Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Screening for Glaucoma: Comparative Effectiveness*

Draft review available for public comment from September 14, 2011 to October 12, 2011.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Public comment/ AAO-AGS	Executive Summary	The condition has a significant individual or population burden. The AHRQ review focuses on the technical aspects of glaucoma screening, including the area under the curve (AUC) of various screening devices such as the HRT II, HRT III, tonometry, etc. What is missing from the document is discussion of the significant burden that untreated glaucoma can have on individuals and would have on society at large	Discussion of the burden of untreated glaucoma was considered outside of the scope of this comparative effectiveness review
Public comment/ Beth Kneib	Executive Summary	ES-6 First paragraph, second sentence, Even though these studies may have most likely been conducted by ophthalmology departments or individual ophthalmologists, it should be noted that they are not the only eye care providers who diagnosis glaucoma. There are many, many optometrists who diagnose and treat glaucoma on a daily basis in the United States	We included studies of all settings in which screening could potentially occur including community screenings, non-eye care health provider settings, eye care provider clinical settings (ophthalmologists and optometrists), and telemedicine.
Peer Reviewer #2	Introduction	Structured abstract- line 18. the authors should change that "It is estimate that half of those with glaucoma..." to "It is estimated that half or more of those with glaucoma.." because the percent of undiagnosed glaucoma in the Hispanic population is 75%, which is more than half (LALES).	We have edited the sentence to "It is estimated that more than half of those who have glaucoma are undiagnosed, leading to the desire to have a population screening for this disease."
Peer Reviewer #3	Introduction	Introduction is generally clear and concise. Suggest including some general literature and consensus statements on glaucoma screening in the introduction and/or discussion–which may be useful to the readers. Healey, PR; Screening for Glaucoma In: Shaarway T, Sherwood MB, Hitchings RA, Crowston JG (eds). Glauocma Medical Diagnosis and Therapy Volume One. Saunders. 2009 pp. 15-23. World Glaucoma Association Glaucoma Screening: Consensus Series 5. edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis 2008. Hardbound. ISBN-10: 90 62992 188. ISBN-13:978-90-6299-218-8 Kugler Publications.	We have revised the text. Thank you for the suggested references.

Commentator & Affiliation	Section	Comment	Response
Public comment/ Pfizer	Introduction	Stratify the Assessment. Stratifying the assessment by patient characteristics known to impact screening Effectiveness: The draft key questions do not explicitly acknowledge the array of patient characteristics that may impact the effectiveness of OAG screening when performed in real-world settings. As previously mentioned, high-risk patient groups are likely to benefit more from glaucoma screening, and further, certain high-risk patients may benefit more from specific techniques. For example, findings from the Ocular Hypertension Treatment Study (OHTS) suggest that African American patients may have a thinner average central corneal thickness, and therefore may benefit more from pachymetry measurement than other populations.5 In addition, research indicates that African American patients are screened less frequently for glaucoma than patients of other ethnicities ratifying the assessment by patient characteristics known to impact screening	We included studies of adult (“adult” as defined by included studies) asymptomatic participants in general or high risk populations. We also noted that "Asymptomatic high risk populations included those not previously tested, diagnosed or presenting with symptoms known to be related to glaucoma but also included those with a family history of glaucoma, specific racial/ethnic groups, older age, and specific ocular or other medical conditions as defined by included studies (e.g., diabetes)."
Public comment/ Pfizer	Introduction	It is critical for AHRQ to account for these variables to reflect real-world practice and to ensure the assessment is meaningful to end users. Therefore, we encourage AHRQ to stratify the analysis by patient characteristics identified in previous research.	We included studies of adult (“adult” as defined by included studies) asymptomatic participants in general or high risk populations. We also noted that "Asymptomatic high risk populations included those not previously tested, diagnosed or presenting with symptoms known to be related to glaucoma but also included those with a family history of glaucoma, specific racial/ethnic groups, older age, and specific ocular or other medical conditions as defined by included studies (e.g., diabetes)."

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Public comment/ Pfizer	Introduction	Comparing the effectiveness both within and across categories of screening Technologies. While we commend AHRQ for including a broad category of screening technologies, we also encourage evaluation of the different techniques used within each screening technology. The background section currently evaluates tonometry, perimetry, direct ophthalmoscopy, and fundus photography or computerized imaging of the posterior pole. However, within each of these technologies there is a multitude of screening techniques, many of which are constantly evolving. For example, indentation tonometry and applanation tonometry are sub-types of tonometry and have important distinctions. Moreover there are even different types of indentation tonometry, such as Schiotz and Pneumatonometry, and applanation tonometry, such as Non-Contact Tonometry, Tonopen, and Godmann Tonometry.	We included studies of the following ocular examinations (screening tests) conducted alone or in any possible combination (including multi-component simultaneous or sequential testing): • Tonometry (contact and non-contact tonometry) • Perimetry (including short-wavelength, high-pass, motion, flicker perimetry, yellow and blue perimetry) • Direct and indirect ophthalmoscopy • Fundus photography or computerized imaging of the posterior pole (optic disc or retinal nerve fiber layer assessments); Also includes optical coherence tomography (OCT), retinal tomography, scanning laser polarimetry. • Pachymetry (corneal thickness measurement) when used in conjunction with another test to diagnose glaucoma. We excluded studies where pachymetry is used alone. We included studies of the following ocular examinations (screening tests) conducted alone or in any possible combination (including multi-component simultaneous or sequential testing): • Tonometry (contact and non-contact tonometry) • Perimetry (including short-wavelength, high-pass, motion, flicker perimetry, yellow and blue perimetry) • Direct and indirect ophthalmoscopy • Fundus photography or computerized imaging of the posterior pole (optic disc or retinal nerve fiber layer assessments); Also includes optical coherence tomography (OCT), retinal tomography, scanning laser polarimetry. • Pachymetry (corneal thickness measurement) when used in conjunction with another test to diagnose glaucoma. We excluded studies where pachymetry is used alone.

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Public comment/ Pfizer	Introduction	Without incorporating effectiveness data on the type of technique used to administer a screening technology, AHRQ will not be evaluating the full spectrum of OAG screening methods. To that end, we suggest that AHRQ stratify the screening technologies by screening technique in its comparative effectiveness review	We included studies of the following ocular examinations (screening tests) conducted alone or in any possible combination (including multi-component simultaneous or sequential testing): • Tonometry (contact and non-contact tonometry) • Perimetry (including short-wavelength, high-pass, motion, flicker perimetry, yellow and blue perimetry) • Direct and indirect ophthalmoscopy • Fundus photography or computerized imaging of the posterior pole (optic disc or retinal nerve fiber layer assessments); Also includes optical coherence tomography (OCT), retinal tomography, scanning laser polarimetry. • Pachymetry (corneal thickness measurement) when used in conjunction with another test to diagnose glaucoma. We excluded studies where pachymetry is used alone. We included studies of the following ocular examinations (screening tests) conducted alone or in any possible combination (including multi-component simultaneous or sequential testing): • Tonometry (contact and non-contact tonometry) • Perimetry (including short-wavelength, high-pass, motion, flicker perimetry, yellow and blue perimetry) • Direct and indirect ophthalmoscopy • Fundus photography or computerized imaging of the posterior pole (optic disc or retinal nerve fiber layer assessments); Also includes optical coherence tomography (OCT), retinal tomography, scanning laser polarimetry. • Pachymetry (corneal thickness measurement) when used in conjunction with another test to diagnose glaucoma. We excluded studies where pachymetry is used alone.
Public comment/ Pfizer	Introduction	There are a number of variables that also impact the availability effectiveness data that AHRQ should also account for to ensure the conduct of a thorough assessment. These variables include factors such as patient preferences, cost, portability of technique, the screening site, and type of personnel administering the screening techniques. Factors such as these impact whether or not some screening techniques are available for population use, and in particular, for use by certain patient populations. We encourage AHRQ to take these factors into consideration, as they will ultimately impact the availability of evidence for the assessment.	The aim of Key Question 2 was to capture patient reported outcomes including quality of life and patient satisfaction. In terms of setting, we included all settings "Settings for this review included community screenings, non-eye care health provider settings, eye care provider clinical settings (ophthalmologists and optometrists), and telemedicine." We did not consider portability nor did we consider the type of personnel administering the examination. We have edited the report, however, to describe the skill required to operate the device as well as issues related to portability. Questions related to cost were considered outside of the scope of this comparative effectiveness review.

