Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Screening for Glaucoma

I. Background and Objectives for the Systematic Review

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program has requested a comparative effectiveness review (CER) of glaucoma screening. The topic was selected through the Effective Health Care Program nomination process and review of the scientific medical literature.

Glaucoma is a leading cause of visual impairment and blindness and is estimated to affect 60.5 million people worldwide by 2010. Glaucoma may be classified by optic nerve damage, visual field loss, and elevated intraocular pressure, but these mechanisms need not occur in tandem to confirm diagnosis. Damage is irreversible, so early detection may prevent severe vision loss. Open-angle glaucoma, the most common subtype of the disease, impacts more than 2.5 million people in the United States with a median age-adjusted prevalence of 4.6% and 1.6% among blacks and whites, respectively (based on year 2000 estimates).

Unfortunately, only half of the prevalent cases of glaucoma have been identified in the U.S. This identification rate is affected by at least two factors. First, glaucoma is an asymptomatic disease that patients do not notice until their disease is advanced and they have severe vision loss. Second, there is no single, simple test to identify people with glaucoma. Because of the large burden of undiagnosed disease and because of the number of people disabled by glaucoma, there is strong interest in developing screening strategies. On the other hand, such strategies have been hampered by the lack of an adequately sensitive and specific test or tests that can be administered on a large scale. Since the last evaluations of glaucoma screening were conducted in the mid 2000s, there have been advances in the devices used to test optic nerve structure and function. Because of this new evidence, it is appropriate to reevaluate the possibility of population-based glaucoma screening.

Ocular examinations such as tonometry, perimetry, and direct ophthalmoscopy are performed alone or as a part of a multicomponent screening test for glaucoma. The U.S. Preventive Services Task Force (USPSTF) concluded in March 2005 that measurement of intraocular pressure and assessment of the
optic nerve head alone have limited effectiveness as population-based screening tools.\(^5,6\) The USPSTF also noted that current methods used to assess visual field loss may be impractical for population-based screening because of the length of time required for testing and the challenge of equipment portability.

New evidence regarding the safety and efficacy of screening for chronic open-angle glaucoma has emerged since the release of the March 2005 USPSTF report. For this reason, there are a number of topics that could be addressed by an updated CER:

- The USPSTF noted that studies of frequency-doubling technology, used to assess visual field loss, were underway at the time of the evidence synthesis for the 2005 guidelines.\(^6\) We will search the literature for new evidence regarding the accuracy (sensitivity and specificity) of frequency-doubling technology and other screening examinations used alone or in combination to aid in the identification of individuals with open-angle glaucoma. We will also summarize the evidence regarding the impact of screening on the prevalence of elevated intraocular pressure and visual impairment and on the progression of visual field loss and optic nerve damage in screened and unscreened populations.
- The goal of treatment for open-angle glaucoma is to “achieve a stable range of measured intraocular pressures deemed likely to retard further optic nerve damage.”\(^6\) We will include intraocular pressure as a screening effectiveness outcome and will also include outcomes such as optic nerve damage, visual field loss, visual impairment, vision-related quality of life, and patient preference.
- With passage of the Affordable Care Act (P. L. 111-148), there is increased potential for promoting equity and access to glaucoma screening for historically underserved populations.\(^7\) The Act promotes prevention by allowing patients to receive evidence-based preventive services without payment. Therefore, determining the efficacy of different screening services in the U.S. has the potential for large health and financial impact.

**Objectives**

The objective of this review is to summarize the evidence regarding the safety and efficacy of screening-based programs for open-angle glaucoma with a specific focus on the effects of screening on visual impairment, patient-reported outcomes, intraocular pressure, visual field loss, optic nerve damage, and
harm/adverse effects. This review will also include a summary of the diagnostic accuracy of screening examinations/tests for open-angle glaucoma.

A detailed description of Food and Drug Administration (FDA) approval status, indications, and warnings for the devices considered for this review is presented in Appendix A.

