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Screening for Glaucoma in Adults: A Systematic Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Structured Abstract

Background: In 2013, the United States Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for primary open angle glaucoma in adults (I Statement). Although the USPSTF found that treatment of increased intraocular pressure (IOP) and early glaucoma reduces progression of visual field defects, it found inadequate evidence on the effects of treatment on the development of impaired vision or quality of life. There was no direct evidence on benefits and harms of glaucoma screening versus no screening.

Purpose: To systematically review the evidence on screening and treatment of glaucoma for populations and settings relevant to primary care in the United States.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE (through February 9, 2021), reviewed the studies in the prior reports, and manually reviewed reference lists. Surveillance was conducted through January 21, 2022.

Study Selection: Randomized controlled trials (RCTs) of screening and referral; studies on diagnostic accuracy of currently utilized screening tests (optical coherence tomography [OCT], optic disc photography, ophthalmoscopy and biomicroscopy, pachymetry, tonometry, and visual fields); and RCTs of medical therapy versus placebo or no treatment, recently approved medical therapies versus older therapies, and selective laser trabeculoplasty versus medical therapy.

Data Extraction: One investigator abstracted data and a second checked accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): A total of 83 studies (N=75,887) were included in this review (30 trials, and 53 diagnostic accuracy studies). Sixteen studies were carried forward from the prior review and 67 studies were new.

One RCT (n=616) found vision screening (including components for glaucoma) by an optometrist was associated with no difference in visual acuity or vision-related quality of life compared with no screening, but greater risk of falls (likelihood of at least 1 fall 65% vs. 50%, relative risk [RR] 1.31, 95% confidence interval [CI] 1.13 to 1.50). No study evaluated effects of referral to an eye health provider versus no referral on vision or other health outcomes. Evidence on accuracy of screening tests for identifying persons with glaucoma was most robust for spectral domain-OCT retinal nerve fiber layer thickness (15 studies, N=4,242, sensitivity 0.79, 95% CI 0.75 to 0.83 and specificity 0.92, 95% CI 0.87 to 0.96), area under the receiver operating characteristic curve (16 studies, N=4,060) 0.90, (95% CI 0.86 to 0.93) and spectral domain-OCT ganglion cell analysis (9 studies, N=1,522, sensitivity 0.74, 95% CI 0.68 to 0.80 and specificity 0.91, 95% CI 0.80 to 0.96), tonometry (13 studies, N=32,892, sensitivity 0.48, 95% CI 0.31 to 0.66 and specificity 0.94, 95% CI 0.90 to 0.96), and the Humphrey Visual Field Analyzer (6 studies, N=11,244, sensitivity 0.87, 95% CI 0.69 to 0.95 and specificity 0.82, 95% CI 0.66 to 0.92). Evidence on other screening tests (swept source-OCT, optic disc photography, ophthalmoscopy and biomicroscopy, and pachymetry) was limited. A pilot study and followup

found telemedicine screening in primary care associated with variable sensitivity for identifying persons with glaucoma but high specificity. Evidence on the accuracy of instruments for identifying patients at higher risk of glaucoma was limited to one study that was of limited applicability to screening because prior diagnosis of glaucoma was one of the key risk factors.

Medical therapy for ocular hypertension and untreated glaucoma was associated with greater reduction in IOP (16 trials, N=3,706, mean difference -3.14 millimeters mercury [mm Hg], 95% CI -4.19 to -2.08), decreased likelihood of glaucoma progression (7 trials, N=3,771, RR 0.68, 95% CI 0.49 to 0.96; absolute risk difference -4.2%), and increased risk of ocular adverse events (2 trials, RR 1.21, 95% CI 1.10 to 1.33 and RR 3.52, 95% CI 2.46 to 5.02) versus placebo or no treatment. One trial (n=461) found no differences between medical therapy versus placebo or no treatment in visual acuity, quality of life, or function. Recently approved medical therapies for glaucoma (netarsudil and latanoprostene bunod) were associated with similar or slightly greater reduction in IOP versus older therapies (6 trials, N=3,128), but increased risk of adverse events. Selective laser trabeculoplasty and medical therapy were associated with similar effects on IOP, visual acuity, visual fields, quality of life, and adverse events (4 trials, N=957).

Limitations: The screening trial had methodological limitations and few patients were referred for glaucoma evaluation; excluded non-English language studies; statistical heterogeneity in pooled analyses on effects of medical therapy versus placebo or no treatment on IOP, though inconsistency was in the magnitude (not direction) of benefit; evidence on effects of treatment on visual impairment, quality of life, and function remains very limited; excluded case-control studies of diagnostic accuracy; evaluation of publication bias limited by small numbers of studies and statistical heterogeneity; most head-to-head comparisons excluded.

Conclusions: Direct evidence on glaucoma screening versus no screening is limited and showed no benefits on vision-related quality of life or function, and increased risk of falls. Screening tests (OCT, visual field assessment) can identify persons with OAG with reasonable accuracy. Treatment for ocular hypertension or untreated OAG is associated with reduction in IOP and reduced risk of glaucoma progression based on visual fields or optic nerve changes, but limited evidence on the association with visual outcome, quality of life, and function indicates no clear effects.

Chapter 1. Introduction and Background

Purpose

This review will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2013 recommendation on screening for primary open-angle glaucoma (POAG) in adults.[1] In 2013, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for POAG in adults (I statement). The USPSTF came to this conclusion because it found no direct evidence on the benefits of screening, inadequate evidence on the effects of treatment of increased intraocular pressure (IOP) or early asymptomatic POAG on the development of impaired vision or quality of life, and potential risk of overdiagnosis and overtreatment. The USPSTF found convincing evidence that treatment of increased IOP and early glaucoma reduces the number of persons who develop small, clinically unnoticeable visual field defects and that treatment of early asymptomatic POAG decreases the number of persons whose visual field defects worsen; however, these were considered intermediate outcomes. The prior USPSTF recommendation was based on comparative effectiveness reviews (CERs) of screening[2] and treatment[3,4] for glaucoma; in this report these are referred to as the "prior screening CER" and the "prior treatment CER."

Condition Background

Condition Definition

Open-angle glaucoma (OAG) is a chronic, progressive neurodegenerative disease of the optic nerve characterized by structural optic disc and/or retinal nerve fiber layer thinning, with associated visual field defects (some authorities consider typical optic nerve changes or visual field defects to be sufficient to diagnosis glaucoma).[5] "Open" refers to an open anterior chamber angle on gonioscopy; this is in contrast to "closed" or narrow-angle glaucoma, which has a different presentation and treatment, and is outside the scope of this review. POAG, the focus of this review, is characterized by the absence of other known secondary causes, such as neovascularization, trauma, uveitis, or steroid use. OAG is generally bilateral, but can be asymmetric. The onset of POAG is often in mid to late adulthood. Although there is an association between elevated IOP (typically defined as ≥21 mm Hg) and OAG, up to 40 percent of patients with OAG do not have elevated IOP.[6-8]

"Glaucoma suspect" is a nonspecific term describing individuals who do not meet criteria for glaucoma, but have findings or risk factors associated with developing OAG.[5] Criteria for glaucoma suspect include a consistently elevated IOP, a suspicious appearance of the optic nerve, a strong family history of OAG, or visual field abnormalities consistent with glaucoma. "Ocular hypertension" refers to the presence of elevated IOP without glaucomatous changes of the optic nerve or visual fields.[9] It can be difficult to distinguish a glaucoma suspect from a patient with early OAG, and prospective followup and repeat diagnostic testing are often necessary to make the distinction.

Prevalence and Burden of Disease/Illness

Glaucoma is the second leading cause of irreversible blindness in the United States (U.S.), and the leading cause in Black and Latino persons.[8,10] Earlier stages of glaucoma can also impact quality of life and function, including ability to drive and risk of motor vehicle crashes.[11] Age-stratified data indicate a decrease in glaucoma related blindness (incidence within 10 years of diagnosis 8.7 per 100,000 for persons diagnosed in 1965 to 1980 and 5.5 per 100,000 for persons diagnosed in 1981 to 2000).[12] The degree to which the observed trend is related to improved treatment/management, earlier diagnosis, or other factors is unclear. The prevalence of POAG in the U.S. is estimated at about 2 percent, based on optic nerve fundus photography assessment of participants in the 2005 to 2008 National Health and Nutrition Examination Survey.[13] In 2011, an estimated 2.71 million persons had OAG; this number was projected to reach 3.7 million in 2020 and 4.3 million in 2025.[14,15] The number of persons with glaucoma increases with age, from an estimated 0.25 million persons 40 to 49 years of age to 1.28 million persons 70 to 79 years of age. In the U.S., Black and Latino persons a threefold or higher prevalence of OAG relative to non-Latino White persons.[8,13,16,17] In the U.S., the proportion of persons 40 years and older with ocular hypertension is estimated at 4.5 percent in non-Latino White and 3.5 percent in Latino persons.[14,16] Data on glaucoma suspect prevalence (not limited to ocular hypertension) are lacking.

Etiology and Natural History

The etiology of OAG is likely multifactorial, and includes genetic factors[18] and age-related neurodegeneration of the optic nerve.[19] The degree of IOP elevation correlates with the rapidity of OAG progression, though the susceptibility of individuals to IOP-related optic nerve damage varies.[5] As noted above, a substantial proportion of patients with OAG have an IOP within the normal range, and some patients with elevated IOP do not develop glaucoma.[20,21] In the Ocular Hypertension Treatment Study (OHTS), 9.5 percent of untreated glaucoma suspects with elevated IOP progressed to glaucoma after 5 years[21] and 29.5 percent after 20 years.[22]

Other factors hypothesized to contribute to the optic nerve damage seen in OAG include a deficient blood supply to the optic nerve, inadequate structural support for the neurons that comprise the optic nerve, and insufficient supplies of neurotrophins. The typical natural history of OAG is of gradual, often insidious, loss of retinal ganglion cells and corresponding loss of peripheral and/or central vision, potentially progressing to blindness. The vision loss is generally irreversible. A study of newly diagnosed OAG glaucoma patients in Olmsted County, Minnesota found that after 20 years, 27 percent were blind in one eye and 9 percent in both eyes.[23] However, the rate of progression varies. Visual field loss is often detectable before visual acuity loss, which usually occurs late in patients with glaucoma. While treatment strategies (currently all based on IOP lowering) can slow the progression of glaucomatous vision loss, some patients continue to lose vision despite apparently adequate IOP lowering.[24]

Risk Factors

A number of risk factors have been identified for OAG, including older age,[25-27] Black or Latino race/ethnicity,[8,16,25,28] family history,[26,29] higher IOP,[8,25] thinner central cornea,[25] optic disc hemorrhage,[30] large optic disc cup-to-disc ratio,[25] and lower ocular perfusion pressure (as determined by systemic blood pressure and IOP).[31]

Rationale for Screening/Screening Strategies

Untreated glaucoma can lead to irreversible vision loss or blindness. Early or mild glaucoma damage to the optic nerve may be asymptomatic and mild visual loss may not be perceived as warranting medical evaluation. Visual field loss from OAG is often not perceived by patients[32] and 50 percent or more of patients with OAG are unaware that they have glaucoma.[8,17,27,33] Therefore, screening could identify patients with asymptomatic or mild OAG who could benefit from early treatment to prevent further visual loss. Screening could also identify patients who are glaucoma suspects and might benefit from treatments or monitoring to prevent progression to OAG and/or vision loss.[21]

Screening for glaucoma is based on a number of tests, including tonometry (for IOP), ophthalmoscopy on dilated eye examination (for evaluation of the optic nerve), perimetry (visual field test), gonioscopy (to measure the angle in the eye where the iris meets the cornea), pachymetry (to measure the thickness of the cornea), and visual acuity testing.[34] Imaging tests, such as optical coherence testing (OCT, which uses low-coherence light to image the retina) and optic disc photography (to view the optic nerve head and/or retina) can supplement the clinical examination. A challenge in screening for glaucoma in primary care settings is that with the exception of visual acuity and certain tonometry tests, primary care clinicians lack training or equipment to perform much of the glaucoma clinical examination, which is typically performed in an eye specialty setting. As previously described, tonometry and visual acuity testing lack sensitivity for glaucoma because a significant proportion of patients have normal IOP and visual acuity changes are a late finding. In addition, diagnostic criteria for glaucoma lack consensus and are difficult to standardize.

Interventions/Treatment

The only known modifiable risk factor for glaucoma is IOP. Therefore, all current glaucoma treatments aim to lower IOP, even in persons with non-elevated IOP. An optimal target IOP has not been identified, and the IOP target is typically individualized, though the American Academy of Ophthalmology (AAO) suggests a reduction in IOP of 25 percent from baseline as a reasonable initial goal in most patients. Current IOP lowering strategies include topical medicated drops (prostaglandin analogs, beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, Rho kinase inhibitors, nitric oxide donators, and less frequently cholinergic agents),[21,35] oral agents (carbonic anhydrase inhibitors, hyperosmotic agents), laser trabeculoplasty,[36,37] laser cyclophotocoagulation,[38,39] and incisional surgery (i.e., trabeculectomy, glaucoma drainage device implantation, and angle-based surgeries).[40,41] The AAO recommends

medications or laser trabeculoplasty as initial therapy in most patients.[5] Topical prostaglandins are currently the most commonly used initial medication for OAG. Selective laser trabeculoplasty (SLT) using a frequency-doubled neodynmium:yttrium-aluminum-garnet laser produces less thermal damage to the trabecular network compared with argon laser trabeculoplasty and is the most commonly used laser trabeculoplasty technique. Surgery is usually reserved for patients with severe visual field loss at baseline or patients with advanced OAG who do not respond to medications or laser trabeculoplasty, due to complications associated with surgery. In patients who are glaucoma suspects, the AAO recommends a shared decision making approach, based on the risk of developing glaucoma, to determine whether to initiate treatment.[5] For persons with ocular hypertension, a risk calculator is available to estimate the risk of developing glaucoma in persons with ocular hypertension.[42]

New developments in treatment for glaucoma since the prior USPSTF recommendation include the approval by the U.S. Food and Drug Administration (FDA) of two new medications for OAG and ocular hypertension: latanoprostene bunod[43] (a nitric oxide-donating medication) and netarsudil[44] (a Rho kinase inhibitor). These are the first new medications approved for glaucoma since 1996. Unlike the majority of medications for OAG that decrease IOP by reducing aqueous production, these medications increase aqueous outflow. The development of newer minimally-invasive surgical procedures for treatment of OAG is ongoing.[45]

Current Clinical Practice/Recommendations of Other Groups

The AAO recommends a baseline comprehensive eye evaluation at age 40. In persons without risk factors for ocular disease, the AAO recommends examinations every 2 to 4 years for persons 40 to 54 years of age, every 1 to 3 years for persons 55 to 64 years of age, and every 1 to 2 years in persons 65 years of age or older.[5] In persons at higher risk for ocular disease, the AAO recommends that decisions regarding when to initiate eye evaluations and the frequency of periodic examinations be based on the risks, but does not provide specific guidance. For glaucoma evaluation, the AAO describes a number of components of the comprehensive eye examination, including visual acuity measurement, pupil examination, anterior segment examination, IOP measurement, gonioscopy, optic nerve head and retinal nerve fiber layer examination, and fundus examination.[5] Diagnostic tests include central corneal thickness measurement, visual field evaluation, and optic nerve hypoplasia and retinal nerve fiber layer imaging.

The American Academy of Family Physicians supports the USPSTF recommendation on glaucoma screening.[46]

Data on the frequency of glaucoma screening in primary care settings are not available, though it is unlikely to be high due to a lack of training and specialized equipment. Data are also not available on the proportion of patients in primary care settings referred for glaucoma screening. An area of ongoing interest is use of telemedicine to facilitate glaucoma screening in primary care settings,[47] and use of artificial intelligence for screening, diagnosis, and classification of glaucoma.[48]

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and Key Questions were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers using the methods developed by the USPSTF.[49] The analytic framework and Key Questions that guided the review are shown in **Figure 1**. In the Key Questions, "OAG" refers to POAG patients and glaucoma suspects. Eleven Key Questions were developed for this review:

Key Questions

1. What are the effects of screening for OAG versus no screening on a) IOP, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
2. What are the harms of screening for OAG versus no screening?
3. What are the effects of referral to an eye health provider versus no referral on a) IOP, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
4. What is the accuracy of screening for diagnosis of OAG?
5. What is the accuracy of instruments for identifying patients at higher risk of OAG?
6. What are the effects of medical treatments for OAG versus placebo or no treatments on a) IOP, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
7. What are the harms of medical treatments for OAG versus placebo or no treatments?
8. What are the effects of newly FDA-approved medical treatments (latanoprostene bunod and netarsudil) versus older medical treatments on a) IOP, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
9. What are the harms of newly FDA-approved medical treatments versus older medical treatments?
10. What are the effects of laser trabeculoplasty for OAG versus no trabeculoplasty or medical treatment on a) IOP, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
11. What are the harms of laser trabeculoplasty for OAG versus no trabeculoplasty or medical treatment?

The Key Questions focus on areas most relevant to inform recommendation on screening in primary care settings and are informed by evidence gaps identified in the prior reviews.[2,3] Key Questions on the effects of screening versus no screening on intermediate outcomes, health outcomes, and harms were carried forward from the prior reviews. A Key Question on the effects of referral to an eye health provider versus no referral was added, because diagnosis of glaucoma is often based on a comprehensive eye examination by an eye health provider. A Key Question on the accuracy of screening for diagnosis of OAG was also carried forward. We added a Key Question on the accuracy of risk prediction instruments to identify persons with OAG. Regarding

therapies, the prior treatment CER[3] included many head-to-head comparisons. In order to focus on the comparisons of most relevance for informing recommendations on screening, we included a Key Question focusing on the effectiveness of first-line medical therapies versus placebo or no therapy. We also included Key Questions of newly FDA-approved therapies compared with older medical therapies and SLT versus first-line therapies or no SLT, as trials comparing these therapies with placebo or no treatment were lacking.

Contextual Question

One Contextual Question was also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

1. What is the association between changes in IOP, visual field loss, visual acuity, or optic nerve damage following treatment for OAG and improvement in visual impairment, quality of life, or function, and what is the association between changes in IOP and visual field loss?

Search Strategies

A research librarian searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE (January 2011 to February 9, 2021), for relevant studies and systematic reviews. The search relied primarily on the previous systematic review for the USPSTF to identify potentially relevant studies published before 2011 (we reassessed all articles included in that systematic review using the eligibility criteria). Search strategies are available in **Appendix A1**. To supplement electronic searches, we reviewed reference lists of relevant articles. Ongoing surveillance was conducted to identify major studies published since February 2021 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on January 21, 2022, and identified no studies affecting review conclusions. One retrospective observational study[50] comparing glaucoma screening to no screening was identified during surveillance but was not eligible for inclusion due to observational design and serious methodological limitations (control group was non-participants/non-responders and study did not control for potential confounders).

Study Selection

At least two reviewers independently evaluated each study to determine eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each Key Question (**Appendix A2**).

Articles were selected for full-text review if they were about OAG or glaucoma suspect in adults 40 years of age or older, were relevant to a Key Question, and met the pre-defined inclusion criteria. We excluded studies of patients with narrow-angle glaucoma, secondary OAG (including exfoliation glaucoma), or advanced glaucoma (e.g., with severely impaired vision). We restricted inclusion to English-language articles and excluded studies published only as

abstracts. Studies of non-human subjects were also excluded, and studies had to report original data.

For screening, we included studies on a complete eye examination (as defined in the studies), various components of a complete eye examination (ophthalmoscopy, perimetry, tonometry, pachymetry, evaluation for afferent pupillary defect), and imaging tests (optic disc photography, optical coherence testing [OCT], and fundus photography). We excluded screening tests that are considered outdated or no longer used, such as the water drinking test, the Heidelberg Retina Tomograph, scanning laser polarimetry, and older OCT technology (time-domain OCT). For treatment, we included first line medical treatments (defined as prostaglandin analogues, beta-blockers, alpha2 agonists, and carbonic anhydrase inhibitors), SLT, and newly FDA-approved medical treatments (latanoprostene bunod and netarsudil). We excluded studies of combination treatment and trabeculectomy, which are not considered first line therapy for ocular hypertension or early glaucoma, and outdated therapies (e.g., argon laser trabeculoplasty). The comparison for screening was no screening and the main comparison for treatment was placebo or no treatment. We also included head-to-head trials that compared latanoprostene bunod or netarsudil with first-line medical therapies. For screening, referral, and treatment, outcomes were IOP, visual field loss, visual acuity, optic nerve damage, visual impairment (defined as visual acuity <20/70 or <20/100), quality of life, function, and harms (e.g., eye irritation, corneal abrasion, infection, anterior synechiae, cataracts), reported at least 4 weeks after initiating the intervention. We included randomized controlled trials (RCTs) of screening and treatment and cohort and cross-sectional studies on screening test diagnostic accuracy. We excluded diagnostic accuracy studies that used a case-control design, due to potential spectrum bias.[51] Telemedicine studies of screening were included if they were conducted in primary care settings. Studies on imaging test diagnostic accuracy that utilized artificial intelligence to analyze images were included if they evaluated a clinical cohort (e.g., did not analyze images in a databank), did not use a case-control design, reported validation testing, and utilized algorithms available for widespread use. Studies on screening accuracy were not restricted by clinical setting, although results from primary care settings were highlighted if available. This report utilized primary studies and systematic reviews were used to identify potentially eligible studies. In accordance with USPSTF methods, studies rated poor quality (see below) were excluded.

The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member.

Predefined criteria were used to assess the quality of individual studies by using criteria developed by the USPSTF. Studies were rated as "good," "fair," or "poor" per USPSTF criteria,

depending on the seriousness of methodological shortcomings (**Appendix A6**).[49] For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis and Analysis

We performed a random effects meta-analysis using the profile likelihood model to summarize the effects of first-line medical treatments versus placebo or no treatment on likelihood of glaucoma progression (based on progression of visual field loss, with or without optic nerve changes), serious adverse events, and withdrawal due to adverse events and mean IOP. Glaucoma progression, serious adverse events, and withdrawal due to adverse events were evaluated as dichotomous outcomes using the relative risk. IOP was evaluated as a continuous outcome using the mean difference. For mean IOP, adjusted differences were utilized when reported; otherwise, the difference in followup IOP was utilized when available, followed by the difference in change from baseline. Further, differences based on per-individual data were used when available. For trials that randomized each individual to a treatment but reported a per-eye analysis (i.e., two eyes per individual), the mean IOP was averaged between the two eyes and the standard deviation (SD) for the mean IOP was calculated by assuming a correlation of 0.5 between an individual's eyes. For trials in which one eye in each individual was randomized to the medical treatment and the other eye received the control treatment, the mean difference based on the within-subject comparison was utilized. If the SD for the within-subject mean difference was not reported, it was calculated based on the reported SD for each treatment group, again, assuming a correlation of 0.5. When the SD for the followup IOP was not reported, it was imputed using the average coefficient of variation from other included trials. Comparable interventions within the same study were combined in the primary analysis, so each study was represented once in a meta-analysis in order to avoid overweighting. Analyses were stratified by the type of medical treatment (alpha agonist, prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor, or mixed) and prespecified study-level subgroup analyses were conducted on the following factors: glaucoma status (OAG, ocular hypertension, or mixed); quality (good or fair); mean IOP (<20 vs. ≥20 mm Hg), and duration of followup (<1 year vs. ≥1 year). For glaucoma progression, a sensitivity analysis restricted to trials that defined progression based on visual field loss (excluding optic nerve changes) was conducted. Statistical heterogeneity was assessed using the Cochran Q-test and I^2 statistic.[52] When at least 10 studies were available for meta-analysis, we tested for small sample effects using graphical (funnel plot) and statistical (Egger's test) methods. All meta-analyses were conducted using Stata 14.2 or Stata/SE 16.1 (Statacorp, College Station, Texas).

For diagnostic accuracy, a bivariate logistic random effects model was used to summarize sensitivity and specificity of screening tests simultaneously for identifying glaucomatous eyes from those without glaucoma (healthy eyes, glaucoma suspect, or ocular hypertension). A bivariate model was used to account for the correlation between sensitivity and specificity, to produce summary values for sensitivity and specificity with corresponding 95 percent confidence intervals (CIs). For the bivariate model, at least four studies were needed to pool. Meta-analysis was restricted to studies that used one eye per individual; studies that used both eyes were not included in the meta-analysis because they did not report the correlation between eyes and inclusion would result in overweighting. When studies reported a range of testing cutoffs, data

based on the most commonly used cutoff (e.g., IOP >21 mm Hg) or closest to it were utilized. For one study[53] that reported sensitivities across multiple specificities without reporting a cutoff, the sensitivity and specificity pair with the fewest misclassifications were utilized. Meta-analysis using a random effects Dersimonian-Laird model was also performed to summarize the area under the receiver operating characteristic (AUROC) curve as reported in individual studies. Stratified analyses were conducted based on the type of control (healthy eye, glaucoma suspect, or ocular hypertension) and study quality (good or fair). Sensitivity analyses were conducted on factors related to specific imaging tests: for retinal nerve fiber layer on spectral domain-OCT, sensitivity analysis was restricted to studies that measured retinal nerve fiber layer based on the mean thickness; for ganglion cell complex on spectral domain-OCT, sensitivity analysis was restricted to studies that utilized measures of the retinal nerve fiber layer, inner plexiform layer, and the ganglion cell layer; and for studies of tonometry, sensitivity analysis was restricted to studies that measured IOP using Goldmann tonometry. Statistical heterogeneity was assessed using the I^2; however, this value is often high and difficult to interpret in diagnostic accuracy studies because it is dependent on sample size and is a univariate measure that does not account for variability in sensitivity or specificity estimates due to threshold effects.

For all Key Questions, the overall strength of evidence was determined using the approach described in the USPSTF Procedure Manual.[49] The strength of evidence was rated "high", "moderate", "low" or "insufficient" based on study quality, consistency of results between studies, precision of estimates, study limitations, and risk of reporting bias.[49] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and Key Questions and to resolve issues around scope for the final evidence synthesis.

AHRQ staff provided oversight for the project, coordinated systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Expert Review and Public Comment

The draft research plan was posted for public comment from February 13, 2020 to March 11, 2010. The comments were reviewed and no changes to the scope or Key Questions were required, though some edits were made for clarity. The eligibility criteria table (**Appendix A2**) was revised to clarify included and excluded diagnostic tests for glaucoma; tests that are no longer used were excluded. A final research plan was posted on the USPSTF's Web site on June 11, 2020.

A draft version of this report was reviewed by content experts and Federal partner representatives (**Appendix A7**), and edits were made for clarity. In addition, the draft was posted for public comment from October 26, 2021 to November 22, 2021. The comments were

reviewed and minor edits were made for clarity. However, no changes to the studies or findings were required.

Chapter 3. Results

A total of 6,225 new references from electronic database searches and manual searches of recently published studies were reviewed and 1,003 full-text papers were evaluated for inclusion. We included a total of 83 studies (in 96 publications) with 75,887 total participants[16,21,35,37,53-144] Sixty-seven studies were newly identified as part of this update and 16 were carried forward from the previous USPSTF reviews. Included studies and quality ratings are described in **Appendix B**.

Key Question 1. What Are the Effects of Screening for OAG vs. No Screening on a) IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage or b) Visual Impairment, Quality of Life, or Function?

Summary

- One trial (N=616) of frail elderly persons found no difference between vision screening, including components for glaucoma, versus no screening on vision outcomes (mean logarithm of the minimum angle of resolution [logMAR] distance visual acuity scores 0.27 vs. 0.25, p=0.32, and mean logMAR near visual acuity scores -0.01 vs. -0.03, p=0.26) and vision-related quality of life (National Eye Institute Visual Function Questionnaire-25 [NEI-VFQ-25] mean composite scores 84.3 vs. 86.4, p=0.49) after 1 year.

Evidence

The prior screening CER included no trials comparing screening with no screening.[2] We identified one good-quality trial (n=616) conducted in Australia comparing vision screening by an optometrist with no screening that included components relevant for diagnosis of glaucoma (IOP, direct ophthalmoscopy, and visual field) as well as other visual testing (visual acuity, contrast sensitivity, and slit lamp examination; **Appendix B Table 1**).[132] In the screened group, interventions for screen-positive persons included referral to an ophthalmologist or public hospital eye clinic and/or an occupational therapist (for home modifications, mobility training, or a cane); those in the control group received no vision assessment or intervention. The mean age was 81 years and 68 percent were female; race and ethnicity were not reported. Thirty-one percent of participants needed help with activities of daily living at baseline and 52 percent were taking more than four medications. At baseline, 46 percent of participants had experienced a fall in the past year. At baseline, mean visual acuity was 0.22 logMAR (Snellen 20/30), the mean NEI-VFQ-25 score was 85.5 (scale 0 to 100, higher is better), 63 percent had cataracts, 39 percent had undergone cataract surgery, and 98 percent wore glasses. Fourteen percent of patients had glaucoma at baseline and 50 percent self-reported vision as "good." In addition to appropriate randomization, the trial blinded outcome assessors and data analysts and attrition was low (11% screening arm and 16% control arm; **Appendix B Table 2**). Nearly half (48.7%)

of the patients in the screening arm were judged to need treatment, though only 5.5 percent of patients judged to need treatment were referred for glaucoma management. Other interventions were new glasses (29.8%), referral for cataract surgery (4.9%), referral for age-related macular degeneration (AMD) (1.6%), and referral to an occupational therapist (7.7%).

At 1 year, there were no differences in vision parameters or vision-related quality of life. Mean distance visual acuity was 0.27 vs. 0.25 logMAR (p=0.32), mean near visual acuity -0.01 vs. -0.03 logMAR (p=0.26), and NEI-VFQ-25 mean composite scores were 84.3 vs. 86.4 (p=0.49). Nearly three-quarters of patients in the control group reported having seen an eye care professional in the 12 months prior to study, which could have attenuated potential benefits of screening.

Key Question 2. What Are the Harms of Screening for OAG vs. No Screening?

Summary

- One trial (n=616) found screening associated with an increased risk for falls versus no screening (incidence rate ratio 1.57, 95% CI 1.20 to 2.05, and risk of one or more falls 65% vs. 50%, RR 1.31, 95% CI 1.13 to 1.50); screening was associated with increased risk for fractures that was not statistically significant (RR 1.74, 95% CI 0.97 to 3.11).

Evidence

No trial in the prior screening CER compared harms of screening with no screening.[2] A previously-described trial[132] of vision screening (including components for identification of glaucoma) versus no screening in frail elderly reported risk of falls and fracture (**Appendix B Table 1**).[72] In the trial, 46 percent of patients had fallen in the past year. Although the trial hypothesized that screening would reduce the risk of falls, screening was associated with increased incidence of falls (758 vs. 516 falls, incidence rate ratio 1.57, 95% CI 1.20 to 2.05), risk of one or more falls (65% vs. 50%, RR 1.31, 95% CI 1.13 to 1.50), and risk of two or more falls (38% vs. 31%, RR 1.24, 95% CI 0.99 to 1.54) versus no screening. Screening was also associated with increased risk of fracture, though the difference was just above the threshold for statistical significance (10% vs. 5.7%, RR 1.74, 95% CI 0.97 to 3.11, p=0.06).

Key Question 3. What Are the Effects of Referral to an Eye Health Provider vs. No Referral on a) IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage or b) Visual Impairment, Quality Of Life, or Function?

No eligible study compared effects of referral to an eye health provider for glaucoma with no referral.

Key Question 4. What Is the Accuracy of Screening for Diagnosis of OAG?

Summary

- Retinal nerve fiber layer thickness on spectral domain-OCT was associated with a pooled sensitivity of 0.79 (95% CI 0.75 to 0.83) and specificity of 0.92 (95% CI 0.87 to 0.96) for distinguishing between glaucomatous eyes and controls, based on 15 studies (N=4,242); the pooled AUROC curve was 0.90 (95% CI 0.86 to 0.93), based on 16 studies (N=4,060).
- Ganglion cell complex thickness on spectral domain-OCT was associated with a pooled sensitivity of 0.74 (95% CI 0.68 to 0.80) and specificity of 0.91 (95% CI 0.80 to 0.96) for distinguishing between glaucomatous eyes and controls, based on nine studies (N=1,522); the pooled AUROC curve was 0.88 (95% CI 0.84 to 0.92), based on six studies (N=765).
- Tonometry was associated with a pooled sensitivity of 0.48 (95% CI 0.31 to 0.66) and specificity of 0.94 (95% CI 0.90 to 0.96), based on 13 studies (N=32,892).
- The Humphrey Visual Field Analyzer was associated with a pooled sensitivity of 0.87 (95% CI 0.69 to 0.95) and specificity of 0.82 (95% CI 0.66 to 0.92) for distinguishing between glaucomatous eyes and controls, based on six studies (N=11,244).
- Evidence on diagnostic accuracy was limited for other screening tests: cup-to-disc ratio on spectral domain-OCT, swept source-OCT, optic disc photography, ophthalmoscopy/biomicroscopy/stereoscopy, pachymetry, and afferent papillary defect.
- One pilot study (n=56) and a followup study (n=256) found a telemedicine screening intervention performed in a primary care setting had variable sensitivity but high specificity for identifying persons with glaucoma compared with a face-to-face evaluation by an ophthalmologist.

