2013).
46. Chang et al (2013) conducted a systematic review and meta-analysis on the accuracy of pupillary light reflex in detecting a relative afferent pupillary defect (RAPD)⁶. Eleven studies (n=7,271) were included, two of which were population-based and nine clinic-based case-control studies. The pooled sensitivity was 63% (95%CI 43% to 80%) and the pooled specificity was 93% (95%CI 85% to 97%). The two population-based studies had low sensitivity scores (9% and 28%) and used the Swinging Light Test to detect RAPD. Some heterogeneity was observed between studies and limitations identified included a lack of standardisation in the testing procedures of pupil assessment and a lack of consistent cut-off levels for each measurement. The inclusion of case-control studies can overestimate test performance.

⁶ Pupillary light reflex (PLR) is an indicator of the afferent input from the retina and optic nerve. Asymmetry in the PLR between the two eyes is referred to as a relative afferent pupillary defect (RAPD) and is often a sign of unilateral or asymmetric impairment of the anterior afferent visual pathways. A RAPD is often clinically detectable in patients with glaucoma (Chang et al 2013)

47. Choudhari et al (2013) considered IOP asymmetry in a population-based study (n=6,310) in India. The participants were all aged over 40 years old and people with known glaucoma were excluded. A diagnosis of IOP asymmetry was made when the difference in IOP between the two eyes was >3mm Hg, and 500 participants had IOP asymmetry. Participants also received an ophthalmic examination and 217 patients were found to have undiagnosed primary glaucoma. The sensitivity of asymmetric IOP to diagnose glaucoma was 20% (95%CI 15% to 26%) and the specificity was 92% (95%CI 91% to 93%). This test was considered to have limited accuracy for detecting glaucoma.
48. Lui et al (2013) explored the value of an automatic glaucoma diagnosis and screening architecture called Automatic Glaucoma Diagnosis Through Medical Imaging Informatics (AGLAIA-MII) in a population-based study of 3,280 people. The AGLAIA-MII tool combines patient personal data (demographic data, ocular examination data (e.g. IOP and corneal thickness) and historical medical data), medical retinal fundus image (optic disc image) and patient's genome information for the purpose of screening. Data from participants of the Singapore Malay Eye Study database was used, and 2,258 participants had sufficient (<5% missing data) data. One hundred individuals were diagnosed with glaucoma. Table 1 summarises the sensitivities and positive predictive values obtained using the different data sources singly or in combination, with the cut-off in each instance set to deliver specificity of 85%. Confidence intervals were not reported.

Table 1: Results from Liu et al (2013) (screening set point)

Data included	Sensitivity	Specificity	PPV
Genome information	54%	85%	14%
Retinal fundus image	42%	85%	12%
Personal data	20%	85%	6%
Genome information and retinal fundus image	65%	85%	17%
Personal data and genome information	64%	85%	16%
Personal data and retinal fundus image	45%	85%	12%
Personal data, genome information and retinal fundus image (AGLAIA-MII)	67%	85%	17%

49. The AGLAIA-MII scenario using all three data sources achieved the highest sensitivity but this is still low for use in population-based screening, and a PPV of 17% suggests that a high number of false positive results would be obtained.

Other considerations in testing for glaucoma

50. Hadwin et al (2013) assessed diagnostic accuracy in 208 UK registered optometrists who completed an optic disc assessment test of 110 images. Participants were selected from 1,256 optometrists who completed an online survey on current practices, through a stratified sample to select optometrists from a wide range of practice environments. Participants classified the images as glaucoma or healthy. The median sensitivity was 92% (95%CI 70% to 100%), the median specificity was 74% (95%CI 62% to 88%) and the median overall accuracy was 80% (95%CI 67% to 88%). The specificity and overall accuracy was higher for participants who undertook any work in a hospital setting.
51. In another study, van der Schoot et al (2013) assessed the accuracy of 109 ophthalmologists from 11 European countries to match optic discs with their corresponding visual fields and classify them as healthy or glaucomatous. Overall, 58.7% images were correctly classified with most mismatches overestimating the visual field damage.

52. The majority of tests for glaucoma considered in this review involve human judgement to distinguish positive and negative results and are therefore open to the possibility of observer bias. For example, Hadwin et al (2013) noted the serious implications of missing a diagnosis of glaucoma, which might create a tendency for practitioners to be over-cautious in referring patients for further assessment.

Summary

53. Studies assessing tests of structure and function were identified, but the sensitivity and specificity scores reported varied widely and no study reported acceptable sensitivity and specificity for use in general population screening. Various cut-off levels were used in the studies and it is not clear that optimum cut-off levels for use in screening have been identified for any tests. Additional studies assessing newer tests and alternative approaches for screening for glaucoma were identified. This included some testing in population-based samples but these also did not achieve sensitivity and specificity scores that would be acceptable for general population screening. Positive predictive values, when reported, were less than 20%. It therefore remains unclear which, if any, of the tests for glaucoma considered would be suitable for a population screening programme.

54. This criterion is not met.

55. The remainder of the NSC criteria relating to testing are not considered further.

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

56. Strategies to reduce visual damage from COAG are based on the reduction of IOP. Longer term clinical observations are also done to monitor signs of progression of visual field defects and optic nerve head damage (NICE 2009).