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Public comment/ Pfizer	Introduction	Refining key questions to capture the appropriate role of screening in the treatment paradigm: It is important to recognize that glaucoma screening in and of itself does not directly impact patient outcomes. Key questions 1, 4, and 5 are all currently phrased to assess the direct impact of screening on visual impairment, intraocular pressure, and the progression of optic nerve damage and visual field loss. Given that screening only impacts outcomes such as these following a glaucoma treatment regimen, Public comment/Pfizer encourages AHRQ to reword key questions 1, 4 and 5 to assess whether early detection reduces the risk of developing outcomes rather than directly influencing the development of these outcomes.	The analytic framework and key questions for the screening comparative effectiveness review incorporate the concept of screening in the context of treatment. The appropriate study to address the key questions would include studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Outcomes would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program).
Public comment/ Pfizer	Introduction	Key question 1: "Does early detection through screening of populations identified to be at risk of open-angle glaucoma reduce the risk of future visual impairment?"	Thank you for your suggested edits to the questions. We are, however, unable to make post hoc modifications to the questions that were the focus of the review
Public comment/ Pfizer	Introduction	Key question 2 "To what extent does screening for open-angle glaucoma change patient-reported outcomes?" Screening for OAG does not typically improve patient-reported outcomes (PROs), but may impact a patient's mental health if they are given a false positive	Thank you for your suggested edits to the questions. We are, however, unable to make post hoc modifications to the questions that were the focus of the review
Public comment/ Pfizer	Introduction	Key question 4: "Does early detection through screening of populations identified to be at risk for open angle glaucoma reduce the risk of developing intraocular pressure?"	Thank you for your suggested edits to the questions. We are, however, unable to make post hoc modifications to the questions that were the focus of the review
Public comment/ Pfizer	Introduction	Key question 5: "Does early detection through screening of populations identified to be at risk for open-angle glaucoma reduce the risk of developing optic nerve damage and visual field loss?	Thank you for your suggested edits to the questions. We are, however, unable to make post hoc modifications to the questions that were the focus of the review

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Peer Reviewer #1	Methods	The main objection I have to the methods used in the screening document is that there is a lack of transparency because much of the search strategy relies on a private database by Li for the systematic reviews of screening. This database is not available except by microfiche at the Johns Hopkins University and thus is not available for perusal and use by others. The search strategy by Li does not appear to be documented in the methods, so it is not available for examination and review.	A summary of the Li dissertation is available via Proquest Dissertation and Theses (http://search.proquest.com/dissertations/docview/847571622/1334C033C261C0CD80D). In the summary Dr. Li notes that "We searched PubMed, EMBASE and The Cochrane Library up to September 2009 to identify systematic reviews..." so the manuscripts were identified via searches of public bibliographic databases. The specific search strategy is embargoed at this time as a related manuscript is currently under consideration for publication. It should be noted that the search that we undertook for identifying systematic reviews published in 2009 and beyond was very similar and identified the same systematic reviews for the period January - September 2009 as were identified by Dr. Li.
Peer Reviewer #2	Methods	It is unclear why studies of risk factors, which usually are derived from population-based studies of prevalence were excluded since many times these studies also evaluate issues of importance regarding the key questions on screening. In addition, these studies are done in the true population at risk. The inclusion of these studies may change the results and conclusions. Without a clear justification for why these studies were excluded, this reviewer is very concerned about selection bias in this report.	As our key questions explore the link between screening and treatment of glaucoma, we were interested in identifying studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Outcomes such as visual impairment, field loss would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program). While we agree that population based studies would inform the evidence base, the study investigators would have had to include information on how well the tests identified those with glaucoma (test accuracy) or followed participants for an extended time (at least 1 year) to determine how well they fare after treatment. A suitable comparison group (as described above) would be necessary to assess whether participation in a screening program leads to improved outcomes
Peer Reviewer #2	Methods	Intraocular pressure is included in the diagnosis of glaucoma. This is no longer considered to be part of the diagnosis because intraocular pressure is a risk factor. Justification for including intraocular pressure in the definition of glaucoma should be provided because this is not consistent with the current definition	We considered studies in which the reference standard for confirmed open angle glaucoma was diagnosis by an ophthalmologist using objective assessments. As you know, a comprehensive clinical eye examination would include measurement of intraocular pressure. Examinations would also include assessment of the visual field, assessment of the optic nerve head and or retinal nerve fiber layer, or review of fundus photographs.

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Peer Reviewer #2	Methods	Only 2 of 169 systematic reviews were eligible for inclusion in this report and the majority were excluded because they did not address the key questions. In addition, the full text was obtained for only 13.5% (630/4680) of the primary study titles and abstracts originally identified. Since it is important to read the whole manuscript because abstracts and titles can be misleading, this reviewer is very concerned about selection bias. Was there an attempt to randomly select full text manuscripts that were not recommended to be included by each reviewer so that an estimate of this error could be obtained?	The screening of titles, abstracts, and full text manuscripts was conducted by two reviewers who reviewed the citations independently and had to agree on inclusion or exclusion based on pre-specified criteria. If they were unable to agree, an adjudicator assisted with reaching a consensus. Citations were excluded at the title or abstract stage primarily because they did not address the appropriate population. As to the systematic reviews, the search strategy identified systematic reviews of both treatment and screening, so 149 were excluded because they either addressed a question of treatment or another ocular condition or both. Please see Figure 1A and 1B for a full listing of the reasons for exclusion.
Peer Reviewer #2	Methods	Why were case series of 100 participants or less excluded? When there are very few manuscripts that are eligible, this Reviewer does not understand the justification for excluding these studies (this Reviewer could not find the justification in the report).	Case series are useful for hypothesis generation but may be fraught with selection bias. As a result, we considered case series with less than 100 participants to be at high risk of selection bias and thus excluded these from our evidence summary.
Peer Reviewer #2	Methods	The exclusion criteria included a criteria for excluding tests not commonly used in the diagnosis of glaucoma. It is not clear how "commonly used" was determined. For example, why the HRT II but not the HRT I? The HRT I is the older version and was included in the OHTS study because it was reliable. Thus this Reviewer does not understand the justification for the exclusion of the HRT I (which this reviewer cannot find in the report!).	Although the software is backwards compatible and HRT I images may be converted to the newer format, HRT I is not frequently used in clinical practice as a diagnostic tool (as it has been replaced with newer technology with a larger field of view). We note that the images from the HRT I are often converted to assess longitudinal changes only (to compare to images taken subsequently with HRT II or III).
Peer Reviewer #2	Methods	The data was not abstracted separately from primary studies but was abstracted from reviews directly. This saves on data collection time but adds a potential for error. Parts of the report read as if they are an extension of the Burr HTA report. Although the Burr report is from the UK, this reviewer is concerned that its findings were not investigated and appear to have been accepted without question. This is not a scientifically valid approach to a review and reads as if the authors have done a short-cut, although the search strategies are explicitly stated.	The appendix includes a quality assessment of the Burr 2007 and Hatt 2006 reviews included in this report. Data from 72 primary studies were abstracted separately and the sensitivity, specificity, and other measures of validity may be found in the appendices. Select primary studies were summarized in narrative of the report with a particular emphasis on studies that identified early disease, and/or examined newer and more frequently reported technologies.
Peer Reviewer #3	Methods	The inclusion and exclusion criteria are generally justifiable.	Thank you for your comment

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	HRT (page ES-5, line 53): It is unclear why manuscripts evaluating HRT 1 were excluded. The HRT 1 is backwards compatible with the HRT2/3 so that they results should be generalizable to the HRT2/3 systems that are most frequently in use today.	Although the software is backwards compatible and HRT I images may be converted to the newer format, HRT I is not frequently used in clinical practice as a diagnostic tool (as it has been replaced with newer technology with a larger field of view). We note that the images from the HRT I are often converted to assess longitudinal changes only (to compare to images taken subsequently with HRT II or III).
Peer Reviewer #3	Methods	Were the HRT II and HRT III studies identified by the instrument in which the images were acquired or the software used in the analysis? I assume that the authors were referring to image acquisition and not analysis. It can be challenging to differentiate between the two. The authors should combine results from HRTII/III as many studies probably acquired images using HRTII, but analyzed images with the latest software version HRT III.	The studies were identified by the instrument in which the images were acquired. As we have not verified that all of the HRT II studies analyzed images with HRT III, we have chosen to keep the discussion of these devices separate.
Peer Reviewer #3	Methods	For example, at least one study (reference #39, Badala, #27 *Burgansky-Eliash* and probably many more) listed as HRTIII on page 22 of the report acquired images using HRT2, but analyzed images with the latest HRT3 software (Badala et al "Confocal scanning laser ophthalmoscopy was performed with the Heidelberg Retina Tomograph (HRT) II and data were analyzed with HRT III software (Heidelberg Engineering GmbH, Heidelberg, Germany)." Other authors did not specify which HRT software version was used (e.g. Medeiros #29 and probably many more). The HRTII and HRTIII results should be interchangeable and there is no evidence that I am aware of that indicates that the results of the two instruments should differ.	The studies were identified by the instrument in which the images were acquired. As we have not verified that all of the HRT II studies analyzed images with HRT III, we have chosen to keep the discussion of these devices separate.
Peer Reviewer #3	Methods	GDx (page ES-5, line 54) In addition, more detail is needed on which GDx systems were excluded – specify that GDx instruments other than GDx VCC, or ECC, (i.e. that did not compensate for corneal birefringence of an individual eye) were excluded.	We have revised the text.
Peer Reviewer #3	Methods	I have several questions about how studies were included/excluded.	Answers below

