

**American Academy of Ophthalmology and the
American Glaucoma Society Joint Comments on:
Comparative Effectiveness of Screening for Glaucoma, xx-EHCxxx**

The American Academy of Ophthalmology is the world's largest association of eye physicians and surgeons—Eye M.D.s—with more than 19,000 members in the U.S. The American Glaucoma Society (AGS), is an organization of over 500 ophthalmologists who specialize in glaucoma care and surgery. The Academy and the AGS appreciate the opportunity to comment upon this draft document. These two organizations have brought together world-renowned glaucoma experts and researchers to analyze and review this draft document, resulting in a broad-based consensus. The deadline for the review of this type of document is wholly inadequate given the amount of data and literature included and more importantly excluded from this report. **Even with the short amount of time to review, we believe that there are gaps in the document that warrant reconsideration in the examination and weighing of the overall effectiveness of screening for glaucoma for the American public. Given the short time allotted for review we strongly encourage AHRQ to meet with representatives from our groups so that additional information can be provided and considered for this review.**

Open-angle glaucoma affects an estimated 2.2 million people in the United States, and that number is likely to increase to 3.3 million in 2020 as the population ages. Overall, there appears to be a threefold higher prevalence of open angle glaucoma in African Americans relative to non-Hispanic Whites in the United States. Glaucoma is the second most common cause of blindness in African Americans. Blindness from glaucoma is at least six times more prevalent in African Americans than in non-Hispanic whites. Evidence on Hispanics/Latinos suggests that they have prevalence rates of OAG that are comparable to African Americans.

It is important to consider screening for open-angle glaucoma because patients are asymptomatic until late in the disease process, when visual loss and functional impairment are irreversible. The populations most at-risk for glaucoma and blindness are also the most vulnerable populations in our society and the least likely to have regular access to “routine” eye care. These factors make intentional outreach strategies for disease detection in these populations necessary. If detected early, patients with primary open angle glaucoma (POAG) can be treated to either slow or prevent the progression of visual field loss. Even mild visual field loss decreases a patient's health-related quality of life.

Although a randomized controlled trial demonstrating the association of screening with improved quality of life and patient reported outcomes may not exist, we believe that there are

similarities between findings seen with the early treatment of glaucoma and reduced disease progression with less visual field loss and reduction in health-related quality of life that should be considered as part of the overall review of glaucoma screening for at-risk populations.

Our concerns regarding the assessment by AHRQ of glaucoma screening are highlighted below:

- **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.**
- **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.**
- **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.**
- **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?**
- **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.**

Our comments and feedback on the questions posed follow.

➤ Executive Summary

The primary objective of the document developed by the Agency for Healthcare Research and Quality (AHRQ) is to, according to the preparers, was to “summarize the evidence regarding the effectiveness and safety of screening on visual impairment, patient reported outcomes, intraocular pressure, visual field loss, optic nerve damage, and adverse effects. This review also includes a summary of the diagnostic accuracy of screening examinations and tests for open-angle glaucoma.”

Under the section entitled Key Question ES-2, the document states that screening for a medical condition in asymptomatic individuals may be considered 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.”

“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.

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 ($\geq 20/200$) 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).

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

Research, Independence for Older Americans: An Investment for Our Nation's Future, 1999). 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).

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.

The medical condition is associated with adverse impacts on the health of the individual.

Results from the Los Angeles Latino Eye Study (LALES) support the observation that early disease with mild to moderate visual field damage adversely impacts the quality of life.

"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.

"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."

"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.

“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

“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.

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.

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.**

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.

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.

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.

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.

➤ Introduction

Some of the Key Questions seem of little importance in determining the societal value of screening for glaucoma. However, Key Questions 3 and 5 are integral to this issue.

➤ Methods

Of the 169 systematic reviews, only 2 were considered relevant. Of the 4680 primary study articles and abstracts, 72 were reviewed for this comparative effectiveness evaluation, which may be a limitation. These 72 articles (all addressing Key Question #3) were published after those primary articles included in the more recent of these two systematic reviews by Burr JM et al. (2007). Therefore, this assessment relies heavily upon the outcomes established in a 2007 United Kingdom/National Health Service Health Technology Assessment by Burr et al. The findings that are provided were a narrative summary. **A meta-analysis, which would have relied on all relevant primary studies, was not performed. The conclusiveness of a narrative summary is not as strong and more open to opinion compared with a formal meta-analysis.**

Separate evaluation of the sensitivity and specificity of screening tests in at-risk adult populations is not presented, which may be due to limitations of the available data. The appropriate target population for screening is an essential issue on which to base outcomes is not addressed by the AHRQ document.

➤ Results

Key Question 1: Does a screening-based program for open-angle glaucoma lead to less visual impairment when compared to no screening program? KQ1b: How does visual

impairment vary when comparing different screening-based programs for open-angle glaucoma?

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.

Key Question 2: Does a screening-based program for open-angle glaucoma lead to improvements in patient-reported outcomes when compared to no screening? KQ2b: How do patient-reported outcomes vary when comparing different screening-based programs for open-angle glaucoma?

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.

Key Question 5: 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? KQ5b: How do optic nerve damage and visual field loss vary when comparing different screening-based programs for open-angle glaucoma?

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.

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.

➤ **Summary and 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.

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.

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

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). 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.

Additional Studies That Could Be Considered for Inclusion in the Final Document:

1. Kymes SM, Lee BS. Preference-based quality of life measures in people with visual impairment. *Optom Vis Sci* 2007;84:809-16.
2. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;119:1050-8.
3. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1171-8.
4. Wren PA, Musch DC, Janz NK, Niziol LM, Guire KE, Gillespie BW. Contrasting the use of 2 vision-specific quality of life questionnaires in subjects with open-angle glaucoma. *J Glaucoma* 2009;18:403-11.
5. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108:1943-53.
6. Hyman LG, Komaroff E, Heijl A, Bengtsson B, Leske MC, Early Manifest Glaucoma Trial G. Treatment and vision-related quality of life in the early manifest glaucoma trial. *Ophthalmology* 2005;112:1505-13.
7. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48-56.
8. Jampel HD, Schwartz A, Pollack I, Abrams D, Weiss H, Miller R. Glaucoma Patients' Assessment of Their Visual Function and Quality of Life. *J Glaucoma* 2002;11:154-63.
9. Suner IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci* 2009;50:3629-35.
10. van Gestel A, Webers CA, Beckers HJ, et al. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye (Lond)* 2010;24:1759-69.
11. McKean-Cowdin R, Wang Y, Wu J, Azen SP, Varma R, Los Angeles Latino Eye Study G. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* 2008;115:941-8 e1.

12. Lee BS, Kymes SM, Nease RF, Jr., Sumner W, Siegfried CJ, Gordon MO. The impact of anchor point on utilities for 5 common ophthalmic diseases. *Ophthalmology* 2008;115:898-903 e4.
13. Saw SM, Gazzard G, Eong KG, Oen F, Seah S. Utility values in Singapore Chinese adults with primary open-angle and primary angle-closure glaucoma. *J Glaucoma* 2005;14:455-62.
14. Kobelt G, Jonsson B, Bergström A, Chen E, Lindén C, Alm A. Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol Scand* 2006;84:363-71.
15. Burr JM, Mowatt G, Hernandez R, et al. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii-iv, ix-x, 1-190.
16. Rein DB, Wittenborn JS, Lee PP, et al. The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009;116:823-32.