II. The Key Questions

Summary of Revisions to the Key Questions

Based on the public comments regarding the key questions submitted to AHRQ, the Evidence-Based Practice Center (EPC) revised the Key Questions and protocol by:

1. Limiting the definition of visual impairment to the definition included in the International Classification of Diseases, 9th Revision, Clinical Modification\(^8\) (hereafter, ICD-9-CM). (Key Question 1)

2. Clarifying that we propose to compare various screening-based programs to no screening program (usual care including, e.g., opportunistic case finding) and to different screening-based programs to determine whether treatment-related outcomes differ among those identified via the various methods under consideration. (Key Questions 1, 2, 4, and 5)

3. Included a statement in the protocol that there is no consensus on the “gold standard” test (or combination of tests) for the identification of open-angle glaucoma.

4. Included “psychological effects related to a glaucoma misdiagnosis” and “harm related to overdiagnosis” as harm-related outcomes. (Key Question 6)

Key Questions

Screening for a medical condition in asymptomatic individuals is thought to be beneficial when 1) the condition has a significant individual or population burden; 2) the medical condition is associated with adverse impacts on the health of the individual; 3) there is an accurate test that detects the condition during the asymptomatic or early clinical stage; 4) treatment at this asymptomatic or early stage improves important health outcomes more than treatment once an individual is symptomatic; and 5) harms of screening and early intervention are limited. Following these requirements, the key questions
for screening for glaucoma will consider and compare, where possible, whether patients were treated or not treated for early stages of glaucoma.

**Key Question 1**

a. Does a screening-based program for open-angle glaucoma lead to less visual impairment (as defined in the ICD-9-CM) when compared to no screening program?

b. How does visual impairment vary when comparing different screening-based programs for open-angle glaucoma?

**Key Question 2**

a. Does a screening-based program for open-angle glaucoma lead to improvements in patient-reported outcomes when compared to no screening?

b. How does visual impairment (as defined in the ICD-9-CM) vary when comparing different screening-based programs for open-angle glaucoma?

**Key Question 3**

What is the predictive value of screening tests for open-angle glaucoma?

**Key Question 4**

a. Does a screening-based program for open-angle glaucoma lead to reductions in intraocular pressure when compared to no screening program?

b. How does intraocular pressure vary when comparing different screening-based programs for open-angle glaucoma?

**Key Question 5**
a. Does a screening-based program lead to a slowing of the progression of optic nerve damage and visual field loss when compared to no screening program?

b. How do optic nerve damage and visual field loss vary when comparing different screening-based programs for open-angle glaucoma?

Key Question 6

What are the harms associated with screening for open-angle glaucoma?

Population(s)

We will include studies of asymptomatic participants aged 40 years and older in general or high-risk populations. High-risk populations include 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).

Interventions/Index Tests

We will include studies of the following ocular examinations (i.e., screening tests) conducted alone or in any possible combination (including multicomponent simultaneous or sequential testing):

- Tonometry
- Perimetry
- Direct ophthalmoscopy
- Fundus photography or computerized imaging of the posterior pole

Comparators/Reference Standards

Key Questions 1, 2, 4, 5, and 6 explore comparisons of the interventions mentioned above (conducted alone or in any possible combination as a part of a screening-based program) to no screening program (usual care including, e.g., opportunistic case finding) and to different screening-based programs (the above-mentioned screening tests conducted alone or in any possible combination). Key Question 3 explores comparisons of screening/diagnostic tests to the gold/reference standards of confirmed open-angle glaucoma at the time of follow-up or open-angle glaucoma that requires treatment (diagnosed by an ophthalmologist by using objective assessments as defined by included studies). We acknowledge that there is no consensus on the gold standard test (or combination of tests) for the identification of patients with open-angle glaucoma. The reference standards for Key Question 3 were adapted from a
diagnostic test accuracy review conducted by Burr and colleagues.9

Outcomes

1. Outcomes for Key Question 1:
   a. **Primary outcome**: The proportion of participants with moderate, severe, and profound visual impairment (as defined in the ICD-9-CM8). We will also consider other measurements of visual impairment as defined by included studies.
   b. **Secondary outcome**: We will also compare visual acuity outcomes (as measured by the Early Treatment Diabetic Retinopathy Study [ETDRS] or the Snellen Eye Test) among the groups of interest as reported in included studies (e.g., mean visual acuity or proportion of participants in prespecified visual acuity categories).