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Peer Reviewer #3	Methods	Not sure what is meant by using “clinical assessment as a reference standard”. From page 5, “the diagnosis should have included a clinical examination with measurement of IOP, assessment of visual field, assessment of the optic nerve head and or RNFL or review of fundus photographs”. However, this criteria seems to have been applied inconsistently to exclude some studies and not others (see comment in Results section “e” of this review). A subjective clinical examination is problematic when it is required to detect glaucoma since reproducibility of the examination is rarely reported. The clinical examination is important to rule out secondary glaucomas and other comorbidities.	We agree with the reviewer and the primary reason for only including studies that incorporated a clinical examination of the subjects was to ensure that any abnormal findings on other tests were indeed due to glaucoma and no other disease.
Peer Reviewer #3	Methods	Exclusion of studies for the reason “infrequently used device” was used to exclude entire studies that compared a device that wasoutside of the scope of this study to one what was included in this study. The authors should consider extracting data on the relevant devices from these articles. a. For example the study “Fortune B et al. “Comparing multifocal VEP and standard automated perirmetry in highrisk Ocular hypertension and early glaucoma” and several others may have relevant data on standard automated perimetry that can be extracted.	As a comparative effectiveness project we attempted to limit our included studies to those that provided information on the relative performance of tests for glaucoma. Some such studies that did not provide such information on two or more tests that met inclusion criteria were therefore excluded.
Peer Reviewer #3	Methods	Are the search strategies explicitly stated and logical? Yes. Search criteria are explicitly stated and logical.	Thank you for your comment
Peer Reviewer #3	Methods	Are the definitions or diagnostic criteria for the outcome measures appropriate? Yes, the outcome measures – sensitivity, specificity and AUROC are appropriate.	Thank you for your comment
Peer Reviewer #3	Methods	Are the statistical methods used appropriate? Due to significant heterogeneity across studies resulting in a large range in the sensitivity, specificity and AUROC values reported, a statistical synthesis of results was not completed.	Thank you for your comment
Peer Reviewer #4	Methods	The search strategies are explicitly stated and logical. The definitions of the outcome measures appropriate. The approach to reviewing the identified potentially eligible studies is standard and appears to have been implemented with fidelity.	Thank you for your comment
Peer Reviewer #4	Methods	The conclusion should state that no links were found between glaucoma screening and improvements ……	NA

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Peer Reviewer #4	Methods	Did the review attempt to assess whether screening tests, if accurate, were feasible for use in the primary care setting? If so, this should be stated.	We did not assess the feasibility of candidate tests in the primary care setting
Peer Reviewer #4	Methods	Was a comparison of the accuracy of different tests for glaucoma a key question? Were any of the key questions directed at assessment of whether there might be individuals at high risk of glaucoma (e.g., blacks) in whom the benefit of screening might be different than in average risk individuals?	Key Question 3 explored the accuracy of candidate tests. We considered for inclusion studies of general and high risk populations
Peer Reviewer #4	Methods	It is not clear why populations not previously tested for glaucoma would be considered to be high risk.	The statement "Asymptomatic high-risk populations included those not previously tested.." was included to emphasize that we were not including studies of persons identified from prior testing as high risk. High risk categories may include specific demographic characteristics such as ethnicity or older age
Peer Reviewer #4	Methods	This is the first description of the interventions (tests) to be considered in the review. The descriptions here should be precise and should be consistent with other sections of the report that describe what tests were considered. For example, later it is made clear that HRT II and HRT III are considered but these tests are not described specifically here.	We have included detailed descriptions of the screening devices in the text of the review.
Peer Reviewer #4	Methods	There appears to be a contradiction between what is stated on line 39 (OCT is described as an included test) and line 51 (OCT 1 and OCT 2 imaging systems are described as excluded).	OCT was an included test, but older technologies not currently used in clinical practice were excluded
Peer Reviewer #4	Methods	On page 10, KQ3 is described as “what is the predictive value of screening tests for open angle glaucoma.” On this page, KQ3 is described in terms of “outcomes”—true positives, true negatives, false positives, and false negatives.” Later in the document, (page 21, line 57) the evidence about the tests is described in terms of accuracy. These should be consistent and/or the reasons for examining sensitivity and specificity rather than predictive value should be stated.	The goal of KQ3 was to identify studies dealing with the predictive value of screenign tests, especially as applied to a screening program. Since virtually all studies report results as sens/spec/ROC, those are the values that dominate the results and discussion.
Peer Reviewer #4	Methods	I don’t understand this sentence: “We considered studies that enrolled healthy volunteers in addition to those with suspected open angle glaucoma but excluded studies of healthy volunteers only.	We excluded studies in which the candidate tests were performed on a sample of healthy volunteers only. We did not exclude studies that enrolled healthy volunteers along with those with suspected glaucoma at the time of screening

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AAO-AGS	Methods	Further, there are a number of variables that also impact the availability effectiveness data that AHRQ should also account for to ensure the conduct of a thorough assessment. These variables include factors such as patient preferences, cost, portability of technique, the screening site, and type of personnel administering the screening techniques. Factors such as these impact whether or not some screening techniques are available for population use, and in particular, for use by certain patient populations. We encourage AHRQ to take these factors into consideration, as they will ultimately impact the availability of evidence for the assessment.	The aim of Key Question 2 was to capture patient reported outcomes including quality of life and patient satisfaction. In terms of setting, we included all settings "Settings for this review included community screenings, non-eye care health provider settings, eye care provider clinical settings, ophthalmologists and optometrists), and telemedicine." We did not consider portability nor did we consider the type of personnel administering the examination. We have edited the report, however, to describe the skill required to operate the device as well as issues related to portability. Questions related to cost were considered outside of the scope of this comparative effectiveness review
Public comment/ Pfizer	Methods	To measure these PROs, we also recommend that AHRQ include a vision-specific mental health scale to evaluate patient-reported quality of life changes before and after screening.	From the methods "We examined at the participants' mean total or relevant item/subscale scores as measured by any validated questionnaire, e.g., National Eye Institute Visual Functioning Questionnaire (NEI-VFQ)…" The NEI-VFQ includes a mental health subscale
Public comment/ Pfizer	Methods	Assessing the impact of delayed detection of glaucoma: We encourage AHRQ to revise key question 6 to assess both the benefits and harms associated with delayed detection of glaucoma. In particular, AHRQ should evaluate the benefit and harms among certain patient populations. Information such as this is useful for patients and providers so they can weigh the benefits and harms against one another when determining the optimal screening technique.	Thank you for your comment. We acknowledge that the inclusion of the benefits of screening would inform the evidence base
Public comment/ Pfizer	Methods	In conclusion, we would like to commend AHRQ for developing these draft key questions and for seeking comment. We look forward to seeing our suggestions incorporated into the final key questions, and we appreciate AHRQ's willingness to partner with healthcare stakeholders, including the life sciences industry, to improve our nation's healthcare. As Pfizer's efforts in this therapeutic area continue, we look forward to further collaboration with the Agency on improving the body of clinical evidence for glaucoma and other important therapeutic areas	Ann's comment: These are not draft key questions - there is some confusion here. Are we sure that we have the correct comments?

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Public comment/ AAO-AGS	Methods	Key Question 1. The definition of visual impairment is visual acuity of 20/70 or less, or visual field of 20 degrees or less. This is end-stage glaucoma. A screening program would have to screen tens of thousands of people to find enough patients who were advanced enough to satisfy the definition of visual impairment and thus to ascertain whether timely intervention would save them from advancing to visual impairment. Consequently, it is an impossible question to answer with applied clinical research. The value of screening must be used to measure a more important and valuable outcome, preventing early visual field loss.	For Key Question 1, we also included visual acuity outcomes (e.g., mean visual acuity or proportion of participants in pre-specified visual acuity categories) as reported in the included studies and as measured with Snellen, or any other valid chart that yields scores that can be converted to Snellen fractions or Logarithm of the Minimum Angle of Resolution values. Had we identified any studies that included visual acuity as an outcome, we would have reported this as well. Outcomes related to changes in visual field would also be captured with Key Question 5.
Public comment/ AAO-AGS	Methods	Key Question 2 presents the problem of finding persons in a screening program who will be followed with regular HRQOL evaluations. This is an impossible question to answer with current existing research.	We acknowledge that we did not identify any studies that addressed this question and suggested that future research improve on the existing evidence base so that there is evidence to determine whether screening impacts patient reported outcomes such as quality of life
Public comment/ AAO-AGS	Methods	Key Question 5 asks whether a screening program results in less visual field and optic nerve damage progression. If that is the desired result, then it is a screening program AND treatment program that must be evaluated in tandem. This would remove the question from a consideration of screening alone, but must include the impact of treatment on early disease.	The analytic framework and key questions for the screening comparative effectiveness review incorporate the concept of screening in the context of treatment. The appropriate study to address the key questions would include studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Outcomes would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program).
Public comment/ AAO-AGS	Methods	Key Question 6: What are the harms associated with screening for open-angle glaucoma? We agree with the document's conclusions that the harms associated with screening are minimal.	Thank you for your comment

Commentator & Affiliation	Section	Comment	Response
Public comment/ AAO-AGS	Methods	Based upon comments concerning the effectiveness of treatment, what would the conclusion be if a screening RCT resulted in a reduced IOP in the screened group? Would that be considered an effective treatment? If one assumes that treatment is effective, the trial would be successful by simply increasing the number of cases found and treatment prescribed. The policy question would be—would the resources devoted to finding cases be offset by the benefit of being able to treat the cases? The authors are understandably reticent to answer the question with a cost-effectiveness approach, so instead they end up with an equivocal answer because they are only looking for a strict definition of visual impairment and quality of life as the definitions.	As to the definitions of the outcomes, in addition to visual impairment, we also included visual acuity outcomes (e.g., mean visual acuity or proportion of participants in pre-specified visual acuity categories) as reported in the included studies and as measured with Snellen, or any other valid chart that yields scores that can be converted to Snellen fractions or Logarithm of the Minimum Angle of Resolution values. Had we identified any studies that included visual acuity as an outcome, we would have reported this as well. Quality of life, as long as a validated instrument was used, would have been reported if identified from existing literature.
Public comment/ AAO-AGS	Methods	The ability to look at all these systems issues is very difficult and resource-intensive in an actual screening program. However, modeling allows you to test these factors and to come up with an optimal screening strategy with calculated costs and benefits for the population	Thank you for your comment
Public comment/ AAO-AGS	Methods	The Scottish health authorities and the Centers for Disease Control and Prevention (CDC) have evaluated these issues in determining the value of glaucoma screening. In Burr et al, the investigators found that mass population screening did not meet British standards for adoption, but that targeted screening of high risk populations would likely be an effective use of societal resources. In the U.S., Rein et al1 (in a CDC funded study) went a step further and determined that an office based strategy for case identification and treatment did meet accepted standards for adoption in most countries (but of course in the U.S., we do not have a clear standard, let alone one based on economic principles).	Thank you for your comment