57. The specific question to be addressed in this review with regards to the treatment of glaucoma is:

- **Is there any high quality evidence demonstrating treatment of glaucoma to be more effective than no treatment?**

58. NICE reviewed the evidence for any treatment versus no treatment for ocular hypertension and COAG as part of the development of CG85 (NICE 2009). Table B4 in the appendix summarises the results of this review.

59. NICE found low to moderate quality evidence that treatment was more effective than no treatment in:

- Reducing the number of ocular hypertensive patients who develop COAG after 5 to 6 years follow up (relative risk (RR) 0.55; 95%CI 0.43 to 0.72)
- Reducing the visual field progression in patients with ocular hypertension after 2 to 10 years follow up (RR 0.65; 95%CI 0.5 to 0.86)
- Reducing the number of COAG patients who show progressive damage after 4 to 5 years follow up (RR 0.78; 95%CI 0.63 to 0.95)

- Reducing the visual field progression in patients with COAG after 4 to 5 years follow up (RR 0.69; 95%CI 0.55 to 0.86)
- Reducing IOP from baseline after 1 to 6 years follow up (mean difference -3.28; 95%CI - 4.5 to -2.06).

60. However, before introducing a population screening programme the UKNSC would expect to have evidence of high quality, not merely low to moderate quality, that treatment of glaucoma is more effective than no treatment. Therefore, we looked for such high quality evidence.

61. For the USPSTF review on screening for glaucoma, Boland et al (2013) reviewed the effectiveness of medical, laser and surgical treatments in adults with OAG with regard to decreasing IOP and preventing optic nerve damage, vision loss and visual impairment. The search included primary studies published up to July 2012 and systematic reviews published up to March 2011. The 99 studies and 23 systematic reviews included in the final analysis considered no treatment, placebo or alternative treatments as comparators. The USPSTF conclusions regarding treatment were (Moyer et al 2013):

“The USPSTF found convincing evidence that treatment of increased intraocular pressure (IOP) and early glaucoma reduces the number of persons who develop small, clinically unnoticeable visual field defects and that treatment of early asymptomatic POAG decreases the number of persons whose visual field defects worsen. However, the USPSTF found inadequate evidence that screening for, or treatment of, increased IOP or early asymptomatic POAG reduces the number of persons who will develop impaired vision or quality of life. ... It found convincing evidence that treatment results in numerous harms, including local eye irritation from medications and risk of complications from surgery, such as early formation of cataracts. The magnitude of these harms for most persons is small.”

62. The updated NSC literature search (October 2014) identified two Cochrane reviews that do not provide evidence comparing treatment to no treatment, but do consider potential treatments for glaucoma, including studies published after the search date for Boland et al's review. Burr et al (2012) considered medical versus surgical interventions for OAG; they identified four randomised controlled trials (RCT) (n=888) involving participants with previously untreated OAG and concluded that “primary surgery lowers IOP more than primary medication but is associated with more eye discomfort”. Sena et al (2013) considered neuroprotection⁷ for the treatment of glaucoma and identified one RCT (n=190) which compared two drugs (brimonidine and timolol). Sena et al concluded that this trial “did not provide evidence that they are effective in preventing retinal ganglion cell death and thus preserving vision in people with OAG”.

63. In conclusion, we did not identify any high quality evidence demonstrating treatment of glaucoma to be more effective than no treatment. This criterion is not met.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

64. NICE CG85 sets out the recommended treatment for people with ocular hypertension (OHT) or suspected COAG based on their IOP, central corneal thickness (CCT) and age (Table 2).

⁷ Neuroprotection for glaucoma refers to any intervention intended to prevent optic nerve damage or cell death (Sena et al 2013)

Table 2: Treatment recommended for people with OHT or suspected COAG (NICE 2009)

CCT	More than 590 micrometres		555-590 micrometres		Less than 555 micrometres		Any
Untreated IOP (mmHg)	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>32
Age (years)	Any	Any	Any	Treat until 60	Treat until 65	Treat until 80	Any
Treatment	No treatment	No treatment	No treatment	BB ^a	PGA	PGA	PGA

^a if beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)

65. NICE specifies that treatment should not be routinely offered to people over the age threshold unless there are likely to be benefits from the treatment in an appropriate timescale. They also specify that the use of age thresholds is only considered appropriate where vision is normal (OHT with or without suspicion of COAG) and the treatment is purely preventative as the threat to the patient's sighted lifetime is considered negligible.

66. If definite COAG (not just suspected COAG) were to develop in such a patient then treatment would be recommended regardless of age, as follows (NICE 2009):

- Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue (PGA)
- Offer people with advanced COAG surgery with pharmacological augmentation (MMC or 5-FU) as indicated
- Offer people who present with advanced COAG and who are listed for surgery interim treatment with a PGA.

67. Further recommendations are provided in CG85 for situations where a patient is intolerant to a treatment, where there is poor adherence to treatment and where disease progression is observed despite treatment. Potential treatment options recommended in these different circumstances include pharmacological treatments, surgery with pharmacological augmentation, laser trabeculoplasty or cyclodiode laser treatment (NICE 2009).

68. In conclusion, UK guidelines exist specifying the treatments to be offered to people with ocular hypertension or suspected chronic OAG. Policies specifically relating to people identified through a screening programme would need to be developed.