Evidence

The prior screening CER[2] included a systematic review[145] and 83 additional studies on the diagnostic accuracy of tests for glaucoma. Since the prior screening CER, several diagnostic tests have been superseded by newer technologies and are not included in this review. For example, for imaging the optic nerve and retinal structures, OCT has superseded Heidelberg retina

tomography and scanning laser polarimetry; for evaluating visual field loss, the Humphrey Field Analyzer has superseded frequency doubling technology. In addition, the prior screening CER included case-control studies, which were excluded from this review, and had an emphasis on comparative diagnostic accuracy, which was not the focus of this review. The prior screening CER concluded that it was unclear whether any one test or combination of tests was suitable for glaucoma screening in the general population, due to the lack of a definitive diagnostic reference standard for glaucoma and heterogeneity in the design and conduct of the studies.

This review includes 53 diagnostic accuracy studies (sample sizes 46 to 8623, N=65,464 in 59 publications.) (**Table 1; Appendix B Tables 3-4**)[16,53-56,59-61,64,65,67-71,73-77,79-81,84-86,88,89,93,95-97,99-102,104-112,116,117,120,122,125,128,130,131,133,135-138,144] The largest groups of studies evaluated spectral domain-OCT (k=29, N=11,434) and tonometry (k=17, N=49,742), followed by visual fields (k=10, N=11,633), ophthalmoscopy/biomicroscopy/stereopscopy (k=3, N=17,519), optic disc photography (k=4, N=3,133), pachymetry (k=2, N=6,129), telemedicine (k=2, N=308), and afferent pupillary defect (k=1, N=107). Most studies evaluated more than one test of diagnostic accuracy. Forty-six studies included a single eye per participant in the analysis, and six studies[75,93,101,112,116,122] allowed two eyes per participant (the number of eyes analyzed was unclear in one study[105]). In most studies, the reference standard was based on findings related to ophthalmic structure (e.g., appearance of optic disc) as well as function (e.g., visual fields), though exact criteria differed (**Appendix B Table 3**).

Mean age ranged from 38.2 years to 82.2 years (median 58 years). The proportion of females enrolled ranged from 13.3 to 72.3 percent (median 55%) in studies that reported gender. Twelve studies reported race/ethnicity. Two studies restricted enrollment to Asian persons,[130,131] one study restricted enrollment to Latino persons,[80] and one study restricted enrollment to White persons.[81] In the other studies, the proportion of White participants ranged from 17 to 99 percent. In two of the studies, the majority of participants (61% and 62%) were Black.[86,110] Studies were conducted in Western Europe (N=16), the U.S. (N=13), and Asia (N=18); two studies were conducted in Turkey and one study each was conducted in Hungary, Australia, New Zealand, and Croatia. The prevalence of glaucoma ranged from 1.1[93] to 73.6[100] percent. Seven studies were rated good quality[56,59,73,80,109,111,122] and the remainder were rated fair quality (**Appendix B Table 5**). Methodological limitations in the fair-quality studies included lack of blinding and uncertain interval between index and reference tests.

Tests of Ophthalmic Structure

The diagnosis of glaucoma is typically made by using tests of both ophthalmic structure and function together. Tests of eye structure include OCT, optic disc photography, and clinical examination with an ophthalmoscope or slit-lamp (biomicroscopy). Thirty studies (N=11,618) evaluated OCT (**Appendix B Tables 3-4**). Four studies were rated good quality (N=2,575)[56,59,73,122] and 27 were rated fair quality (N=8,859)[53-55,64,67,71,75,76,79,81,93,96,97,99-101,104-106,116,120,125,128,131,136,144] (**Appendix B Table 5**).

Optical Coherence Tomography

There are three types of OCT: time domain, spectral domain, and swept source. Time domain-

OCT represents the earliest technology and became commercially available in 1996.[146] Time domain-OCTs have a movable reference light and can produce 400 axial scans of the eye per second. Time domain-OCT was not included in this review as it has been superseded by spectral domain-OCT, which entered the market in 2006, uses a fixed reference light, and can produce 50,000 axial scans per second, resulting in images with greater resolution.[146] Swept source is the latest OCT technology and is even faster than spectral domain-OCT (200,000 or more axial scans per second), but is not yet in widespread use. The primary parameters used on OCT are the thickness of the retinal nerve fiber layer and the ganglion cell complex.

The prior screening CER included 48 studies of OCT. Based on average retinal nerve fiber layer estimates on OCT, sensitivity ranged from 24 to 96 percent and specificity ranged from 66 to 100 percent. Many studies (k=34) in the prior screening CER used time domain-OCT and are not included in this review. Two studies of spectral domain-OCT were carried forward from the prior USPSTF report (k=2, n=283),[55,131] and we identified 27 new studies (N=14,199). Twenty-nine studies (N=14,482) evaluated spectral domain-OCT[53-56,59,64,67,71,73,75,76,79,81,93,96,97,99-101,104,106,116,120,122,125,128,136,144] and three studies (n=120, 145, and not reported) assessed swept source-OCT.[104-106]

Retinal Nerve Fiber Layer Thickness

Retinal nerve fiber layer thickness on spectral domain-OCT was associated with a pooled sensitivity of 0.79 (95% CI 0.75 to 0.83) and specificity of 0.92 (95% CI 0.87 to 0.96) for diagnosing eyes with glaucoma versus no glaucoma (healthy eyes, glaucoma suspect, and/or ocular hypertension), based on 15 studies (N=4,242)[53,54,56,59,64,71,73,76,81,99,104,106,128,131,136] (**Table 2, Figures 2-3**). Pooled estimates were similar when the analysis was limited to studies in which the control group was healthy eyes (9 studies, N=2,404, sensitivity 0.81, 95% CI 0.74 to 0.86 and specificity 0.96, 95% CI 0.89 to 0.99).[53,54,56,73,81,99,104,106,131] Pooled estimates were also similar when the analysis was limited to studies that measured retinal nerve fiber layer based on the mean overall thickness as opposed to mean inferior,[81] mean outer/inferior,[71,104] or mean temporal/inferior retinal nerve fiber layer thickness[53,54] (12 studies, N=3,819, sensitivity 0.79, 95% CI 0.74 to 0.84 and specificity 0.90, 95% CI 0.85 to 0.93),[56,59,64,71,73,76,99,104,106,128,131,136] and when results were limited to the 12 fair-quality studies (N=1,880, sensitivity 0.80, 95% CI 0.74 to 0.85; specificity 0.94, 95% CI 0.88 to 0.97).[53,54,64,71,76,81,99,104,106,128,131,136] In three good-quality studies (N=2,400),[56,59,73] sensitivity ranged from 0.69 to 0.81 and specificity ranged from 0.79 to 0.94. One study (n=129) also reported accuracy of retinal nerve fiber layer thickness for diagnosing ocular hypertension versus healthy eyes (sensitivity 0.08, 95% CI 0.005 to 0.63; specificity 1.00, 95% CI 0.96 to 1.00).[81]

Five studies on diagnostic accuracy of retinal nerve fiber layer thickness on spectral domain-OCT were not pooled because they were based on the inter-eye retinal nerve fiber layer thickness asymmetry[79] or because they evaluated more than one eye per participant.[75,93,101,122] Details of these studies are shown in **Appendix B Tables 3 and 4**.

Retinal nerve fiber layer on spectral domain-OCT was associated with high discrimination for distinguishing glaucomatous eyes from non-glaucoma, with a pooled AUROC curve of 0.90 (95% CI 0.86 to 0.93, I^2=96%), based on 16 studies (N=4,060)[53-56,59,64,71,76,96,97,99,100,104,106,120,128

(**Figure 4**). Discrimination was similar for the two good-quality studies (N=1,944, pooled AUROC 0.87, 95% CI 0.80 to 0.94, I^2=86%)[56,59] and 14 fair-quality studies (N=2,116, pooled AUROC 0.90, 95% CI 0.86 to 0.94, I^2=97%).[53-55,64,71,76,97,99,100,104,106,120,128] All studies reported an AUROC greater than or equal to 0.83, with the exception of two studies that reported an AUROC of 0.78.[54,71] Results were similar in a sensitivity analysis restricted to studies that utilized overall mean retinal nerve fiber layer thickness (12 studies, N=3,634, AUROC 0.92, 95% CI 0.89 to 0.94, I^2=80%**)** and in an analysis stratified according to whether the non-glaucoma group was healthy eyes (10 studies, N=2,262, AUROC 0.92, 95% CI 0.89 to 0.94, I^2=84%),[53-56,96,99,100,104,106,120] glaucoma suspects (4 studies, N=496, AUROC, 0.90, 95% CI 0.86 to 0.94, I^2=51%),[64,76,96,99] or ocular hypertension (3 studies, N=319, AUROC 0.80, 95% CI 0.71 to 0.89, I^2=87%)[54,71,96] (**Figure 5**).

Three studies (N=364) of retinal nerve fiber layer reported a pooled AUROC of 0.76 (95% 0.63 to 0.90, I^2=83%) for discrimination of glaucoma suspect from healthy eyes.[55,96,97] One study (n=122) of retinal nerve fiber layer reported an AUROC of 0.64 (95% CI 0.54 to 0.75) for discrimination of ocular hypertension from healthy eyes.[96] Four other studies reported discrimination of retinal nerve fiber layer but were not pooled due to inadequate data (N=1,335)[73,125,136,144] or because they enrolled more than one eye in some participants (N=659).[67,75,116] Details are shown in **Appendix B Tables 3 and 4**.

Ganglion Cell Complex

The ganglion cell complex is composed of three thickness areas which can be imaged using OCT: the retinal nerve fiber layer, the inner plexiform layer, and the ganglion cell layer. Ganglion cell complex on spectral domain-OCT was associated with a pooled sensitivity of 0.74 (95% CI 0.68 to 0.80) and pooled specificity of 0.91 (95% CI 0.80 to 0.96) for identifying individuals with glaucoma, based on nine studies (N=1,522)[53,54,71,73,76,81,104,106,136] (**Table 3; Figures 6 and 7**). Estimates were similar when three studies[71,76,136] in which persons with ocular hypertension or glaucoma suspects were excluded from the analysis (6 studies, N=1,145, sensitivity 0.76, 95% CI 0.66 to 0.83 and specificity 0.92, 95% CI 0.86 to 0.96). Estimates were also similar when studies that reported only the ganglion cell layer or inner plexiform layer[71,76,104,106] were excluded (5 studies, N=998, pooled sensitivity 0.73, 95% CI 0.60 to 0.83 and pooled specificity 0.95, 95% CI 0.87 to 0.98). One good-quality study (n=456) reported sensitivity of 0.62 (95% CI 0.41 to 0.80) and specificity of 0.93 (95% CI 0.91 to 0.96);[73] in eight fair-quality studies (N=542) pooled sensitivity was 0.75 (95% CI 0.68 to 0.81) and pooled specificity was 0.91 (95% CI 0.78 to 0.97).[53,54,71,76,81,104,106,136]

Six fair-quality studies found ganglion cell complex, ganglion cell layer, and inner plexiform layer associated with high discrimination for distinguishing glaucoma from non-glaucoma (N=765, AUROC 0.88, 95% CI 0.84 to 0.92, I^2=68%)[53,54,75,96,104,106] (**Figure 8**). Results were similar when the non-glaucoma groups were stratified as healthy eyes (5 studies, N=564, AUROC 0.87, 95% CI 0.82 to 0.92, I^2=70%),[53,54,96,104,106] glaucoma-suspect eyes (2 studies, N=354, AUROC 0.84, 95% CI 0.69 to 1.00, I^2=92%),[75,96] or eyes with ocular hypertension (2 studies, N=224, AUROC 0.76, 95% CI 0.70 to 0.82, I^2=0%)[54,96] (**Figure 9**). Results were also similar when the analysis was restricted to two studies that assessed the ganglion cell complex (N=211, AUROC 0.87, 95% CI 0.73 to 1.00, I^2=89%).[53,54] Five studies could not be pooled due

to inadequate data (e.g., reported sensitivity, specificity and/or AUROC without confidence intervals, only reported odds ratios),[71,122,125,136] or did not report standard AUROC.[73] Four studies were not pooled because they enrolled more than one eye in some participants.[67,75,93,101] Details are provided in **Appendix B Tables 3-4**.

Cup-to-Disc Ratio

One study (N=286) found the cup-to-disc ratio on spectral domain-OCT associated with sensitivity of 0.84 (95% CI 0.77 to 0.89) and specificity of 0.72 (95% CI 0.60 to 0.81) for identifying persons with glaucoma versus healthy eyes. The cup-to-disc ratio threshold for a positive test was not specified.[81]

Three studies (n=1,870) found the spectral domain-OCT vertical cup-to-disc ratio associated with an AUROC that ranged from 0.74 to 0.94[100,101,144] (**Table 4**). These studies were not pooled because they enrolled more than one eye in some participants[101,144] and one did not report SD.[144]

Swept Source–OCT

Swept source-OCT utilizes a longer wavelength than spectral domain-OCT to visualize deeper structures and is faster than spectral domain-OCT.

Two studies (reported in 3 publications, N=266) assessed the diagnostic accuracy of swept-source OCT using retinal nerve fiber layer thickness.[104-106] One study found wide-field retinal nerve fiber layer thickness map associated with sensitivity of 0.95 (95% CI 0.90 to 0.98) and specificity of 0.89 (95% CI 0.75 to 0.97) for distinguishing between participants with glaucoma and participants with healthy eyes.[106] The other study reported an AUROC for distinguishing persons with glaucoma from those with healthy eyes of 0.85 (95% CI 0.78 to 0.92) for the retinal nerve fiber layer outer/inferior sector and 0.83 (95% CI 0.75 to 0.90) for the outer/temporal sector of the ganglion cell inner plexiform layer.[104] Another article (n=not reported; 184 eyes)[105] reported an AUROC of 0.85 (95% CI 0.78 to 0.91) for discriminating between early perimetric glaucoma and healthy eyes of 0.85 (95% CI 0.78 to 0.91) for the retinal nerve fiber layer thickness and 0.87 (95% CI 0.80 to 0.92) for the ganglion cell inner plexiform layer (inferior temporal).

Optic Disc Photography

Four studies (N=3,133) reported diagnostic accuracy of cup-to-disc ratio on optic disc photography, separate from OCT.[64,74,86,107] One study (n=2,631) screened participants with indirect ophthalmoscopy as well as disc photographs to assess the optic disc[107] (**Table 5**).

Two studies reported similar discrimination of cup-to-disc ratio on optic disc photography, with AUROCs of 0.85 (95% CI 0.74 to 0.96) and 0.81 (95% CI 0.74 to 0.92).[64,74] In one of these studies, sensitivity was 0.64 (95% CI 0.45 to 0.81) and specificity was 0.73 (95% CI 0.45 to 0.92) for distinguishing persons with glaucoma from glaucoma suspects; the cup-to-disc ratio threshold was not reported.[64] Two studies did not report discrimination; in one study sensitivity was 0.18 (95% CI 0.09 to 0.31) and specificity was 0.67 (95% CI 0.62 to 0.71) based on a cup-

to-disc ratio threshold of 0.4.[107] In the other study, sensitivity was 0.71 (95% CI 0.54 to 0.85) and specificity was 0.49 (95% CI 0.44 to 0.55) for distinguishing between glaucoma and nonglaucoma, based on a cup-to-disc ratio of 0.65 for average-sized or large discs and 0.5 for small discs.[86]

Ophthalmoscopy, Biomicroscopy, and Stereoscopy

Five studies reported accuracy of cup-to-disc ratio on ophthalmoscopy, biomicroscopy, and stereoscopy (N=17,519)[80,84,107,130,135] (**Table 6**). Studies were not pooled because the methods used to determine cup-to-disc ratio as well as the cutoffs to define a positive screen varied. Although specificity was high in all studies, sensitivity varied widely (range 0.18 to 0.92).

Pachymetry

Two studies (N=6,129) reported the diagnostic accuracy of corneal thickness on pachymetry.[60,80] One study (n=6,082) reported a sensitivity of 0.16 (95% CI 0.11 to 0.21) and specificity of 0.91 (95% CI 0.90 to 0.92) for distinguishing between glaucoma and non-glaucoma within a Latino population using a central corneal thickness of less than or equal to 504µm.[80] The other study (n=47) reported an AUROC of 0.55 (standard error [SE] 0.08) for pachymetry; sensitivity and specificity were not reported.[60]

Tests of Ophthalmic Function

Tests of optic nerve function include measurements of IOP through tonometry and visual field assessment.

Visual Fields

The Humphrey Field Analyzer has superseded frequency doubling technology as standard of care for the assessment of visual fields. Although the Humphrey Field Analyzer was often used as part of the reference standard for the diagnosis of glaucoma, 10 studies (N=11,633) reported diagnostic accuracy of the Humphrey Field Analyzer against a reference standard.[64,74,80,88,89,95,108,112,117,122] In these studies, Humphrey Field Analyzer methods varied: five studies used the Swedish Interactive Threshold Algorithm-Standard 24-2,[64,74,80,108,122] two use the 76-point 30 degree suprathreshold,[88,89] and one study each used the Full Field 120 Protocol,[95] the 630 Armaly Full Field Test,[112] and the Central 30-2 (Goldmann III stimulus).[117]

The Humphrey Field Analyzer was associated with pooled sensitivity of 0.87 (95% CI 0.69 to 0.95) and pooled specificity of 0.82 (95% CI 0.66 to 0.92), based on six studies (N=11,244)[64,80,88,95,108,117] (**Figures 10 and 11**). There were too few studies of specific Humphrey Field Analyzer methods to conduct a meaningful analysis stratified by method (**Table 7**). One good-quality study (N=6,082)[80] reported a sensitivity of 0.88 (95% CI 0.83 to 0.92) and specificity of 0.64 (95% CI 0.63 to 0.65) using SITA-Standard 24-2.

The mean deviation on the SITA-Standard 24-2 was associated with a pooled AUROC (0.83, 95% CI 0.70 to 0.97, I^2=88%), based on three studies (N=288).[64,74,108] (**Figure 12**) and the pattern standard deviation was associated with an AUROC of 0.87 (95% CI 0.76 to 0.99), based on two studies (N=242)[74,108] (**Figure 13**). One other study found the 76-point 30 degree suprathreshold associated with an AUROC of 0.87 (CI not reported).[89]

One study (n=175; 280 eyes) found the Humphrey Field Analyzer, Swedish Interactive Threshold associated with sensitivity of 0.70 (95% CI 0.63 to 0.77) and specificity of 0.95 (95% CI 0.89 to 0.98).[122] Another study (n=104; 182 eyes) found the Humphrey Field Analyzer, Armaly full field test associated with a sensitivity of 0.64 (95% CI 0.56 to 0.72) and specificity of 0.64 (95% CI 0.48 to 0.78).[112] Because these studies included more than one eye of some participants, they were not included in pooled analysis.

Afferent Pupillary Defect

One study (N=107) tested afferent pupillary defect using the swinging flashlight test.[69] Sensitivity was 0.67 (95% CI 0.54 to 0.78) and specificity was 0.83 (95% CI 0.67 to 0.92). Sensitivity and specificity were similar when 40 participants without prior cataract surgery were excluded from the analysis (sensitivity 0.69, 95% CI 0.50 to 0.83; specificity 0.89, 95% CI 0.72 to 0.96).

Tests of IOP Measurement

Tonometry

Seventeen studies (n=49,742) evaluated the accuracy of tonometry for identifying glaucoma.[60,65,68,70,73,77,80,84,86,89,93,102,107,117,133,135,138] Tonometry was associated with a pooled sensitivity of 0.48 (95% CI 0.31 to 0.66) and pooled specificity of 0.94 (95% CI 0.90 to 0.96) for diagnosing glaucoma from non-glaucomatous or healthy eyes, based on 13 studies (N=32,892)[65,68,73,77,80,84,86,102,107,117,133,135,138] (**Figures 14 and 15; Table 8**). The IOP cutoff was 21 to 22 mm Hg in all studies except for two, which used cutoffs of 22.6[84] and 25 mm Hg.[93] Results were similar when one study[138] that compared diagnostic accuracy for probable glaucoma with not probable glaucoma was excluded from the analysis (12 studies, N=28,726, pooled sensitivity 0.47, 95% CI 0.29 to 0.66 and pooled specificity 0.94, 95% CI 0.90 to 0.97). When stratified by tonometry method, sensitivity was higher for Goldmann tonometry (4 studies, N=11,690; sensitivity 0.66, 95% CI 0.36 to 0.87) [65,77,80,102] than for other methods (9 studies, N=21,202, sensitivity 0.39, 95% CI 0.22 to 0.58) (**Table 8**). However, the sensitivity estimate for Goldmann tonometry was imprecise. Specificity was similar regardless of tonometry technique. Results were also similar when the analysis was limited to fair-quality studies (11 studies, N=26,305, pooled sensitivity 0.54, 95% CI 0.34 to 0.72 and specificity 0.94, 95% CI 0.89 to 0.97).[65,68,77,84,86,95,102,107,117,135,138] Only two studies were rated good quality[73,80] (sensitivity 0.24, 95% CI 0.19 to 0.30 and 0.19, 95% CI 0.07 to 0.39 and specificity 0.97, 95% CI 0.97 to 0.97 and 0.89, 95% CI 0.86 to 0.92). One study that included more than one eye per individual (n=3,039, eyes=6,060) reported a sensitivity of 0.07 (95% CI 0.01 to 0.19) and specificity of 0.99 (95% CI 0.99 to 0.99) for glaucoma versus non-glaucoma, based on an IOP threshold of >25 mm Hg using a rebound tonometer.[93] Two studies (N=418) found tonometry associated with low

sensitivity (0.01, 95% CI 0.00 to 0.05 and 0.27, 95% CI 0.20 to 0.36) and high specificity (0.98, 95% CI 0.94 to 1.00 and 0.81, 95% CI 0.73 to 0.88) for distinguishing glaucoma suspects versus healthy controls.[86,117]

In three studies (N=4,684), discrimination of tonometry based on the AUROC ranged from 0.66 to 0.78.[60,77,89] All three studies used Goldmann applanation tonometry (**Figures 16 and 17**).

One study (N=6,310) that evaluated intereye IOP asymmetry on tonometry[70] was not pooled; details are shown in **Appendix B Tables 3 and 4**.

Other

Telemedicine Screening

Two studies examined the diagnostic accuracy of a telemedicine screening intervention called Technology-based Eye Care Services used in the Veteran Affairs Healthcare System.[109-111] The first was a small pilot study (n=52) where screening was conducted in primary care clinics and consisted of distance auto-refraction, visual acuity, tonometry, pachymetry, and a pupil exam for depth, reactivity, afferent papillary defect, and fundus. A blinded ophthalmologist reviewed screening findings and made recommendations for the participant. These recommendations were compared with the diagnosis and recommendations of a physician who conducted a face-to-face exam, which was considered the reference standard. In the pilot study, the technology-based exam was associated with sensitivity of 0.64 (95% CI 0.35 to 0.87) and specificity of 0.95 (95% CI 0.82 to 0.99).

A subsequent, larger (n=256) followup study followed a similar protocol as the pilot study.[111] Most participants were male (87%) and Black (61%) and over a quarter of participants had a history of eye trauma (28%) or a family history of eye diagnosis or blindness (25%). Participants had no known ocular disease; those with "glaucoma suspect" history and documented visual field changes or prior treatment were excluded. Two ophthalmologists reviewed the screening findings and accuracy was compared against a face-to-face exam. On the face-to-face exam, 26.6% (68/256) were diagnosed with glaucoma or glaucoma suspect; other conditions diagnosed were cataracts referred for surgery (3.9%), macular degeneration (2.3%), diabetic retinopathy (3.1%), and other diagnoses resulting in referral (43.8%). Compared with a face-to-face exam, the sensitivity of the technology-based exam to identify persons with glaucoma varied between readers (0.72, 95% CI 0.60 to 0.82 and 0.47, 95% CI 0.35 to 0.6), though specificity was high with both readers (0.91, 95% CI 0.87 to 0.95 and 0.97, 95% CI 0.94 to 0.99). The addition of spectral domain-OCT to the screening protocol did not improve diagnostic accuracy.[110]

Key Question 5. What Is the Accuracy of Instruments for Identifying Patients at Higher Risk of OAG?

Summary

- One cross-sectional study (n=145) that was not in the prior CER found a questionnaire associated with low sensitivity (0.20, 95% CI 0.03 to 0.56) but high specificity (0.96, 95% CI 0.91 to 0.99) for identifying persons with glaucoma.

Evidence

One fair-quality, cross-sectional study (n=145) not in the prior screening CER[2] reported the diagnostic accuracy of a weighted screening questionnaire for identifying persons with glaucoma (**Appendix B Tables 6-8**).[117] In the instrument, the highest weights were assigned for taking steroid medication and having a previous glaucoma diagnosis; less highly weighted risk factors were previous eye injury or stroke, age, race, prior eye surgery, high blood pressure, being nearsighted, and family history of diabetes or glaucoma. Two out of ten participants with glaucoma were correctly identified as having glaucoma based on the questionnaire alone (sensitivity 0.20, 95% CI 0.03 to 0.56), and 116 out of 121 correctly identified as not having glaucoma (specificity 0.96, 95% CI 0.91 to 0.99). The study was conducted in the U.S., but applicability to screening was likely limited because previous glaucoma diagnosis was one of the most heavily weighted risk factors.

Key Question 6. What Are the Effects of Medical Treatments for OAG vs. Placebo or No Treatments on a) IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage or b) Visual Impairment, Quality of Life, or Function?

Summary

- Treatment was associated with greater reduction in IOP compared with placebo or no treatment (16 trials, N=3,706, mean difference -3.14 mm Hg, 95% CI -4.19 to -2.08, I^2=95%); there was an interaction between drug class and effects of medical therapy on IOP (p for interaction <0.0005), though estimates favored treatment for all drug classes.
- Treatment with topical therapy decreased risk of glaucoma progression compared with placebo or no treatment at 24 to 120 months (7 trials, N=3,771, RR 0.68; 95% CI 0.49 to 0.96, I^2=53%; absolute risk difference [ARD] -4.8%, 95% CI -8.5 to -1.0).
- Evidence on effects of medical therapy on quality of life was very limited, with one trial (n=461) reporting no differences between latanoprost and placebo in general or vision-related quality of life measured using the EuroQol-5D (EQ-5D) (1.7 vs. 1.7, p=0.98), Short Form Health Survey-36 (SF-36) (4.8 vs. 5.0, p=0.94), Glaucoma Quality of Life-15

(GQL-15) (2.7 vs. 3.2 p=0.66), or Glaucoma Activity Limitation-9 (GAL-9) (3.0 vs. 3.2 p=0.87) scales at 24 months.

Evidence

The prior treatment CER[3] primarily focused on head-to-head comparisons of glaucoma treatment, but included a systematic review that found medical (topical) therapy for ocular hypertension associated with reduced risk of onset of visual field defects compared with placebo or no treatment (10 trials, N=3,648, odds ratio [OR] 0.62, 95% CI 0.47 to 0.81).[147] For this review, we included 13 placebo-controlled trials and four trials of medical therapy compared with no treatment[21,123,126,143] in patients with OAG or ocular hypertension. Nine trials[21,78,87,92,94,114,126,127,143] were in the systematic review utilized in the prior treatment CER and we identified eight additional trials,[35,62,63,121,123,124,134,142] including the U.K. Glaucoma Treatment Study[35] (UKGTS), which reported effects on quality of life and visual acuity in addition to IOP and visual field progression (**Appendix B Table 9**).

Across trials, sample sizes ranged from 20 to 1,636 participants (N=4,665). Mean age ranged from 55 to 74 years and 34 to 75 percent of participants were female. In 10 trials that reported race/ethnicity, the proportion of White participants ranged from 68 to 100 percent. Two trials enrolled patients with untreated, newly diagnosed OAG (excluding advanced disease and pigment dispersion),[35,63] three trials enrolled mixed populations with OAG or ocular hypertension (proportion with OAG 40%, 76%, and not reported),[62,124,142] and 12 trials enrolled patients with ocular hypertension (elevated IOP but normal visual fields; often also normal optic discs). OAG or ocular hypertension was diagnosed using a variety of tests, including perimetry, tonometry, gonioscopy, and visualization of the optic nerve by ophthalmoscopic examination and/or imaging; only the UKGTS[35] utilized OCT (primarily time domain-OCT) as part of the diagnostic evaluation. Mean baseline IOP ranged from 19.6 to 27.3 mm Hg; mean baseline IOP was <22 mm Hg in the two trials[35,63] of patients with early untreated OAG and ≥22 mm Hg in the other trials. Treatment was a beta-blocker in 10 trials (timorol in 6 trials,[78,87,121,126,143] levobunolol in 2 trials,[62,123] and betaxolol in 2 trials[92,121]) a carbonic anhydrase inhibitor in five trials (dorzolamide in 4 trials,[63,114,115,124,142] and brinzolamide in 1 trial[124]), a prostaglandin analogue (latanaprost) in one trial,[35] and an alpha agonist (brimonidine) in one trial.[134] One trial did not evaluate a specific drug but allowed various topical therapies, with a target IOP ≤24 mm Hg or ≥20 percent IOP reduction.[21] The duration of followup ranged from 1.5 months[63,121] to 120 months,[87] with followup >1 year in 10 trials. One study was multinational,[114,115] and the others were conducted in the U.S.,[21,62,78,94,121,124,127,134,142] U.K.,[35,92,143] Sweden,[63,87] Italy,[123] and Canada.[126]

In 12 trials,[21,35,62,63,78,87,92,114,115,121,124,126,142] randomization and analysis was per individual (2 of which enrolled only one eye[63,92]); one trial[127] randomized by individual but reported a per-eye analysis; and three trials[94,134,143] randomized one eye in each individual (with the other eye serving as the control). One trial[123] reported a per-eye analysis, but randomization by eye or individual was unclear. Four trials were rated good quality,[35,92,115,127] and 12 were rated fair quality[21,62,78,87,94,121,123,124,126,134,142,143] (**Appendix B Table 10**). Methodological limitations in the fair-quality trials included unclear reporting of randomization, allocation concealment, and blinding methods, and high attrition in some studies.

Intraocular Pressure

Mean IOP was the most commonly reported outcome, reported in all but two trials.[21,35,62,63,87,92,94,115,121,123,126,127,134,142,143] Overall, treatment was associated with greater reduction in IOP compared with placebo or no treatment (16 studies, N=3,706, mean difference -3.14 mm Hg, 95% CI -4.19 to -2.08, I^2=95%) (**Figure 18**). Statistical heterogeneity was substantial, though inconsistency was in the magnitude of effect but not the direction of effect, with all trials reporting effects on IOP that favored treatment (range -0.70 to -7.00 mm Hg). A funnel plot did not indicate small sample effects (Egger's test p=0.16) (**Figure 19**), but results were difficult to interpret due to statistical heterogeneity. There was an interaction between drug class and effects of medical therapy on IOP (p for interaction <0.0005), though estimates favored treatment for all drug classes. Beta blockers were associated with a pooled mean difference of -3.75 mm Hg (95% CI -5.43 to -2.06; I^2=92%), based on nine trials (N=455); prostaglandin analogues with a mean difference of -2.70 mm Hg (95% CI -3.34 to -2.06), based on one trial (n=516); alpha agonists with a mean difference of -2.30 mm Hg (95% CI -3.52 to -1.08), based on one trial (n=30); and carbonic anhydrase inhibitors with a mean difference of -1.20 mm Hg (95% CI -2.30 to -0.61), based on four trials (N=1,635). One trial (n=1,636) found treatment to target using various medications associated with a mean difference of -4.60 mm Hg (95% CI -4.85 to -4.35). Estimates also consistently favored medical therapy, with differences ranging from -2 to -4 mm Hg, when analyses were stratified according to ocular hypertension, untreated OAG, or mixed status at baseline (**Figure 20**), baseline IOP (<20 mm Hg vs. ≥20 mm Hg) (**Figure 21**), and quality (fair vs. good) (**Figure 22**), or duration (<1 year vs. ≥1 year) (**Figure 23**), though statistically significant interactions were present (**Table 9**). In the OHTS, effects of medication compared with placebo on IOP were almost identical in Black persons and persons of other races.[148]

Progression of Glaucomatous Changes

Nine trials reported effects of topical medical therapies compared with placebo or no treatment on risk of glaucoma progression (**Appendix B Table 9**).[21,35,78,87,92,94,114,115,126,143] Glaucoma progression was defined as progression of visual field defects,[35,78] progression to a glaucoma diagnosis (among those with ocular hypertension, based on visual field defects or optic disc changes),[87,92,126] or progression of visual field defects or optic disc changes.[21,114,115] Definitions and measurement methods for progression of visual field loss varied, but were based on the development of focal or reproducible visual field defects or by the development of any reproducible visual field defect (**Appendix B Table 9**). No trial reported the proportion of patients with overall visual field loss exceeding a minimum clinically important threshold such as a change in mean deviation of >3 to 5 decibels (dB, a measure of light intensity when testing visual fields).[149]

Treatment with topical therapy decreased risk of glaucoma progression compared with placebo or no treatment (seven trials, N=3,771, RR 0.68; 95% CI 0.49 to 0.96, I^2=53%; ARD -4.8%, 95% CI -8.5% to -1.0%; **Figure 24**) at 24 to 120 months. Estimates were similar in the new UKGTS trial,[150] which evaluated patients with untreated OAG (n=461, RR 0.59, 95% CI 0.41 to 0.86), and trials included in the prior treatment CER of patients with ocular hypertension (6 trials, N=3,310, RR 0.71, 95% CI 0.46 to 1.08; I^2=57%) (**Figure 25**). Results were also similar in fair-

quality studies (4 trials, N=1,978, RR 0.57, 95% CI 0.33 to 1.00, I^2=44%) and good-quality studies (3 trials, N=1,793, RR 0.76, 95% CI 0.52 to 1.30, I^2=15%; **Figure 26**). There was no interaction between medication type (p for interaction=0.30) or study quality (p for interaction=0.36) and effects on risk of glaucoma progression. Two trials[94,143] (ns=34 and 62) were not included in the meta-analysis because they randomized one eye in each individual and reported a per-eye analysis, but both found treatment associated with decreased risk of progression (RR 0.63, 95% CI 0.17 to 2.39 and RR 0.38, 95% CI 0.13 to 1.16). An analysis restricted to progression of visual field defects (excluding optic disc changes as a criterion for progression) produced similar results (6 trials, N=3,679, RR 0.73, 95% CI 0.53 to 1.05, I^2=25%; **Figure 27**).[21,35,78,92,114,126] In the UKGTS, latanaprost was associated with a small and non-statistically significant difference in overall visual field loss, measured by the mean deviation (-0.23 vs. 0.14 dB, p=0.07); there was no difference in visual acuity (-0.01 vs. -0.02 logMAR, p=0.9).[35] In the OHTS, there was no interaction between race and risk of progression from ocular hypertension to OAG (hazard ratio [HR] 0.50, 95% CI 0.28 to 0.90 for Black patients, and HR 0.36, 95% CI 0.23 to 0.57 for other races; p for interaction=0.40).[148]

Quality of Life

Evidence on effects of medical therapy on quality of life was very limited. In the UKGTS (n=461),[90] there were no differences between latanoprost and placebo in general or vision-related quality of life measured using the EQ-5D (1.7 vs. 1.7, p=0.98), SF-36 (4.8 vs. 5.0, p=0.94), GQL-15 (2.7 vs. 3.2 p=0.66), or GAL-9 scales (3.0 vs. 3.2 p=0.87) at 24 months followup.