Commentator & Affiliation	Section	Comment	Response
Public comment/ AAO-AGS	Methods	The key difference between these two reports is that Burr was considering bringing the equipment into the community (i.e., screening in malls, churches and senior centers) and Rein was examining an office-based approach. Thus, it seems that the question of screening in this AHRQ document was examined in a simplistic manner. A study that would examine the question in the manner that the investigators propose would not provide an answer that the health system requires.	As the inclusion criteria for the Burr review, "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."
Public comment/ Mariela Shirley	Methods	analysis does not consider different populations with glaucoma; particularly those with trauma-induced open angle glaucoma. This sub-group may be younger in age and allow for more longitudinal studies regarding the longer term benefits of widespread screening, ongoing screening schedules, and early intervention.	Traumatic glaucoma is outside the scope of this review.
Public comment/ Mariela Shirley	Methods	Need more research on traumatically induced glaucoma secondary to sports-related injury. There needs to be a best practices or policy regarding screening and appropriate intervals for follow up. For example, in younger populations there may be as much as a 2 yr interval between visits to ophthalmologists. Also, in individuals with a family history of glaucoma, what are the recommendations regarding screening and early intervention (and at what point re IOP levels)?	Thank you for your suggestions of other potential high-risk populations. Our report presents a review of the evidence and does not make recommendations.
Public comment/ Mariela Shirley	Methods	Glaucoma Professional Societies such as the Optometric Glaucoma Society should comment on the paper regarding this topic and/or Optometric research should be included in the study/report.	Optometric journals that are indexed in MEDLINE, EMBASE or LILACS were searched for this comparative effectiveness review. Optometric journals or conference proceedings (Journal of the American Optometric Association, Optometry and Vision Science, American Academy of Optometry annual conference proceedings) that are included in the Cochrane CENTRAL register of trials would have also been searched for this review
Public comment/ Beth Kneib	Methods	Should include optometric journals and glaucoma society expert research.	Optometric journals that are indexed in MEDLINE, EMBASE or LILACS were searched for this comparative effectiveness review. Optometric journals or conference proceedings (Journal of the American Optometric Association, Optometry and Vision Science, American Academy of Optometry annual conference proceedings) that are included in the Cochrane CENTRAL register of trials would have also been searched for this review

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	KQ1. Consider the EMGT as a RCT evaluating the outcomes of a screening program. Leske MC, Heijl A; Hyman L et al. Early Manifest Glaucoma Trial Design and Baseline Data. Ophthalmology 1999;106:2144–2153 “Early manifest glaucoma is asymptomatic, and patients usually are identified and immediately treated at later stages of the disease. Therefore, EMGT required special efforts to recruit previously untreated glaucoma patients who were detected in four ways: 1. At a large-scale population-based screening of specific age cohorts. 2. Among patients followed from the screening. 3. Among patients followed at the clinical centers. 4. Among patients referred from eye specialists in clinical practice	Although EMGT identified participants from a screening program who were randomized to treatment or careful follow-up, there was no comparable group of participants who were identified via case finding or referral only (or identified via a different type of screening-based program)and were diagnosed and treated for glaucoma. This specific comparison group is required to address the key questions of interest for this comparative effectiveness review.
Peer Reviewer #1	Results	The Los Angeles Latino Eye Study could also be considered as a population screening program study. A census of all residential households in 6 census tracts in La Puente California was completed to identify individuals eligible to be included in the study. The study found lower vision-related QOL in those with glaucoma, including those previously unaware that they had glaucoma but identified through the study. McKean-Cowdin R; Wang Y; Wu J et al. Impact of Visual Field Loss on Health-Related Quality of Life in Glaucoma. The Los Angeles Latino Eye Study. Ophthalmology 2008; 115:941-8.	We have included a discussion of the Los Angeles Latino Eye Study for the key question addressing the diagnostic accuracy of candidate screening tests as a manuscript was published in January 2011 addressing this question.
Peer Reviewer #1	Results	It would be important to consider screening in settings other than the general population. Glaucoma detection may be most effective when targeted at populations at high risk. Detection of glaucoma through comprehensive eye evaluations may be more useful and cost-effective when it is targeted at populations at high risk for glaucoma, such as older adults, those with a family history of glaucoma, Hispanics and African Americans. In these populations, where glaucoma prevalence is 4% to 6%, positive predictive value of glaucoma screening is 49% or higher. One article evaluated a protocol for detection of glaucoma in African Americans over 40 years old: Vistamehr S; Shelsta HN, Palmisano PC et al. Glaucoma Screening in a High-risk Population. J Glaucoma 2006; 15:534-40	We considered for inclusion studies of general and high risk populations