69. The remainder of the NSC criteria relating to treatment are not considered further.

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials (RCT) that the screening programme is effective in reducing mortality or morbidity

70. The specific question to be addressed in this review is:

- **Are there any data from RCTs assessing whether a screening programme for glaucoma would be effective in reducing morbidity?**

71. A Cochrane review, originally published in 2006 and assessed as up-to-date with a new search for studies in January 2009, searched for RCTs evaluating population-based

screening programmes for OAG with a minimum one year follow up. The authors did not identify any RCTs on screening for glaucoma and concluded that there is insufficient evidence to recommend population-based screening for OAG (Hatt et al 2006).

72. A systematic review on the effectiveness of screening for glaucoma (Ervin et al 2012) searched for studies (RCTs, quasi-RCTs, cohort studies or case-control studies) of adult asymptomatic patients in general or high-risk populations. The key questions considered included:
- Does a screening-based programme for OAG lead to less visual impairment when compared with no screening programme?
 - Does a screening-based programme for OAG lead to improvements in patient-reported outcomes when compared to no screening?
 - Does a screening-based programme for OAG lead to reductions in intraocular pressure when compared with no screening programme?
 - Does a screening-based programme for OAG lead to a slowing of the progression of optic nerve damage and visual field loss when compared with no screening programme?
73. The authors did not identify any review or study that “provided evidence for direct or indirect links between glaucoma screening and visual field loss, visual impairment, optic nerve damage, intraocular pressure or patient-reported outcomes” (Ervin et al 2012).
74. No RCTs on screening for glaucoma were identified by the literature search for this review.
75. A long-term cohort study was identified (Åström et al 2014). This involved individuals from one district in Sweden who were born in 1915 (n=856) and compared the proportion of diagnosed OAG in a randomly selected group who were screened (n=389, of which 339 completed screening) with a group who were not screened (n=467). Screening was performed every seven years with an ophthalmic examination during the 21-year follow up period. Suspected glaucoma cases were monitored between screening intervals. During the follow-up period, 33 new cases of OAG were identified in the screened group and 31 in the unscreened group. Glaucoma cases in the unscreened group were identified through a retrospective review of medical records. Diagnoses of glaucoma were confirmed through reassessment of visual field tests, descriptions of the optic head nerve and IOP. No statistically significant difference was found in the number of diagnosed OAG cases between the screened and unscreened groups (intention-to-screen analysis). This was a fairly small study and medical records for only 290 of the unscreened group were identified. This suggests that some cases of glaucoma in the unscreened group may have been missed. This study did not assess severity or progression rate of OAG.
76. Burr et al (2014) published a paper assessing the value of conducting a glaucoma screening RCT in the UK. Four possible screening strategies were considered compared to no screening. All strategies used an inception cohort aged 40, with sensitivity analysis considering the impact of varying the screening start age, the uptake of screening, the cost of sight impairment, and enhancing current eye care. The four strategies differed in the tests performed and the pathways for those testing positive, with either a diagnostic refinement step, using a specialised optometrist to examine screen positives, or no referral refinement with screen test positives referred to a hospital-based glaucoma service. The four strategies were:
- The population to be screened are invited to a primary care setting to receive tonometry and optic nerve photography by a technician or nurse who has received some training. Screen positives are referred to the hospital eye service
 - As above, but the tests used are tonometry and a visual field test (perimetry)

- c. Screening with tonometry and optic nerve photography. Screen positives are examined by a specialised optometrist, who makes a diagnosis. Diagnostic test positives are referred to the hospital eye service
 - d. Screening with tonometry and a visual field test (perimetry) with further diagnostic refinement and screen positives examined by a specialised optometrist who makes a diagnosis. Diagnostic test positives are referred to the hospital eye service.
77. Burr et al (2014) found that glaucoma screening of a population selected on age is unlikely to be considered cost-effective and suggested that further research to understand and quantify the cost of sight impairment is a priority before proceeding to a large RCT evaluating a glaucoma screening or surveillance programme. Other particular areas of uncertainty were around test performance and uptake of either screening or current eye care. They concluded that:
- “A glaucoma screening trial in the UK is unlikely to be the best use of research resources. Further research to quantify the costs of sight impairment falling on the NHS and personal services is a priority [*best collected within a prospective cohort study*]. Further development of glaucoma tests and research into strategies to promote the uptake of screening or current eye care such as through the use of a behavioural intervention would be worthwhile”.
78. We did not identify any RCTs on screening for glaucoma. This criterion is not met.
79. The remainder of the criteria relating to the screening programme are not considered further.

Implications for policy

- **Have any studies identified a test with acceptable sensitivity and specificity for screening the general population, and with optimum cut-off levels?**
80. Studies assessing tests of structure and function were identified, but the sensitivity and specificity scores reported varied widely and no study reported acceptable sensitivity and specificity for use in general population screening. Only two of the six studies assessing structural tests had more than 200 participants. Although the two studies assessing function had larger sample sizes, the number of people identified as having glaucoma was small in all of the studies. Various cut-off levels were used in the studies and it is not clear that optimum cut-off levels for use in screening have been identified for any tests. Confirmation of glaucoma at follow-up was used as the reference standard, but in many studies, this was only performed for people suspected of having glaucoma. This may have led to cases being missed, resulting in overestimates of the sensitivity and specificity of the screening tests.
81. Additional studies assessing newer tests and alternative approaches for screening for glaucoma were identified. This included some testing in population-based samples but these also did not achieve sensitivity and specificity scores that would be acceptable for general population screening. Positive predictive values, when reported, were less than 20%.
82. It therefore remains unclear which, if any, of the tests for glaucoma considered would be suitable for a population screening programme.