Key Question 7. What Are the Harms of Medical Treatments for OAG vs. Placebo or No Treatments?

Summary

- There were no significant differences in risk of serious adverse events (3 trials, N=3,140, RR 1.14, 95% CI 0.60 to 1.99; I^2=32%), withdrawal due to adverse events (5 trials, N=648, RR 2.40, 95% CI 0.71 to 19.32; I^2=0%), or any adverse event (2 trials, N=1,538, RR 1.56, 95% CI 0.59 to 4.03; I^2=82%).
- Two trials found treatment associated with increased risk of ocular adverse events (primarily itching, irritation, tearing, dryness, or taste issues) compared with placebo (RR 1.21, 95% CI 1.10 to 1.33 in a trial of various treatments and RR 3.52, 95% CI 2.46 to 5.02 in a trial of dorzolamide).

Evidence

Eight trials (in 9 publications) of medical treatments compared with placebo or no treatment reported harms (**Appendix B Table 9**).[21,35,62,78,114,115,124,127,142] There were no statistically significant differences in risk of serious adverse events (three trials, N=3,140, RR 1.14, 95% CI 0.60 to 1.99; I^2=32%; **Figure 28**),[21,35,114,115] withdrawal due to adverse events (five trials, N=648, RR 2.40, 95% CI 0.71 to 19.32; I^2=0%; **Figure 29**),[35,62,78,127,142] or any adverse event (two trials,

N=1,538, RR 1.56, 95% CI 0.59 to 4.03; I^2=82%).[35,114,115] However, estimates were imprecise and the estimate for any adverse event was based on two trials, with substantial statistical heterogeneity (RR 1.04; 95% CI 0.73 to 1.47 in a trial of latanaprost[35] and RR 2.30, 95% CI 1.69 to 3.12 in a trial of dorzolamide[114,115]). Two trials found treatment associated with increased risk of ocular adverse events compared with placebo (RR 1.21, 95% CI 1.10 to 1.33 in a trial of various treatments[114,115] and RR 3.52, 95% CI 2.46 to 5.02[21] in a trial of dorzolamide). The most common ocular adverse events were localized itching, irritation, tearing, dryness, or taste issues. Because of extreme statistical heterogeneity (I^2=94%), the pooled estimate was unreliable and not reported. The OHTS found no interaction between race and likelihood of experiencing one or more serious adverse events (p for interaction=0.16) or any adverse event (p for interaction=0.58) with medical treatment compared with placebo.[148]

Key Question 8. What Are the Effects of Newly FDA-Approved Medical Treatments (Latanoprostene Bunod and Netarsudil) vs. Older Medical Treatments on a) IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage or b) Visual Impairment, Quality of Life, or Function?

Summary

- Three trials (N=1,875) found netarsudil to be noninferior to timolol for IOP lowering at 3 to 12 months.
- A pooled analysis of two trials (N=985) found netarsudil and latanaprost to be associated with similar effects on IOP (mean diference 0.3 mm Hg) and likelihood of IOP ≤18 mm Hg 57.4% vs. 65.5%) at 12 months.
- One trial (N=413) found latanoprostene bunod 0.024 or 0.040 percent associated with slightly greater effects on IOP (difference 1.2 mm) compared with latanoprost at short-term (1 month) followup.
- Two trials (N=840) found latanoprostene bunod associated with slightly greater IOP reduction compared with timolol at 3 months (difference -1.0 to -1.3 mm Hg).
- A pooled analysis of two trials (N=840) found latanoprostene bunod associated with increased likelihood of IOP ≤18 (20.2% vs. 11.2%; p=0.001) and IOP reduction ≥25 percent (22.9% vs. 19.0%; p<0.001) at 3 months.

Evidence

Eight trials and two meta-analyses evaluated the effects of latanaprostene bunod or netarsudil compared with an older glaucoma medication (**Appendix B Table 11**).[57,58,66,91,98,113,129,139-141] The Rho Kinase Elevated IOP Treatment (ROCKET) trials compared netarsudil with timolol (ROCKET-1 and ROCKET-2[129] and ROCKET-4 [98] trials); the VOYAGER study compared different doses of latanaprostene bunod with latanaprost;[140] the LUNAR[113] and APOLLO[139,141] trials (acronyms not defined) compared latanaprostene bunod with timolol; and the MERCURY-1[58,66] and MERCURY-2[57] trials (acronym not defined) compared netarsudil with latanaprost.

Sample sizes ranged from 411 to 985 (N=4,113). The mean age ranged from 61 to 66 years and 50 to 68 percent of participants were female. All trials enrolled mixed populations of patients with OAG or ocular hypertension. The proportion of patients with OAG in the ROCKET trials ranged from 62 to 68 percent and in the MERCURY-1 and MERCURY-2 trials ranged from 72 to 77 percent; the three trials of latanaprostene bunod did not report the proportion of patients with OAG. Mean baseline IOP ranged from 20.7 to 26.7 mm Hg. The duration of followup was 3 months in all trials except for three, which had 1-[140] or 12-month followup.[66,91] All trials were multinational except for the MERCURY trials, which were conducted in the U.S. Three trials (LUNAR, APOLLO, and MERCURY-2)[57,113,141] were rated good quality and five trials were rated fair quality.[66,91,98,129,140] Methodological limitations in the fair-quality trials included unclear reporting of randomization, allocation concealment, and blinding of outcome assessors; the ROCKET and MERCURY-1 trials also had high and differential attrition (**Appendix B Table 12**).[91,98,129] All of the trials focused on the outcome of IOP.

The ROCKET trials (N=1,875) found netarsudil to be noninferior to timolol in mean IOP reduction at 3 months (3 trials) and 12 months (1 trial).[91] The MERCURY-1 trial (N=480) found netarsudil and latanaprost associated with similar reduction in IOP (mean difference 0.3 mm Hg for netarsudil vs. latanaprost) and likelihood of achieving IOP ≤18 mm Hg RR (57.4% vs. 65.5%, RR 0.73; 95% CI 0.61 to 0.88) at 12 months.[66]

The short-term (1 month) VOYAGER trial (n=413) found latanaprostene bunod 0.024% and 0.04% associated with greater reduction in IOP compared with latanaprost (mean differences 1.23 mm Hg, 95% CI 0.37 to 2.10; 0.04% and 1.16 mm Hg, 95% CI 0.29 to 2.03, respectively) and increased likelihood of IOP ≤18 (68% vs. 64% vs. 47%, $p<0.05$ for both latanaprostene bunod doses vs. latanaprost).[140] Two trials (LUNAR and APOLLO, N=840) found latanaprostene bunod associated with greater IOP reductions than timolol.[113,141] In a pre-planned pooled analysis, mean differences in IOP ranged from -1.0 to -1.3 mm Hg at 3 months ($p<0.001$).[139] Latanaprostene was also associated with a higher likelihood of IOP ≤18 at week 2, week 6, and 3-month timepoints (20.2% vs. 11.2%; $p=0.001$) and IOP reduction ≥25 percent at all timepoints (2.9% vs. 19.0%; $p<0.001$).

Key Question 9. What Are the Harms of Newly FDA-Approved Medical Treatments vs. Older Medical Treatments?

Summary

- Netarsudil was associated with increased risk of ocular adverse events (3 trials, N=1,875, RRs ranged from 1.69 to 2.07), withdrawal due to adverse events (3 trials, N=1,875, RRs ranged from 4.73 to 38.20), and any adverse event (1 trial, n=708, 80% vs. 60%, RR 1.33, 95% CI 1.20 to 1.47) compared with timolol.
- Netarsudil also associated with increased risk of any adverse event (1 trial, n=480, RR 1.45, 95% CI 1.27 to 1.66), ocular adverse events (1 trial, n=480, RR 1.76, 95% CI 1.50 to 2.07) and withdrawal due to adverse events (1 trial, n=480, RR 12.82, 95% CI 4.71 to 34.85) compared with latanaprost at 12 months.

- One trial (n=413) found latanaprostene bunod and latanaprost associated with similar likelihood of any adverse events and withdrawals due to adverse events.
- Two trials (N=840) found latanaprostene bunod associated with increased risk of ocular adverse events compared with timolol (pooled RR 1.72; 95% CI 1.22 to 2.42); estimates for withdrawal due to adverse events were imprecise.

Evidence

Eight head-to-head trials and two meta-analyses reported adverse events associated with newly approved glaucoma medications compared with older medications (**Appendix B Table 11**).[57,58,66,91,98,113,129,139-141] In the ROCKET trials (k=3, N=1,875), netarsudil was associated with increased risk of ocular adverse events compared with timolol.[91,98,129] The most common ocular adverse events were conjunctival redness or hemorrhage, corneal deposits (cornea verticillata, typically asymptomatic and without effects on vision), blurry vision, tearing, and itching. The proportion of patients with ocular adverse events ranged from 73 to 88 percent with netarsudil and from 41 to 50 percent with timolol; RRs ranged from 1.51 to 2.07 at 3 to 12 months (ARDs ranged from 26% to 38%). Netarsudil was also associated with increased likelihood of withdrawal due to adverse events (RRs ranged from 4.73 to 38.20; ARDs ranged from 8% to 34%), though estimates were imprecise. One trial found netarsudil associated with increased likelihood of any adverse event compared with timolol (80% vs. 60%, RR 1.33, 95% CI 1.20 to 1.47).[98]

Netarsudil was also associated with increased risk of any adverse event (RR 1.45, 95% CI 1.27 to 1.66) and ocular adverse events (RR 1.76, 95% CI 1.50 to 2.07) at 12 months compared with latanaprost, based on one trial (n=480).[66] Netarsudil was also associated with increased risk of withdrawal due to adverse events compared with latanaprost at 3 months (2 trials, N=986, RR 7.40, 95% CI 2.94 to 18.65)[57] and 12 months (one trial, n=480, RR 12.82, 95% CI 4.71 to 34.85).[66]

One short-term (1 month) trial (n=413) found no differences between latanaprostene bunod and latanaprost in risk of any adverse event or withdrawal due to adverse events.[140] Two trials (N=840) found latanaprostene bunod associated with increased risk of ocular adverse events compared with timolol (pooled RR 1.72, 95% CI 1.22 to 2.42).[139] Estimates for withdrawal due to adverse events were imprecise (RR 1.96; 95% CI 0.22 to 17.40 and RR 0.48, 95% CI 0.12 to 1.88).

Key Question 10. What Are the Effects of Laser Trabeculoplasty for OAG vs. No Trabeculoplasty or Medical Treatment on a) IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage or b) Visual Impairment, Quality of Life, or Function?

Summary

- The large (n=718), good-quality Laser in Glaucoma and Ocular Hypertension (LiGHT) trial reported SLT and medical therapy were associated with similar effects on IOP, visual acuity, visual field, general quality of life, and glaucoma-specific utility, symptoms, and quality of life at 3 years.
- Three smaller, fair-quality trials found SLT and medical therapy similar for IOP at 4 to 12 months and 5 years; the trials did not evaluate other ocular and health outcomes.

Evidence

The prior treatment CER[3] included two trials[103,151] (N=220) comparing SLT with medical therapy. One trial[103] was carried forward for this update but the other[151] was ineligible because a high proportion of patients had capsular glaucoma and use of an outdated intervention (argon laser). Three additional trials (in four publications; N=925) not included in the prior treatment CER of SLT compared with a topical prostaglandin analogue were added for this update (**Appendix B Table 13**).[37,82,118,119]

The largest study was the LiGHT trial, which enrolled 718 participants with OAG or ocular hypertension and visual acuity ~20/120 or better.[37,82] In the medical therapy arm of LiGHT, patients received stepped therapy with prostaglandins as initial therapy, followed by beta blockers, topical carbonic anhydrase inhibitors, or alpha agonists. Patients were excluded if they had prior surgery or were currently on or had prior exposure to glaucoma medical therapy. Forty-five percent of patients were female and mean age was 63 years. Seventy percent of patients were White, 20 percent Black, and 7.1 percent Asian. Mean baseline IOP was 24.5 mm Hg; the majority of randomized patients were diagnosed with OAG (77.3%) compared with ocular hypertension (22.7%). Of those with OAG, disease severity was most commonly assessed as mild (88.6%), followed by moderate (20.1%) and severe (10.4%).

The sample sizes in three smaller trials (including the trial in the prior treatment CER)[103] ranged from 32 to 167 participants; 48 percent to 55 percent were female.[103,118,119] Mean ages ranged from 52 years to 66 years and mean baseline IOP ranged from 22.8 mm Hg to 29.3 mm Hg. The proportion of patients with OAG ranged from 43 to 59 percent and the proportion with ocular hypertension ranged from 41 to 57 percent. All studies excluded patients with prior laser or glaucoma surgery. In two trials,[103,118] patients were randomized to 360° SLT; in the other trial,[119] patients were randomized to 90°, 180°, or 360° SLT. The duration of followup ranged from 4

months to 5 years. Three trials were conducted in the United Kingdom (U.K.)[37,82,118,119] and one in Hong Kong.[103]

One RCT[37,82] was rated good quality; the remaining three were rated fair quality (**Appendix B Table 14**).[103,118,119] Methodological limitations in the fair-quality trials included unclear reporting of randomization, allocation concealment, and blinding methods.

IOP

The good-quality, large (n=718) LiGHT trial found 360° SLT and medical therapy associated with very similar mean IOP at 3 years (16.6 [SD 3.62] vs. 16.3 [SD 3.87] mm Hg).[37,82] Among those randomized to SLT, 74.1 percent received one treatment per eye, 25.7 percent received two treatments, and 0.2 percent received three treatments. Medical therapy was associated with more treatment escalations than SLT. SLT and medical therapy were also associated with very similar proportions of eyes at target IOP, based on Canadian Target IOP Workshop criteria (95.0% vs. 93.1%). Among those who achieved target IOP at 3 years, 78.2 percent of eyes randomized to SLT did not require medication compared with 3 percent of patients randomized to medical therapy.[37,82] Race/ethnicity was not a predictor of response to SLT (22% of participants were Black, 6.5% were Asian, and 68% were White).[36]

Three smaller trials (n=32, 40, and 167) reported results for IOP that were consistent with LiGHT.[103,118,119] One trial[118] (n=40) found 360° SLT and medical therapy associated with similar mean reduction from baseline in IOP at 4 to 6 months (6.2 [SE 0.8] vs. 7.8 [SE 0.8] mm Hg, $p>0.05$). Similar results were reported in a trial[103] (n=32) comparing mean IOP reduction in SLT with medical therapy at 5 years (8.6 [SD 6.7] vs. 8.7 [SD 6.6] mm Hg, $p>0.05$). Two trials found 360° SLT and medical therapy associated with similar likelihood of ≥20 percent reduction in IOP from baseline at 4 to 6 months (75% vs. 73%; adjusted OR, 1.65, 95% CI 0.52 to 6.07)[118] or 12 months (82% vs. 90%).[119] In one trial (n=167),[119] there was no difference between 360° SLT and medical therapy in likelihood of achieving ≥20 percent IOP reduction (82% vs. 90%). However, 90° and 180° SLT were both associated with decreased likelihood of ≥20 percent IOP reduction compared with medical therapy (34% vs. 65% vs. 90%, respectively, $p<0.001$ for 90° vs. medical therapy and $p<0.01$ for 180° vs. medical therapy).[119]

Other Ocular Outcomes

The LiGHT trial found 360° SLT and medical therapy associated with similar mean visual acuity at 3 years (0.07 [SD 0.18] vs. 0.08 [SD 0.17] logMAR).[37,82] SLT and medical therapy were also associated with similar visual field mean deviation (-3.21 [SD 3.76] vs. -3.19 [SD 3.92] dB). Effects on visual acuity and visual fields were similar when patients stratified according to whether they had ocular hypertension or mild, moderate, or severe OAG at baseline. The other trials did not report visual acuity or other visual outcomes.

Quality of Life and Function

The LiGHT trial found SLT and medical therapy associated with similar quality of life at 3 years, as measured using the EQ-5D-5 (0.90 [SD 0.16] vs. 0.89 [SD 0.18]; adjusted mean

difference 0.02, 95% CI -0.00 to 0.03).[37,82] SLT and medical therapy were also associated with very similar glaucoma-specific utility, symptoms, and quality of life, based on the Glaucoma Utility Index (GUI) (0.89 [SD 0.13] vs. 0.89 [SD 0.13]), Glaucoma Symptom Scale (GSS) (83.1 [SD 17.7] vs. 83.3 [SD 17.3]), and the GQL-15 (19.8 [SD 7.2] vs. 19.8 [SD 7.8]).[37,82] The other trials did not report visual acuity or other visual outcomes.

Key Question 11. What Are the Harms of Laser Trabeculoplasty for OAG vs. No Trabeculoplasty or Medical Treatment?

Summary

- The LiGHT trial reported similar adverse and serious adverse event rates between SLT and medical therapy; evidence on harms from three smaller trials was limited.

Evidence

The LiGHT trial found no differences between SLT and medical therapy in patients experiencing any adverse event (73.3% vs. 71.8%) or any serious adverse event (18.0% vs. 18.8%) **(Appendix B Table 13)**.[37,82] SLT and medical therapy were associated with similar risk of ocular adverse events such as ocular irritation, retinal hemorrhage, or floaters (52% vs. 61%) and serious ocular adverse events such as trauma, central retinal artery occlusion, or choroidal neovascularization (2.2% vs. 1.7%). In the SLT group, 34.4 percent of patients experienced SLT-related transient adverse events, including discomfort, transient blurred vision, transient photophobia, and hyperemia. Evidence on harms of SLT compared with medical therapy from other trials was limited, due to suboptimal reporting and imprecision.[103,118,119]

Contextual Question 1. What Is the Association Between Changes in IOP, Visual Field Loss, Visual Acuity, or Optic Nerve Damage Following Treatment for OAG and Improvement in Visual Impairment, Quality of Life, or Function, and What Is the Association Between Changes in IOP and Visual Field Loss?

As described in the prior treatment CER,[3] evidence is available on the association between decreased IOP following treatment and decreased visual field loss. However, evidence on the association between changes in intermediate outcomes (IOP, visual field loss, visual acuity, or optic nerve damage) following treatment for OAG and improvement in health outcomes remains limited. Other information that may aid in interpreting intermediate outcomes include standards for classifying the severity of impaired visual acuity; limited evidence is available on minimum clinically important differences for visual acuity and visual field loss.

As described in the Results, there was direct evidence that treatment for OAG or ocular hypertension compared with placebo or no treatment is associated with decreased risk of progression of (variably defined) visual field loss (see Key Question 6). Studies have also evaluated the association between the degree of IOP lowering following treatment for POAG or ocular hypertension and decreased visual field loss. In these analyses, greater IOP reduction or lower IOP has consistently been associated with reduced likelihood of visual field or glaucoma progression. Several studies have focused on cohorts of patients enrolled in RCTs of glaucoma treatment. One analysis evaluated patients (n=738) in the Advanced Glaucoma Intervention Study (AGIS), which enrolled patients with OAG that could not be adequately controlled by medications alone. Patients had baseline visual acuity of 20/80 or better and the minimum Visual Field Defect Score ranged from 1 to 16 (0 to 20 scale, 20 indicates insufficient vision to count fingers at 30 cm). Patient eyes were randomized to argon laser trabeculoplasty or trabeculectomy.[152] The analysis found higher average IOP associated with greater visual field loss at 24, 60, and 84 months, with a 1 mm Hg increase in average IOP associated with an increase in the Visual Field Defect Score of 0.08 to 0.18, after adjusting for age, intervention sequence, age, diabetes, gender, baseline IOP, and baseline Visual Field Defect Score.

Subsequent studies also found an association between degree of IOP lowering following treatment and decreased visual field loss in less advanced glaucoma. The Early Manifest Glaucoma Trial (EMGT) enrolled persons (n=255) with previously untreated glaucoma.[153] Patients with advanced visual field defects, visual acuity worse than 0.5 (20/40), or mean IOP greater than 30 mm Hg were excluded. Patients were randomized to argon laser trabeculoplasty plus topical betaxolol or no immediate treatment. The outcome was glaucoma progression, defined as a composite outcomes based on perimetric criteria for visual field loss or photographic criteria for optic disc progression. At 6 years, greater decrease in IOP from baseline to 3 months was associated with decreased risk of glaucoma progression (per 1 mm Hg, HR 0.90, 95% CI 0.86 to 0.94) and higher mean IOP at followup was associated with increased risk of glaucoma progression (per 1 mm Hg, HR 1.13, 95% CI 1.07 to 1.19), after adjusting for baseline IOP, presence of exfoliation, baseline visual field loss, and age. Similar results were found at longer (up to 11 years) followup.[154] The European Glaucoma Prevention Study (EGPS), which randomized persons (n=1,077) with ocular hypertension to dorzolamide or placebo, found greater reduction in mean followup IOP associated with decreased risk of progression to OAG during 5-year followup (per 1 mm Hg, HR 0.89, 95% CI 0.80 to 0.98), after adjusting for treatment arms and baseline predictive factors.[155] Greater increase in mean followup IOP (per 1 mm Hg, HR 1.12, 95% CI 1.03 to 1.22) and area under the curve of IOP (mm Hg per year, HR 1.09, 95% CI 1.06 to 1.12) were associated with increased risk of progression to OAG. A limitation of the analyses from EGPS and EMGT is that they did not exclude patients randomized to placebo or no immediate treatment, potentially reducing the directness of findings to treated patients, though both reported estimates adjusted for treatment arm. Long-term (12 to 15 year) analyses from cohort studies of treated patients with normal tension glaucoma also found an association between greater IOP reduction and risk of glaucoma progression.[156,157]

The prior treatment CER found no direct evidence on the association between improvements in intermediate outcomes (IOP, visual fields, visual acuity, or optic nerve damage) following treatment for OAG or ocular hypertension and improvement in visual impairment, quality of life, or function.[3] However, the prior treatment CER noted that cross-sectional studies not meeting

inclusion criteria indicated an association between more severe visual field loss with more visual impairment and worse patient reported outcomes. Although such studies can evaluate correlations between intermediate and health outcomes, they cannot demonstrate causality or the association between changes in IOP following treatment and subsequent outcomes, due to the lack of longitudinal followup.

As in the prior treatment CER, we identified no studies on the association between improvements in intermediate outcomes and health outcomes. Studies published since the prior USPSTF review were consistent with previous findings with regard to the association between greater visual field loss and reduced vision-related quality of life or function, but were cross-sectional or did not evaluate the association between treatment-related changed in visual fields and function.[158-160]

We identified no studies on the association between improvements in optic nerve damage following treatment and health outcomes. The association between increased optic nerve damage and greater visual field loss has been described in numerous articles, but this represents an association between two intermediate outcomes.[161-166]

Evidence on minimum clinically important differences for visual field loss is limited. One longitudinal study found a mean deviation >5 dB visual field loss or >3 dB visual field gain associated with clinically meaningful losses or gains in vision-specific quality of life (defined as a change of ≥5 points on the 0 to 100 composite NEI-VFQ).[149] Effects of visual field changes varied according to baseline vision status, with similar levels of visual field change associated with greater impact on quality of life in persons with pre-existing vision loss.

As noted in the 2016 USPSTF review on screening for impaired visual acuity, standards for classifying severity of impaired visual acuity are available. For example, visual acuity of 20/70 or better is classified as mild or no impairment by the World Health Organization.[167] The International Council of Ophthalmology uses a slightly lower (20/63 or better) threshold for mildly impaired visual acuity.[168] However, effects of even mildly impaired visual acuity are variable and can have a significant impact on quality of life. The best-corrected visual acuity acceptable for driving in most U.S. states is 20/40.[169] Therefore, even relatively small changes in even "mild" impaired visual acuity could have a clinically important impact, depending on baseline visual acuity and type of work or other activities in which an individual is engaged.

As described in the 2016 USPSTF review on screening for impaired visual acuity,[170] minimum clinically important differences for visual acuity have been described. Although definitions for a clinically important change in visual acuity vary across studies, a difference of at least 15 letters (equivalent to 3 lines on the Early Treatment Diabetic Retinopathy Study [ETDRS]), representing a doubling of the visual angle, is a commonly reported outcome in studies assessing visual acuity, and has been used to indicate a clinically meaningful difference.[171,172] This threshold is based primarily on studies that evaluate effects of changes in visual acuity on vision-related function. Studies using the NEI-VFQ to assess vision-related function, though not necessarily in patients with glaucoma, found a difference of 4 to 10 points to be clinically meaningful to patients, corresponding to a 10- to 15-letter change in visual acuity.[172-175]

Chapter 4. Discussion

Summary of Review Findings

Table 10 summarizes the evidence reviewed for this update. The prior screening CER[2] that informed the 2012 USPSTF recommendation included no studies comparing glaucoma screening with no screening. We identified one trial of frail elderly persons not included in the prior screening CER that found no difference when comparing vision screening by an optometrist (including components relevant for diagnosis of glaucoma) with no screening on vision outcomes or vision-related quality of life.[132] In this trial, vision screening was not specific for glaucoma, imaging was not utilized as part of screening, and the proportion of patients referred for glaucoma management was small (5.5% of those judged to need treatment). In addition, most patients in the no screening arm had seen an eye care professional in the prior year, which could have attenuated potential benefits of screening. Unexpectedly, the trial found screening associated with an increased risk of falls (number needed to screen 6.7 for 1 additional person falling), with a non-statistically significant increased risk of fractures. The reason for the increase in falls was unclear, but could be related to difficulty adapting to large corrections in vision or use of multifocal lenses. No study evaluated outcomes comparing referral to an eye health provider with no referral. Although one new study comparing screening with no screening was published prior to finalization of this report, it did not meet inclusion criteria because it was observational and had serious methodological limitations (control group was nonparticipants/nonresponders, and study did not perform statistical adjustment for potential confounders). In addition, the proportion of glaucoma patients with exfoliation glaucoma was very high (>50%), with uncertain applicability to primary care screening.[50]

For diagnostic accuracy, our review found spectral domain-OCT and visual field assessment using the Humphrey Automated Field Analyzer to be associated with reasonable accuracy for identifying persons with glaucoma compared with a comprehensive eye exam. Although visual field assessment generally requires referral to an eye specialty setting, OCT could be ordered from a primary care clinic and has potential as a standalone screening test. Swept source-OCT, a newer OCT technology with increased scan speed and resolution compared with spectral domain-OCT, appears to offer improved visualization of ocular structures, but evidence on diagnostic accuracy for glaucoma is currently limited.[176] Tonometry for measurement of IOP was associated with high specificity but low sensitivity, indicating that it is insufficient as a standalone screening test. The low sensitivity of tonometry was consistent with data indicating that a significant proportion of patients with glaucoma have normal IOP. The gold standard for tonometry is the Goldmann Applanation Tonometer, which is not widely used in primary care settings. Evidence on other screening tests, including swept source-OCT, optic disc photography, ophthalmoscopy and biomicroscopy, and pachymetry was more limited. Our review differs from and expands upon the prior screening CER,[2] which included case-control studies, included screening tests no longer in use, focused on head-to-head comparisons of screening modalities, did not perform meta-analysis, and did not include more recent studies on spectral domain-OCT. A persistent challenge in interpreting studies on diagnostic accuracy of screening is the variability and lack of standardization in the reference standard.

An ophthalmic telemedicine screening program was associated with inconsistent sensitivity but high specificity for identifying persons with glaucoma compared with a face-to-face evaluation.[109-111] Although telemedicine screening was performed in a Veterans Affairs primary care setting, potential barriers to more widespread implementation include the need to install specialized instruments and utilize trained technicians. One study evaluated the accuracy of a risk assessment instrument for identifying persons with glaucoma, but reported low sensitivity and was conducted over 30 years ago, with no subsequent validation.[117] The risk assessment instrument also may be of limited applicability to screening because one of the primary risk factors was a previous glaucoma diagnosis.

Our findings on the effectiveness of medications for early OAG and ocular hypertension are generally consistent with the prior treatment CER,[3] which found moderate evidence that medical and surgical treatments can lower IOP and reduce risk of progression by visual field and optic nerve criteria, but no studies on effects of treatments on visual impairment or patient reported outcomes. Our review differs from the prior treatment CER by focusing on comparisons involving treatment versus placebo or no treatment and conducting meta-analysis. We included several new trials conducted since the prior treatment CER that evaluated effects on visual acuity and vision-related function or quality of life. Most notable were the addition of the large UKGTS,[35] which compared latanoprost with placebo in persons with untreated glaucoma, and LiGHT,[37,82] which compared SLT with topical medications. Our meta-analysis found topical medications associated with decreased risk of glaucoma progression, defined by visual field or optic disc changes, with a number needed to treat of 20.8 to prevent one case of progression over 2 to 10 years. Results were similar when the analysis was restricted to trials that defined glaucoma progression based on visual field changes (excluding optic disc changes). However, these results are difficult to interpret because methods for defining visual field changes varied and were based on the development of focal visual field deficits or any visual field loss; no trial evaluated the proportion of patients who met a minimum clinically important different threshold[149] for overall visual field loss. In the UKGTS, there were no differences between medications and placebo in mean visual field loss or visual acuity.[35]

Medications were also associated with greater reduction in IOP compared with placebo or no medication, with a pooled difference of about 3 mm Hg. Although there was statistical heterogeneity in the IOP meta-analysis, the inconsistency was in the magnitude rather than direction of effects, as results favored therapy in all studies and for all specific classes and medications. Across individual studies and in various stratified analyses, effects of medications on mean IOP generally ranged from 2 to 3 mm Hg. Data on harms of topical medical therapies was limited, but did not indicate an increased risk of serious adverse events, though non-serious ocular adverse events (e.g., redness, irritation, itching, burning, tearing) were more common. Newly-approved topical medications for glaucoma (netarsudil and latanaprost bunod) were associated with similar or greater IOP reducing effects compared with older medications, but increased risk of adverse events. New data on effects of medical treatment for glaucoma on quality of life was available from the UKGTS,[90] which found no differences between latanoprost and placebo in general or vision-related quality of life at 2 years. For SLT compared with medical therapy, LiGHT found effects of SLT and medical therapy associated with similar effects on IOP, visual acuity, visual field, and quality of life, with no differences in serious adverse events or ocular adverse events.[37,82] Results of smaller trials comparing SLT and medical

therapy were consistent with LiGHT. Our findings regarding treatment are most applicable to patients with ocular hypertension or early, untreated OAG, the populations typically enrolled in the trials.

As in the prior treatment CER, interpretation of effects of treatment on IOP and glaucoma progression is a challenge because of a lack of evidence on the association between improvements in these and other intermediate outcomes (e.g., optic nerve damage) following treatment for OAG or ocular hypertension and improvement in visual impairment, quality of life, or function. Although cross-sectional studies indicated an association between more severe visual field loss and greater visual impairment and patient reported outcomes, such studies cannot demonstrate causality and do not evaluated the association between changes in IOP following treatment and subsequent outcomes.