2. Outcomes for Key Question 2:

   Mean total or relevant item/subscale scores of the participants as measured by any validated questionnaire—for example, the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ)—for the following **patient-reported outcomes** will be compared among the treatment groups of interest:
   a. Vision-related quality of life, that is, vision-related functional loss as well as the impact of functional loss on activities of daily living (**Primary outcome**).
   b. Patient satisfaction (**Secondary outcome**).

3. Outcomes for Key Question 3:

   The number of participants in the following categories:
   a. True positives, true negatives, false positives, and false negatives (**Primary outcome**).
   b. Studies that include sensitivity and specificity values only will also be considered. Testability—the ability to perform the test, including measures among those administering the test as well as those being tested—will also be compared among the interventions of interest (**Secondary outcome**).

4. Outcome for Key Question 4:

   The difference in the mean intraocular pressure among the groups of interest

5. Outcomes for Key Question 5:
a. The proportion of participants with progressive optic nerve damage as defined by included studies and as observed via fundus photography or other imaging of the posterior pole.

b. The proportion of participants with progression of visual field loss as defined by included studies.

6. Outcome for Key Question 6:

The proportion of participants experiencing the following adverse events will be compared among the treatment groups of interest (adapted from the USPSTF5):

a. Eye irritation
b. Corneal abrasions
c. Infection (e.g., endophthalmitis)
d. Distortion of sense of taste (due to anesthetic use)
e. Exam apprehension
f. Psychological effects related to a glaucoma diagnosis or misdiagnosis
g. Harms related to overdiagnosis

We will also include a discussion of other potential benefits of screening, including detection of additional ocular conditions (e.g., diabetic retinopathy, cataract, visual impairment) and increased awareness of glaucoma (educational benefits).

Timing

Outcomes for Key Questions 1, 2, 4, 5, and 6 will be assessed at 1 year of follow-up and at annual intervals thereafter. There will be no minimum length of follow-up for outcomes related to Key Question 3.

Settings

- Community screenings
- Health care provider clinical settings not related to eye care
- Eye care provider (ophthalmologists and optometrists) clinical settings
- Telemedicine
III. Analytic Framework

Figure 1: The above figure is a modified version of a larger framework depicting the impact of both screening and treatment for open-angle glaucoma. This figure focuses on the screening aspects of the framework and depicts the key questions within the context of the inclusion criteria described in the following sections. In general, the figure illustrates how screening-based programs (which may incorporate treatment when indicated) may reduce visual impairment (KQ1), improve patient-reported outcomes (KQ2), reduce intraocular pressure (KQ4), and possibly slow the progression of optic nerve damage, visual field loss, or both (KQ5). The figure also illustrates the potential predictive value of candidate screening tests to detect open-angle glaucoma and open-angle glaucoma suspects (KQ3). Finally, the potential harms of screening (KQ6) are illustrated in the framework.

*Defined by the American Academy of Ophthalmology as “individual[s] with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing primary open-angle glaucoma.”9

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

For Key Questions 1 through 6, we will include randomized controlled trials (RCTs), quasi-randomized controlled trials, and observational studies (to include cohort and case control studies). Key Question 3 may also include cross-sectional studies; it will include study designs in which all tests (including the index, comparator, and reference standard) are performed on all participants and in which participants are randomized to one test (among the index and potential comparator[s]) but all obtain the reference
standard. Narrative summaries of case reports and case series (including more than 100 participants) will also be presented for Key Question 6. The specific populations, interventions, and outcomes of interest are described in Section II.