- **Is there any high quality evidence demonstrating treatment of glaucoma to be more effective than no treatment?**

83. NICE (2009) found low to moderate quality evidence, but not high quality evidence, that treatment was more effective than no treatment. We found no studies published since the NICE guideline which provide high quality evidence that the treatment of glaucoma is more effective than no treatment.

- **Is there any data from RCTs assessing whether a screening programme for glaucoma would be effective in reducing morbidity?**

84. Two systematic reviews published in 2006 and 2012 did not identify any RCTs (or other studies) assessing the effectiveness of screening for glaucoma. We found no RCTs assessing whether a screening programme for glaucoma would be effective in reducing morbidity.

Implications for research

85. This review concluded that it is unclear which, if any, of the tests for glaucoma considered would be suitable for a population screening programme.

86. A study comparing potential screening tests for glaucoma could provide further evidence on the most appropriate test, or combination of tests, and appropriate cut-off levels.

Appendix A

Literature search update on screening for glaucoma

Paula Coles, Information Scientist, (1) August 2012 and (2) October 2014

SOURCES SEARCHED: (1) Medline (OvidSP), Embase, PsycINFO, Web of Science and the Cochrane Library. (2) Medline, Embase and the Cochrane Library.

DATE OF SEARCHS: (1) January 2005 to July 2012; (2) January 2012 to 16th October 2014.

SEARCH STRATEGY:

'Accuracy of tests' Medline search

1. Glaucoma, Open-Angle/ (9291)
2. Glaucoma/ (28927)
3. Ocular Hypertension/ (4686)
4. Intraocular Pressure/ (27242)
5. glaucoma.tw. (37264)
6. poag.tw. (1904)
7. ((ocular or intraocular) adj3 (hypertension or pressure)).tw. (23259)
8. corneal thickness.tw. (3300)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (64780)
10. Ophthalmoscopy/ (6958)
11. exp Tomography, Optical/ (10496)
12. Tomography/ (8657)
13. Tonometry, Ocular/ (5728)
14. Manometry/ (17394)
15. Diagnostic Techniques, Ophthalmological/ (4239)
16. (photograph\$ or stereophoto\$).tw. (33169)
17. (stereoscop\$ or monoscop\$).tw. (4037)
18. (retina\$ adj3 (tomograph\$ or tomogram\$)).tw. (1094)
19. (coherence adj3 (tomograph\$ or tomogram\$)).tw. (9691)
20. ophthalmoscop\$.tw. (6751)
21. tomograph\$.tw. (212974)
22. heidelberg.tw. (3458)
23. scan\$ laser polarimet\$.tw. (532)
24. nerve\$ fib\$ analy\$.tw. (174)
25. retina\$ nerve fib\$.tw. (2201)
26. planimet\$.tw. (3843)
27. (retina\$ adj5 analy\$).tw. (3773)
28. (stereo\$ adj3 photo\$).tw. (1338)
29. (slp or oct or hrt).tw. (21253)
30. tonomet\$.tw. (6041)
31. perimet\$.tw. (10336)
32. humphrey.tw. (1833)
33. frequency doubling.tw. (882)
34. goldmann.tw. (2161)
35. (sap or fdt or swap or okp or gat or nct).tw. (11327)
36. (applanation or tonopen or tono pen).tw. (2723)
37. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (336828)
38. 9 and 37 (13775)
39. Glaucoma, Open-Angle/di [Diagnosis] (1908)
40. Glaucoma/di [Diagnosis] (5274)
41. Ocular Hypertension/di [Diagnosis] (1039)
42. 39 or 40 or 41 (7306)
43. 38 or 42 (17146)

44. "Sensitivity and Specificity"/ (248817)
45. roc curve/ (22748)
46. "Predictive Value of Tests"/ (121022)
47. exp Diagnostic Errors/ (86443)
48. "Reproducibility of Results"/ (233163)
49. Diagnosis, Differential/ (354389)
50. early diagnosis/ (9806)
51. 44 or 45 or 46 or 47 or 48 or 49 or 50 (903488)
52. 43 and 51 (3165)
53. animal/ or nonhuman/ (4963387)
54. human/ (12343636)
55. 53 not 54 (3640602)
56. 52 not 55 (3063)
57. limit 56 to yr="2005 -Current" (1478)