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	This Reviewer has a similar issue with KQ2 which requires a validated vision-specific quality of life questionnaire. By not including studies on risk factors, the authors have eliminated the majority of the studies that would investigate quality of life with a validated instrument such as the NEI-VFQ. In addition, the NEI-VFQ has 25 or 51 questions and can take 30 minutes or more to complete, which would be hardly appropriate for a true screening study. Thus, this reviewer does not know why a non-vision specific instrument could be used such as the SF-36.	Studies that examine risk factors only would not have adequately addressed Key Question 2. The appropriate study to address Key Question 2 would include studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Quality of life and other patient reported outcomes would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program).
Peer Reviewer #2	Results	In addition, for KQ1, KQ2, KQ4, KQ5 and KQ6,there appears to be a requirement for follow-up since all of these outcomes occur over a specified period of time. For example, in KQ5 progressive optic nerve damage and progressive visual field loss require at least 6 months to confirm that there has been progression. Or are the authors trying to state that progression has been inferred.	In the methods we stated that "We assessed outcomes for Key Questions 1, 2, 4, and 5 at one year of follow-up and at annual intervals thereafter."
Peer Reviewer #2	Results	For KQ6, this Reviewer is very confused about how a person could get endophthalmitis from a screening since none of the screening tests are designed to create an incision in the eye at this time. Why not include the occurrence of acute angle closure attacks after dilation as an example of a harm? If population-based studies were included in this review, the authors could find information about the occurrence of this harm.	We noted that we planned to include other harms as reported in included studies so the occurrence of acute angle closure attacks would have been reported if identified from the literature. For questions of harm, observational study designs (e.g., cohort and case control studies) are appropriate for rare harms as well as those that would possibly occur over time. These study designs were included for Key Question 6
Peer Reviewer #2	Results	The investigators did not obtain data that was relevant but was not reported in the primary studies that they did review. In meta-analyses and reviews, it is the standard practice for investigators to contact the authors of studies in an attempt to get not reported (NR) data; this was not done and means that the results are less helpful. In addition, this limits the amount of relevant information that can be gleaned from this report because of the missing data.	We acknowledge that we were unable to contact investigators, but are unsure of what relevant data are perceived as missing for specific key questions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	In addition, the reviewers did not include the population-based studies. It would have been very helpful to this Reviewer to have had more information on the studies that were excluded because they did not have information on the KQs. The tables on the studies that were included are helpful but this Reviewer would like to know more about the studies that were excluded because this was the majority of the studies.	A table of excluded studies (with reasons for exclusion) is included with the appendices
Peer Reviewer #3	Results	Is the amount of detail presented in the results section appropriate? Yes, level of detail is generally appropriate	Thank you for your comment
Peer Reviewer #3	Results	Page ES-11: should report separately the number of GDx VCC and GDx ECC included – and summarize separately.	In the results section of the Executive Summary we note that "Twenty-four studies included an investigation of GDx with variable corneal compensation…" "Three studies examined the GDx with enhanced corneal compensation." These devices are summarized separately
Peer Reviewer #3	Results	I would have like to see an attempt to analyze studies stratified by severity of disease. I know this is not easy to do since the reporting of severity varies by study. However, most studies do provide some information on disease severity – usually the mean of the visual field MD.	Details about disease severity are included in the tables. We are limited in ability to conduct synthesis due to heterogeneity
Peer Reviewer #3	Results	Perhaps 2 groups: studies with a mean visual field MD > (better than) -5.0 dB compared to studies with a mean visual field MD worse than -5.0dB. The heterogeneity of results may be largely explained by the severity of glaucoma cases included in the studies. If heterogeneity is reduced by categorizing studies by severity, statistical analysis may be possible.	Details about disease severity are included in the tables. We are limited in ability to conduct synthesis due to heterogeneity. We will consider this further.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Are the characteristics of the studies clearly described? The terminology used in the "population category (IOP)" column of the "Study Design and Population Characteristics" table which begins on page 91 is inconsistent. The terminology "glaucoma", "early glaucoma","moderate glaucoma" needs consistent application – and needs the addition of "advanced glaucoma". From the mean deviation column, some studies were clearly "early glaucoma", but the table does not indicate that (e.g. #30 Fang MD -2.28 db; 1022, Hong, MD=-1.98 dB). Other studies are listed as "early glaucoma" (e.g. #1473 Kanamori MD-3.55) with MDs similar to others that are just listed as "glaucoma" (e.g.#1621 Leung MD - -0.61 is this a typo?, #1233 Sample, MD=-2.89 db).	We revised the text. In general, we took the definition of population as provided by the study
Peer Reviewer #3	Results	Terminology sometimes is "POAG" or "glaucoma patients" instead of glaucoma. Standard definitions should be used that do not rely on the terminology used in the manuscript.	This should now be corrected in text
Peer Reviewer #3	Results	The numbering of the 72 studies in the tables in the Appendices is confusing as the numbers do not correspond to the reference list (page 26+).	The tables were corrected.
Peer Reviewer #3	Results	The severity of glaucoma included in the study (as described in "bi" above, early glaucoma, moderate glaucoma etc), should be carried over to the "Outcomes Table" which begins on Page 121 – this will help the reader evaluate the results.	The tables were corrected.
Peer Reviewer #3	Results	Recommend that information on whether the study required visual field damage, optic disc damage or both should be included in the Appendix "Outcomes Table" – perhaps as a footnote to provide the reader with more complete information while assessing the results. Studies that defined glaucoma using visual fields and evaluating the diagnostic accuracy of visual function may be overstating the results. Once again – the problem of no gold standard / reference standard can lead to biased results.	The tables were corrected
Peer Reviewer #3	Results	Are the key messages explicit and applicable? Yes. Messages are explicit – but I believe some analysis by severity of disease may be warranted. (see above comments in this section)	Thank you for your suggestions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Are figures, tables and appendices adequate and descriptive? In general tables and appendices are adequate – a few suggestions to improve readability:	Thank you for your comment.
Peer Reviewer #3	Results	Table 1: Indicate that these 72 studies were those that were not already included in the Burr systematic review.	We edited the results as follows "We included 72 primary studies addressing the diagnostic accuracy of candidate screening tests for the detection of OAG that were not included in the Burr 2007 systematic review (Key Question 3 - Evidence Tables 3 to 7 in Appendix C). (See Figure 2)."
Peer Reviewer #3	Results	Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? Studies using the HRT1 or HRT classic should have been included as the results should be generalizable to HRT2/3 results.	Although the software is backwards compatible and HRT I images may be converted to the newer format, HRT I is not frequently used in clinical practice as a diagnostic tool (as it has been replaced with newer technology with a larger field of view). We note that the images from the HRT I are often converted to assess longitudinal changes only (to compare to images taken subsequently with HRT II or III).
Peer Reviewer #3	Results	I did a quick spot check of a handful of excluded studies and found several studies that I thought should be included: (Caveat: I acknowledge that I am not familiar with all the criteria used to include/exclude studies – but want to bring these to your attention)	Thank you for your comment.
Peer Reviewer #3	Results	It is unclear whether some criteria were applied consistently – specifically the issue of “use of clinical assessment as a reference standard”.	This was corrected and reference standard was defined based on 5 criteria (IOP, visual field, optic nerve assessment-disc photos and clinical exam
Peer Reviewer #3	Results	113(2) Girkin et al. “Comparison of Moorfields classification using CSLO and subjective optic disc classification in detecting glaucoma in blacks and whites” was excluded because it did “not use a clinical assessment as a reference standard”; visual field loss was the criteria applied and a clinical exam was required for all participants. I believe this study should be included.	For inclusion criteria, the studies had to have clinical assessment AND any of the other parameters. The diagnosis had to have included a clinical examination with measurement of intraocular pressure, assessment of visual field, assessment of the optic nerve head and/or retinal nerve fiber layer, or review of fundus disc photographs. The studies mentioned had just one parameter without clinical assessment.
Peer Reviewer #3	Results	I may be interpreting this criteria incorrectly, but there are several other appropriately included manuscripts that also did not include a clinical assessment as a reference standard including: 729 (56) Nouri-Mahdavi, K 2008 seemed to use early glaucoma by disc and early glaucoma by visual field as criteria. 30: Medeiros et al used visual field damage for defining glaucoma.	For inclusion criteria, the studies had to have clinical assessment AND any of the other parameters. The diagnosis had to have included a clinical examination with measurement of intraocular pressure, assessment of visual field, assessment of the optic nerve head and/or retinal nerve fiber layer, or review of fundus disc photographs. The studies mentioned had just one parameter without clinical assessment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	I believe all the abovementioned studies (and perhaps others) should be included. It should be noted that some investigators advocate not using functional features in the definition of glaucoma when evaluating results of functional tests and vice versa to avoid overstating the diagnostic accuracy of the test under evaluation. Better description of this criteria would help to clarlify how this criteria was applied.	For inclusion criteria, the studies had to have clinical assessment AND any of the other parameters. The diagnosis had to have included a clinical examination with measurement of intraocular pressure, assessment of visual field, assessment of the optic nerve head and/or retinal nerve fiber layer, or review of fundus disc photographs. The studies mentioned had just one parameter without clinical assessment.
Peer Reviewer #3	Results	Not sure why "Testing in house scoring system" was a reason for excluding: "Rao et al. Comparison of the diagnostic capability of the Heidelberg Retina Tomographs 2 and 3 for glaucoma in the Indian population". Data was reported in the abstract for standard commercially available parameters using the standard normative database in addition to the commercially available Indian normative database.	For inclusion criteria, the studies had to have clinical assessment AND any of the other parameters. The diagnosis had to have included a clinical examination with measurement of intraocular pressure, assessment of visual field, assessment of the optic nerve head and/or retinal nerve fiber layer, or review of fundus disc photographs. This study mentioned had just one parameter without clinical assessment.
Peer Reviewer #4	Results	The amount of detail presented in the results section seems appropriate.	Thank you for your comment.
Peer Reviewer #4	Results	The characteristics of the studies are described adequately in the accompanying tables and the amount of detail in the text of the report seems appropriate.	Thank you for your comment.
Peer Reviewer #4	Results	The figures, tables and appendices are adequate and descriptive.	Thank you for your comment.
Peer Reviewer #4	Results	I am not aware of any studies that ought to have been included and the included studies appear to meet the stated eligibility criteria.	Thank you for your comment.
Peer Reviewer #6	Results	Given that there is no evidence for many of the questions the most emphasis should be on how best to graphically display the findings from the diagnostic accuracy studies. Perhaps some grid tables or scatter figures might allow one to see the comparisons better.	Although we chose not to include scatter figures, we have included summary tables for each device with information regarding the population(s) studied, devices compared, and reference standard.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion	Regarding the conclusion, it is misleading to state on page 6 line 49 that "we did not find direct or indirect links between glaucoma screening and visual field loss, etc". Because there were no English studies found for 5 of the 6 key questions, it would be better to reflect this lack of information in the Conclusion and to state that there were no English studies identified for 5 of the 6 key questions. As the current conclusion is written, it is too strong and does not present the true uncertainty of the finding. In a scientific review it is very misleading when the uncertainty of the findings is not addressed in the conclusions. In addition, the authors should address the limitations of this current report and how their approach could have biased the findings. The report is written as if it is has more validity and accuracy than it does.	We have edited the discussion to note that the decision to exclude non-English literature as a limitation of our findings.
Peer Reviewer #3	Discussion	Are the implications of the major findings clearly stated? Generally yes – but more discussion on the sources of heterogeneity should be included. Does the variation in severity of disease explain much of the heterogeneity of results?	We have edited the discussion to note that the decision to exclude non-English literature as a limitation of our findings
Peer Reviewer #3	Discussion	Page 14 lines 29-31: What does the following summary statement need for more heterogeneity refer to? “The lack of a definitive diagnostic reference standard for glaucoma and the need for more heterogeneity in the design and conduct of diagnostic test accuracy studies, prevents a coherent synthesis of data and therefore limits conclusive statements regarding these tests.” This contradicts the statement in the Conclusion on pages 22-23 “Two significant barriers that remain in terms of identifying and characterizing potential glaucoma screening tests are the lack of a definitive diagnostic reference standard for glaucoma and the heterogeneity in the design of the studies. Because of these, the ranges of sensitivities, specificities, and areas under the ROC curve are large and prevent a coherent synthesis.” Some editing is required here.	We have edited the statement as follows ""The lack of a definitive diagnostic reference standard for glaucoma and the need for more homogeneity in the design and conduct of diagnostic test accuracy studies, prevents a coherent synthesis of data and therefore limits conclusive statements regarding these tests.”
Peer Reviewer #3	Discussion	Are the limitations of the review/studies described adequately? Most limitations are mentioned.	Thank you for your comment

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion	In the discussion, did the investigators omit any important literature? Three studies are cited in the discussion. Suggest including some general literature on glaucoma screening in the introduction and/or discussion–which may be useful to the readers. 1. Healey, PR; Screening for Glaucoma In: Shaarway T, Sherwood MB, Hitchings RA, Crowston JG (eds). Glaucoma Medical Diagnosis and Therapy Volume One. Saunders. 2009 pp. 15-23. 2. World Glaucoma Association Glaucoma Screening: Consensus Series 5. edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis 2008. Hardbound. ISBN-10: 90 62992 188. ISBN-13:978-90-6299-218-8 Kugler Publications. The authors may want to include mention of this 2008 consensus document on glaucoma screening developed by the World Glaucoma Association. Although not entirely evidence-based it provides important background information on the issue.	We have revised the text. Thank you for the suggested references
Peer Reviewer #4	Discussion	The implications of the major findings seem to be that there is no evidence in support of the use of any test to screen for glaucoma because the positive and negative predictive values of the tests being considered to be used for screening are not known and may be low. The discussion could point out that the evidence suggests that screening for glaucoma does not now meet one of standards used widely to decide whether to screen (page 11, lines 29-30)--3) there is an accurate test that detects the condition during the asymptomatic or early clinical stage; The section on future research seems overly prescriptive. It is not clear that a matched study is the only or the best way to gather the kind of information that would permit one to decide what the predictive value is of any test potentially useful for screening in an asymptomatic population at risk of glaucoma.	Thank you for your comment
Peer Reviewer #4	Discussion	It would seem that the most critical research need is for studies that evaluate the predictive value of tests being considered for use in screening in populations that are being considered for screening. The validity of this type of research as information to inform decisions about screening is critically dependent on having a gold-standard for the diagnosis of glaucoma.	We have included the suggestion of well-designed studies assessing predictive value. These studies should include participants that one would encounter in a screening setting.