Limitations

Our evidence review has some limitations. First, we excluded non-English language studies, which could introduce language bias. Although we identified one RCT of medical therapy published in Japanese, it was small (n=16) and would not impact conclusions.[177] Second, there was statistical heterogeneity in pooled analyses on effects of medical therapy compared with placebo or no treatment on IOP. However, as described above, inconsistency was in the magnitude but not direction of effect, which favored medical therapy across studies. In addition, differences in IOP lowering effects were small, generally ranging from 1 to 2 mm Hg. Because of anticipated heterogeneity, we utilized a random effects model for pooling. Third, statistical heterogeneity was present in pooled analyses of sensitivity and specificity. However, standard methods for measuring statistical heterogeneity do not account for the variability in estimates related to threshold effects. Despite the statistical heterogeneity, results were robust in stratified and sensitivity analyses. Fourth, direct evidence on benefits and harms comparing screening with no screening and comparing effects of treatment with no treatment for ocular hypertension or early OAG on visual impairment, quality of life, and function remains very limited, though the UKGTS study found no effects on quality of life or function. Fifth, we excluded case-control studies of diagnostic accuracy, which reduced the evidence available for evaluating screening tests, but reduced potential spectrum bias. Sixth, evaluations of publication bias through graphical or statistical methods was limited by small numbers of studies or statistical heterogeneity. However, we did not identify unpublished studies likely to impact findings. Seventh, unlike the prior screening and treatment CERs,[2,3] we excluded most head-to-head comparisons, which might provide indirect evidence regarding the diagnostic accuracy of screening tests and outcomes of treatment. However, we included trials comparing newly FDA-approved medications with older medications and comparing SLT with medical therapy, because the new medications and SLT are considered first-line treatments and placebo- and sham-controlled trials are not available.

Emerging Issues/Next Steps

Latanoprostene bunod (a nitric oxide-donating medication) was FDA-approved in 2017 and

netarsudil (a Rho kinase inhibitor) was approved in 2019. These medications are the first in their respective classes for treatment of glaucoma and decrease IOP primarily by increasing outflow (rather than reducing aqueous production). Although some trials comparing latanoprostene bunod with netarsudil are available, additional studies with longer-term followup are needed to verify benefits and harms. The development of newer minimally-invasive surgical procedures for treatment of OAG is ongoing,[45] including angle-based surgeries (Kahook dual blade and gonioscopy-assisted transluminal trabeculotomy), micro-shunting surgeries (Xen gel stent), and micropulse laser therapy.

With regard to screening tests, OCT technology has evolved rapidly with respect to scanning speed and resolution, which may lead to improvements in diagnostic accuracy (e.g., with use of swept source-OCT).[178] Although OCT may have some potential as a standalone screening test for glaucoma,[179] evidence on the effects of screening with OCT are not available, and evidence on effects of treatments in persons diagnosed using OCT is limited. An area of high interest and a rapidly expanding evidence base is the use of artificial intelligence to analyze and categorize data from OCT and other screening tests,[48] potentially improving diagnostic accuracy and facilitating implementation of screening. However, we did not identify studies utilizing artificial intelligence that were eligible for our review, because they utilized (non-clinical) imaging databanks, used a case-control design, lacked validation testing, or did not evaluate algorithms available for widespread use. The FDA has published a proposed regulatory framework to evaluate artificial intelligence and machine learning as a medical device;[180] as yet no artificial intelligence technologies have been approved for diagnosis of glaucoma.

Relevance for Priority Populations

Glaucoma disproportionately impacts Black persons, and to a lesser extent, Latino persons, relative to non-Latino White persons. Black persons have the highest prevalence of glaucoma, a higher rate of glaucoma progression and blindness, and earlier presentation of glaucoma.[17,181] Race-related disparities have been reported in glaucoma management and adherence to care,[182-184] and disparities exist with regard to access to care. Evidence on how race or ethnicity impacts effectiveness of treatment is limited. In the OHTS, in which 25 percent of participants were Black, there was no interaction between race and effects of medical treatment compared with placebo on IOP, likelihood of progression from ocular hypertension to OAG, or adverse events.[148] Although Black participants were at increased risk of progression to OAG in univariate analysis, race was not a predictor when analyses adjusted for other demographic factors, markers of glaucoma severity, and comorbidities. In LiGHT, in which 22 percent of participant were Black, 6.5 percent were Asian, and 68 percent were White, race/ethnicity was not a predictor of response to SLT.[36] In UKGTS, approximately 5 percent of participants were Black and 3.1 percent were Asian; no analysis was performed on the interaction between race/ethnicity and effects of latanoprost compared with placebo.[35] Two trials that did not meet inclusion criteria because they evaluated surgery (one trial also enrolled persons with advanced glaucoma) found that Black participants had worse outcomes than White participants who had surgery first.[185,186]

Future Research

Important gaps remain in the evidence on screening for glaucoma. Additional trials comparing screening with no screening that utilize contemporary screening and diagnostic modalities (e.g., spectral domain-OCT or swept source-OCT) and include vision-related outcome, function, and quality of life would provide direct evidence on effects of screening. Research is also needed to determine optimal screening approaches, such as strategies that target higher-risk populations compared with screening of all adults. Research on the accuracy of instruments for identifying persons at increased risk of glaucoma would be useful for informing screening strategies. Studies are needed to verify the diagnostic accuracy of current screening tests when applied to screened populations. Studies are needed to better understand the utility of artificial intelligence to aid in the analysis and interpretation of screening tests, using validated algorithms in clinical cohorts of patients that are available for use in clinical practice (ideally, FDA-approved). Telehealth approaches to screening that can be implemented in primary care settings could potentially facilitate access and are particularly relevant in the post-COVID-19 era. Studies on the effects of referral to glaucoma screening from primary care compared with no referral are lacking and would help clarify outcomes associated with referral. Research is needed to better understand the long-term effects of treatment on visual impairment, quality of life, and function; to understand how effects of treatment vary by race/ethnicity; and to verify that benefits of treatment are retained in persons diagnosed with OAG using newer imaging methods. Longer-term studies of the recently approved medications netarsudil and latanoprostene bunod would help clarify benefits and harms relative to older first-line therapies.

Conclusions

Direct evidence comparing glaucoma screening with no screening is limited and showed no benefits on vision-related quality of life or function, and increased risk of falls. Screening tests (OCT, visual field assessment) can identify persons with OAG with reasonable accuracy. Treatment for ocular hypertension or untreated OAG is associated with reduction in IOP and reduced risk of glaucoma progression based on visual fields or optic nerve changes, but limited evidence on the association with visual outcome, quality of life, and function indicates no clear effects.

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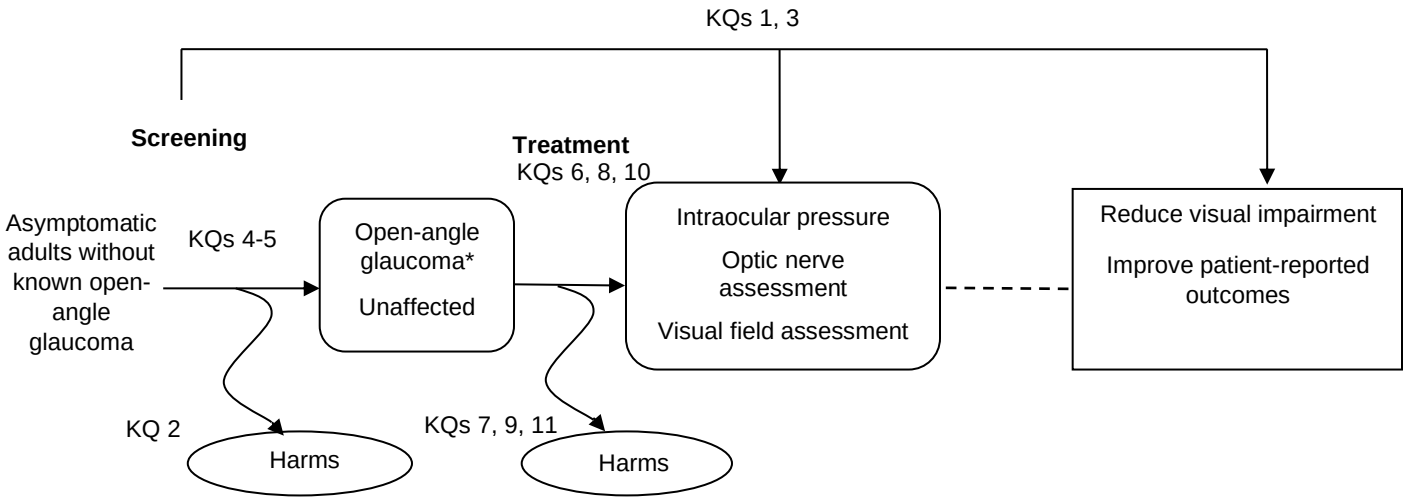
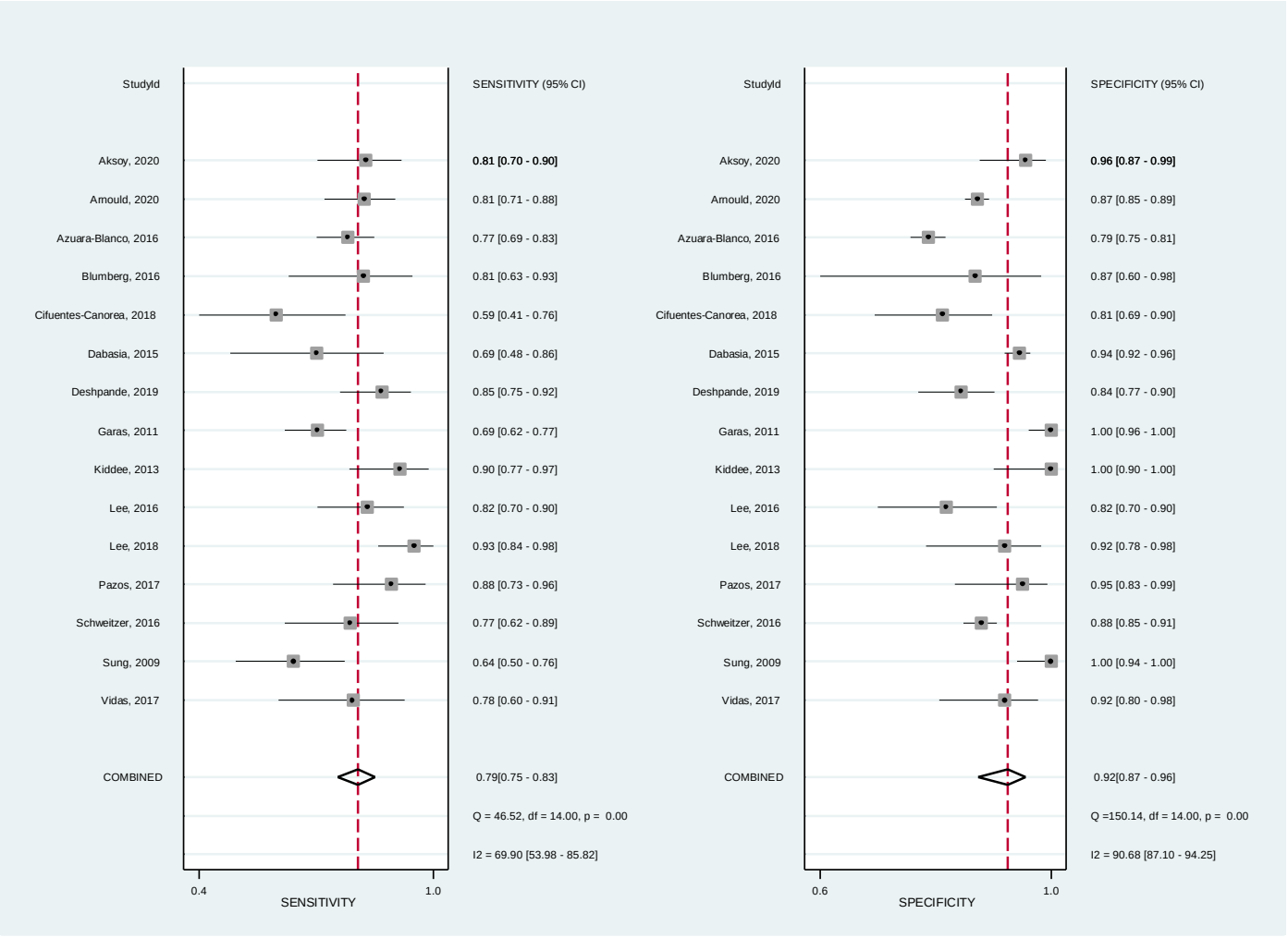
Figure 1. Analytic Framework and Key Questions: Glaucoma



*Includes open-angle glaucoma suspects.
Note: Subpopulations of interest include those defined by age, sex, race/ethnicity, and setting (e.g., rural or urban), etc.
Abbreviation: KQ = Key Question.

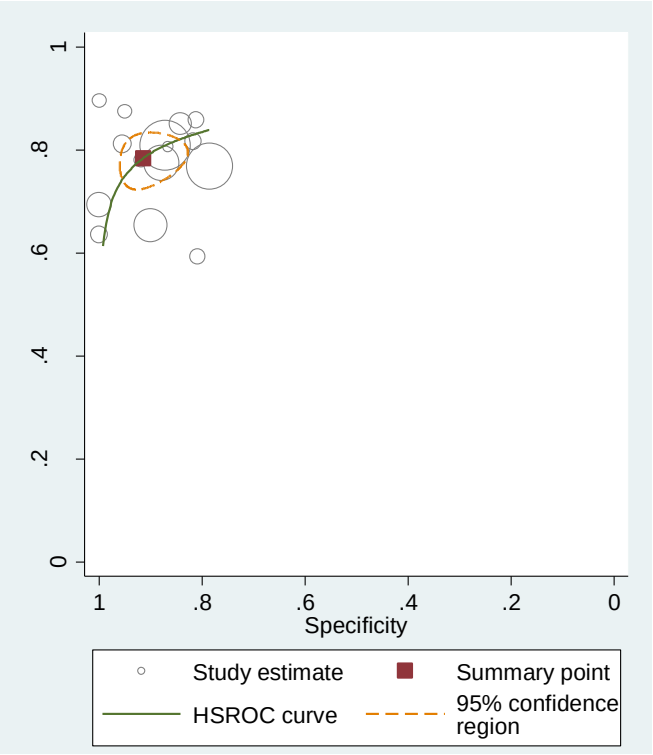
Key Question 1. What are the effects of screening for open angle glaucoma versus no screening on a) intraocular pressure, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
Key Question 2. What are the harms of screening for open angle glaucoma versus no screening?
Key Question 3. What are the effects of referral to an eye health provider versus no referral on a) intraocular pressure, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
Key Question 4. What is the accuracy of screening for diagnosis of open angle glaucoma?
Key Question 5. What is the accuracy of instruments for identifying patients at higher risk of open angle glaucoma?
Key Question 6. What are the effects of medical treatments for open angle glaucoma versus placebo or no treatments on a) intraocular pressure, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
Key Question 7. What are the harms of medical treatments for open angle glaucoma versus placebo or no treatments?
Key Question 8. What are the effects of newly U.S. Food and Drug Administration-approved medical treatments (latanoprostene bunod and netarsudil) versus older medical treatments on a) intraocular pressure, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
Key Question 9. What are the harms of newly U.S. Food and Drug Administration-approved medical treatments versus older medical treatments?
Key Question 10. What are the effects of laser trabeculoplasty for open angle glaucoma versus no trabeculoplasty or medical treatment on a) intraocular pressure, visual field loss, visual acuity, or optic nerve damage or b) visual impairment, quality of life, or function?
Key Question 11. What are the harms of laser trabeculoplasty for open angle glaucoma versus no trabeculoplasty or medical treatment?

Figure 2. Glaucoma vs. Control, Spectral Domain-OCT Sensitivity and Specificity for Retinal Nerve Fiber Layer Thickness



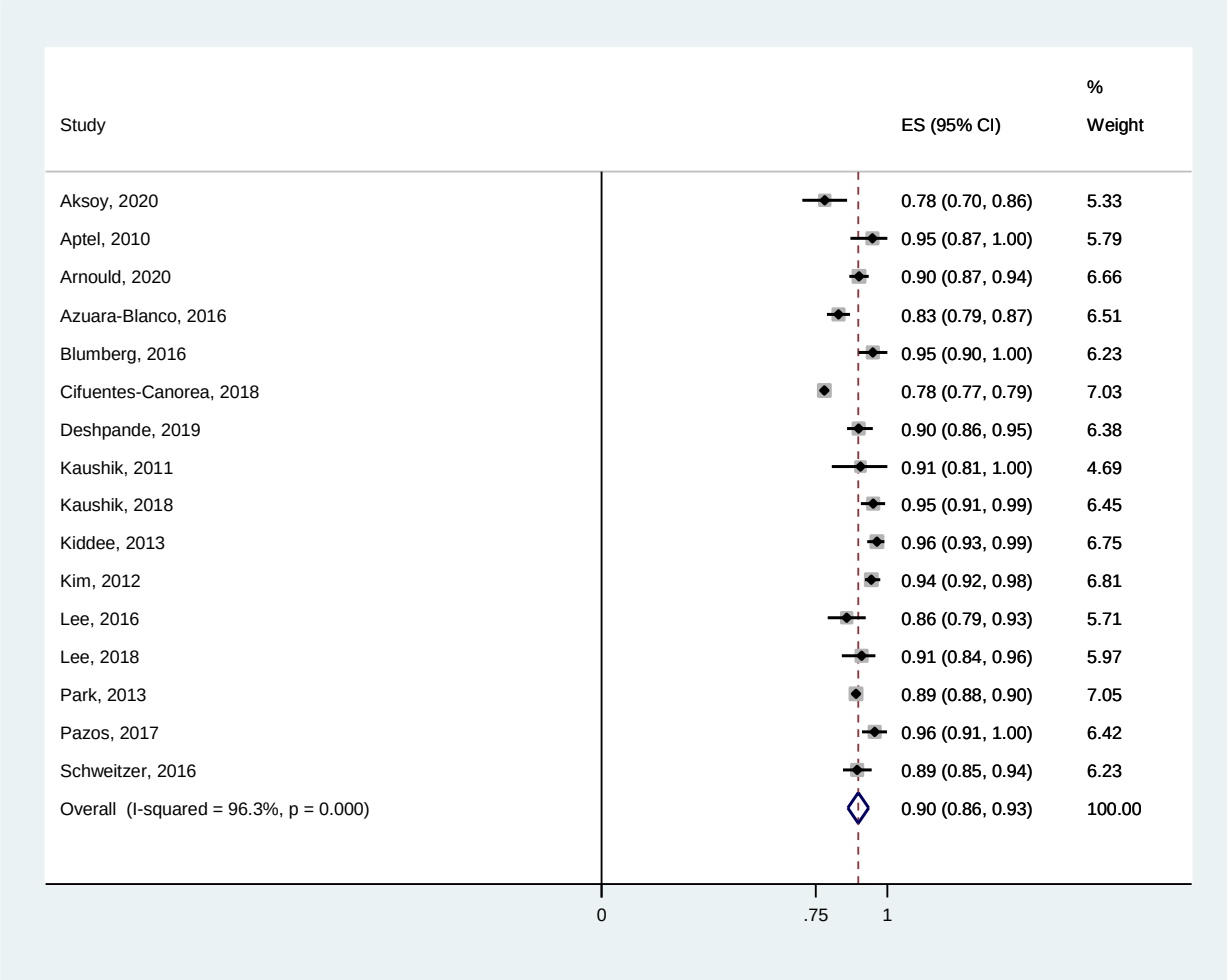
Abbreviations: CI = confidence interval; df = degrees of freedom; OCT = optical coherence tomography.

Figure 3. Glaucoma vs. Control, Spectral Domain-OCT Retinal Nerve Fiber Layer Thickness



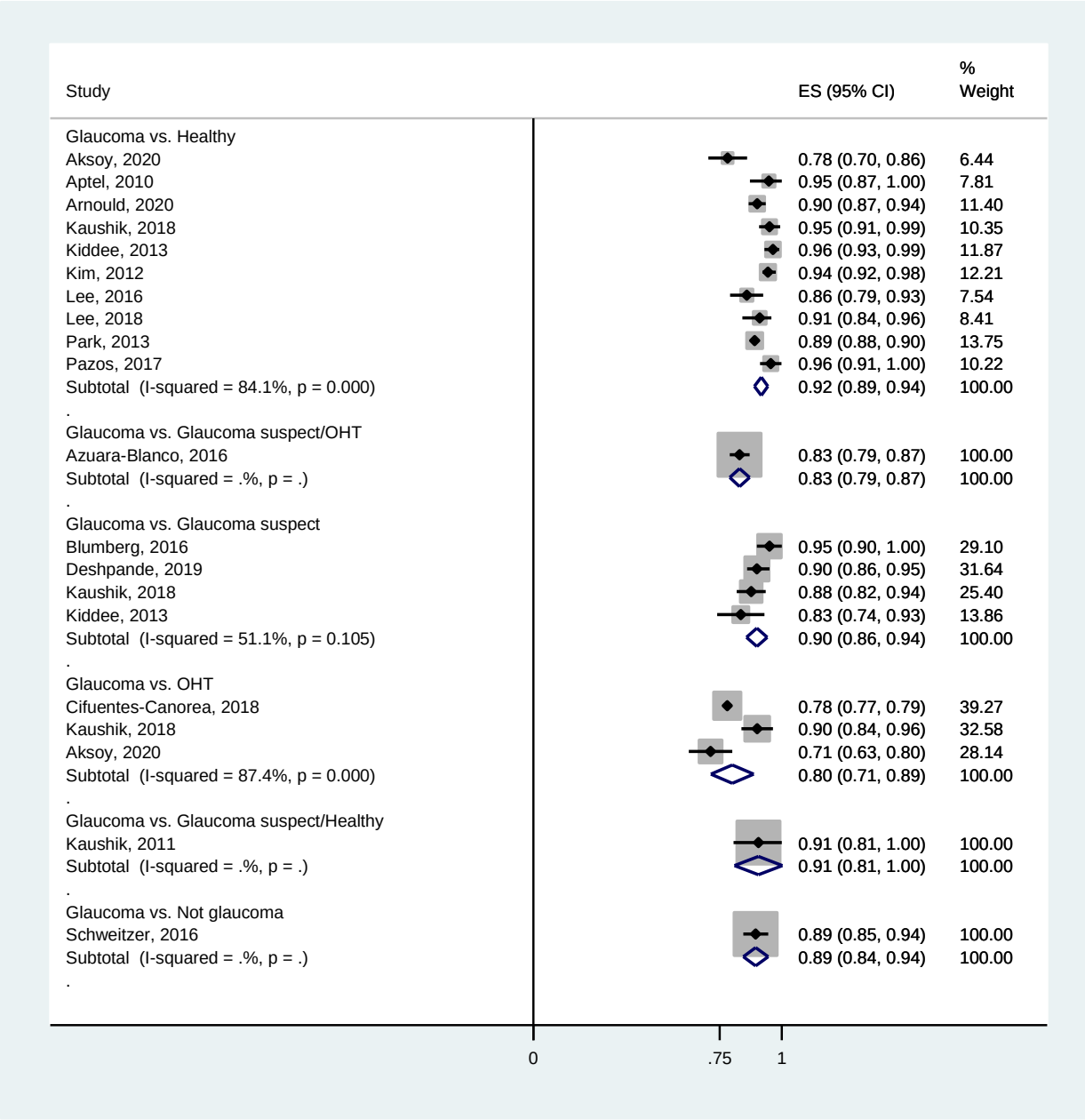
Abbreviations: HSROC = hierarchical summary receiver operating characteristic; OCT = optical coherence tomography.

Figure 4. AUROC, Spectral Domain-OCT Retinal Nerve Fiber Layer Thickness by Comparison



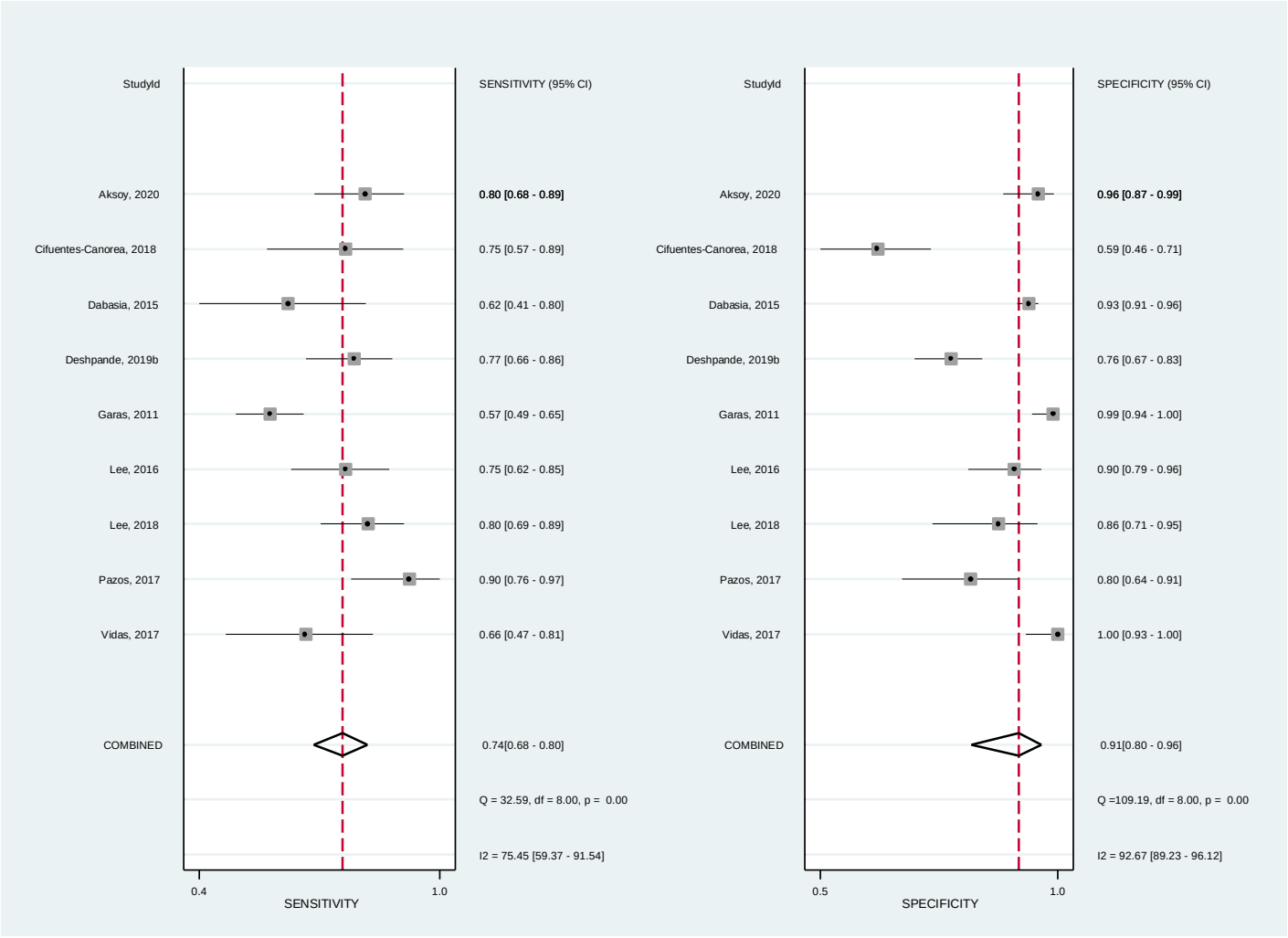
Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ES = estimate; OCT = optical coherence tomography.

Figure 5. AUROC Curves, Spectral Domain-OCT Retinal Nerve Fiber Layer Thickness



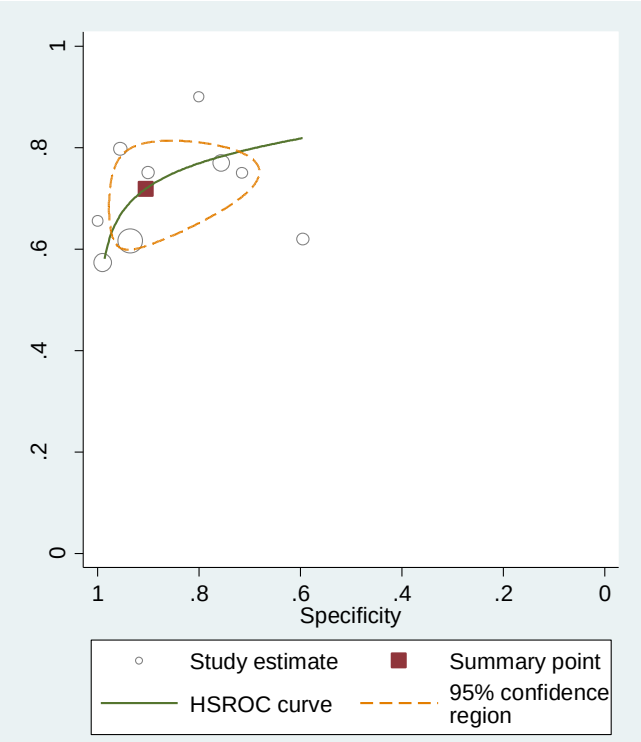
Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ES = estimate; OCT = optical coherence tomography.

Figure 6. Glaucoma vs. Control, Spectral Domain-OCT Sensitivity and Specificity for Ganglion Cell Complex Thickness



Abbreviations: CI = confidence interval; df = degrees of freedom; OCT = optical coherence tomography.

Figure 7. Glaucoma vs. Control, Spectral Domain-OCT Ganglion Cell Complex Thickness



Abbreviations: HSROC = hierarchical summary receiver operating characteristic; OCT = optical coherence tomography.