'Acceptability of tests' Medline search

1. Glaucoma, Open-Angle/ (9291)
2. Glaucoma/ (28927)
3. Ocular Hypertension/ (4686)
4. Intraocular Pressure/ (27242)
5. glaucoma.tw. (37264)
6. poag.tw. (1904)
7. ((ocular or intraocular) adj3 (hypertension or pressure)).tw. (23259)
8. corneal thickness.tw. (3300)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (64780)
10. Ophthalmoscopy/ (6958)
11. exp Tomography, Optical/ (10496)
12. Tomography/ (8657)
13. Tonometry, Ocular/ (5728)
14. Manometry/ (17394)
15. Diagnostic Techniques, Ophthalmological/ (4239)
16. (photograph\$ or stereophoto\$).tw. (33169)
17. (stereoscop\$ or monoscop\$).tw. (4037)
18. (retina\$ adj3 (tomograph\$ or tomogram\$)).tw. (1094)
19. (coherence adj3 (tomograph\$ or tomogram\$)).tw. (9691)
20. ophthalmoscop\$.tw. (6751)
21. tomograph\$.tw. (212974)
22. heidelberg.tw. (3458)
23. scan\$ laser polarimet\$.tw. (532)
24. nerve\$ fib\$ analy\$.tw. (174)
25. retina\$ nerve fib\$.tw. (2201)
26. planimet\$.tw. (3843)
27. (retina\$ adj5 analy\$).tw. (3773)
28. (stereo\$ adj3 photo\$).tw. (1338)
29. (slp or oct or hrt).tw. (21253)
30. tonomet\$.tw. (6041)
31. perimet\$.tw. (10336)
32. humphrey.tw. (1833)
33. frequency doubling.tw. (882)
34. goldmann.tw. (2161)
35. (sap or fdt or swap or okp or gat or nct).tw. (11327)
36. (applanation or tonopen or tono pen).tw. (2723)
37. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (336828)
38. 9 and 37 (13775)
39. Glaucoma, Open-Angle/di [Diagnosis] (1908)

40. Glaucoma/di [Diagnosis] (5274)
41. Ocular Hypertension/di [Diagnosis] (1039)
42. 39 or 40 or 41 (7306)
43. 38 or 42 (17146)
44. "Sensitivity and Specificity"/ (248817)
45. roc curve/ (22748)
46. "Predictive Value of Tests"/ (121022)
47. exp Diagnostic Errors/ (86443)
48. "Reproducibility of Results"/ (233163)
49. Diagnosis, Differential/ (354389)
50. early diagnosis/ (9806)
51. 44 or 45 or 46 or 47 or 48 or 49 or 50 (903488)
52. 43 and 51 (3165)
53. animal/ or nonhuman/ (4963387)
54. human/ (12343636)
55. 53 not 54 (3640602)
56. 52 not 55 (3063)
57. 56 (3063)
58. limit 57 to yr="2005 -Current" (1478)
59. exp "Patient Acceptance of Health Care"/ (144511)
60. exp Consumer Satisfaction/ (68953)
61. Patient Dropouts/ (6025)
62. ((patient\$ or consumer\$) adj3 (satisfaction or attitude\$ or perception\$ or preference\$ or compliance or participat\$ or acceptab\$ or refus)).tw. (70391)
63. 59 or 60 or 61 or 62 (209025)
64. 43 and 63 (160)
65. limit 64 to yr="2005 -Current" (92)

'Effectiveness of screening' Medline search

1. Glaucoma, Open-Angle/ (9291)
2. Glaucoma/ (28927)
3. Ocular Hypertension/ (4686)
4. Intraocular Pressure/ (27242)
5. glaucoma.tw. (37264)
6. poag.tw. (1904)
7. ((ocular or intraocular) adj3 (hypertension or pressure)).tw. (23259)
8. corneal thickness.tw. (3300)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (64780)
10. Mass Screening/ (74668)
11. Vision Screening/ (1552)
12. Vision Tests/ (8394)
13. screen\$.tw. (394439)
14. 10 or 11 or 12 or 13 (425809)
15. 9 and 14 (2433)
16. exp clinical trial/ (682090)
17. Random Allocation/ (74701)
18. Comparative Study/ (1583408)
19. random\$.tw. (601166)
20. compara\$.tw. (461342)
21. (control adj (group\$ or subject\$ or patient\$)).tw. (321457)
22. 16 or 17 or 18 or 19 or 20 or 21 (2876223)
23. 15 and 22 (685)
24. limit 23 to yr="2005 -Current" (275)