Commentator & Affiliation	Section	Comment	Response
Public comment/ AAO-AGS	Discussion	While the questions of screening and treatment are treated separately, they are highly related. From a health system perspective, we should not screen for a condition for which we have no treatment. If there is effective treatment, then screening should be considered in the context of the benefit of treatment.	The analytic framework and key questions for the screening comparative effectiveness review incorporate the concept of screening in the context of treatment. The appropriate study to address the key questions would include studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Outcomes would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program).
Peer Reviewer #2	Future Research Needs	This Reviewer finds the future research section rather vague. For example, one of the 2 reports on systemic reviews that was included in this report was a Cochrane review that only looked at Randomized Controlled Trials (RCTs), which is an extremely expensive study design for a disease of low prevalence in the general population. Because there were no RCTs of screening versus no screening, this Cochrane report by Hatt could draw no conclusions. It is thus not surprising that there still are no conclusions because a RCT on screening has not been done. A RCT on screening versus no screening should be recommended as future research. This should be written as a specific suggestion.	We have included the suggestion of a randomized controlled trial in the future research section
Peer Reviewer #2	Future Research Needs	In the future research section visual fields and optic nerve head appearance are described as intermediate outcomes but do the authors mean that visual fields and optic nerves should be followed for progression? If yes, what would be the appropriate time period? 6 months? 10 years? The final outcomes of visual impairment and patient-reported outcomes could be determined at one time point unless the authors are recommending long-term follow-up. This should be clarified.	In our inclusion criteria, we outlined a minimum of one year for the assessment of outcomes. We have clarified this in the future research section

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Future Research Needs	The request for a standard diagnosis does not add very much to the future research section, because there already is a standard diagnosis that does not include intraocular pressure but does include both visual field and optic nerve head changes (see Blue Mountains Study or LALES) but since these epidemiological studies appear to have been excluded from this review, it is not surprising that the authors ask for a standard diagnosis. The ophthalmic epidemiologists try to present their data so that the information from one study can be applied to another (BES, BMS, LALES, Beaver Dam). Of course, trying to mandate that everyone uses the same diagnosis is very difficult because of free will so the best approach is to ask all investigators to provide the data used for their classifications, which may then require re-classification so that there is consistency in meta-analyses or reviews. To do this, the authors would need to call the study investigators so that they can minimize missing data or not reported data.	Thank you for your comment
Peer Reviewer #3	Future Research Needs	Is the future research section clear and easily translated into new research? Yes, this section is clearly written.	Thank you for your comment
Peer Reviewer #2	Applicability	The lack of a scientific and unbiased approach limits the clinical meaningfulness of this report. Although the report is well structured and organized, the conclusions cannot be used to inform policy and/or practice decisions because there were no studies identified for 5 of the 6 KQs.	Thank you for your comment
Peer Reviewer #3	Applicability	Is the report well structured and organized? In general, the report is well structured and organized.	Thank you for your comment
Peer Reviewer #3	Applicability	Are the main points clearly presented? Yes the main points are clearly presented through the key questions, summaries etc.	Thank you for your comment
Peer Reviewer #3	Applicability	Can the conclusions be used to inform policy and/or practice decisions? Yes, unfortunately the literature is insufficient in many areas to address the issues critical to identify how best to screen for glaucoma.	Thank you for your comment
Peer Reviewer #4	Applicability	The Executive Summary and body of the report are virtually identical in many places and not much different in length. This probably is because the report format is defined rigidly, but the redundancy makes the report more overwhelming than it might need to be.	The EPC feels this is a question for AHRQ

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Applicability	See comments above. The conclusions could be a bit more hard-hitting. The evidence reviewed here seems to show that there is no evidence to support screening for glaucoma using currently available tests because the ability tests being considered for use in screening in the asymptomatic population to predict who does and does not have glaucoma has not been established.	Thank you for your comment
Peer Reviewer #1	General Comments	Early Visual Field Defects Impact Patients Quality of Life. This doesn't consider the significant society costs and burdens of missing the identification of patients with glaucoma. It may be impossible to design and fund a study that is the focus of this report: directly linking the improvement of visual acuity and patient-reported outcomes through a randomized controlled trial because one group would need to be screened and treated if needed and followed for a long time, 10+	Thank you for your comment
Peer Reviewer #1	General Comments	First, the investigators of the NIH funded Los Angeles Latino Eye Study (LALES) have demonstrated that visual field loss in even one eye (with multivariate analyses) has a clinically significant decrement in patient reported visual functioning (on the standard National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) instrument) at – 4 dB of visual field loss and that subsequent loss results in a linear decrease in VFQ scores	We are aware of cross-sectional studies examining related issues, such as vision loss and visual functioning. We identified no studies that addressed the questions in our review, except for the question addressing diagnostic accuracy (KQ3). We have included a discussion of the Los Angeles Latino Eye Study for the key question addressing the diagnostic accuracy of candidate screening tests as a manuscript was published in January 2011 addressing this question.
Peer Reviewer #1	General Comments	At the University of Alabama at Birmingham they showed that even when the worse eye has a minimal level of field loss (4 or less on the AGIS scoring system), significant decrements of quality of life exist compared to published population norms, supporting the findings of the LALES study. Thus, the presence of early visual field loss in even one eye is associated with a measurable impact on patient quality of life.	We are aware of cross-sectional studies examining related issues, such as vision loss and visual functioning. We identified no studies that addressed the questions in our review, except for the question addressing diagnostic accuracy (KQ3).
Peer Reviewer #1	General Comments	General health, is diminished in older patients generally. Key areas of visual functioning decrement compared to age and general health adjusted population normals from the initial reference group in the development of the NEI-VFQ (Mangione CM, Lee PP, Pitts J, et al. Psychometric Properties of the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116:1496-1504)	A summary of the benefits of regular eye examinations and the relationship to quality of life was considered outside of the scope of this comparative effectiveness review

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	Gutierrez et al demonstrated that vision-related functioning begins to decline with early visual field loss in a linear manner. While there are several different grading schemes available to detect visual field loss worsening, what is consistent is that worse visual field performance is associated with worse visual functioning regardless of the system used.	We are aware of cross-sectional studies examining related issues, such as vision loss and visual functioning. We identified no studies that addressed the questions in our review, except for the question addressing diagnostic accuracy (KQ3).
Peer Reviewer #1	General Comments	Significant Visual Field Loss Exists at the Time of Detection, Particularly in the Absence of Screening. Published data that suggests that the absence of detection of glaucoma from means other than typical patient self-presentation results in significant levels of visual impairment at the time of detection "Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. Ophthalmology 1998; 105: 2099-104."	We are aware of cross-sectional studies examining related issues, such as the study mentioned. We identified no studies that addressed the questions in our review, except for the question addressing diagnostic accuracy (KQ3).
Peer Reviewer #1	General Comments	Treatment of glaucoma with Early visual field defect is CostEffective: Not only can visual impairment and blindness due to glaucoma be virtually eliminated with early, appropriate care, but that starting treatment at – 4 dB is also highly cost-effective	Discussion of the cost effectiveness of treatment of glaucoma was considered outside of the scope of this comparative effectiveness review
Peer Reviewer #1	General Comments	Additional Benefits of Screening for Glaucoma: cataract, age-related macular degeneration, and diabetic eye disease. Papers have clearly demonstrated that treatment of the first two conditions are highly cost-effective	Discussion of the cost effectiveness of treatment of other ocular conditions identified via screening (for glaucoma or other conditions) was considered outside of the scope of this comparative effectiveness review
Peer Reviewer #1	General Comments	Need for Increased Levels of Eye Examination in the Elderly: Evidencevii suggests that vision loss in the elderly frequently goes undiagnosed and is associated with falls, fractures, vehicular accidents, and other conditions that are devastating to the individual and extremely costly both to the health care system and to society. Yet, we also now know that we have serious gaps in longitudinal patterns of care in the United States for those aged 65 and older	A summary of the evidence related to vision loss in the elderly and the frequency of eye examinations in this population was considered outside of the scope of this comparative effectiveness review