**B. Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies To Answer the Key Questions**

We will search the following databases for primary studies: MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences), and CENTRAL (the Cochrane Central Register of Controlled Trials). We will develop a search strategy for MEDLINE, to be accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. This search strategy will be adapted for searches of EMBASE (using EMTREE terms) and CENTRAL.

We will search the literature without imposed language, sample size, or date restrictions.

We will search reference lists of included studies, relevant review articles, and related systematic reviews to identify any additional studies for inclusion. We will search MEDION (www.mediondatabase.nl) for related diagnostic accuracy reviews (Key Question 3). We will also use the Science Citation Index–Expanded database to identify additional studies that may have cited trials included in this review. Conference proceedings or journals will not be hand searched.

The MEDLINE search strategy to be used is:


We will search LILACS by using the terms glaucoma$ AND (screen$ OR diagn$).

Primary authors of included studies will be contacted to provide missing information regarding study methodology, missing standard deviations, intention to treat data, or other data as appropriate. If no response is received within 6 weeks, we will assess the study based upon the available data provided in the published article.
C. Data Abstraction and Management

Potentially relevant citations will be screened by using DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), a Web-based systematic review software. Citations identified by the search strategies will be uploaded to DistillerSR and managed in the following manner: Two reviewers will independently assess titles and abstracts resulting from the literature searches according to the inclusion criteria stated in Section IV-B. The titles and abstracts will be classified as “include”, “exclude,” or “unsure.” Disagreements regarding eligibility are identified by DistillerSR and will be resolved by discussion with each reviewer by providing a rationale based on the review of titles, abstracts, and/or full text articles. The two reviewers will retrieve the full text for titles and abstracts classified as “unsure” by both reviewers or classified as “unsure” by one reviewer and “include” by a second reviewer and reassess the studies for inclusion. The authors of studies classified as “unsure” will be contacted for further clarification, as appropriate, after examining the full text according to the guidelines described in Section IV-A. Any disagreements regarding inclusion after full text review will be resolved through discussion, and unresolved conflicts will be adjudicated during a team meeting of investigators and advisors. Studies labeled as “exclude” by both review authors will be excluded from the review and the reasons for exclusion documented. Studies labeled “include” will be further assessed for methodological quality as described in Section IV-D.

Two reviewers will extract descriptions of the study methods to include the population, intervention(s) (including the index test[s], comparator[s], and reference standard for Key Question 3) and outcomes of interest by using a form designed by the team investigators, advisors, and senior research methodologist. Disagreements will be resolved through discussion. Data will be entered independently by two reviewers into a database designed specifically for this CER.
D. Assessment of Methodological Quality of Individual Studies

We will use the Cochrane Collaboration’s tool for assessing the risk of bias of randomized and quasi-randomized trials. Two authors will independently assess the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions and will evaluate the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of participants, study investigators, outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Masking of investigators and participants might not be possible with some of the interventions being examined, but it will be noted when mentioned.

Judgments for each criterion will be reported as “Yes” (low risk of bias), “No” (high risk of bias), or “Unclear” (information is insufficient to assess). Two reviewers will resolve disagreements through discussion. We will contact the authors of the studies for additional information on issues that were unclear from information available in the original reports. In case of failure to communicate with the primary investigators, or if there is no response within 6 weeks, we will assess the methodological quality on the basis of the available information.

We will use the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of observational studies to include cohort and case control studies. The NOS includes domains to assess the quality of study group selection (representativeness, case definitions), comparability of cohorts/cases and controls on the basis of design or analysis, and ascertainment of exposure(s) or outcome(s). One star is awarded for the four selection questions and three stars for the ascertainment of exposure/outcome questions. Up to two stars are awarded for the comparability domain.