'Economic evaluation of screening' Medline search

1. Glaucoma, Open-Angle/ (9291)
2. Glaucoma/ (28927)
3. Ocular Hypertension/ (4686)
4. Intraocular Pressure/ (27242)
5. glaucoma.tw. (37264)
6. poag.tw. (1904)
7. ((ocular or intraocular) adj3 (hypertension or pressure)).tw. (23259)
8. corneal thickness.tw. (3300)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (64780)
10. Mass Screening/ (74668)
11. Vision Screening/ (1552)
12. Vision Tests/ (8394)
13. screen\$3.tw. (394439)
14. 10 or 11 or 12 or 13 (425809)
15. 9 and 14 (2433)
16. Glaucoma, Open-Angle/di [Diagnosis] (1908)
17. Glaucoma/di [Diagnosis] (5274)
18. 16 or 17 (7070)
19. Ophthalmoscopy/ (6958)
20. exp Tomography, Optical/ (10496)
21. Tomography/ (8657)
22. Tonometry, Ocular/ (5728)
23. Manometry/ (17394)
24. Diagnostic Techniques, Ophthalmological/ (4239)
25. (photograph\$ or stereophoto\$).tw. (33169)
26. (stereoscop\$ or monoscop\$).tw. (4037)
27. (retina\$ adj3 (tomograph\$ or tomogram\$)).tw. (1094)
28. (coherence adj3 (tomograph\$ or tomogram\$)).tw. (9691)
29. ophthalmoscop\$.tw. (6751)
30. tomograph\$.tw. (212974)
31. heidelberg.tw. (3458)
32. scan\$ laser polarimet\$.tw. (532)
33. nerve\$ fib\$ analy\$.tw. (174)
34. retina\$ nerve fib\$.tw. (2201)
35. planimet\$.tw. (3843)
36. (retina\$ adj5 analy\$).tw. (3773)
37. (stereo\$ adj3 photo\$).tw. (1338)
38. (slp or oct or hrt).tw. (21253)
39. tonomet\$.tw. (6041)
40. perimet\$.tw. (10336)
41. humphrey.tw. (1833)
42. frequency doubling.tw. (882)
43. goldmann.tw. (2161)
44. (sap or fdt or swap or okp or gat or nct).tw. (11327)
45. (applanation or tonopen or tono pen).tw. (2723)
46. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (336828)
47. 9 and 46 (13775)
48. 15 or 18 or 47 (18146)
49. exp "Costs and Cost Analysis"/ (165257)
50. exp Economics, Medical/ 13282
51. Economics/ or exp Economics, Hospital/ (44114)
52. xp models, economic/ (8648)
53. exp Decision Theory/ (8786)
54. "Quality of Life"/ (99791)

55. quality-adjusted life years/ (5689)
 56. Health Status Indicators/ (17943)
 57. cost\$.ti. (72146)
 58. (cost\$ adj2 (effective\$ or utilit\$ or benefit\$ or minimis\$)).ab. (70164)
 59. (quality adj1 life).tw. (3140)
 60. quality adjusted life.tw. (4898)
 61. disability adjusted life.tw. (958)
 62. (QOL or HRQOL or QALY\$ or DALY\$ or HYE\$).tw. (25504)
 63. (decision\$ adj2 (tree\$ or analy\$ or model\$)).tw. (10668)
 64. (markov or monte carlo).tw. (32191)
 65. 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
 427577
 66. 48 and 65 (242)
 67. limit 66 to yr="2005 -Current" (142)

Similar searches also carried out in Embase, PsycINFO, Cinahl, and Cochrane Library.
 The results of these searches are presented in Table A1.

Table A1: Search 1 (August 2012):

	Accuracy of tests	Acceptability of tests	Effectiveness of Screening	Economic evaluation of screening	Total
Medline	1,478	92	275	142	1,987
Embase	1,311	142	312	268	2,033
Cochrane Library	638	---	66	55	759
Web of Science	1,911	58	270	279	2,519
PsycINFO	---	33	---	---	33
Total					7,731

A simple search of the NICE website was also conducted to identify NICE guidance regarding the management of glaucoma. One guideline was retrieved.

After de-duplication 4,242 unique, potentially relevant results remained. These were sifted for relevance to the criteria for a screening programme and glaucoma by the NSC, focussing on the test and screening as these were the areas that did not meet the criteria for a screening programme in the Burr et al HTA. These were classified into several categories (Table A2). Since the condition and the treatment were not the focus of this review they have not been classified further. A total of 1,294 results were passed to the reviewer for further assessment.

Table A2: Categorisation of the search 1 results (August 2012)

Systematic reviews and meta-analyses	
The condition (7)	
The test (14)	
The treatment (28)	
The screening programme (13)	62
Guidelines and recommendations	7
Non-systematic reviews	12
The condition	192
The test	
Structure (380)	
Optical coherence tomography (124)	
Heidelberg retina tomography (56)	
Scanning laser polarimetry (48)	
Electroretinogram (23)	726

Ophthalmoscopy (11) Miscellaneous (21) Combinations and/or comparisons (97) Function (140) Perimetry (47) Frequency doubling technology (42) Combinations and/or comparisons (51) Intraocular pressure (97) Structure/function/intraocular pressure (74) Reviews (15) Personnel (12) Surveys (4) Acceptability (3) Biomarkers (1)	
The treatment	220
Adherence to/acceptance of guidelines and interventions	26
The screening programme Reviews (6) High-risk populations (22) Opportunistic case-finding (5) Enhanced referral (6) Costs (7)	46
Total	1,291

The updated search in October 2014 generated a further 2,148 references (Table A3).

Table A3: Search 2 (October 2014):

	Accuracy	Acceptability	Cost-effectiveness	Screening	Total
Medline	664	54	87	102	851
Embase	556	64	122	330	962
Cochrane Library	---	---	---	335	335
Total					2,148

After automatic and manual de-duplication, 1,455 unique references were sifted for relevance to the review.

Inclusions and exclusions: As in previous reviews, accuracy and acceptability of the test for diagnosing glaucoma and screening. Systematic reviews for treatment were also included.

180 references were deemed to be relevant and were passed to the reviewer (Table A4).