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	Demonstrated Benefits of Regular Eye Exams on Patient Quality of Life Various economic evaluations of the costs and benefits of glaucoma screening have already concluded that glaucoma screening can be cost-effective, given the costs of treatment of more severe glaucoma cases and the disability of glaucoma-related blindness: Tuck MW, Crick RP. The cost-effectiveness of various modes of screening for primary open-angle glaucoma. Ophthalmic Epidemiology 1997; 4:3-17	A summary of the benefits of regular eye examinations and the relationship to quality of life was considered outside of the scope of this comparative effectiveness review
Peer Reviewer #1	General Comments	In summary, there are benefits and value to screening for glaucoma in high-risk populations; 1) There is a clinically meaningful decrement in visual function and vision-related quality of life for patients with early / minimal unilateral visual field loss (fellow eye normal)2) Relying on patient self-presentation for care as opposed to periodic eye provider assessments to detect glaucoma results in patients having significant visual field loss well in excess of a – 4 dB threshold when detected 3) Treatment of glaucoma starting at – 4 dB is highly cost-effective	Thank you for your comments regarding this comparative effectiveness review. No additional response will be included here as we have addressed these comments in prior responses
Peer Reviewer #2	General Comments	The report is not clinically meaningful because the conclusion overstates the findings (see below) and because of a potential selection bias in which manuscripts were included in this report. As the current conclusion is written on page 6, it is too strong and does not present the true uncertainty of the findings. In a scientific review it is very misleading when the uncertainty of the findings is not addressed in the conclusions.	We've responded to the specific comments referenced here.
Peer Reviewer #2	General Comments	It is debatable whether the key questions are appropriate since many of the studies were excluded because they did not address the key questions. This could be because the investigators of these studies did not specifically mention a key component of the question (for example visual impairment in Key Question 1)	We understand that all outcomes discussed in a manuscript are not always included in the title or abstract. The literature search strategies were not designed to exclude studies if terms related to the outcomes of the review were not included in the title or abstract (see Chapter 6, section 6.4.2 in the Cochrane Handbook). During our screening of titles and abstracts, citations were not excluded based on outcomes (such as visual impairment). The inclusion of outcomes of interest were assessed at the full text stage

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Peer Reviewer #2	General Comments	Because this report relies on prior systematic reviews and does not include reviews of the primary data or population-based prevalence studies, all of the biases of those prior reviews are present in this report	Where possible, we did not duplicate effort but instead systematically identified and summarized high-quality systematic reviews. Please see Whitlock et al. (PMID 18490690) and specific AHRQ-EPC guidance on this practice (PMID: 21433402). We have revised text to clarify the summary of existing systematic reviews in relation to summaries of individual studies. We assessed the quality of the systematic reviews and set minimum quality criteria for inclusion in the review based on the review inclusion criteria, number and type of bibliographic databases searched, assessments of risk of bias, and analysis methods.
Peer Reviewer #4	General Comments	The target population for this report is likely to be primary care physicians, optometrists and opticians, and the public and policy-makers interested in screening for eye disease and prevention of visual loss and blindness. The target audience may not have a deep understanding of the many tests that are available as possible tests to be used to screen for glaucoma. For this reason, it would be useful to have added, perhaps as an appendix, a fairly detailed description of each of the technologies that are considered to be potentially useful to screen for glaucoma at this time, how they work to detect glaucoma, and how suitable they are for use in screening by primary care physicians.	We have included detailed descriptions of the screening devices in the text of the review.
Peer Reviewer #4	General Comments	The report should identify tests that, if used for screening, would likely involve a specially trained individual.	In the descriptions of the devices, we include discussion of the skill level required to operate the device and interpret the findings
Peer Reviewer #4	General Comments	Clearly the authors of the report know the definitions of sensitivity, specificity, positive predictive value, and negative predictive value. The authors also know that the positive and negative predictive values (and false and true positives and negatives) for a test are affected by the prevalence of the disease in the population studied and that these predictive values will be lower in a screening population than in patients with a suspicion of disease or with symptoms.	We acknowledge that the inclusion of studies that have included participants with known or suspected glaucoma will result in potential overestimates of the predictive value of the tests under examination

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Peer Reviewer #4	General Comments	Both in the ES and the body of the report, there is very little description of the limitations in what can be gleaned about the accuracy of a test used as a screening test for glaucoma based on literature that has evaluated the tests using study designs that compare patients with glaucoma or people with a suspicion of having glaucoma compared with “healthy people.” This fact will be clear to “experts” but readers of the report are not all experts.	In the discussion we note the following "Many of the diagnostic studies include healthy volunteers as well as those known to have glaucoma at the time of screening. Including participants who are not representative of those one reasonably expects to encounter in a screening setting may lead to biased estimates of diagnostic performance and limit the generalizability of findings. "
Peer Reviewer #4	General Comments	My own reading of the exhaustive review of the literature is that there are no studies that have evaluated directly the predictive value of any of the tests in an asymptomatic screening population. If true, the report needs to more clearly state that the extant literature evaluating the performance characteristics of the tests being considered for use to screen for glaucoma in asymptomatic people provides no information on the positive and negative predictive value of the tests in the screening situation. It should then go on to state that studies of the tests being considered for screening, when used to diagnose glaucoma, yield estimates of sensitivity and specificity and accuracy that are highly variable and that no single test emerges as better than any other in diagnosis of glaucoma.	The Los Angeles Latino Eye Study (LALES) screened a population-based sample of Latinos who were 40 years or older and lived in La Puente, California. The study investigators published a summary of the accuracy of candidate tests in January 2011. A discussion of LALES has been included in this review. We will reemphasize in the discussion, as discussed in the body of the report (Burr 2007), that "that given the 'impr+H26ecision in 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.'"
Peer Reviewer #6	General Comments	Very detailed and clearly written. I agree with the study, population intervention and outcome inclusion/exclusion criteria. The conclusions appear to be supported by the evidence. In particular the group did a good job walking the reader through the various screening tests and summarizing findings. For the presentation (and possibly this report) it would be useful to somehow create a figure/scatter diagram that graphically represents the different tests and their sensitivity/specificity. In particular focusing on tests most likely to be available to primary care providers (I assume that photography is not widely available	While we agree that a figure of this type would be an appropriate way to display the sensitivity and specificities of the candidate tests, we chose not to include such a display in the report as among the included studies discussed in this review, each device/test may include several estimates of sensitivity/specificity depending on the parameters reported, and the reader would be unable to effectively glean much from a display under these circumstances. This would require several displays for each device (by parameter reported) and each figure may include only one study.
Public comment/ AAO-AGS	General Comments	The AHRQ review focused on the technical aspects of glaucoma screening and overlooks the significant burden that untreated glaucoma and associated blindness has on individuals. This includes the economic, social and functional impacts on elderly patients as well as on society in aggregate	Discussion of the burden of untreated glaucoma was considered outside of the scope of this comparative effectiveness review

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Public comment/ AAO-AGS	General Comments	The report did not include studies that examined the value of detecting early disease as compared with late stage disease where the outcomes are worse. This would under represent the value of screening	We included studies that examined the detection of early disease
Public comment/ AAO-AGS	General Comments	Glaucoma specialists agree that population screening for glaucoma without targeting high-risk groups is not useful. However, identifying or incentivizing high risk groups to have a comprehensive eye examination as a "screening" will have higher yield. Moreover, the fact that there are high-risk populations that are appropriate targets for screening is an essential issue which was not addressed	General and high risk population screening studies were considered for inclusion in this comparative effectiveness review
Public comment/ AAO-AGS	General Comments	The report failed to ask an important question: would the resources devoted to detecting cases be offset by the benefit of being able to treat the affected individuals at an early stage of disease?	Discussion of this question was considered outside of the scope of this comparative effectiveness review
Public comment/ AAO-AGS	General Comments	Finally, the report did not include consideration of the importance of an effective treatment administered early in the disease course. From a health system perspective, we agree that screening for a condition for which we have no treatment is unreasonable. If there is effective treatment, then screening should be considered in the context of the benefit of treatment. The report on treatment shows that there are effective treatments, so screening should be an aim of health care delivery.	The analytic framework and key questions for the screening comparative effectiveness review incorporate the concept of screening in the context of treatment. The appropriate study to address the key questions for the screening review would include studies of screened versus non screened populations (or screened via one method versus another method) who then go on to treatment (if diagnosed with open angle glaucoma). Outcomes would be assessed and compared among those who were identified via a screening based program versus those identified by other means (e.g., opportunistic case finding, referral, and different screening based program).