For Key Question 3, we will use the QUADAS checklist, which is specific to risk-of-bias assessments of diagnostic accuracy studies. The QUADAS tool includes 14 items that evaluate numerous domains including representativeness, inclusion/exclusion criteria, choice of reference standard, masked interpretation of results of tests and reference standard, and study withdrawal. Judgments for each checklist item will be reported as “Yes,” “No,” or “Unclear.”

E. Data Synthesis

If there is appreciable variability in the studies with regard to interventions, follow-up intervals, or assessments of outcomes, we will not combine the results in a meta-analysis and will instead present a narrative summary.

Source: www.effectivehealthcare.ahrq.gov
Published Online: November 16, 2010
Assessments of heterogeneity

We will assess the clinical, methodological, and statistical heterogeneity of included studies. We will evaluate clinical and methodological heterogeneity by examining potential variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes. The \( I^2 \) statistic (%), the Chi-square test for heterogeneity, and the degree of overlap in confidence intervals of the included studies will be examined as appropriate to assess statistical heterogeneity. Heterogeneity will be further investigated by using receiver operating characteristic (ROC) curves (Key Question 3).

Assessment of reporting biases

A funnel plot will be used to assess reporting biases in conjunction with study characteristics or other factors that may contribute to asymmetry of the plot.

Measures of treatment effect

We will calculate summary risk ratios or odds ratios as appropriate for dichotomous outcomes. For Key Question 3, we will calculate diagnostic odds ratios. We will verify normality of continuous outcomes and calculate mean differences; standardized mean differences will be calculated if continuous outcomes are measured by using different scales.

Data synthesis

If the \( I^2 \) statistic suggests considerable heterogeneity (a threshold will be established before undertaking any analyses) or if there are insufficient data (less than three studies), we will not combine the results in a meta-analysis and will instead present a narrative summary. If considerable heterogeneity does not exist based on the \( I^2 \) statistic and an inspection of the forest plot, we will combine the results of included trials in a meta-analysis by using fixed or random effects methods as appropriate.

Subgroup analysis

If there are sufficient data, we will conduct subgroup analyses by stage or severity of disease, by relevant demographic characteristics (e.g., age, race/ethnicity), and by other factors as outlined in Populations. We will also consider a subgroup analysis of studies that include asymptomatic participants who have been previously tested or treated.

F. Grading the Evidence for Each Key Question

We will assess the quantity, quality, and consistency of the body of available evidence by addressing Key Questions 1 through 6. We will use an evidence-grading scheme recommended by the GRADE Working
Group, adapted by AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, and recently published in the *Journal of Clinical Epidemiology*. We will consider the strength of the study designs; randomized controlled trials will be graded as having the highest level of evidence followed by observational studies as having the lowest. If an outcome is evaluated by at least one randomized controlled trial and by observational studies, our evidence grade will be based firstly on the randomized controlled trials and secondly on the quality of the cohort studies. If an outcome is evaluated by one or no randomized controlled trials, our evidence grade will be based on the single randomized controlled trial and the best available observational study.

We will assess the quality and consistency of the best available evidence, including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision as described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and by Owens and colleagues. For each outcome of interest, two reviewers will grade the major outcomes for each Key Question and then the entire team will discuss their recommendations and reach consensus.

**V. References**


VI. Definition of Terms

Definitions and abbreviations are listed in Appendix B.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For comparative effectiveness reviews (CERs), the key questions are posted for public comment and finalized after the comments were reviewed. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the Evidence-based Practice Center (EPC) and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is to be reviewed.

IX. Technical Expert Panel (TEP)

The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived to be healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, study designs, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report, and recommend approaches to specific issues as requested by the EPC. The TEP does not perform analysis of any kind nor does it contribute to the writing of the report.
X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewers may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. For some specific reports, such as reports requested by the Office of Medical Applications of Research at the National Institutes of Health, there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published 3 months after the publication of the evidence report.

It is our policy not to release the names of the peer reviewers or TEP members until the final report is published so that they can maintain their objectivity during the review process.