Table A4: Categorisation of the search 2 results (October 2014)

Systematic reviews and guidelines The test (4) Screening / case finding (3) Treatment (8)	15
Non-systematic reviews	2
Diagnostic delay	2
The test Intraocular pressure (or with ultrasound) (9) Structural tests (84)	147

Optical coherence tomography (55) Scanning laser tomography (5) Optic disc photography (4) Pupillography (3) Other structural tests (5) 2 or more structural tests combined (12) Functional tests (20) Electrophysiological tests (9) Perimetry (4) Other functional tests (3) 2 or more functional tests (4) Structural and functional tests combined (18) Personnel (9) Algorithms (7)	
Screening / case finding	14
Total	180

Appendix B

Table B1: Summary of modified QUADAS quality assessment checklist (Burr et al 2007): results for glaucoma screening tests

Item	Chan et al 2013	Bengtsson et al 2012	Garas et al 2011	Healy et al 2010	Tóth et al 2008	Andreou et al 2007	Kamdeu Fansi et al 2011	Iwase et al 2007
1. Was the spectrum of patients representative of the patients who will receive the test in practice?								
a. Was the sample selected from an unscreened population with a glaucoma prevalence between >0 and 20%? (If No go to b)	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Yes
b. Is the sample constructed from previously undiagnosed glaucoma patients referred from primary care or are the cases and controls representative of those detected in primary care?	n/a	n/a	n/a	n/a	n/a	Yes	n/a	n/a
2. Is the reference standard follow-up confirmation of glaucoma?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Did the whole sample or a random sample of the sample receive verification using a reference standard of diagnosis?	Yes	No	No	Yes	No	Yes	Yes	No
4. Did patients receive the same reference standard regardless of the index test result?	No	No	No	Yes	No	Yes	Yes	No
5. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? (e.g. in a HRT-II study if clinical assessment of optic disc was part of reference standard it will be regarded as independent reference standard and scored yes)	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
6. Were the index test results interpreted without knowledge of the results of the reference standard? (studies in which cut-off is calculated by a machine and subjective decision is involved should be scored yes)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
7. Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Unclear
8. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?								

a. For screening studies: index test results alone	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
b. For diagnostic studies: may include information from ophthalmic examination and/or co-morbidity	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
9. Were uninterpretable/ intermediate/ incomplete tests results reported?	Yes 1078/1219 8 (9%)	Yes 2/15 (13%)	Yes ONH: 21/227 (9%) GCC: 23/227 (10%)	Yes 70/174 (4%)	Yes GDx: 19/236 eyes (8%) HRT: 44/236 eyes (19%)	Yes GDx: 13/112 (12%) HRT: 6/112 (5%)	Yes 56/550 (10%)	Yes 252/5832 eyes (4%)
10. Were withdrawals from the study explained? (Withdrawals are participants who entered the study but did not get both tests)	Yes 1078/1291 8 eyes (8%)	Yes 18/170 (11%)	Yes 10/146 (7%)	Yes 30/1952 (1.5%)	Yes 18/136 (13%)	Unclear	Yes 49/550 (9%)	Yes 14/2977 (0.5%)
11. Is the technology of the index test used in the study still current?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Did the study provide a clear definition of what was considered to be a 'positive' result?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was the definition of a positive index test result determined before the study was carried out?	Yes	No	Unclear	No	Unclear	GDx: No HRT II: Unclear	No	Yes

GCC – Ganglion cell complex; GDx – scanning laser polarimetry; HRT – Heidelberg retinal tomograph; ONH – Optic nerve head

Table B2: Studies assessing structural tests as potential screening tests for glaucoma

Study	Population	Index test	Reference standard	Cut-off	Sensitivity	Specificity	Number of 'yes' on QUADAS	Comments
Chan et al 2013 Singapore	Participants in the Singapore Malay Eye Study (n=3,280) and Singapore Indian Eye Study (n=3,400) recruited through age-stratified random sampling of ethnic Malays and Indians living in Singapore during the study period. Age 40 to 80 years. Total n = 6,459 (11,840 eyes had images suitable for analysis).	HRT II (ISNT rule and variants ⁸)	Classification of glaucoma cases by a senior glaucomatologist.	Various	4.7% to 93.5%	15.7% to 98.2%	11/13	194 participants with glaucoma. Very wide range of scores with the different ISNT rule variants. No single algorithm had a combination of high sensitivity and specificity. PPV scores ranged from 2.1% to 8.4%. NPV scores ranged from 97.9% to 99.1%. Glaucoma suspects and 1 in 5 non-glaucoma suspect patients received gonioscopy and automated perimetry.
Bengtsson et al 2012 Sweden	307 randomly selected people living in two primary medical care districts. Age >50 years. N participated = 170.	Stratus OCT Cirrus OCT	Follow-up confirmation of glaucoma (for people with possible glaucoma or abnormal test result).	Various	67% to 100%	65% to 100%	8/13	9 participants with glaucoma; very wide 95% confidence intervals. Results for a sample of clinical glaucoma patients not included.
Garas et al 2011 Hungary	146 reported for an advertised free screening programme.	RTVue-100 OCT	Follow-up confirmation of glaucoma (for people with possible	Various	11.1% to 55.6%	89.0% to 99.6%	10/13	9 participants with glaucoma. Confidence intervals not reported. Criteria for damage were set

⁸ "The ISNT rule states that in normal eyes, the thickness of the neuroretinal rim along the cardinal meridians of the optic disc, that is the rim width, decreases in the order inferior (I) > superior (S) > nasal (N) > temporal (T), and that the neuroretinal rim in glaucomatous optic discs violate this quantitative relationship". The 4 variants of the ISNT rule do not involve the nasal rim e.g. (I>S>T; I>T; and S>T, I>T, and S>T) (Chan et al 2013).