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Public comment/ AAO-AGS	General Comments	Visual Impairment Carries a Significant Emotional Impact. It has been noted that more than 70% of individuals fear blindness. Fear of blindness is viewed as worse than being deaf, having to use a wheelchair, or losing a limb (Statistics on Visual Impairment, 2002). Another survey found that only cancer and heart disease are feared more than blindness (Glaucoma Research Foundation). Finally, it should be noted that patients with severe visual loss (> 20/200) would trade 39% of their remaining years for permanent normal vision. This trade-off is similar to patients with severe angina and severe stroke (Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss: A time tradeoff utility analysis comparison with medical health states. Ophthalmology 2003; 110:1076-1081).	Thank you for your comment
Public comment/ AAO-AGS	General Comments	Visual Impairment Carries a Serious Functional Impact on Elderly Patients. Glaucoma has increased prevalence in the aged, and thus its impact on this group of the elderly should be emphasized. Visual impairment is one of the four most significant contributors to loss of independence among older individuals (Alliance for Aging AAO-AGS on Screening for Glaucoma AHRQ Review 10/12/2011 4 Research, Independence for Older Americans: An Investment for Our Nation's Future, 1999).	Thank you for your comment
Public comment/ AAO-AGS	General Comments	Visual impairment also contributes to driving accidents (Keltner JL, Johnson CA. Ophthalmology, 1980; 87:785-792; Johnson CA, Keltner JL. Arch Ophthalmol. 1983; 101:371-375; Keltner JL, Johnson CA. Ophthalmology. 1987; 94:1180-1188) and falls (Guse CE, Porinsky R. WMJ, 2003;102:37-42; Brennan M. Generations, 2003; 27:52-56).	Thank you for your comment

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Public comment/ AAO-AGS	General Comments	Visual Impairment Has a Significant Financial Impact on the American Economy. "*It was+ estimated that the annual total financial burden of major adult visual disorders is $35.4 billion ($16.2 billion in direct medical costs, $11.1 billion in other direct costs, and $8 billion in productivity losses) and that the annual governmental budgetary impact is $13.7 billion." (Rein DB, Zhang P, Wirth KE et al. The economic burden of major adult visual disorders in the United States. Arch Ophthalmol 2006 Dec; 124(12): 1754-60). The potential impact of the failure to detect blinding disease is not known but is certainly sizeable.	Thank you for your comment
Public comment/ AAO-AGS	General Comments	The medical condition is associated with adverse impacts on the health of the individual. "Losses in VF of more than 5 dB [decibels] and gains of more than 3 dB were associated with clinically meaningful losses and gains in vision-specific health-related quality of life (HRQOL), respectively. Areas of vision-specific HRQoL most affected by greater losses in VF were driving, dependency, role-functioning, and mental health." Patino CM, Varma R, Azen SP et al. The impact of change in visual field on health-related quality of life the Los Angeles Latino Eye Study. Ophthalmology. 2011 Jul; 118(7):1310-7.	Thank you for your comment
Public comment/ AAO-AGS	General Comments	"A trend of worse National Eye Institute Visual Function Questionnaire - 25 (NEI-VFQ) scores for most subscales was observed with worse VF loss (using both monocular and calculated binocular data). Open-angle glaucoma participants with VF loss had lower scores than participants with no VF loss."	Thank you for your comment
Public comment/ AAO-AGS	General Comments	"Greater severity of VF loss in persons with OAG impacts vision-related QOL. This impact was present in persons who were previously unaware that they had glaucoma. Prevention of VF loss in persons with glaucoma is likely to reduce loss of vision-related QOL."McKean-Cowdin R, Wang Y, Wu J et al. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. Ophthalmology. 2008 Jun; 115(6): 941-948.	Thank you for your comment

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Public comment/ AAO-AGS	General Comments	"HRQOL is diminished even in persons with relatively mild VFL on the basis of MD scores." McKean-Cowdin R, Varma R, Wu J et. al. Severity of visual field loss and health related quality of life. Am J Ophthalmol. 2007 Jun; 143:1013-23	Thank you for your comment
Public comment/ AAO-AGS	General Comments	"Relative to persons with no visual impairment (VI), persons with bilateral mild and unilateral or bilateral moderate/severe VI report greater difficulties in performing most vision-dependent daily activities and experience vision-related dependency and poorer vision-related mental health." Varma R, Wu J, Chong K. et al. Impact of severity and bilaterality of visual impairment on health-related quality of life. Ophthalmology. 2006 Oct; 113(10):1846-53.	Thank you for your comment
Public comment/ AAO-AGS	General Comments	These papers report that mild to moderate visual field changes are important milestones in progressive glaucoma. Early detection is important to reduce the risk of advanced disease and loss of quality of life and productivity.	Thank you for your comment
Public comment/ AAO-AGS	General Comments	The AHRQ document relies on reports from 2006 and 2007 in concluding that there is no evidence that proves screening influences outcomes. Much of the document focuses on diagnostic tests that could be used in screening that were not reviewed in the 2007 report, noting that "Despite accommodating the potential for evidence that could lead stepwise from screening to final outcomes, we were also unable to find evidence that provided support for or against glaucoma screening." The draft report did not discuss studies that examined identifying early disease compared with late stage disease when the visual, functional, and quality of life outcomes would be worse.	We searched for studies that were published after 2006 (Key Question 5) and 2007 (Key Question 3). We did not identify any new studies to address Key Question 5 and identified 72 additional studies for Key Question 3
Public comment/ AAO-AGS	General Comments	The general consensus among glaucoma specialists is that population screening for glaucoma without targeting high-risk groups is not useful. However, refining strategies to identify high risk groups to have a comprehensive eye examination as a "screening" will have higher yields. There is an important distinction between population-based screening and office-based screening, and it's not clear from the report if office-based screening was considered in the 2007 analysis by Burr.	We included studies that examined the detection of early disease

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Public comment/ AAO-AGS	General Comments	The AHRQ document includes office-based examination as screening for glaucoma among those settings for which there is no evidence of effectiveness. The basis for this statement is short-sighted.	We included studies of all settings in which screening could potentially occur including community screenings, non-eye care health provider settings, eye care provider clinical settings (ophthalmologists and optometrists), and telemedicine.
Public comment/ AAO-AGS	General Comments	The AHRQ report does not consider that office-based eye examinations are not limited to detection of glaucoma. In fact, in many patients who present for "screenings," other treatable eye disease is detected, especially in the professional office-based setting, and represents a significant opportunity for preventing other visual impairment from many causes.	Discussion of comprehensive eye examinations to detect conditions other than glaucoma was considered outside of the scope of this comparative effectiveness review
Public comment/ AAO-AGS	General Comments	It is important to understand that this document does not conclude that screening for glaucoma is not useful or beneficial. Rather, it states that evidence linking screening with outcomes is lacking. A screenable disease should have an effective treatment for which glaucoma does, and the link between treatment and visual field/optic nerve progression has been more definitively established than documented in this report.	Thank you for your comment

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Public comment/ Pfizer	General Comments	Revising the analytic framework to reflect real-world clinical practice; We encourage AHRQ to revise the draft analytic framework to reflect how glaucoma screening is conducted in real-world practice. Currently, AHRQ lists “asymptomatic adults” in the draft analytic framework as the patient population of interest for the assessment. However, in current practice, glaucoma screening typically involves first identifying a population at higher risk for glaucoma (e.g., either due to advanced age or ethnicity), then measurement of the intra-ocular pressure (IOP), and examination of the optic nerve through a dilated pupil. Those patients identified to be at higher risk for the disease (either due to presence of risk factors, or an abnormal IOP or eye examination) then go on to a more definitive functional or structural assessment of the disease, which is often performed by a specialist.1 High-risk populations (such as patients of advanced age, of certain ethnicities, with a family history of disease, a history of diabetes or elevated intra-ocular pressure) are more likely to develop OAG and therefore are more likely to benefit from screening. Therefore, we encourage AHRQ to revise the analytic framework to reflect that basic population screening techniques, such as identifying whether a patient has certain risk factors, are deemed clinically relevant in order to appropriately identify which patients will benefit most from a more sophisticated glaucoma screening.	We included studies of adult (“adult” as defined by included studies) asymptomatic participants in general or high risk populations. We also noted that "Asymptomatic high risk populations included those not previously tested, diagnosed or presenting with symptoms known to be related to glaucoma but also included those with a family history of glaucoma, specific racial/ethnic groups, older age, and specific ocular or other medical conditions as defined by included studies (e.g., diabetes)."
Peer Reviewer #4	General Comments	The Executive Summary and body of the report are virtually identical in many places and not much different in length. This probably is because the report format is defined rigidly, but the redundancy makes the report more overwhelming than it might need to be.	The EPC feels this is a question for AHRQ
Peer Reviewer #6	General Comments	I like the recommendations for future research...do you think your current findings allow you to be a bit more detailed in laying out the specifics re: population, intervention, outcomes of greatest importance to close the information gap...it is a bit general.	We have reviewed all text and revised accordingly

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Peer Reviewer #4	General Comments	The conclusions could be a bit more hard-hitting. The evidence reviewed here seems to show that there is no evidence to support screening for glaucoma using currently available tests because the ability tests being considered for use in screening in the asymptomatic population to predict who does and does not have glaucoma has not been established.	Thank you for your comment
Peer Reviewer #3	General Comments	Suggestion: Tables in the Appendix describing methods can be consolidated to reduce the number of tables. It is helpful that excluded manuscripts are listed with reasons for exclusion. Suggest including full citations of the excluded manuscripts and reformatting to improve readability.	We have consolidated the appendices tables as much as possible to improve readability
Peer Reviewer #3	General Comments	Recommendation: Excellent synthesis of a difficult topic. Suggest that a review of consistency of application of inclusion/exclusion criteria is needed and/or clarification of the inclusion/exclusion critieria	Thank you for your comment. We have responded to the suggestion to review specific aspects of the application of inclusion/exclusion criteria
Peer Reviewer #3	Appendices	The Tables in the Appendix are numerous –some consolidation will improve readability. Suggest combining some of the tables together so that the information about the methods is summarized fewer tables so that the reader does not have to flip between several tables to obtain the information. I understand that organizing this much information is challenging but I found the appendices in the Burr systematic review easier to read than the appendices in this draft AHRQ report.	We have consolidated the appendices tables as much as possible to improve readability