Figure 8. Ganglion Cell Analysis

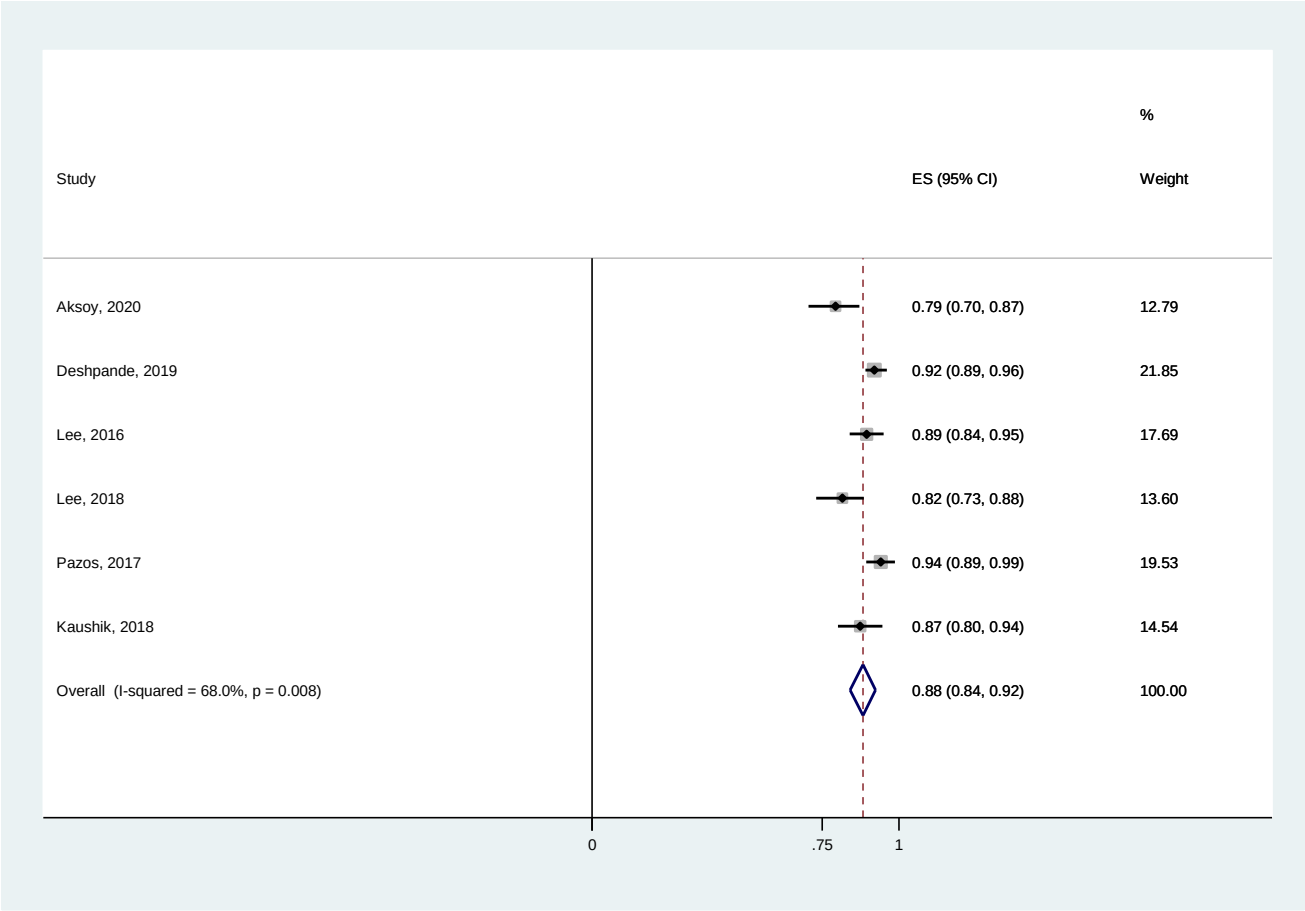


Figure 9. Ganglion Cell Analysis by Control Group

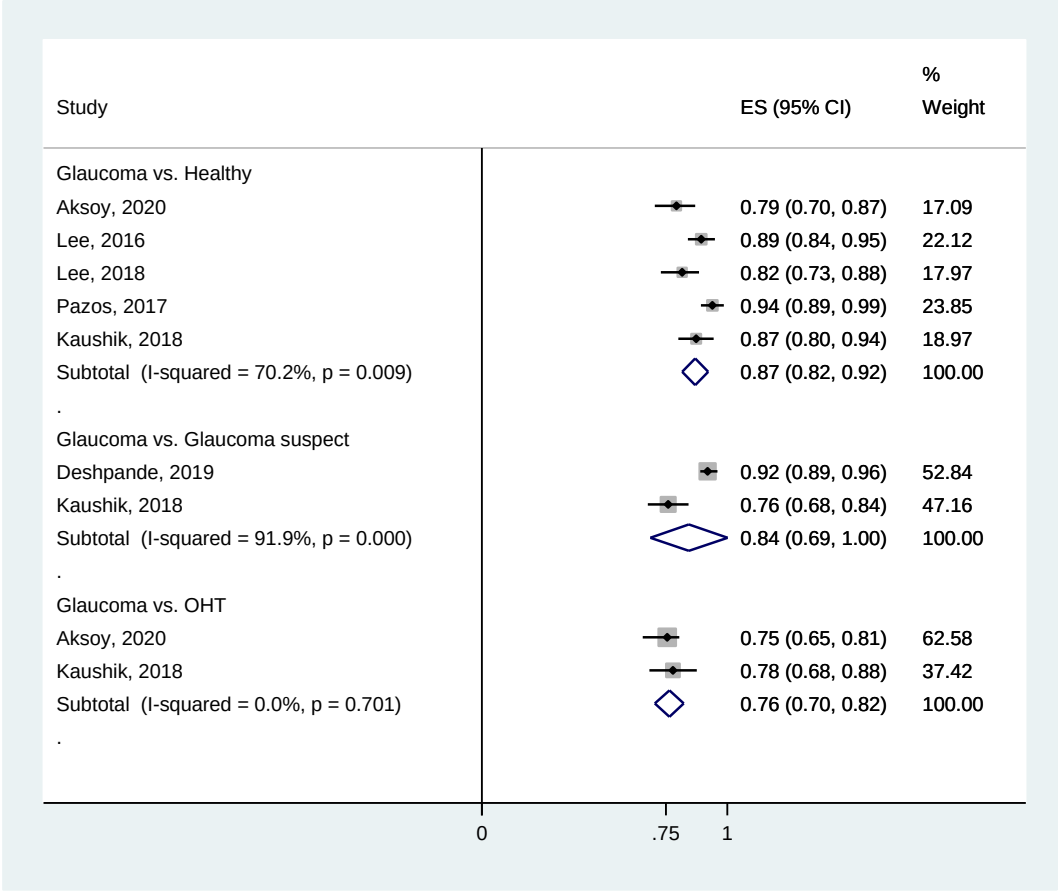
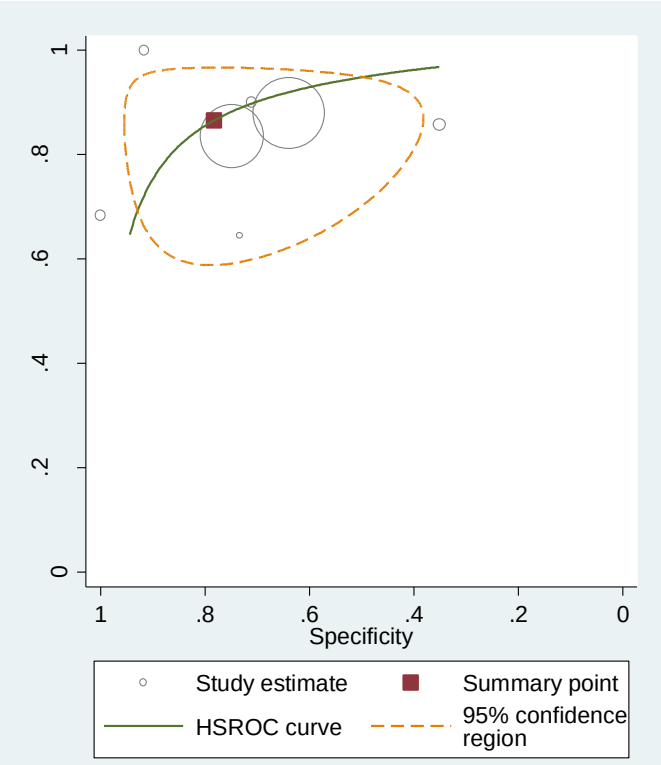
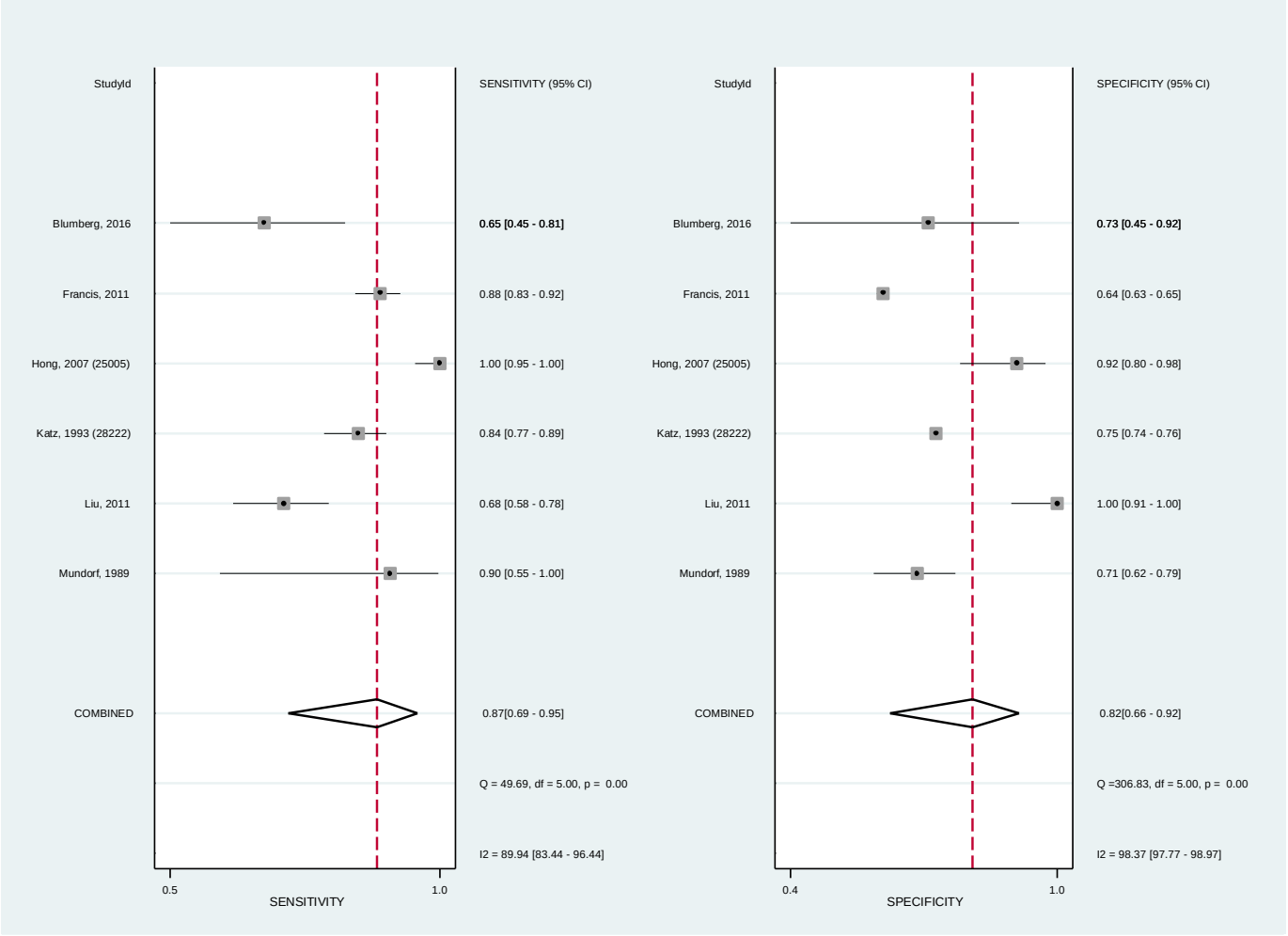


Figure 10. Glaucoma vs. Control, Humphrey Field Analyzer Visual Field



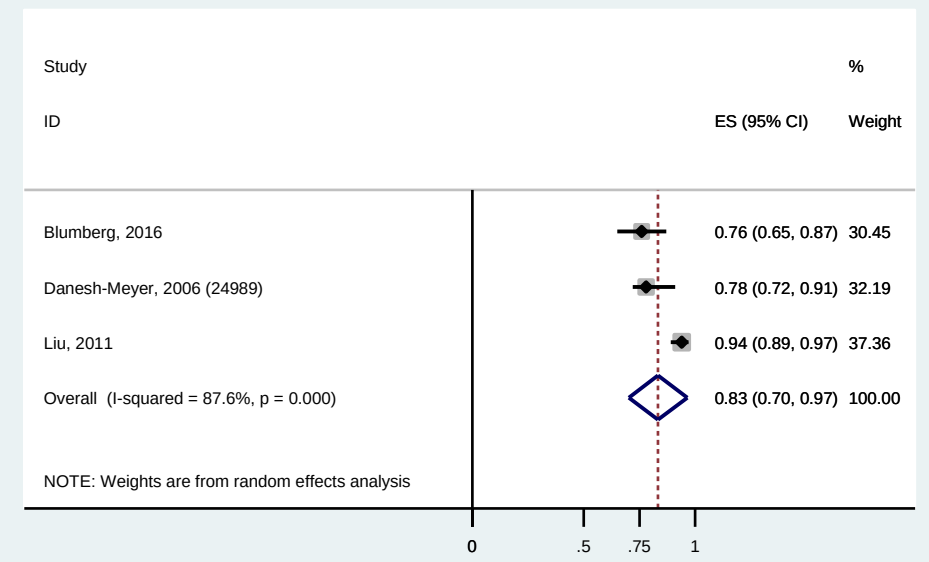
Abbreviation: HSROC = hierarchical summary receiver operating characteristic.

Figure 11. Glaucoma vs. Control, Visual Field Sensitivity and Specificity



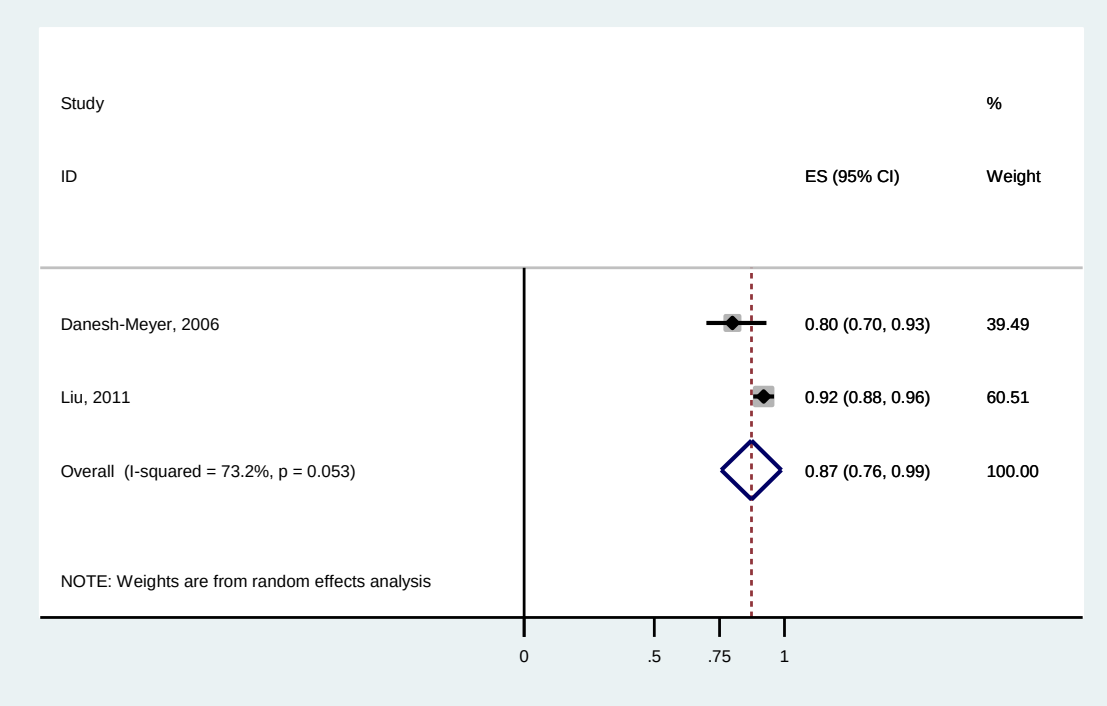
Abbreviations: CI = confidence interval; df = degrees of freedom.

Figure 12. Glaucoma vs. Control, AUROC Humphrey Field Analyzer Visual Field Mean Deviation



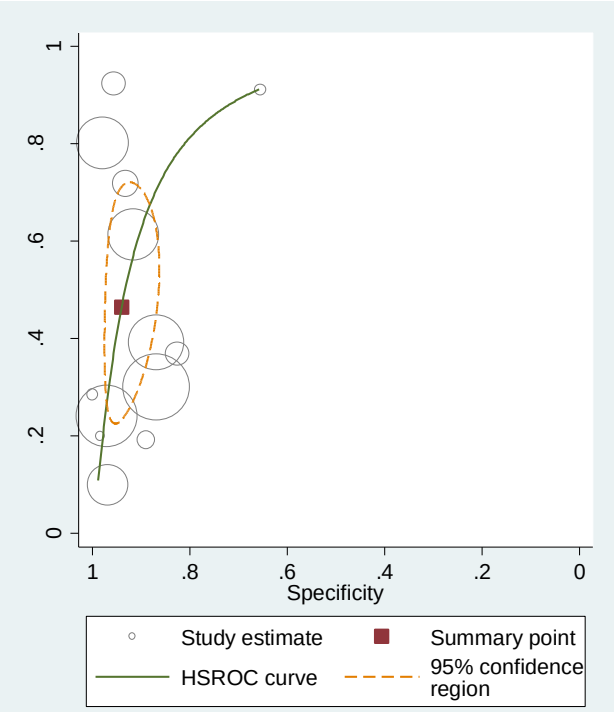
Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ES = estimate.

Figure 13. Glaucoma vs. Control, AUROC Humphrey Field Analyzer Visual Field Pattern Standard Deviation



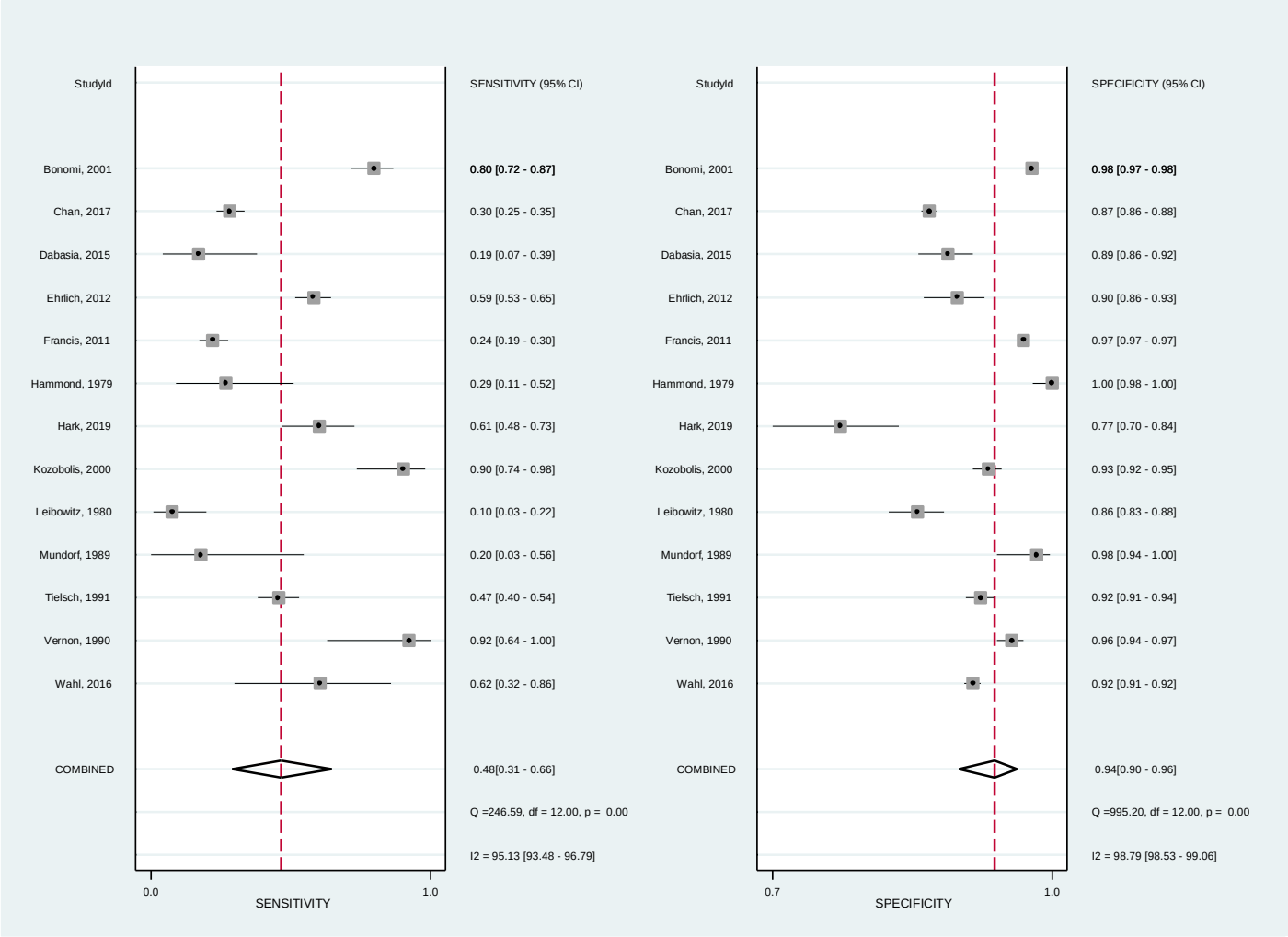
Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; ES = estimate.

Figure 14. Glaucoma vs. Control Tonometry



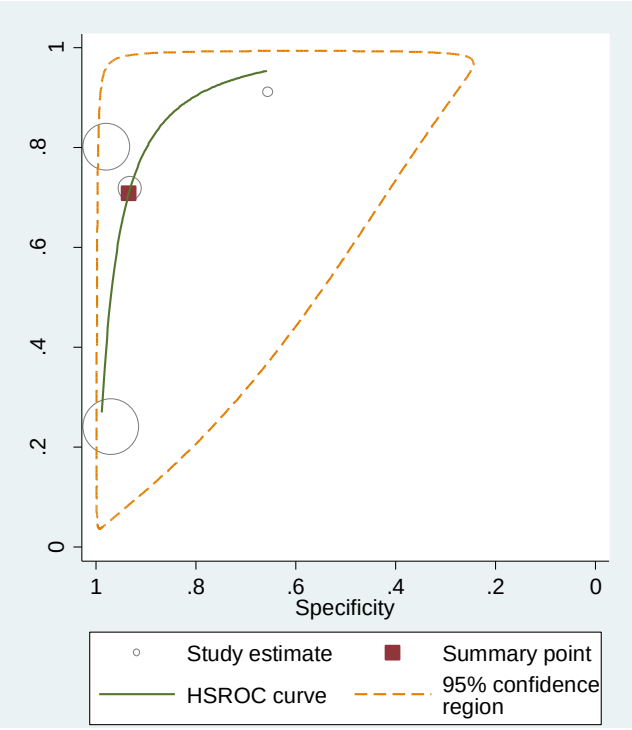
Abbreviation: HSROC = hierarchical summary receiver operating characteristic.

Figure 15. Glaucoma vs. Control Tonometry Sensitivity and Specificity



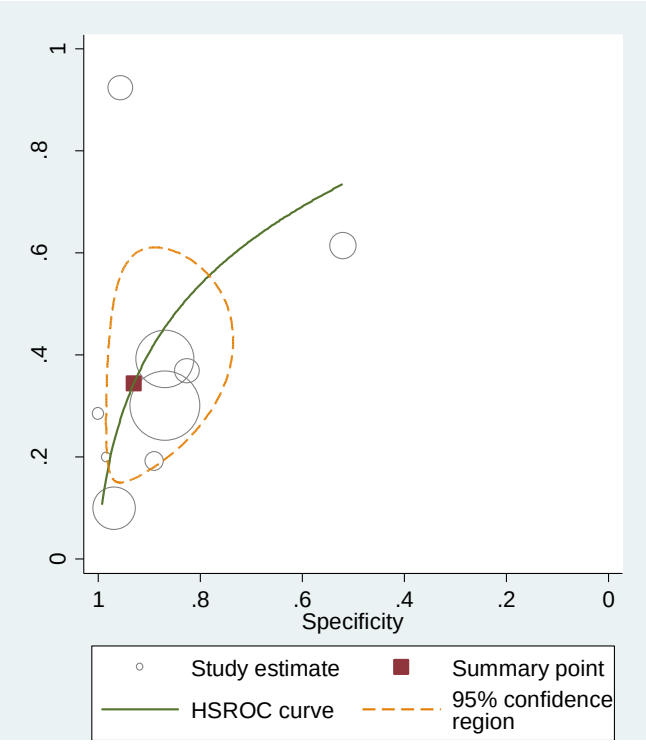
Abbreviations: CI = confidence interval; df = degrees of freedom.

Figure 16. Glaucoma vs. Control, Goldman Applanation Tonometry



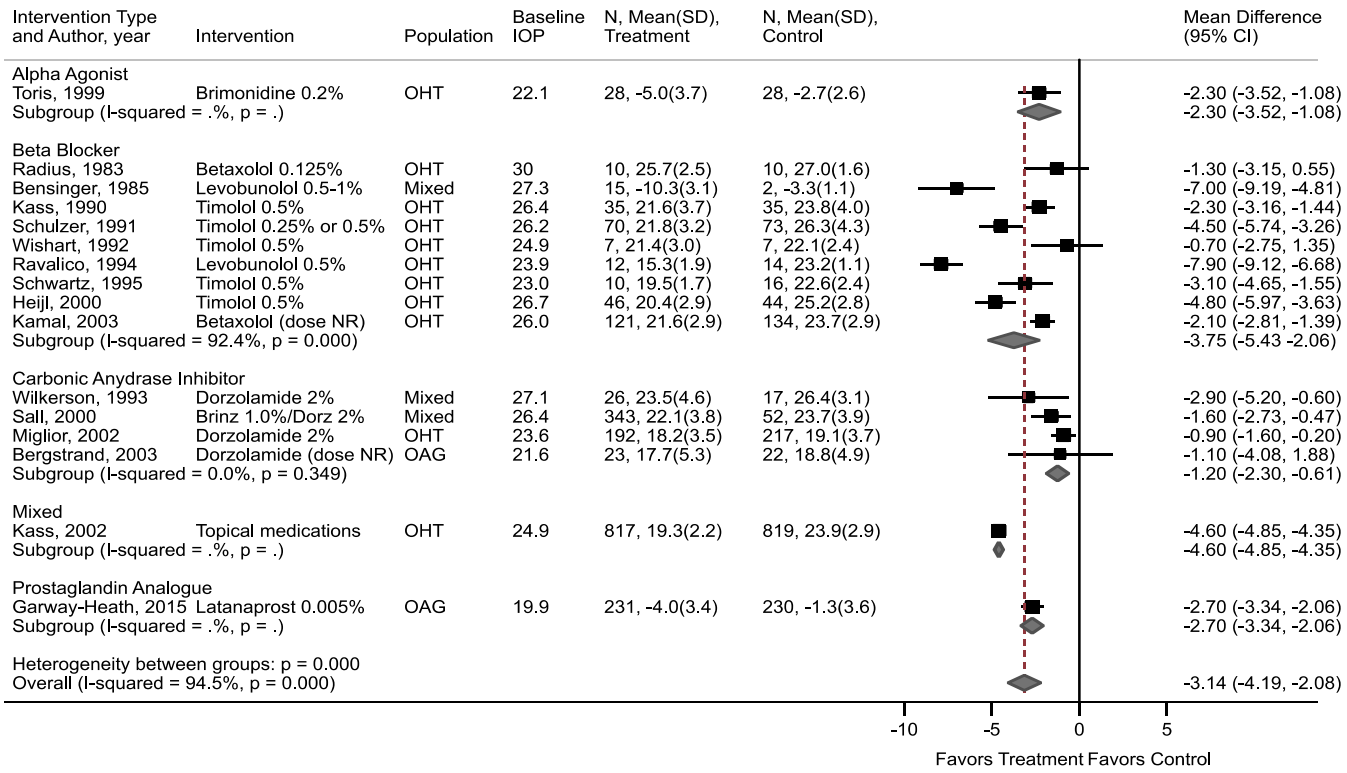
Abbreviations: HSROC = hierarchical summary receiver operating characteristic.

Figure 17. Glaucoma vs. Control, Other Tonometry Techniques



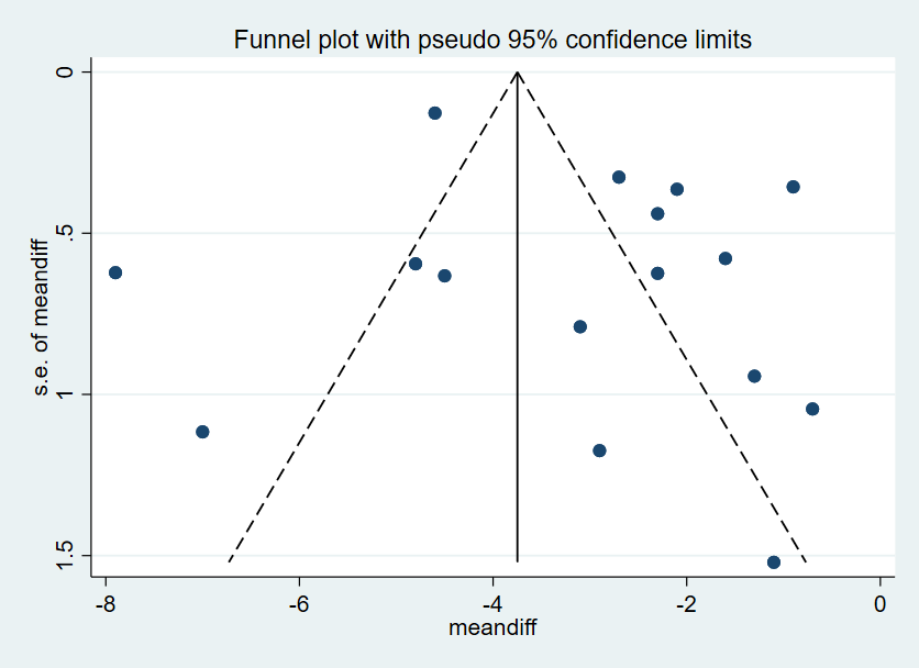
Abbreviations: HSROC = hierarchical summary receiver operating characteristic.

Figure 18. Medical Treatment vs. Placebo/No Treatment on IOP, by Drug Class



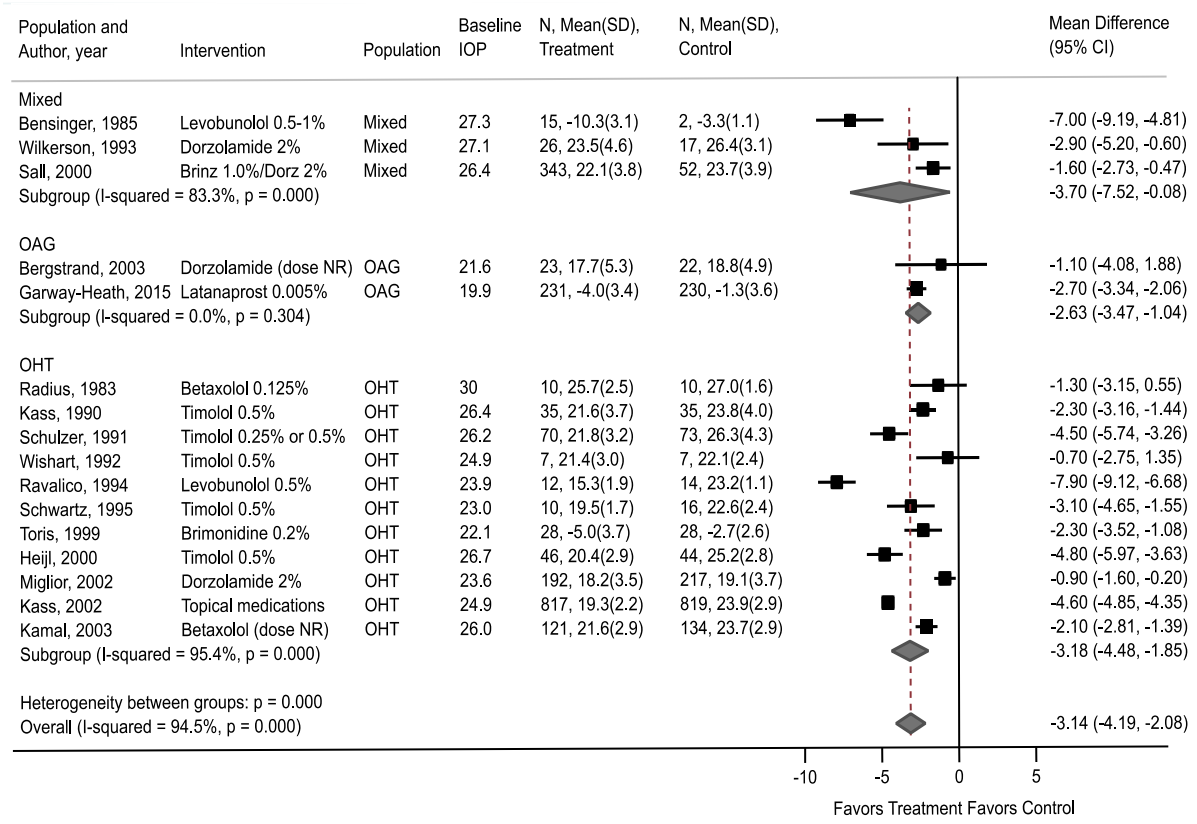
Abbreviations: CI = confidence interval; IOP = intraocular pressure; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

Figure 19. IOP Funnel Plot



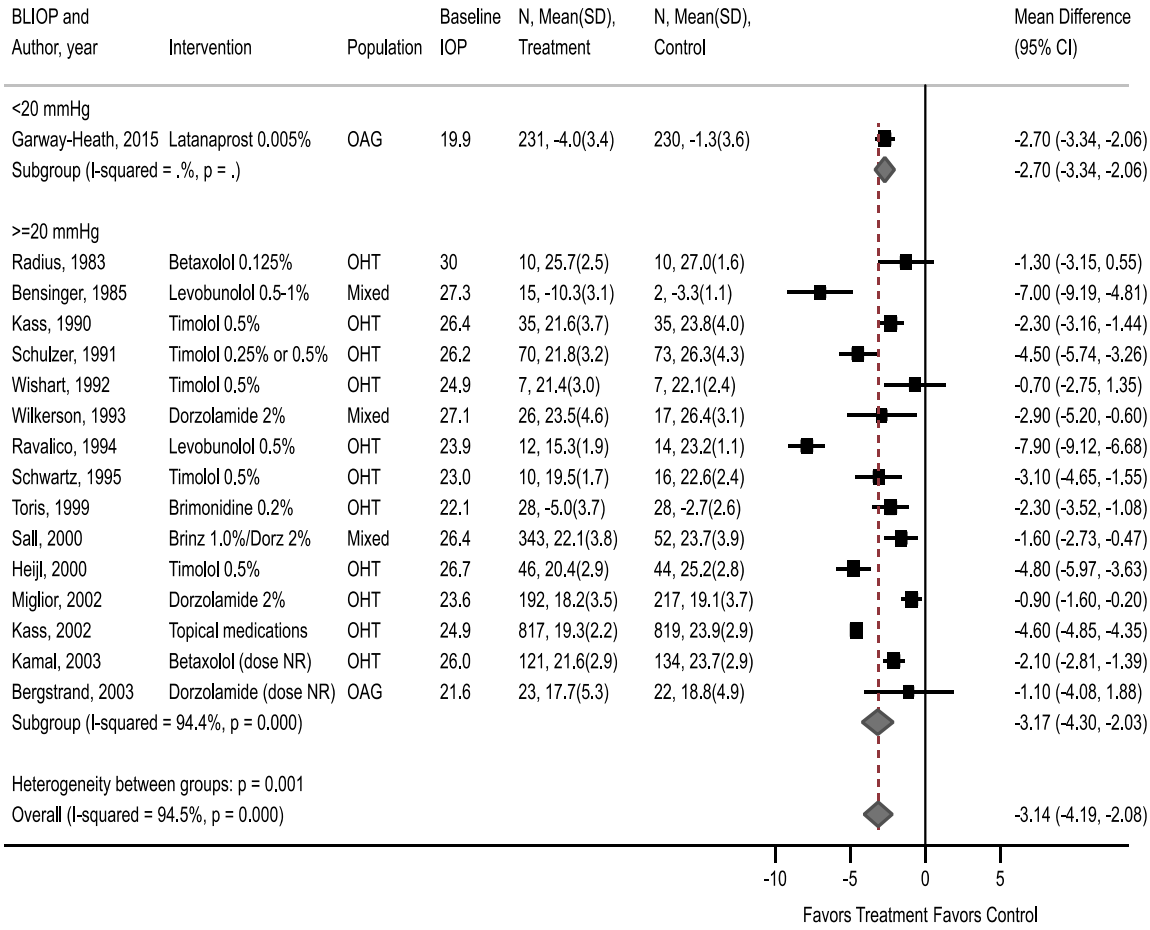
Abbreviations: IOP = intraocular pressure; s.e. = standard error.