	For RTVue- 100 OCT n=133 (256 eyes).		glaucoma or abnormal test result).					in advance of the study, however several different criteria were considered.
Healy et al 2010 Australia	1,952 survivors from the Blue Mountains Eye Study Cohort – invited for 10-year follow up examination. Mean age = 74 years. For HRT N = 1,644	HRT II	Confirmation of glaucoma on the basis of visual field loss which matched the optic disc changes, and gonioscopy. Period of follow-up before confirming diagnosis is unclear.	Various	40.7% to 66.7%	73.7% to 91.3%	9/13	105 participants with glaucoma (30 had already been diagnosed through early screening cycles). Confidence intervals not reported. Authors concluded that this test is not sufficiently specific for use in glaucoma screening.
Tóth et al 2008 Hungary	136 reported for an advertised free screening programme. For testing N=123 (218 eyes)	GDx-VCC HRT II	Follow-up confirmation of glaucoma (for people with possible glaucoma or abnormal test result).	GDx-VCC: various HRT II: various Combination of GDx-VCC and HRT II: various	14.3% to 56.5% 0.0% to 92.9% 7.1% to 92.9%	71.0% to 98.9% 39.9% to 93.8% 58.5% to 100%	10/13	13 participants with glaucoma. Confidence intervals not reported. Criteria for damage were set in advance of the study, however several different criteria were considered.
Andreou et al 2007 UK	New patients referred to a primary eye care clinic with a possible diagnosis of glaucoma. N = 112	GDx HRT II	Follow-up confirmation of glaucoma or non- glaucoma (for all participants).	GDx of 50 HRT II (outside normal limits):	80% (95%CI 59% to 93%) 79% (95%CI 60% to 92%)	72% (95%CI 61% to 80%) 70% (95% CI 60% to 78%)	11/13	23 participants with glaucoma. The population for this study may not reflect a screening population. Various GDx cut-off values were tested before determining that 50 gave the best level of agreement with the clinicians diagnosis

GDx- scanning laser polarimetry; HRT – Heidelberg retinal tomograph; NPV – negative predictive value; OCT – optical coherence tomography; PPV – positive predictive value; VCC – variable corneal compensation

Table B3: Studies assessing function tests as potential screening tests for glaucoma

Study	Population	Index test	Reference standard	Cut-off	Sensitivity	Specificity	Number of 'yes' on QUADAS	Comments
Kamdeu Fansi et al 2011 Canada	Participants recruited from groups at high risk of glaucoma. Age > 50 years N = 550	FDT Screening Mode C-20-5 algorithm	Follow-up confirmation of glaucoma or non-glaucoma (for all participants).	Various	40.7% to 78.9%	66.0% to 70.0%	12/13	Criteria for glaucoma were set in advance of the study, however several different criteria were considered. 39 eyes had glaucoma. 95% confidence intervals for sensitivity very wide. Authors concluded that this test has poor validity, even in a high risk population.
Iwase et al 2007 Japan	A random sample of people aged > 40 years resident in a city in Japan. N = 3,021 (5,784 eyes)	FDT C-20-1 screening protocol	Follow-up confirmation of glaucoma (for people with abnormal test result).	At least 1 abnormal point on the C-20-1 screening protocol of FDT perimetry.	55.6% (95%CI 48.1% to 63.0%)	92.7% (95%CI 92.0% to 93.4%)	9/13	95 participants with glaucoma. Authors concluded that this test is not sufficiently sensitive for detecting glaucoma, especially early damage.

FDT - Frequency doubling technology

Table B4: Summary of the evidence comparing any treatment with no treatment

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of ocular hypertensive patients developing COAG (follow up 5-6 years)	82/1353 (6.1%)	149/1360 (11%)	0.55 (0.43 to 0.72)	49 fewer per 1,000 (from 31 fewer to 63 fewer)	Low (2 RCTs)
Number of COAG patients showing progressive damage (follow up 4-5 years)	80/190 (42.1%)	109/205 (53.2%)	0.78 (0.63 to 0.95)	117 fewer per 1,000 (from 27 fewer to 197 fewer)	Low (2 RCTs)
Visual field progression in patients with ocular hypertension (follow up 2-10 years)	81/1726 (4.7%)	124/1730 (7.2%)	0.65 (0.5 to 0.86)	25 fewer per 1,000 (from 10 fewer to 36 fewer)	Moderate (8 RCTs)
Visual field progression in COAG patients (follow up 4-5 years)	68/190 (35.8%)	102/205 (49.8%)	0.69 (0.55 to 0.86)	154 fewer per 1,000 (from 70 fewer to 224 fewer)	Moderate (2 RCTs)
Mean change in IOP from baseline (follow up 1-6 years)	1136	1137	N/a	Mean difference -3.28 (-4.5 to -2.06)	Low (5 RCTs)

Adapted from NICE CG85 (2009) pp 111-112

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