Figure 20. Medical Treatment vs. Placebo/No Treatment on IOP, by Population



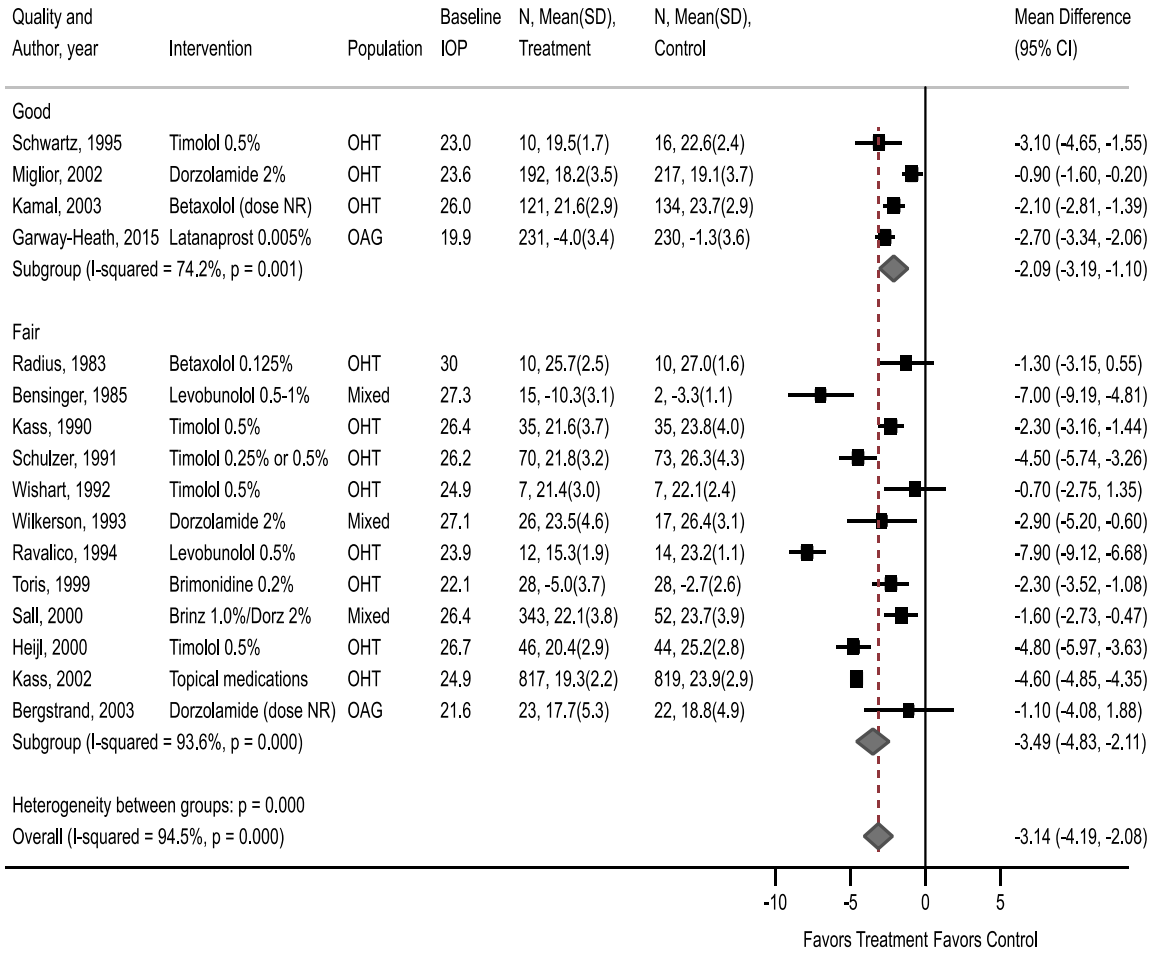
Abbreviations: CI = confidence interval; IOP = intraocular pressure; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

Figure 21. Medical Treatment vs. Placebo/No Treatment on IOP, by Baseline IOP



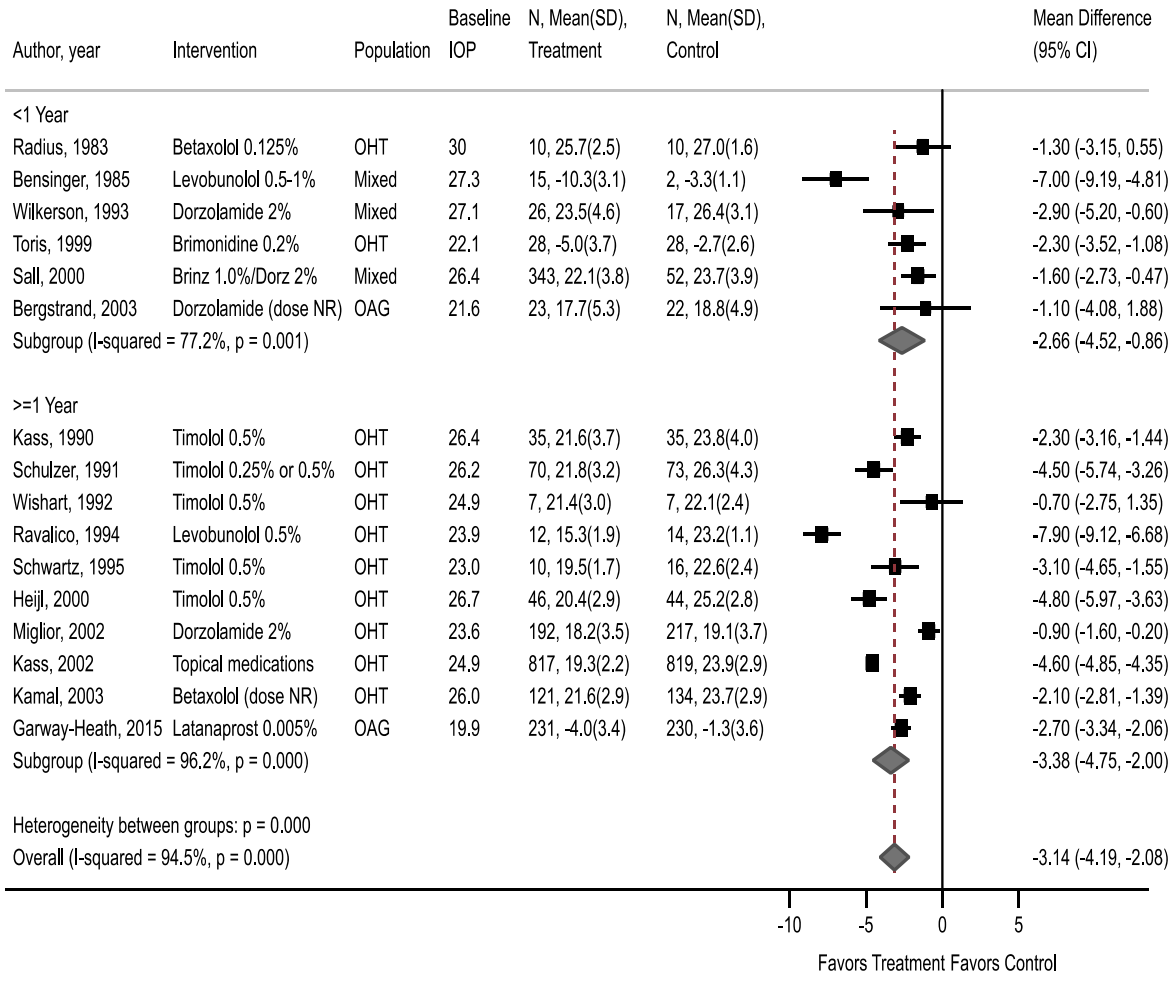
Abbreviations: BLIOP = baseline intraocular pressure; CI = confidence interval; IOP = intraocular pressure; mm Hg = millimeters mercury; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

Figure 22. Medical Treatment vs. Placebo/No Treatment on IOP, by Quality



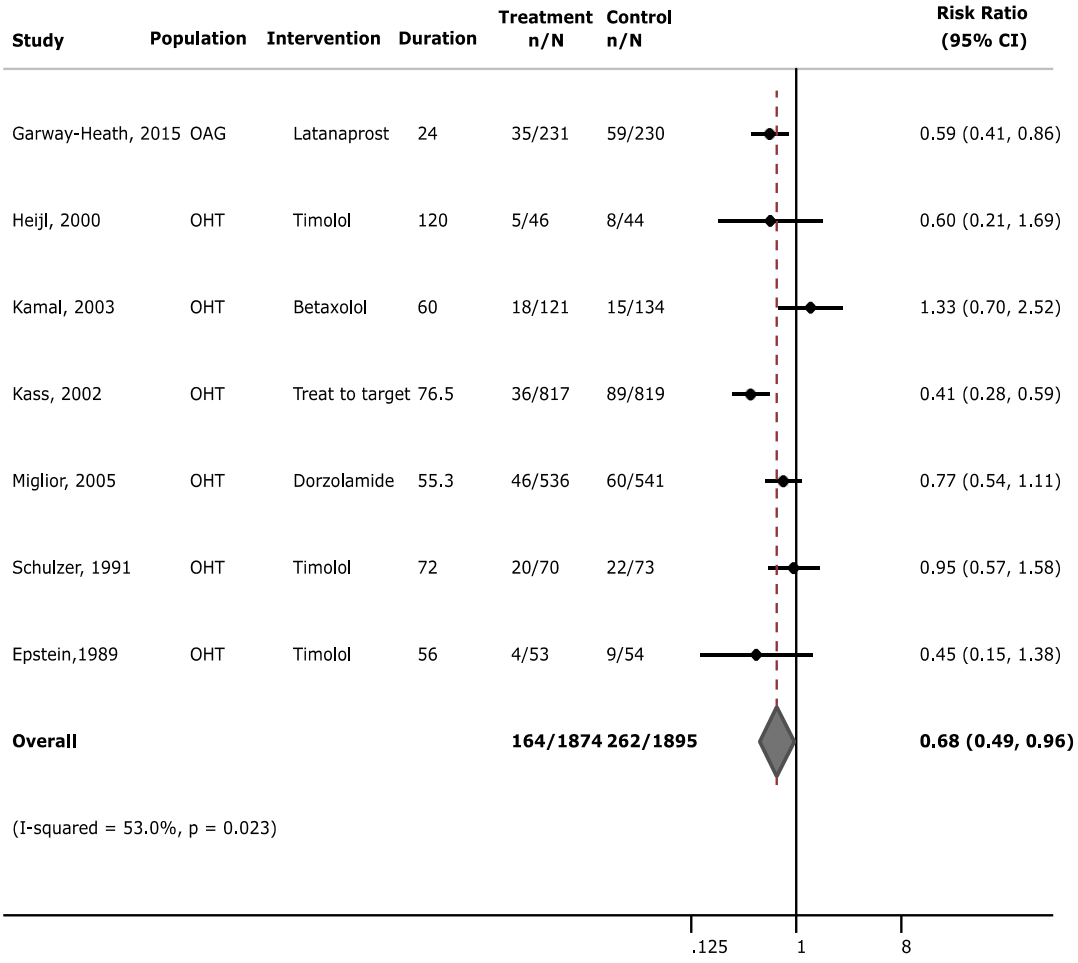
Abbreviations: CI = confidence interval; IOP = intraocular pressure; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

Figure 23. Medical Treatment vs. Placebo/No Treatment on IOP, by Duration



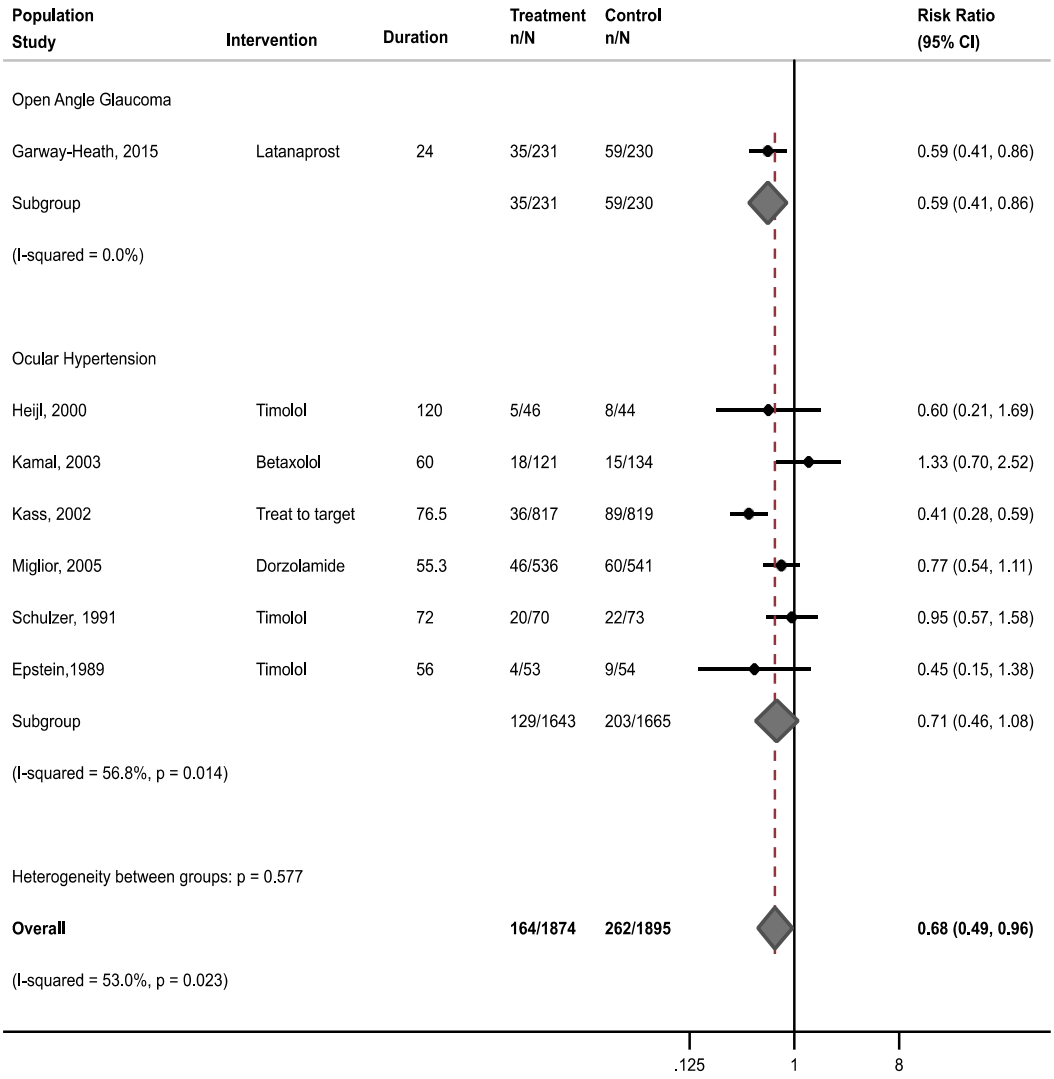
Abbreviations: CI = confidence interval; IOP = intraocular pressure; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

Figure 24. Medical Treatment vs. Placebo/No Treatment on Progression to Glaucoma



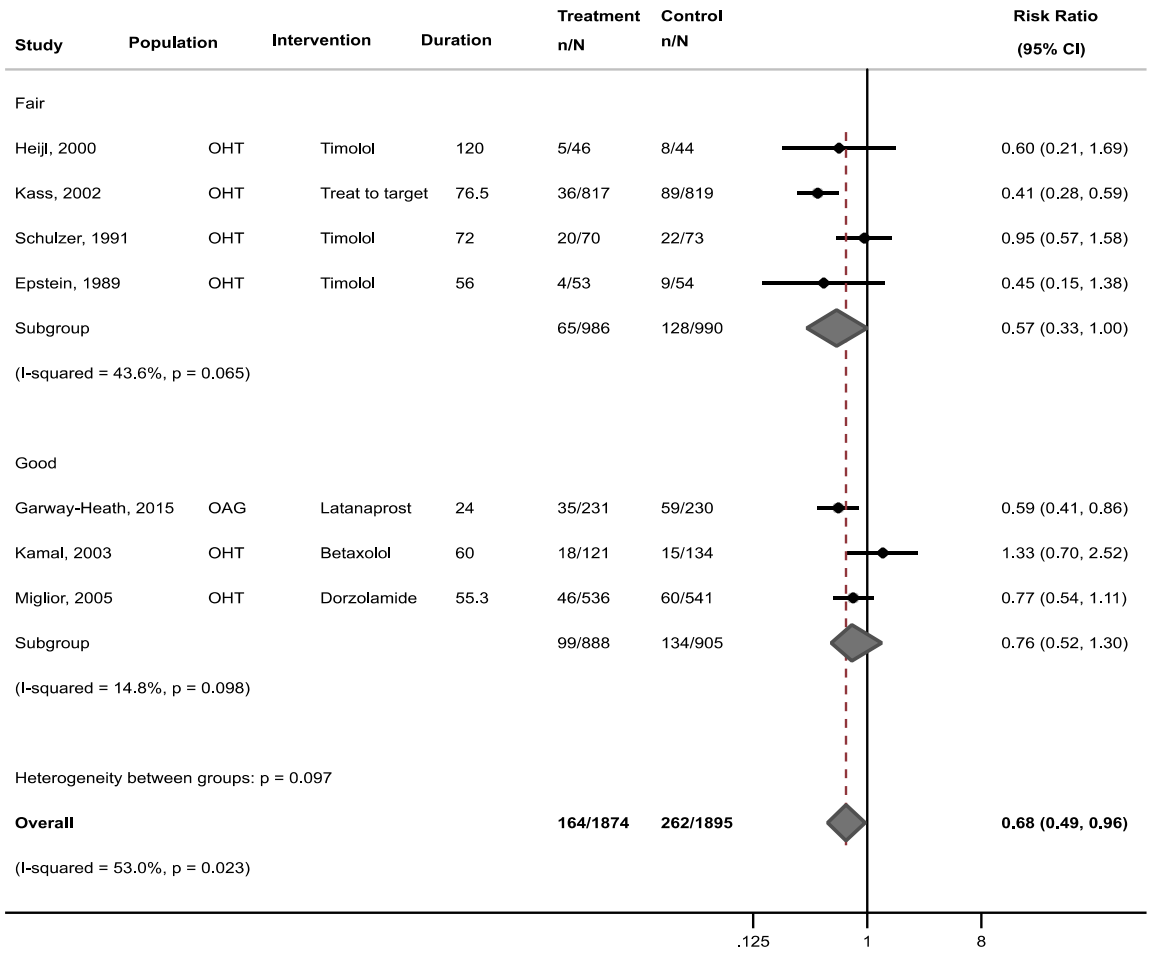
Abbreviations: CI = confidence interval; OAG = open angle glaucoma; OHT = ocular hypertension.

Figure 25. Medical Treatment vs. Placebo/No Treatment on Progression to Glaucoma, by Population



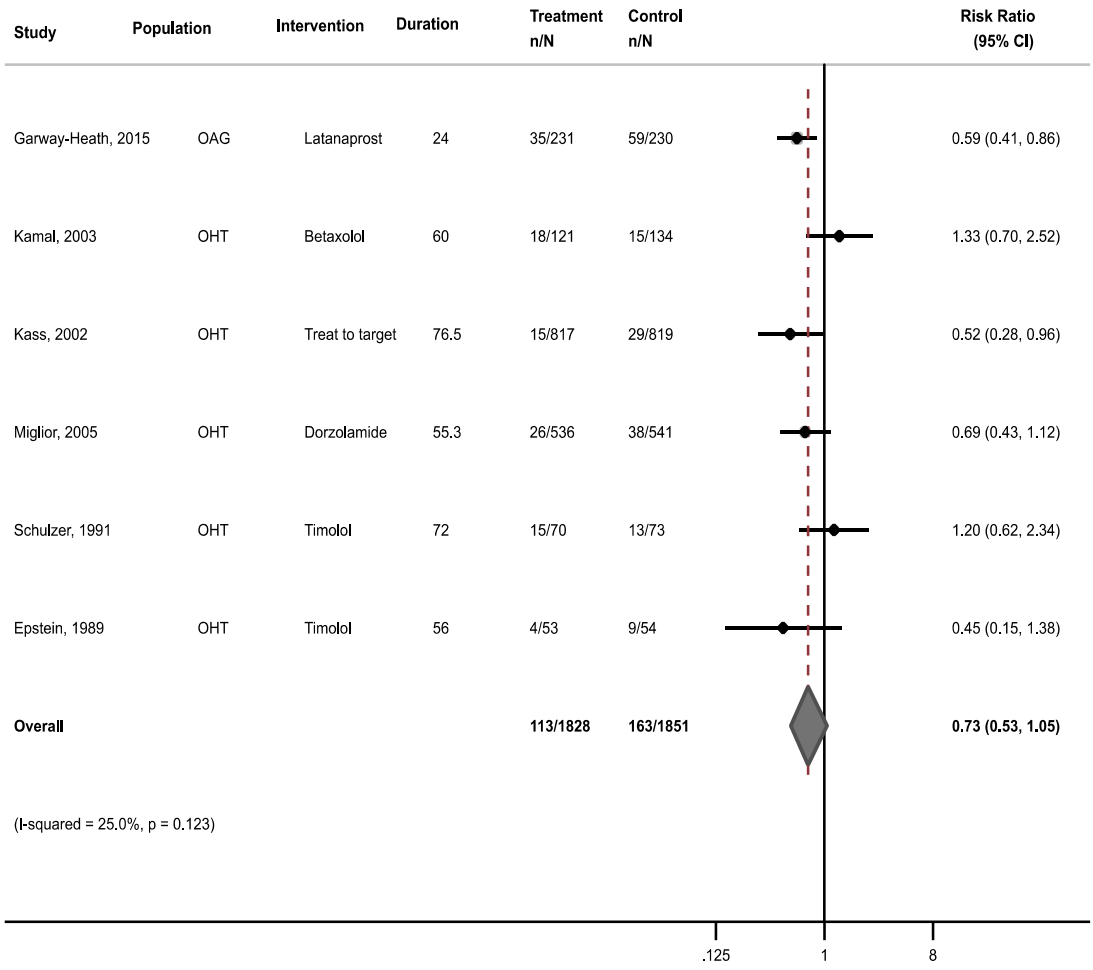
Abbreviation: CI = confidence interval.

Figure 26. Medical Treatment vs. Placebo/No Treatment on Progression to Glaucoma, by Quality



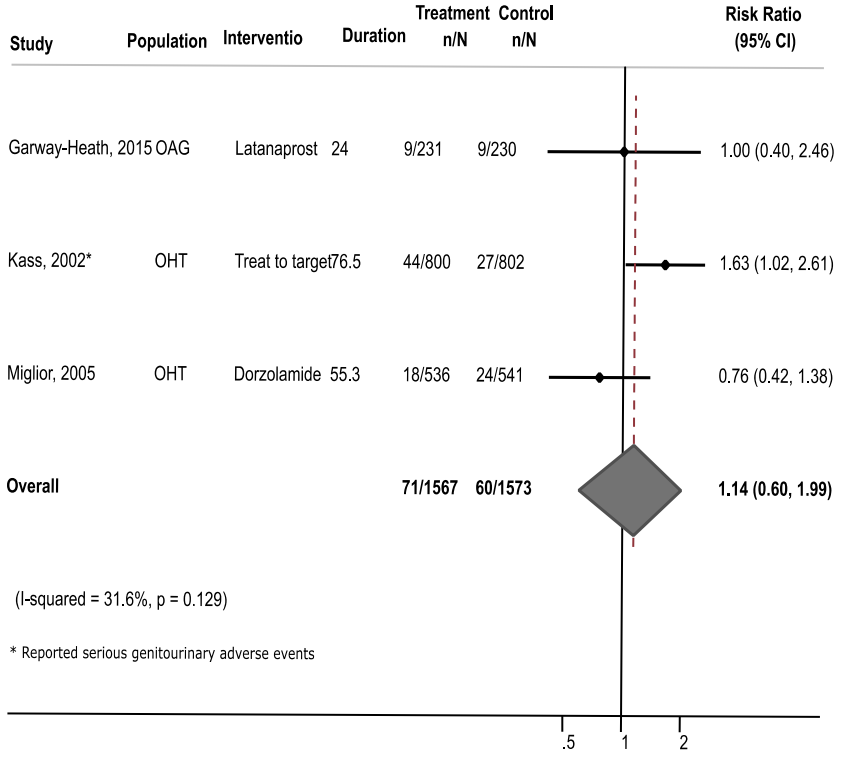
Abbreviations: CI = confidence interval; OAG = open angle glaucoma; OHT = ocular hypertension.

Figure 27. Medical Treatment vs. Placebo/No Treatment on Progression of Visual Field Defects



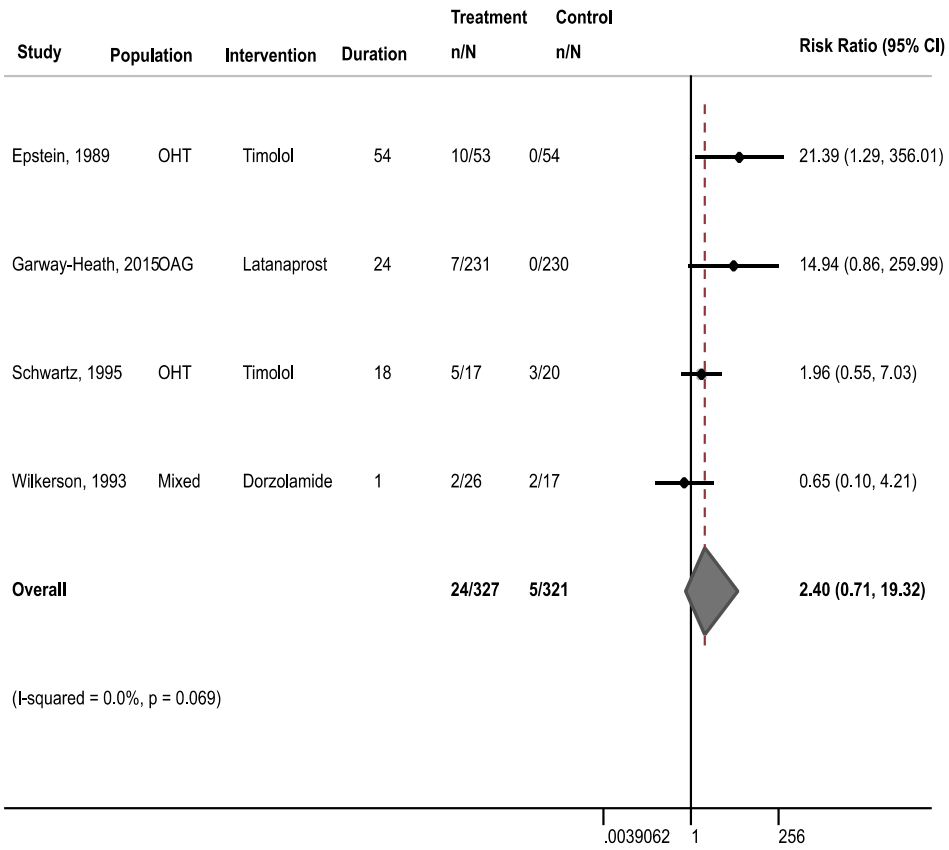
Abbreviations: CI = confidence interval; OAG = open angle glaucoma; OHT = ocular hypertension.

Figure 28. Medical Treatment vs. Placebo/No Treatment on Serious Adverse Effects



Abbreviations: CI = confidence interval; OAG = open angle glaucoma; OHT = ocular hypertension.

Figure 29. Medical Treatment vs. Placebo/No Treatment on IOP Withdrawals Due to Adverse Effects



Abbreviations: CI = confidence interval; IOP = intraocular pressure; OAG = open angle glaucoma; OHT = ocular hypertension.

Table 1. Diagnostic Accuracy, Pooled Analyses

Sensitivity and Specificity

Pooled analysis	# trials	N	Sensitivity (95% CI)	Specificity (95% CI)
RNFL thickness	**15**	**4242**	**0.79 (0.75 to 0.83)**	**0.92 (0.87 to 0.96)**
• Healthy eye controls	9	2404	0.81 (0.74 to 0.86)	0.96 (0.89 to 0.99)
• Glaucoma suspect controls	3	1130	Range 0.77 to 0.85	Range 0.79 to 0.87
• Ocular hypertension + healthy controls	1	81	0.78 (0.60 to 0.91)*	0.92 (0.80 to 0.98)*
• Ocular hypertension controls	2	228	0.59 and 0.80	0.81 and 0.96
• Not glaucoma	1	532	0.77 (0.62 to 0.89)	0.88 (0.85 to 0.91)
• Restricted to overall mean RNFL	12	3819	0.79 (0.74 to 0.84)	0.90 (0.85 to 0.93)
• Good quality	3	2400	Range 0.65 to 0.81	Range 0.79 to 0.90
• Fair quality	12	1880	0.80 (0.74 to 0.85)	0.94 (0.88 to 0.97)
GCC thickness	**9**	**1522**	**0.74 (0.68 to 0.80)**	**0.91 (0.80 to 0.96)**
• Healthy eye controls	6	1145	0.76 (0.66 to 0.83)	0.92 (0.86 to 0.96)
• Glaucoma suspect controls	1	201	0.77 (0.66 to 0.86)*	0.76 (0.67 to 0.83)*
• Ocular hypertension controls	1	95	0.75 (0.57 to 0.89)*	0.59 (0.46 to 0.71)*
• Healthy + ocular hypertension controls	1	81	0.66 (0.47 to 0.81)*	1.00 (0.93 to 1.00)*
• Restricted to studies that utilized inner plexiform layer or ganglion cell layer	5	998	0.73 (0.60 to 0.83)	0.95 (0.87 to 0.98)
• Good quality	1	456	0.62 (0.41 to 0.80)*	0.93 (0.91 to 0.96)*
• Fair quality	8	542	0.75 (0.68 to 0.81)	0.91 (0.78 to 0.97)
Intraocular pressure	**13**	**32892**	**0.48 (0.31 to 0.66)**	**0.94 (0.90 to 0.96)**
• Healthy or non-glaucoma controls	12	28726	0.47 (0.29 to 0.66)	0.94 (0.90 to 0.97)
• Probable glaucoma vs. not probable glaucoma	1	4166	0.61 (0.56 to 0.67)*	0.92 (0.91 to 0.92)*
• Goldmann tonometry	4	11690	0.66 (0.36 to 0.87)	0.95 (0.92 to 0.98)
• Other tonometry methods	9	21202	0.39 (0.22 to 0.58)	0.93 (0.87 to 0.97)
• Good quality	2	6587	0.24 (0.19 to 0.30) 0.19 (0.07 to 0.39)	0.97 (0.97 to 0.97) 0.89 (0.86 to 0.92)
• Fair quality	11	26305	0.54 (0.34 to 0.72)	0.94 (0.89 to 0.97)
HFA visual fields	**6**	**11244**	**0.87 (0.69 to 0.95)**	**0.82 (0.66 to 0.92)**
• Good quality	2	6082	0.88 (0.83 to 0.92)*	0.64 (0.64 to 0.65)*
• Fair quality	5	5162	Range 0.65 to 1.00†	Range 0.64 to 1.00†

AUROC

Pooled analysis	# trials	N	AUROC (95% CI)
RNFL thickness	***16***	***4060***	***0.90 (0.86 to 0.93)***
• Healthy eye controls	10	2262	0.92 (0.89 to 0.94)
• Glaucoma suspect controls	4	496	0.90 (0.86 to 0.94)
• Ocular hypertension controls	3	319	0.80 (0.71 to 0.89)
• Glaucoma suspect + healthy controls	1	91	0.91 (0.81 to 1.00)*
• Glaucoma suspect + ocular hypertension controls	1	883	0.83 (0.79 to 0.87)*
• Not glaucoma	1	532	0.89 (0.85 to 0.94)*
• Overall mean RNFL	12	3634	0.92 (0.89 to 0.94)
• Good quality	2	1944	0.87 (0.80 to 0.94)
• Fair quality	14	2116	0.90 (0.86 to 0.94)

Table 1. Diagnostic Accuracy, Pooled Analyses

Pooled analysis	# trials	N	AUROC (95% CI)
Ganglion cell analysis	**6**	**765**	**0.88 (0.84 to 0.92)**
• Healthy eye controls	5	564	0.87 (0.82 to 0.92)
• Glaucoma suspect	2	354	0.84 (0.69 to 1.00)
• Ocular hypertension	2	224	0.76 (0.70 to 0.82)
• Restricted to studies of ganglion cell complex	2	211	0.87 (0.72 to 1.00)
HFA visual fields			
• HFA SITA-Standard 24-2 mean deviation	3	288	0.830.70 to 0.97)
• HFA SITA-Standard 24-2 pattern standard deviation	2	242	0.87 (0.76 to 0.99)

Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; GCC = ganglion cell complex; HFA = Humphrey Field Analyzer; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; SITA = Swedish Interactive Thresholding Algorithm.

* Estimate from a single study (not pooled).

† Pooled estimate was not produced because the model did not converge.

Table 2. Sensitivity and Specificity, Spectral Domain-OCT Retinal Nerve Fiber Layer Thickness

Author, year	N	Glaucoma	Control	Sensitivity (95% CI)	Specificity (95% CI)
Aksoy, 2020[54]	131	Early glaucoma	Healthy	0.81 (0.70 to 0.90)	0.96 (0.87 to 0.99)
Aksoy, 2020[54]	133	Early glaucoma	OHT	0.80 (0.68 to 0.89)	0.96 (0.88 to 0.99)
Arnould, 2020[56]	1061	Glaucoma	Healthy	0.81 (0.71 to 0.88)	0.87 (0.85 to 0.89)
Azuara-Blanco, 2016[59]	883	Glaucoma	Glaucoma Suspect + OHT	0.77 (0.69 to 0.83)	0.79 (0.75 to 0.81)
Blumberg, 2016[64]	46	Glaucoma	Glaucoma Suspect	0.81 (0.63 to 0.93)	0.87 (0.60 to 0.98)
Cifuentes-Canorea, 2018[71]	95	Early glaucoma	OHT	0.59 (0.41 to 0.76)	0.81 (0.69 to 0.90)
Dabasia, 2015[73]	456	POAG	Healthy	0.69 (0.48 to 0.86)	0.94 (0.92 to 0.96)
Deshpande, 2019[76]	201	Early glaucoma	Glaucoma suspect	0.85 (0.75 to 0.92)	0.84 (0.77 to 0.90)
Garas, 2011[81]	250	Perimetric + PPG	Healthy	0.69 (0.62 to 0.77)	1.00 (0.96 to 1.00)
Kiddee, 2013	83	Glaucoma	Healthy	0.90 (0.77 to 0.97	1.00 (0.90 to 1.00)
Lee, 2016[164]	120	POAG	Healthy	0.82 (0.70 to 0.90)	0.82 (0.70 to 0.90)
Lee, 2018a[106]	146*	Early glaucoma	Healthy	0.93 (0.84 to 0.98)	0.92 (0.78 to 0.98)
Pazos, 2017[53]	80	Early glaucoma	Healthy	0.88 (0.73 to 0.96)	0.95 (0.83 to 0.99)
Schweitzer, 2016[128]	532	Glaucoma	Nonglaucoma	0.77 (0.62 to 0.89)	0.88 (0.85 to 0.91)
Sung, 2009[131]	115	Glaucoma	Healthy	0.64 (0.50 to 0.76)	1.00 (0.94 to 1.00
Vidas, 2017[136]	81	Glaucoma	No glaucoma	0.78 (0.60 to 0.91)	0.92 (0.80 to 0.98)

Abbreviations: CI = confidence interval; OCT = optical coherence tomography; OHT = ocular hypertension; POAG = primary open angle glaucoma; PPG = preperimetric glaucoma (no visual field defects).
*Includes 36 patients with preperimetric glaucoma; n=108 in the analysis.

Table 3. Sensitivity and Specificity, Spectral Domain-OCT Ganglion Cell Complex Thickness

Author, year	N	Glaucoma	Control	Sensitivity (95% CI)	Specificity (95% CI)
Aksoy, 2020[54]	131	Early glaucoma	Healthy	0.80 (0.68 to 0.89)	0.96 (0.87 to 0.99)
Aksoy, 2020[54]	133	Early glaucoma	OHT	0.82 (0.71 to 0.90)	0.96 (0.88 to 0.99)
Cifuentes-Canorea, 2018[71]	95	Early glaucoma	OHT	0.75 (0.57 to 0.89)	0.59 (0.46 to 0.71)
Dabasia, 2015[73]	456	POAG	Healthy	0.62 (0.41 to 0.80)	0.93 (0.91 to 0.96)
Deshpande, 2019[76]	201	Early glaucoma	Glaucoma suspect	0.77 (0.66 to 0.86)	0.76 (0.67 to 0.83)
Garas, 2011[81]	250	Perimetric + PPG	Healthy	0.57 (0.49 to 0.65)	0.99 (0.94 to 1.00)
Lee, 2016[104]	120	POAG	Healthy	0.75 (0.62 to 0.85)	0.90 (0.79 to 0.96)
Lee, 2018[106]	108	Early glaucoma	Healthy	0.80 (0.69 to 0.89)	0.86 (0.71 to 0.95)
Pazos, 2017[53]	80	Early glaucoma	Healthy	0.90 (0.76 to 0.97)	0.80 (0.64 to 0.91)
Vidas, 2017[136]	81	Glaucoma	OHT + Healthy	0.66 (0.47 to 0.81)	1.00 (0.93 to 1.00)

Abbreviations: CI = confidence interval; OCT = optical coherence tomography; OHT = ocular hypertension; POAG = primary open angle glaucoma; PPG = preperimetric glaucoma (no visual field defects).

Table 4. Glaucoma vs. Control, Spectral Domain-OCT Cup-to-Disc Ratio

Author, year	N	Control	AUROC (95% CI)
Kim, 2012[100]	106	Healthy	0.74 (0.72 to 0.83)
Koh, 2018[101]	1061*	Healthy	0.94 (0.91 to 0.98)
Xu, 2017[144]	703*	Healthy	0.91 (not reported)

Abbreviations: AUROC = area under the receiver operating characteristic curve; CI = confidence interval; OCT = optical coherence tomography.
*These studies enrolled one or more eyes per participant, n=number of participants.

Table 5. Glaucoma vs. Control, Optic Disc Photography Cup-to-Disc Ratio

Author, year	N	Control	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blumberg, 2016[64]	46	Glaucoma suspect	0.85 (0.74 to 0.96)	0.64 (0.45 to 0.81)	0.73 (0.45 to 0.92)
Danesh-Meyer, 2006[74]	110	Non-glaucoma	0.81 (0.74 to 0.92)	---	---
Hark, 2019[86]	345	Non-glaucoma CDR>0.65 medium and large discs, >0.5 for small discs	---	0.71	0.51
Leibowitz, 1980[107]	2631	Non-glaucoma CDR>0.4	---	0.18 (0.09 to 0.31)	0.67 (0.62 to 0.71)

Abbreviations: AUROC = area under the receiver operating characteristic curve; CDR = cup-to-disc ratio; CI = confidence interval.

Table 6. Ophthalmoscopy/Biomicroscopy/Stereoscopy Cup-to-Disc Ratio

Author, year	N	Method CDR Cutoff	Control	Sensitivity (95% CI)	Specificity (95% CI)
Vernon, 1990[135]	854	Ophthalmoscopy CDR >0.7	Glaucoma Suspect	0.56 (0.31 to 0.78)	0.99 (0.98 to 0.99)
Liebowitz, 1980[107]	2631	Ophthalmoscopy + disc photos; CDR>0.4	Non-glaucoma	0.18 (0.09 to 0.31)	0.67 (0.62 to 0.71)
Francis, 2011[80]	5749	Biomicroscopy CDR≥0.8	Non-glaucoma	0.60 (0.54 to 0.67)	0.98 (0.975 to 0.982)
Hammond, 1979[84]	188	Ophthalmoscopy CDR≥0.5	Non-glaucoma	0.86 (0.42 to 1.00)	0.95 (0.91 to 0.98)
Soh, 2020[130]	8097	Stereoscopy + disc photos; CDR>0.6 or CDR asymmetry>0.2	Healthy eyes	0.91; 0.95 (CDR asymmetry)	0.92; 0.91 (CDR asymmetry)

Abbreviations: CDR = cup to disc ratio; CI = confidence interval.

Table 7. Glaucoma vs. Control, Humphrey Field Analyzer Sensitivity and Specificity

Author, Year	N	Method Threshold	Control	Sensitivity (95% CI)	Specificity (95% CI)
Francis, 2011[80]	6082	SITA-Standard 24-2 GHT abnormal; MD, PSD < 5%	Non-glaucoma	MD 0.88 (0.83 to 0.92 PSD 0.76 (0.70 to 0.81)	MD 0.64 (0.63 to 0.65) PSD 0.78 (0.77 to 0.79)
Hong, 2007[88]	120	30-2 Swedish interactive threshold GHT abnormal; PDP <5%; PSD<5%	Healthy	1.00 (0.95 to 1.00)	0.92 (0.80 to 0.98)
Tielsch 1991[133] Katz, 1993[95]	4733	Full Field 120 Protocol ≥17 defects or ≥8 defects in any quadrant	Non-glaucoma	0.84 (0.77 to 0.89)	0.75 (0.91 to 1.00)
Liu, 2011[108]	132	SITA-Standard 24-2 ≥3 non-edge-contiguous point defects with ≥1 on side of horizontal meridian in PDP	Healthy	0.68 (0.58 to 0.78)	1.00 (0.91 to 1.00)
Mundorf, 1989[117]	131	Central 30-2 (Goldman III Stimulus) ≥4 defects in any quadrant or defect pattern consistent with glaucoma	Healthy	0.90 (0.55 to 1.00)	0.79 (0.58 to 0.91)

Abbreviations: CI = confidence interval; GHT = global hemifield test; MD = mean deviation; PDP = pattern deviation plot; PSD = pattern standard deviation; SITA = Swedish Interactive Thresholding Algorithm.

Table 8. Tonometry Sensitivity and Specificity Glaucoma vs. Control

Author, year	N	Method	Control	Sensitivity (95% CI)	Specificity (95% CI)
Mundorf, 1989[117]	131	Schiotz tonometer	Healthy	0.20 (0.03 to 0.56)	0.98 (0.94 to 1.00)
Kozobolis, 2000[102]	1107	GAT	Non-glaucoma	0.90 (0.74 to 0.98)	0.93 (0.92 to 0.95)
Hark, 2019[85]	887	Rebound tonometry	Non-glaucoma	0.61 (0.48 to 0.73)	0.77 (0.70 to 0.84)
Dabasia, 2015[73]	505	Ocular Response Analyzer	Non-glaucoma	0.19 (0.07 to 0.39)	0.89 (0.86 to 0.92)
Tielsch, 1991[133] Katz, 1993[95]	4735	Not Reported	Non-glaucoma	0.47 (0.40 to 0.54)	0.92 (0.91 to 0.94)
Wahl, 2016[138]	4166	Noncontact AT555	Not probable glaucoma	0.62 (0.32 to 0.86)	0.92 (0.91 to 0.92)
Vernon, 1990[135]	874	Pulsair noncontact	Non-glaucoma	0.92 (0.64 to 1.00)	0.96 (0.94 to 0.97)
Leibowitz, 1980[107]	2631	Schiotz tonometer	Non-glaucoma	0.10 (0.03 to 0.22)	0.86 (0.83 to 0.88)
Hammond, 1979[84]	197	Schiotz tonometer	Non-glaucoma	0.29 (0.11 to 0.52)	1.00 (0.98 to 1.00)
Francis, 2011[80]	6082	GAT	Non-glaucoma	0.24 (0.19 to 0.30)	0.97 (0.97 to 0.97)
Ehrlich, 2012[77]	204	GAT	Healthy	0.59 (0.53 to 0.65)	0.90 (0.86 to 0.93)
Chan, 2017[68]	7076	Ocular Response Analyzer	Healthy	0.30 (0.25 to 0.35)	0.87 (0.86 to 0.88)
Bonomi, 2001[65]	4297	GAT	Healthy	0.80 (0.72 to 0.87)	0.98 (0.97 to 0.98)

Abbreviations: AT555 = autotonometer model 555; CI = confidence interval; GAT = Goldmann applanation tonometry.

Table 9. Medical Treatment vs. Placebo/No Treatment, Pooled Analyses

Analysis	Number of trials	N	Estimate (95% CI)	I^2
Intraocular Pressure	***16***	***3,706***	***MD -3.14 (-4.19 to -2.08)***	***95%***
Drug class ($P_{interaction}$<0.0005)				
• Beta-blockers	9	455	MD -3.75 (-5.43 to -2.06)	92%
• Prostaglandin	1	516	MD -2.70 (-3.34 to -2.06)	NA
• Alpha agonists	1	30	MD -2.30 (-3.52 to -1.08)	NA
• Carbonic anhydrase inhibitors	4	1,635	MD -1.20 (-2.30 to -0.61)	0%
• Mixed/various medications	1	817	MD -4.60 (-4.85 to -4.35)	NA
Baseline population ($P_{interaction}$<0.0005)				
• OHT	11	2,745	MD -3.178 (-4.48 to -1.85)	95%
• Untreated OAG	2	506	MD -2.63 (-3.47 to -1.04)	0%
• Mixed status	3	455	MD -3.704 (-7.515 to -0.083)	83%
Baseline IOP ($P_{interaction}$<0.001)				
• <20 mm Hg	1	461	MD -2.70 (-3.34 to -2.06)	NA
• ≥20 mm Hg	15	3,245	MD -3.17 (-4.30 to -2.03)	94%
Quality ($P_{interaction}$<0.0005)				
• Fair	12	2,555	MD -3.49 (-4.83 to -2.11)	94%
• Good	4	1,151	MD -2.09 (-3.19 to -1.10)	74%
Duration ($P_{interaction}$<0.0005)				
• <1 year	6	576	MD -2.66 (-4.52 to -0.86)	77%
• ≥1 year	10	3,130	MD -3.38 (-4.75 to -2.00)	96%
Progression	***7***	***3,771***	***RR 0.68 (0.49 to 0.96)***	***53%***
Population ($P_{interaction}$=0.71)				
• OAG	1	461	RR 0.59 (0.41 to 0.86)	0%
• OHT	6	3,310	RR 0.71 (0.46 to 1.08)	57%
Quality ($P_{interaction}$=0.36)				
• Fair	4	1,978	RR 0.59 (0.31 to 1.20)	54%
• Good	3	1,793	RR 0.76 (0.52 to 1.30)	15%
Progression of visual field defects	6	3,679	RR 0.73 (0.53 to 1.05)	25%
Adverse Effects				
Serious adverse events	3	3,140	RR 1.14 (0.60 to 1.99)	32%
Withdrawal due to adverse events	5	648	RR 2.40 (0.71 to 19.32)	0%

Abbreviations: CI = confidence interval; MD = mean difference; mm HG = millimeters mercury; NA = not applicable; OAG = open angle glaucoma; OHT = ocular hypertension; RR = risk ratio.

Table 10. Summary of Evidence – Glaucoma

Key Question	Studies Observations (N) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 1. Benefits of screening	1 trial (not in prior screening CER) N=616	One trial of frail elderly persons found no difference between vision screening (including components for glaucoma) versus no screening on visual acuity (mean logMAR distance acuity 0.27 vs. 0.25, p=0.32, and mean logMAR near visual acuity scores -0.01 vs. -0.03, p=0.26) or vision-related quality of life (NEI-VFQ-25 mean composite scores 84.3 vs. 86.4, p=0.49) after 1 year.	Unable to assess consistency Reasonably precise	Screening intervention evaluated other visual conditions in addition to glaucoma; small proportion of those judged to need treatment referred for glaucoma management; nearly three-quarters of control group saw eye care professional in last year	Low for no benefit	Screening conducted by optometrist; screening included components not commonly performed in primary care (ophthalmoscopy, visual field); population was frail elderly persons in Australia with high risk of falls
KQ 2. Harms of screening	1 trial (not in prior screening CER) N=616	One trial of frail elderly persons found screening associated with increased risk for falls versus no screening (incidence rate ratio 1.57 [95% CI, 1.20 to 2.05]); effects on risk of fractures was not statistically significant RR, 1.74 [95% CI, 0.97 to 3.11]).	Unable to assess consistency (1 study) Reasonably precise	See KQ 1	Low for harm	See KQ 1
KQ 3. Effects of referral	No studies	-	-	-	Insufficient	-

Table 10. Summary of Evidence – Glaucoma

Key Question	Studies Observations (N) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 4. Accuracy of screening	53 diagnostic accuracy studies (6 in prior screening CER, 47 new) N=65,464	SD-OCT (RNFL): Pooled sensitivity 0.79 (95% CI 0.75 to 0.83) and specificity 0.92 (95% CI 0.87 to 0.96) (15 studies, N=4242); pooled AUROC 0.90 (95% CI 0.86 to 0.93) (16 studies, N=4060) SD-OCT (GCC): Pooled sensitivity 0.74 (95% CI 0.68 to 0.80) and specificity 0.91 (95% CI 0.80 to 0.96) (9 studies, N=1522); pooled AUROC 0.88 (95% CI 0.84 to 0.92 (6 studies, N=765) Tonometry: Pooled sensitivity 0.48 (95% CI 0.31 to 0.66) and specificity 0.94 (95% CI 0.90 to 0.96) (13 studies, N=32,892); AUROC ranged from 0.66 to 0.78 (3 studies, N=4,684) Visual fields (HFA): Pooled sensitivity 0.87 (95% CI 0.69 to 0.95) and specificity 0.82 (95% CI 0.66 to 0.92) (6 studies, N=11244); pooled AUROC 0.83 (95% CI 0.70 to 0.97) (3 studies, N=288) Evidence on other screening tests limited Telemedicine screening was associated with variable sensitivity and high specificity compared with a face to face examination (2 studies, N=308)	Some inconsistency present. Imprecision for sensitivity of tonometry and specificity of visual fields; otherwise reasonably precise	Most studies rated fair quality; variability in comparison groups (healthy, glaucoma suspect, OHT); variability in measurement and diagnostic thresholds	Moderate	Focused on current screening tests; OCT technology is evolving and data on SS-OCT limited; prevalence of glaucoma ranged from 1.1% to 73.6%; some screening tests not available or frequently conducted in primary care; most studies conducted in the United States, Europe and Asia
KQ 5. Accuracy of instruments	1 cross-sectional study (not in prior screening CER) N=145	One study (n=145) found a questionnaire had low sensitivity (0.20, 95% CI 0.03 to 0.56) but high specificity (specificity 0.96, 95% CI 0.91 to 0.99) for identifying persons with glaucoma	Unable to assess consistency (1 study) Imprecision for sensitivity	Single fair-quality study published in 1989; no further validation available	Low	Study conducted in the United States; limited applicability to screening because previous glaucoma diagnosis was one of the most heavily weighted risk factors

Table 10. Summary of Evidence – Glaucoma

Key Question	Studies Observations (N) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 6. Effects of treatments vs. placebo/no treatments	17 trials (9 in prior treatment CER, 8 new) N=4,737	IOP: Topical medical treatment associated with greater reduction in IOP versus placebo or no treatment (16 studies, N=3,706, mean difference -3.14 mm Hg, 95% CI -4.19 to -2.08, I^2=95%) Likelihood of glaucoma progression: Topical medical treatment associated with decreased risk (7 studies, N=3,771, RR 0.68, 95% CI 0.49 to 0.96, I^2=53%; ARD -4.2%) Quality of life, visual acuity: No difference (1 study, n=461)	Inconsistency present in magnitude (not direction) of effect for IOP Precise	Most studies rated fair-quality; variability in randomization and analysis by individual or by eye; variability in definitions for glaucoma progression	Moderate for benefit	Focused on first-line therapies in current practice; trials enrolled patients with OHT or untreated early OAG; mean baseline IOP elevated in most studies; studies were conducted in the United States, Europe, and Canada
KQ 7. Harms of treatments vs. placebo/no treatments	8 trials (3 in prior treatment CER, 5 new) N=3,928	No differences between medical therapy versus placebo/no treatment in risk of serious adverse events, withdrawal due to adverse events, or any adverse event Medical therapy associated with increased risk of ocular adverse events versus placebo in two trials (RR 1.21, 95% CI 1.10 to 1.33 and RR 3.52, 95% CI 2.46 to 5.02)	Inconsistency present for withdrawal due to adverse events and any adverse events Imprecise	Harms not reported in most trials of medical therapies versus placebo or no treatment and inconsistent reporting in trials that reported harms	Low	See KQ 6
KQ 8. Effects of new vs. older treatments	8 trials (this KQ was not addressed in the prior treatment CER) N=4,113	Recently approved medical therapies (netarsudil and latanoprostene bunod) were associated with similar or greater effects on IOP versus older medications	Consistent Precise	Most trials rated fair quality; duration of follow-up 3 months in most trials (range 1 to 12 months); evidence on effects on vision, function, and quality of life not available	Moderate for similar or greater effects of new treatments	Trials conducted in multinational settings; trials enrolled mixed populations of patients with OAG or OHT

Table 10. Summary of Evidence – Glaucoma

Key Question	Studies Observations (N) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 9. Harms of new vs. older treatments	8 trials (this KQ was not addressed in the prior treatment CER) N=4,113	Netarsudil associated with increased risk of ocular adverse events (3 trials, N=1875, RRs 1.51 to 2.07), withdrawal due to adverse events (3 trials, N=1875, RRs 4.73 to 38.20), and any adverse event (1 trial, n=708, RR 1.33, 95% CI 1.20 to 1.47) versus timolol Latanoprostene bunod and latanoprost associated with similar likelihood of any adverse events and withdrawal due to adverse events (1 trial, n=413). Latanoprostene bunod associated with increased risk of ocular adverse events versus timolol (pooled RR 1.72, 95% CI 1.22 to 2.42)	Consistent Imprecision for some estimates	Most trials rated fair quality; duration of follow-up 3 months in most trials (range 1 to 12 months)	Moderate	See KQ 8
KQ 10. Effects of SLT	4 trials (1 in prior treatment CER and 3 new) N=957	The large (n=718), LiGHT trial found SLT and medical therapy associated with similar effects on IOP, visual acuity, visual fields, general quality of life, and glaucoma specific quality of life and function Three smaller trials reported results consistent with LiGHT for IOP	Consistent for IOP; unable to assess for other outcomes Precise	Most evidence from 1 trial	Moderate for similar effects of SLT and medical therapy	Patients in LiGHT had OAG with visual acuity ~20/120 or better and no prior surgery or glaucoma medical therapy; LiGHT was conducted in the United Kingdom; patients randomized to medical therapy in LiGHT received a variety of medications to achieve a target IOP
KQ 11. Harms of SLT	4 trials (1 in prior treatment CER and 3 new) N=957	One trial (n=718) found no differences between SLT versus medical therapy in risk of serious adverse events or any adverse event Evidence on harms from other trials of SLT versus medical therapies was limited by suboptimal reporting and imprecision	Unable to assess consistency (1 study) Reasonably precise	Evidence on harms based on 1 trial; other trials had suboptimal reporting and imprecision	Moderate for no differences	See KQ 11

Abbreviations: ARD = adjusted risk difference; AUROC = area under the receiver operating characteristic curve; CER = comparative effectiveness review; CI = confidence interval; GCC = ganglion cell complex; HFA = Humphrey Field Analyzer; IOP = intraocular pressure; KQ = key question; LiGHT = Laser in Glaucoma and ocular HyperTension study; logMAR = logarithmic minimum angle of resolution; mm Hg = millimeters mercury; NEI-VFQ = National Eye Institute Vision Function Questionnaire; OAG = open angle

glaucoma; OCT = optical coherence tomography; OHT = ocular hypertension; RNFL = retinal nerve fiber layer; RR = relative risk; SD-OCT = spectral domain optical coherence tomography; SLT = selective laser trabeculoplasty; SS-OCT = swept source optical coherence tomography.

Database: Ovid MEDLINE(R)

Screening

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,kf.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,kf.
5 or/1-4
6 Mass Screening/
7 early diagnosis/
8 screen*.ti,ab,kf.
9 or/6-8
10 5 and 9
11 limit 10 to yr="2011 -Current"
12 (random* or control* or trial or cohort or case* or prospective or retrospective or systematic or "meta analysis" or "metaanalysis").ti,ab,kf,tw,pt,sh.
13 11 and 12
14 limit 13 to english language

Referral

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,kf.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,kf.
5 or/1-4
6 exp "Referral and Consultation"/
7 refer*.ti,ab,kw.
8 6 or 7
9 5 and 8
10 (random* or control* or trial or cohort or case* or prospective or retrospective or systematic or "meta analysis" or "metaanalysis").ti,ab,kf,tw,pt,sh.
11 9 and 10
12 limit 11 to english language

Diagnostic Accuracy

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,kf.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,kf.
5 or/1-4
6 (screen* or test* or diagnos*).ti,ab,kf.
7 5 and 6
8 exp "Sensitivity and Specificity"/
9 (sensitivity or specificity or accuracy or predict* or reliability).ti,ab,kf.
10 8 or 9
11 7 and 10

12 limit 11 to yr="2011 -Current"
13 limit 12 to english language

Treatment
1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,kf.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,kf.
5 or/1-4
6 (apraclonidine or brimonidine or timolol or betaxolol or levobunolol or metipranolol or brinzolamide or methazolamide or dorzolamide or acetazolamide or travaprost or bimatoprost or latanoprost* or tafluprost or netarsudil).ti,ab,kf,sh.
7 ("alpha 2 agonist*" or "alpha2 agonist*" or "beta blocker*" or "carbonic anahydrast inhibitor*" or "prostaglandin analogue*").ti,ab,kf.
8 (trabeculoplasty or trabeculectomy or phacotrabeculoplasty or phacotrabeculectomy).ti,ab,kf,sh.
9 or/6-8
10 5 and 9
11 limit 10 to yr="2011 -Current"
12 (random* or control* or trial or cohort or case* or prospective or retrospective or systematic or "meta analysis" or "metaanalysis").ti,ab,kf,tw,pt,sh.
13 11 and 12
14 limit 13 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Screening
1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,hw.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,hw.
5 or/1-4
6 Mass Screening/
7 early diagnosis/
8 screen*.ti,ab,hw.
9 or/6-8
10 5 and 9
11 limit 10 to yr="2011 -Current"
12 limit 11 to english language
13 conference abstract.pt.
14 "journal: conference abstract".pt.
15 "journal: conference review".pt.
16 "http://.www.who.int/trialsearch*".so.
17 "https://clinicaltrials.gov*".so.
18 13 or 14 or 15 or 16 or 17
19 12 not 18

Appendix A1. Search Strategies

Referral

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,hw.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,hw.
5 or/1-4
6 exp "Referral and Consultation"/
7 refer*.ti,ab,hw.
8 6 or 7
9 5 and 8
10 conference abstract.pt.
11 "journal: conference abstract".pt.
12 "journal: conference review".pt.
13 "http://.www.who.int/trialsearch*".so.
14 "https://clinicaltrials.gov*".so.
15 10 or 11 or 12 or 13 or 14
16 9 not 15
17 limit 16 to medline records
18 16 not 17

Diagnostic Accuracy

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,hw.
3 Ocular Hypertension/
4 "ocular hypertension".ti,ab,hw.
5 or/1-4
6 (screen* or test* or diagnos*).ti,ab,hw.
7 5 and 6
8 exp "Sensitivity and Specificity"/
9 (sensitivity or specificity or accuracy or predict* or reliability).ti,ab,hw.
10 8 or 9
11 7 and 10
12 limit 11 to yr="2011 -Current"
13 limit 12 to english language
14 conference abstract.pt.
15 "journal: conference abstract".pt.
16 "journal: conference review".pt.
17 "http://.www.who.int/trialsearch*".so.
18 "https://clinicaltrials.gov*".so.
19 14 or 15 or 16 or 17 or 18
20 13 not 19

Treatment

1 Glaucoma, Open-Angle/
2 glaucoma*.ti,ab,hw.
3 Ocular Hypertension/

4 "ocular hypertension".ti,ab,hw.
5 or/1-4
6 (apraclonidine or brimonidine or timolol or betaxolol or levobunolol or metipranolol or brinzolamide or methazolamide or dorzolamide or acetazolamide or travaprost or bimatoprost or latanoprost* or tafluprost or netarsudil).ti,ab,hw,sh.
7 ("alpha 2 agonist*" or "alpha2 agonist*" or "beta blocker*" or "carbonic anahydrast inhibitor*" or "prostaglandin analogue*").ti,ab,hw.
8 (trabeculoplasty or trabeculectomy or phacotrabeculoplasty or phacotrabeculectomy).ti,ab,hw,sh.
9 or/6-8
10 5 and 9
11 limit 10 to yr="2011 -Current"
12 limit 11 to english language
13 conference abstract.pt.
14 "journal: conference abstract".pt.
15 "journal: conference review".pt.
16 "http://.www.who.int/trialsearch*".so.
17 "https://clinicaltrials.gov*".so.
18 13 or 14 or 15 or 16 or 17
19 12 not 18

Database: EBM Reviews - Cochrane Database of Systematic Reviews

All KQs
1 glaucoma*.ti,ab.
2 "ocular hypertension".ti,ab.
3 "eyes and vision".gw.
4 1 or 2
5 3 and 4
6 limit 5 to last 10 years
7 limit 6 to full systematic reviews

Appendix A2. Inclusion and Exclusion Criteria

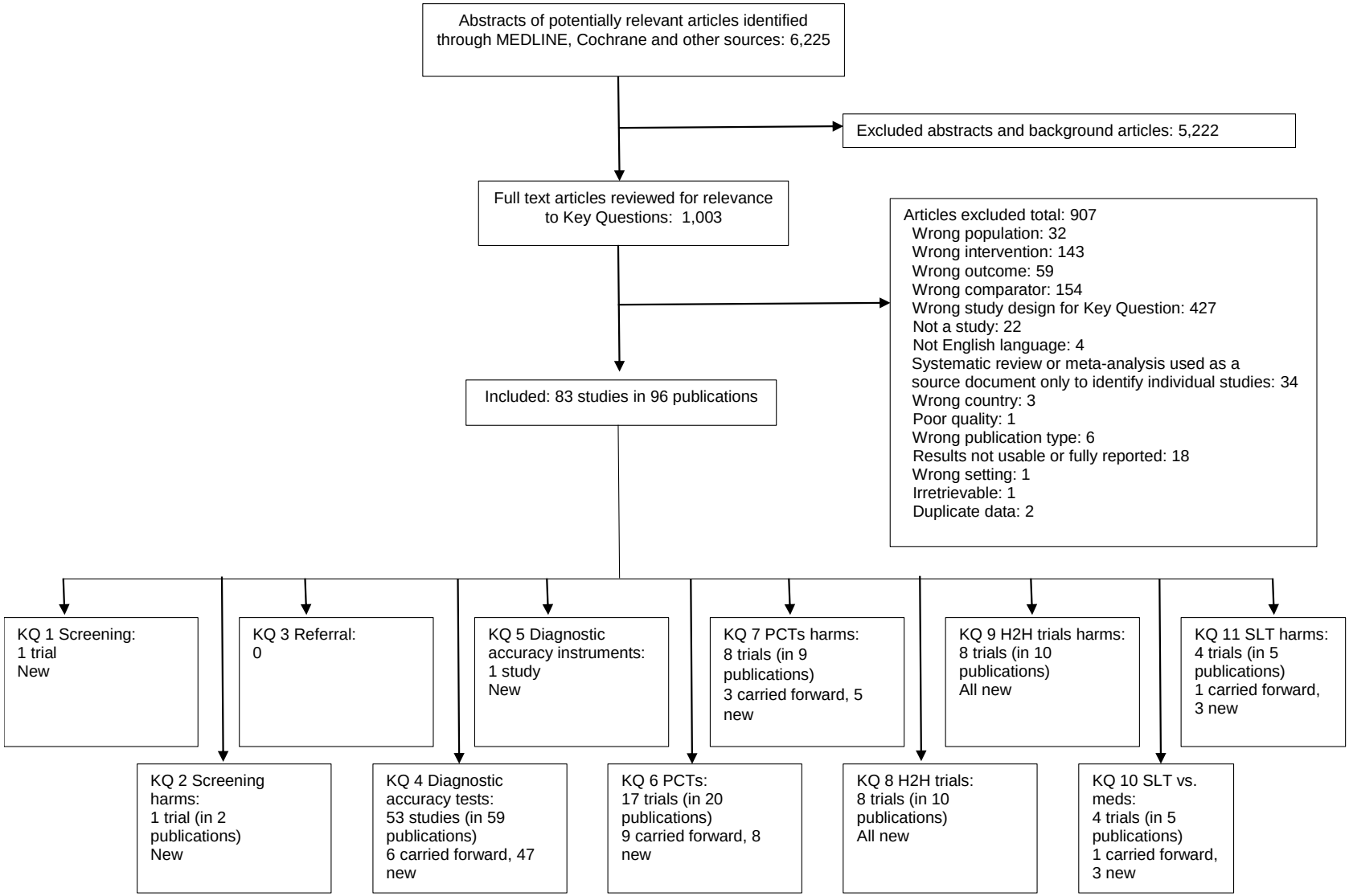
Category	Inclusion	Exclusion
Definition of disease	POAG; glaucoma defined by presence of glaucomatous optic disc changes and RNFL changes, with or without associated visual field changes or elevated IOP Glaucoma suspect: Patients do not meet criteria for glaucoma but have a consistently elevated IOP, a suspicious appearance of the optic nerve, or visual field abnormalities consistent with glaucoma	-
Populations	KQs 1-5: Asymptomatic adults 40 years of age or older without visual symptoms KQs 6-11: Adults with screen-detected, asymptomatic, or early POAG	KQs 1-5: Patients with visual symptoms, case-control studies of patients known to have OAG and normal controls KQs 6-11: Patients with OAG and severe visual field or visual deficits; patients with narrow-angle glaucoma, secondary glaucoma, juvenile glaucoma, other glaucoma
Interventions	KQs 1-2, 4-5: Screening with a comprehensive eye examination (as defined in the studies) by an eye health provider; screening tests performed in primary care or applicable to primary care; and instruments for identifying persons at increased risk of OAG KQ3: Referral to an eye specialist KQ4: Diagnostic tests that are currently used: 1. Comprehensive eye exam 2. Ophthalmoscopy, direct and indirect 3. Optic disc photography, including non-digital and digital monoscopic and steroscopic photography, and planimetric 4. Perimetry, including high-pass, motion, flicker perimetry, yellow and blue perimetry a. White-on-white standard automated perimetry, including suprathershold and threshold (classic Humphrey visual field) 5. Tonometry, contact and non-contact tonometry a. GAT b. Non-contact tonometer (air puff) c. Tonopen 6. OCT and OCT angiography 7. Fundus photography or computerized imaging of the posterior pole, optic disc or RNFL 8. Pachymetry, when used in conjunction with another test to diagnose glaucoma 9. Afferent pupillary defect 10. GCC measurements KQs 6-11: • First line medical treatments (prostaglandin analogues, beta-blockers, alpha2 agonists, and carbonic anahydrast inhibitors) • SLT • Latanoprostene bunod • Netarsudil	KQ4: Screening tests that are no longer used KQs 6-11: Second line medical therapies, surgery, argon trabeculoplasty, non-FDA approved therapies, therapies not commonly used as first-line therapy in U.S. practice

Appendix A2. Inclusion and Exclusion Criteria

Category	Inclusion	Exclusion
Comparisons	KQs 1-2: No screening KQ3: No referral KQs 4-5: Reference standard for OAG (as defined in the studies) KQs 6-11: Placebo, no therapy, or first-line medical therapies (for SLT, latanoprostene bunod, and netarsudil)	Comparisons involving second line medical therapies or surgery Other eye in same patient as the control for diagnostic accuracy
Outcomes	KQs 1-3, 6-11: IOP, visual field loss, VA, optic nerve damage, visual impairment (defined as VA <20/70 or <20/100), quality of life, function, harms (e.g., eye irritation, corneal abrasion, infection, anterior synechiae, cataracts) KQs 4-5: Measures of diagnostic accuracy	Other (non-listed) outcomes
Timing	KQs 6-11: ≥4 weeks duration of followup	
Setting	Studies conducted in high income studies applicable to U.S. practice; include studies performed in primary care (including use of telemedicine) and specialty settings	
Study Design	RCTs of screening and treatment; cohort studies for harms of treatment if RCTs not available; population-based cohort or cross-sectional studies of diagnostic accuracy; high-quality systematic reviews	Case series, case reports, case-control studies
Study Quality	Fair or good-quality studies	Poor quality studies

Abbreviations: FDA = U.S. Food and Drug Administration; GAT = Goldmann Applanation Tonometer; GCC = ganglion cell complex; IOP = intraocular pressure; OAG = open angle glaucoma; OCT = optical coherence tomography; POAG = primary open angle glaucoma; RCTs = randomized controlled trials; RNFL = retinal nerve fiber layer; SLT = selective laser trabeculoplasty; U.S. = United States; VA = visual acuity.

Appendix A3. Literature Flow Diagram



Note: Studies are included for more than one Key Question.
Abbreviations: H2H = head to head; KQ = key question; PCTs = placebo controlled trials; SLT = selective laser trabeculoplasty.

Appendix A4. Included Studies

1. Aksoy FE, Altan C, Yilmaz BS, et al. A comparative evaluation of segmental analysis of macular layers in patients with early glaucoma, ocular hypertension, and healthy eyes. J Fr Ophtalmol. 2020;43(9):869-78. doi: 10.1016/j.jfo.2019.12.020. PMID: 32839014.
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and glaucoma patients. PLoS One. 2018;13(4):e0196112. doi: 10.1371/journal.pone.0196112. PMID: 29672563.

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Appendix A5. Excluded Studies

1. Abdel-Hamid L. Glaucoma detection from retinal images using statistical and textural wavelet features. J Digit Imaging. 2020;33(1):151-8. doi: 10.1007/s10278-019-00189-0. PMID: 30756264. Excluded for wrong study design for key question.
2. Abrams LS, Scott IU, Spaeth GL, et al. Agreement among optometrists, ophthalmologists, and residents in evaluating the optic disc for glaucoma. Ophthalmology. 1994;101(10):1662-7. doi: 10.1016/s0161-6420(94)31118-3. PMID: 7936564. Excluded for wrong intervention.
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14. Akashi A, Kanamori A, Nakamura M, et al. Comparative assessment for the ability of Cirrus, RTVue, and 3D-OCT to diagnose glaucoma. Invest Ophthalmol Vis Sci. 2013;54(7):4478-84. doi: 10.1167/iovs.12-11268. PMID: 23737470. Excluded for wrong study design for key question.
15. Al-Akhras M, Barakat A, Alawairdhi M, et al. Using soft computing techniques to diagnose glaucoma disease. J Infect Public Health. 2021;14(1):109-16. doi: 10.1016/j.jiph.2019.09.005. PMID: 31668615. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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25. An G, Omodaka K, Tsuda S, et al. Comparison of machine-learning classification models for glaucoma management. J Healthc Eng. 2018;2018:6874765. doi: 10.1155/2018/6874765. PMID: 30018755. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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Appendix A5. Excluded Studies

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117. Chang DS, Xu L, Boland MV, et al. Accuracy of pupil assessment for the detection of glaucoma: a systematic review and meta-analysis. Ophthalmology. 2013;120(11):2217-25. doi: 10.1016/j.ophtha.2013.04.012. PMID: 23809274. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
118. Chang RT, Knight OJ, Feuer WJ, et al. Sensitivity and specificity of time-domain versus spectral-domain optical coherence tomography in diagnosing early to moderate glaucoma. Ophthalmology. 2009;116(12):2294-9. doi: 10.1016/j.ophtha.2009.06.012. PMID: 19800694. Excluded for wrong study design for key question.
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122. Chen HY, Chang YC, Wang IJ, et al. Comparison of glaucoma diagnoses using stratus and cirrus optical coherence tomography in different glaucoma types in a Chinese population. J Glaucoma. 2013;22(8):638-46. doi: 10.1097/IJG.0b013e3182594f42. PMID: 22595933. Excluded for wrong study design for key question.
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125. Chen R, Yang K, Zheng Z, et al. Meta-analysis of the efficacy and safety of latanoprost monotherapy in patients with angle-closure glaucoma. J Glaucoma. 2016;25(3):e134-44. doi: 10.1097/IJG.0000000000000158. PMID: 25383466. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
126. Chen TC, Hoguet A, Junk AK, et al. Spectral-domain OCT: helping the clinician diagnose glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology. 2018;125(11):1817-27. doi: 10.1016/j.ophtha.2018.05.008. PMID: 30322450. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
127. Chen X, Zhao Y. Diagnostic performance of isolated-check visual evoked potential versus retinal ganglion cell-inner plexiform layer analysis in early primary open-angle glaucoma. BMC Ophthalmol. 2017;17(1):77. doi: 10.1186/s12886-017-0472-9. PMID: 28532392. Excluded for wrong study design for key question.
128. Chen XW, Zhao YX. Comparison of isolated-check visual evoked potential and standard automated perimetry in early glaucoma and high-risk ocular hypertension. Int J Ophthalmol. 2017;10(4):599-604. doi: 10.18240/ijo.2017.04.16. PMID: 28503434. Excluded for wrong study design for key question.
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130. Chen Z, Peng P, Shen H, et al. Region-segmentation strategy for bruch's membrane opening detection in spectral domain optical coherence tomography images. Biomed Opt Express. 2019;10(2):526-38. doi: 10.1364/BOE.10.000526. PMID: 30800497. Excluded for wrong outcome.
131. Chen Z, Zheng X, Shen H, et al. Combination of enhanced depth imaging optical coherence tomography and fundus images for glaucoma screening. J Med Syst. 2019;43(6):163. doi: 10.1007/s10916-019-1303-8. PMID: 31044289. Excluded for wrong study design for key question.
132. Cheng JW, Cheng SW, Gao LD, et al. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. PLoS One. 2012;7(9):e45079. doi: 10.1371/journal.pone.0045079. PMID: 23028770. Excluded for wrong comparator.
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136. Cheng L, Ding Y, Duan X, et al. Ocular pulse amplitude in different types of glaucoma using dynamic contour tonometry: diagnosis and follow-up of glaucoma. Exp Ther Med. 2017;14(5):4148-52. doi: 10.3892/etm.2017.5074. PMID: 29104631. Excluded for wrong study design for key question.
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138. Chi SC, Kang YN, Hwang DK, et al. Selective laser trabeculoplasty versus medication for open-angle glaucoma: systematic review and meta-analysis of randomised clinical trials. Br J Ophthalmol. 2020;104(11):1500-7. doi: 10.1136/bjophthalmol-2019-315613. PMID: 32051136. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

Appendix A5. Excluded Studies

139. Chien JL, Ghassibi MP, Patthanathamrongkasem T, et al. Glaucoma diagnostic capability of global and regional measurements of isolated ganglion cell layer and inner plexiform layer. J Glaucoma. 2017;26(3):208-15. doi: 10.1097/IJG.0000000000000572. PMID: 27811573. Excluded for wrong study design for key question.
140. Chiselita D. Evaluation of the role of travoprost 0.004% ophthalmic solution in the management of open angle glaucoma and ocular hypertensive patients. Oftalmologia. 2007;51(2):81-6. PMID: 17937041. Excluded for wrong comparator.
141. Chiselita D, Antohi I, Medvichi R, et al. Comparative analysis of the efficacy and safety of latanoprost, travoprost and the fixed combination timolol-dorzolamide; a prospective, randomized, masked, cross-over design study. Oftalmologia. 2005;49(3):39-45. PMID: 16408674. Excluded for wrong comparator.
142. Chiselita D, Cantemir A, Pantalon AD. Selective laser trabeculoplasty-short term efficacy and safety profile in open angle glaucoma or ocular hypertension treatment. Rom J Ophthalmol. 2015;59(3):148-53. PMID: 26978882. Excluded for poor quality.
143. Chiselita D, Pantalon AD, Cantemir A, et al. Translating data and measurements from stratus to cirrus OCT in glaucoma patients and healthy subjects. Rom J Ophthalmol. 2016;60(3):158-64. PMID: 29450341. Excluded for wrong study design for key question.
144. Cho JW, Sung KR, Hong JT, et al. Detection of glaucoma by spectral domain-scanning laser ophthalmoscopy/optical coherence tomography (SD-SLO/OCT) and time domain optical coherence tomography. J Glaucoma. 2011;20(1):15-20. doi: 10.1097/IJG.0b013e3181d1d332. PMID: 20436370. Excluded for wrong study design for key question.
145. Choi EY, Li D, Fan Y, et al. Predicting global test-retest variability of visual fields in glaucoma. Ophthalmol Glaucoma. 2020;10:10. doi: 10.1016/j.ogla.2020.12.001. PMID: 33310194. Excluded for wrong population.
146. Choi YJ, Jeoung JW, Park KH, et al. Clinical use of an optical coherence tomography linear discriminant function for differentiating glaucoma from normal eyes. J Glaucoma. 2016;25(3):e162-9. doi: 10.1097/IJG.0000000000000210. PMID: 25580887. Excluded for wrong study design for key question.
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150. Christopher M, Abramoff MD, Tang L, et al. Stereo photo measured ONH shape predicts development of POAG in subjects with ocular hypertension. Invest Ophthalmol Vis Sci. 2015;56(8):4470-9. doi: 10.1167/iovs.14-16142. PMID: 26193923. Excluded for wrong outcome.
151. Christopher M, Belghith A, Bowd C, et al. Performance of deep learning architectures and transfer learning for detecting glaucomatous optic neuropathy in fundus photographs. Sci Rep. 2018;8(1):16685. doi: 10.1038/s41598-018-35044-9. PMID: 30420630. Excluded for wrong study design for key question.
152. Christopher M, Bowd C, Belghith A, et al. Deep learning approaches predict glaucomatous visual field damage from OCT optic nerve head en face images and retinal nerve fiber layer thickness maps. Ophthalmology. 2020;127(3):246-356. doi: 10.1016/j.ophtha.2019.09.036. PMID: 31718841. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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161. Cook R, Thomas V, Martin R, et al. Laser eye procedure is safe and effective as an early treatment for glaucoma. BMJ. 2019;366:l4235. doi: 10.1136/bmj.l4235. PMID: 31292128. Excluded for not a study.
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163. Correa-Perez ME, Lopez-Miguel A, Miranda-Anta S, et al. Precision of high definition spectral-domain optical coherence tomography for measuring central corneal thickness. Invest Ophthalmol Vis Sci. 2012;53(4):1752-7. doi: 10.1167/iovs.11-9033. PMID: 22395881. Excluded for wrong outcome.
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167. Cucherat M, Stalmans I, Rouland JF. Relative efficacy and safety of preservative-free latanoprost (T2345) for the treatment of open-angle glaucoma and ocular hypertension: an adjusted Indirect comparison meta-analysis of randomized clinical trials. J Glaucoma. 2014;23(1):e69-75. doi: 10.1097/IJG.0b013e3182a075e6. PMID: 23881267. Excluded for wrong comparator.
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173. Daka Q, Trkulja V. Efficacy and tolerability of mono-compound topical treatments for reduction of intraocular pressure in patients with primary open angle glaucoma or ocular hypertension: an overview of reviews. Croat Med J. 2014;55(5):468-80. PMID: 25358880. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.

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174. Damato BE, Ahmed J, Allan D, et al. The detection of glaucomatous visual field defects by oculo-kinetic perimetry: which points are best for screening? Eye (Lond). 1989;3 (Pt 6):727-31. doi: 10.1038/eye.1989.112. PMID: 2630353. Excluded for wrong study design for key question.
175. Damji KF, Shah KC, Rock WJ, et al. Selective laser trabeculoplasty v argon laser trabeculoplasty: a prospective randomised clinical trial. Br J Ophthalmol. 1999;83(6):718-22. doi: 10.1136/bjo.83.6.718. PMID: 10340983. Excluded for wrong comparator.
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178. Dave P, Shah J. Diagnostic accuracy of posterior pole asymmetry analysis parameters of spectralis optical coherence tomography in detecting early unilateral glaucoma. Indian J Ophthalmol. 2015;63(11):837-42. doi: 10.4103/0301-4738.171965. PMID: 26669335. Excluded for wrong country.
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190. Dhar SK, Raji K, Sandeep S, et al. Study of correlation between stereopsis and retinal nerve fiber layer thickness in cases of glaucoma. Med J Armed Forces India. 2021;77(1):63-9. doi: 10.1016/j.mjafi.2020.01.004. PMID: 33487868. Excluded for wrong study design for key question.

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193. Digiuni M, Manni G, Vetrugno M, et al. An evaluation of therapeutic noninferiority of 0.005% latanoprost ophthalmic solution and xalatan in patients with glaucoma or ocular hypertension. J Glaucoma. 2013;22(9):707-12. doi: 10.1097/IJG.0b013e318259b47c. PMID: 22595934. Excluded for wrong comparator.
194. Dirks MS, Noecker RJ, Earl M, et al. A 3-month clinical trial comparing the IOP-lowering efficacy of bimatoprost and latanoprost in patients with normal-tension glaucoma. Adv Ther. 2006;23(3):385-94. doi: 10.1007/bf02850159. PMID: 16912020. Excluded for wrong comparator.
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196. Dominguez-Duenas F, Plaza-Espinosa L, Mundo-Fernandez EE, et al. Early glaucoma screening using the ibopamine provocative test. J Glaucoma. 2016;25(5):e441-5. doi: 10.1097/IJG.0000000000000343. PMID: 26709501. Excluded for wrong study design for key question.
197. Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. J Glaucoma. 1998;7(4):247-52. doi: 10.1097/00061198-199808000-00006. PMID: 9713782. Excluded for wrong comparator.
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203. Eguia MD, Tsamis E, Zemborain ZZ, et al. Reasons why OCT global circumpapillary retinal nerve fiber layer thickness is a poor measure of glaucomatous progression. Transl Vis Sci Technol. 2020;9(11):22. doi: 10.1167/tvst.9.11.22. PMID: 33150048. Excluded for wrong outcome.
204. Ekstrom C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open-angle glaucoma. A population-based five-year follow-up study. Acta Ophthalmol (Copenh). 1993;71(2):189-95. doi: 10.1111/j.1755-3768.1993.tb04989.x. PMID: 8333264. Excluded for wrong outcome.
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206. El-Assal K, Foulds J, Dobson S, et al. A comparative study of glaucoma referrals in southeast Scotland: effect of the new general ophthalmic service contract, eyecare integration pilot programme and NICE guidelines. BMC Ophthalmol. 2015;15:172. doi: 10.1186/s12886-015-0161-5. PMID: 26643710. Excluded for wrong outcome.
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208. Elahi S, Rao HL, Dumitru A, et al. Predictors of success in selective laser trabeculoplasty: data from the lausanne laser trabeculoplasty registry. J Glaucoma. 2020;29(7):550-5. doi: 10.1097/IJG.0000000000001534. PMID: 32398589. Excluded for wrong study design for key question.
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217. Evans DW, Bartlett JD, Houde B, et al. Latanoprost-induced stabilization of central visual function in patients with primary open-angle glaucoma. J Ocul Pharmacol Ther. 2008;24(2):224-9. doi: 10.1089/jop.2007.0106. PMID: 18355134. Excluded for wrong comparator.
218. Eyawo O, Nachega J, Lefebvre P, et al. Efficacy and safety of prostaglandin analogues in patients with predominantly primary open-angle glaucoma or ocular hypertension: a meta-analysis. Clin Ophthalmol. 2009;3(1):447-56. Excluded for wrong comparator.
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221. Fama F, Santamaria S. Comparison of the ocular effects of three beta-blockers: timolol, carteolol, and betaxolol. Ann Ophthalmol. 1996;28(5):317-20. Excluded for wrong comparator.
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Appendix A5. Excluded Studies

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Appendix A5. Excluded Studies

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Appendix A5. Excluded Studies

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382. Kim KE, Kim SH, Jeoung JW, et al. Comparison of ability of time-domain and spectral-domain optical coherence tomography to detect diffuse retinal nerve fiber layer atrophy. Jpn J Ophthalmol. 2013;57(6):529-39. doi: 10.1007/s10384-013-0270-8. PMID: 24000036. Excluded for wrong study design for key question.
383. Kim KE, Kim SH, Oh S, et al. Additive diagnostic role of imaging in glaucoma: optical coherence tomography and retinal nerve fiber layer photography. Invest Ophthalmol Vis Sci. 2014;55(12):8024-30. doi: 10.1167/iovs.14-15237. PMID: 25414196. Excluded for wrong study design for key question.
384. Kim KN, Jeoung JW, Park KH, et al. Comparison of the new rebound tonometer with goldmann applanation tonometer in a clinical setting. Acta Ophthalmol. 2013;91(5):e392-6. doi: 10.1111/aos.12109. PMID: 23521889. Excluded for wrong comparator.
385. Kim NR, Hong S, Kim JH, et al. Comparison of macular ganglion cell complex thickness by Fourier-domain OCT in normal tension glaucoma and primary open-angle glaucoma. J Glaucoma. 2013;22(2):133-9. doi: 10.1097/IJG.0b013e3182254cde. PMID: 21701394. Excluded for wrong study design for key question.
386. Kim NR, Kim CY, Kim H, et al. Comparison of goldmann applanation tonometer, noncontact tonometer, and TonoPen XL for intraocular pressure measurement in different types of glaucomatous, ocular hypertensive, and normal eyes. Curr Eye Res. 2011;36(4):295-300. PMID: 21284505. Excluded for wrong study design for key question.

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389. Kim YJ, Kang MH, Cho HY, et al. Comparative study of macular ganglion cell complex thickness measured by spectral-domain optical coherence tomography in healthy eyes, eyes with preperimetric glaucoma, and eyes with early glaucoma. Jpn J Ophthalmol. 2014;58(3):244-51. doi: 10.1007/s10384-014-0315-7. PMID: 24610541. Excluded for wrong study design for key question.
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396. Kita Y, Soutome N, Horie D, et al. Circumpapillary ganglion cell complex thickness to diagnose glaucoma: a pilot study. Indian J Ophthalmol. 2017;65(1):41-7. doi: 10.4103/ijo.IJO_437_16. PMID: 28300739. Excluded for wrong study design for key question.
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398. Klamann MK, Grunert A, Maier AK, et al. Comparison of functional and morphological diagnostics in glaucoma patients and healthy subjects. Ophthalmic Res. 2013;49(4):192-8. doi: 10.1159/000345074. PMID: 23306647. Excluded for wrong study design for key question.
399. Klein BE, Johnson CA, Meuer SM, et al. Nerve fiber layer thickness and characteristics associated with glaucoma in community living older adults: prelude to a screening trial? Ophthalmic Epidemiol. 2017;24(2):104-10. doi: 10.1080/09286586.2016.1258082. PMID: 28032805. Excluded for wrong study design for key question.
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401. Kobayashi H, Kobayashi K. A correlation between latanoprost-induced conjunctival hyperemia and intraocular pressure-lowering effect. J Glaucoma. 2011;20(1):3-6. doi: 10.1097/IJG.0b013e3181d26024. PMID: 20520573. Excluded for wrong study design for key question.
402. Kobayashi H, Kobayashi K. A comparison of the intraocular pressure lowering effect of adjustable suture versus laser suture lysis for trabeculectomy. J Glaucoma. 2011;20(4):228-33. Excluded for wrong intervention.
403. Koh JEW, Acharya UR, Hagiwara Y, et al. Diagnosis of retinal health in digital fundus images using continuous wavelet transform (CWT) and entropies. Comput Biol Med. 2017;84:89-97. doi: 10.1016/j.compbiomed.2017.03.008. PMID: 28351716. Excluded for wrong study design for key question.
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406. Konstas AG, Kozobolis VP, Tersis I, et al. The efficacy and safety of the timolol/dorzolamide fixed combination vs latanoprost in exfoliation glaucoma. Eye (Lond). 2003;17(1):41-6. doi: 10.1038/sj.eye.6700257. PMID: 12579169. Excluded for wrong comparator.
407. Kook MS, Cho HS, Yang SJ, et al. Efficacy of latanoprost in patients with chronic angle-closure glaucoma and no visible ciliary-body face: a preliminary study. J Ocul Pharmacol Ther. 2005;21(1):75-84. doi: 10.1089/jop.2005.21.75. PMID: 15718831. Excluded for wrong study design for key question.
408. Kopczynski CC, Heah T. Netarsudil ophthalmic solution 0.02% for the treatment of patients with open-angle glaucoma or ocular hypertension. Drugs Today. 2018;54(8):467-78. doi: 10.1358/dot.2018.54.8.2849627. PMID: 30209441. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
409. Kopic A, Biuk D, Barac J, et al. Retinal nerve fiber layer thickness in glaucoma patients treated with multiple intravitreal anti-VEGF (bevacizumab) injections. Acta Clinica Croatica. 2017;56(3):406-14. doi: 10.20471/acc.2017.56.03.07. PMID: 29479906. Excluded for wrong study design for key question.
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461. Li Z, He Y, Keel S, et al. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. Ophthalmology. 2018;125(8):1199-206. doi: 10.1016/j.ophtha.2018.01.023. PMID: 29506863. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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474. Liu H, Li L, Wormstone IM, et al. Development and validation of a deep learning system to detect glaucomatous optic neuropathy using fundus photographs. JAMA Ophthalmol. 2019;137(12):1353-60. doi: 10.1001/jamaophthalmol.2019.3501. PMID: 31513266. Excluded for wrong study design for key question.
475. Liu JHK, Slight JR, Vittitow JL, et al. Efficacy of latanoprostene bunod 0.024% compared with timolol 0.5% in lowering intraocular pressure over 24 hours. Am J Ophthalmol. 2016;169:249-57. doi: 10.1016/j.ajo.2016.04.019. PMID: 27457257. Excluded for wrong outcome.
476. Liu HN, Chen XL, Li X, et al. Efficacy and tolerability of one-site versus two-site phaco-trabeculectomy: a meta-analysis of randomized controlled clinical trials. Chin Med J (Engl). 2010;123(15):2111-5. PMID: 20819551. Excluded for wrong intervention.
477. Liu JL, McAnany JJ, Wilensky JT, et al. M&S smart system contrast sensitivity measurements compared with standard visual function measurements in primary open-angle glaucoma patients. J Glaucoma. 2017;26(6):528-33. doi: 10.1097/IJG.0000000000000659. PMID: 28333894. Excluded for wrong outcome.
478. Liu L, Tan O, Ing E, et al. Sectorwise visual field simulation using optical coherence tomographic angiography nerve fiber layer plexus measurements in glaucoma. Am J Ophthalmol. 2020;212:57-68. doi: 10.1016/j.ajo.2019.11.018. PMID: 31770516. Excluded for wrong comparator.
479. Liu MM, Cho C, Jefferys JL, et al. Use of optical coherence tomography by nonexpert personnel as a screening approach for glaucoma. J Glaucoma. 2018;27(1):64-70. doi: 10.1097/IJG.0000000000000822. PMID: 29194196. Excluded for wrong study design for key question.
480. Liu S, Wang B, Yin B, et al. Retinal nerve fiber layer reflectance for early glaucoma diagnosis. J Glaucoma. 2014;23(1):e45-52. doi: 10.1097/IJG.0b013e31829ea2a7. PMID: 23835671. Excluded for wrong study design for key question.
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485. Loon SC, Liew G, Fung A, et al. Meta-analysis of randomized controlled trials comparing timolol with brimonidine in the treatment of glaucoma. Clin Exp Ophthalmol. 2008;36(3):281-9. doi: 10.1111/j.1442-9071.2008.01720.x. Excluded for wrong comparator.
486. Lopes F, Matsubara I, Almeida I, et al. Using enhanced depth imaging optical coherence tomography - derived parameters to discriminate between eyes with and without glaucoma: a cross-sectional comparative study. Ophthalmic Res. 2021;64(1):108-15. doi: 10.1159/000508952. PMID: 32454499. Excluded for wrong study design for key question.
487. Loureiro M, Matos R, Sepulveda P, et al. Intravitreal injections of bevacizumab: the impact of needle size in intraocular pressure and pain. J Curr Glaucoma Pract. 2017;11(2):38-41. PMID: 28924336. Excluded for wrong comparator.
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493. Macky TA. Bimatoprost versus travoprost in an Egyptian population: a hospital-based prospective, randomized study. J Ocul Pharmacol Ther. 2010;26(6):605-10. doi: 10.1089/jop.2010.0068. PMID: 21034177. Excluded for wrong comparator.
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496. Maheshwari S, Kanhangad V, Pachori RB, et al. Automated glaucoma diagnosis using bit-plane slicing and local binary pattern techniques. Comput Biol Med. 2019;105:72-80. doi: 10.1016/j.compbiomed.2018.11.028. PMID: 30590290. Excluded for wrong study design for key question.
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499. Maier PC, Funk J, Schwarzer G, et al. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. BMJ. 2005;331(7509):134-6. doi: 10.1136/bmj.38506.594977.E0. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
500. Manalastas PIC, Zangwill LM, Daga FB, et al. The association between macula and ONH optical coherence tomography angiography (OCT-A) vessel densities in glaucoma, glaucoma suspect, and healthy eyes. J Glaucoma. 2018;27(3):227-32. doi: 10.1097/IJG.0000000000000862. PMID: 29303870. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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529. Medeiros FA, Zangwill LM, Bowd C, et al. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. Am J Ophthalmol. 2005;139(1):44-55. doi: 10.1016/j.ajo.2004.08.069. PMID: 15652827. Excluded for wrong study design for key question.
530. Medeiros FA, Zangwill LM, Bowd C, et al. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and stratus OCT optical coherence tomograph for the detection of glaucoma. Arch Ophthalmol. 2004;122(6):827-37. doi: 10.1001/archopht.122.6.827. PMID: 15197057. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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560. Mvoulana A, Kachouri R, Akil M. Fully automated method for glaucoma screening using robust optic nerve head detection and unsupervised segmentation based cup-to-disc ratio computation in retinal fundus images. Comput Med Imaging Graph. 2019;77:101643. doi: 10.1016/j.compmedimag.2019.101643. PMID: 31541937. Excluded for wrong study design for key question.
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575. Nakatani Y, Higashide T, Ohkubo S, et al. Evaluation of macular thickness and peripapillary retinal nerve fiber layer thickness for detection of early glaucoma using spectral domain optical coherence tomography. J Glaucoma. 2011;20(4):252-9. doi: 10.1097/IJG.0b013e3181e079ed. PMID: 20520570. Excluded for wrong study design for key question.
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577. National Eye Health Education Program. Eye-Q Test. https://www.nei.nih.gov/sites/default/files/nehep-pdfs/EyeQTest_for_Toolkit.pdf. Accessed Februrary 12, 2020. Excluded for wrong intervention.
578. Nazareth T, Rocha J, Scoralick ALB, et al. Retinal sensitivity thresholds obtained through easyfield and Humphrey perimeters in eyes with glaucoma: a cross-sectional comparative study. Clin Ophthalmol. 2020;14:4201-7. doi: 10.2147/OPTH.S280692. PMID: 33299296. Excluded for wrong outcome.
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580. Netland PA, Weiss HS, Stewart WC, et al. Cardiovascular effects of topical carteolol hydrochloride and timolol maleate in patients with ocular hypertension and primary open-angle glaucoma. Night Study Group. Am J Ophthalmol. 1997;123(4):465-77. doi: 10.1016/s0002-9394(14)70172-2. PMID: 9124243. Excluded for wrong comparator.
581. Nezu N, Usui Y, Saito A, et al. Machine learning approach for intraocular disease prediction based on aqueous humor immune mediator profiles. Ophthalmology. 2021;20:20. doi: 10.1016/j.ophtha.2021.01.019. PMID: 33484732. Excluded for wrong population.
582. Ng M, Racette L, Pascual JP, et al. Comparing the full-threshold and Swedish interactive thresholding algorithms for short-wavelength automated perimetry. Invest Ophthalmol Vis Sci. 2009;50(4):1726-33. doi: 10.1167/iovs.08-2718. PMID: 19074800. Excluded for wrong intervention.
583. Nicolela MT, Drance SM, Broadway DC, et al. Agreement among clinicians in the recognition of patterns of optic disk damage in glaucoma. Am J Ophthalmol. 2001;132(6):836-44. doi: 10.1016/s0002-9394(01)01254-5. PMID: 11730646. Excluded for wrong comparator.
584. Nieves-Moreno M, Martinez-de-la-Casa JM, Bambo MP, et al. New normative database of inner macular layer thickness measured by spectralis OCT used as reference standard for glaucoma detection. Transl Vis Sci Technol. 2018;7(1):20. doi: 10.1167/tvst.7.1.20. PMID: 29497582. Excluded for wrong study design for key question.
585. Niwas SI, Lin W, Kwoh CK, et al. Cross-examination for angle-closure glaucoma feature detection. IEEE J Biomed Health Inform. 2016;20(1):343-54. doi: 10.1109/JBHI.2014.2387207. PMID: 25561599. Excluded for wrong study design for key question.
586. Nixon DR, Simonyi S, Bhogal M, et al. An observational study of bimatoprost 0.01% in treatment-naive patients with primary open angle glaucoma or ocular hypertension: the CLEAR trial. Clin Ophthalmol. 2012;6:2097-103. doi: 10.2147/OPTH.S35394. PMID: 23269858. Excluded for wrong study design for key question.
587. Niziol LM, Gillespie BW, Musch DC. Association of fellow eye with study eye disease trajectories and need for fellow eye treatment in Collaborative Initial Glaucoma Treatment Study (CIGTS) participants. JAMA Ophthalmol. 2018;136(10):1149-56. doi: 10.1001/jamaophthalmol.2018.3274. PMID: 30098162. Excluded for wrong outcome.
588. Nolan WP, Ganzorig S, Undraa A, et al. Randomized controlled trial of screening for primary angle-closure in Mongolia. Iovs. 2000;41. Excluded for wrong publication type.
589. Nouri-Mahdavi K, Nikkhou K, Hoffman DC, et al. Detection of early glaucoma with optical coherence tomography (StratusOCT). J Glaucoma. 2008;17(3):183-8. doi: 10.1097/IJG.0b013e31815768c4. PMID: 18414102. Excluded for wrong study design for key question.
590. Nouri-Mahdavi K, Nowroozizadeh S, Nassiri N, et al. Macular ganglion cell/inner plexiform layer measurements by spectral domain optical coherence tomography for detection of early glaucoma and comparison to retinal nerve fiber layer measurements. Am J Ophthalmol. 2013;156(6):1297-307.e2. doi: 10.1016/j.ajo.2013.08.001. PMID: 24075422. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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Appendix A5. Excluded Studies

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752. Simmons ST, Earl ML. Three-month comparison of brimonidine and latanoprost as adjunctive therapy in glaucoma and ocular hypertension patients uncontrolled on beta-blockers: tolerance and peak intraocular pressure lowering. Ophthalmology. 2002;109(2):307-14; discussion 14-5. doi: 10.1016/s0161-6420(01)00936-8. PMID: 11825814. Excluded for wrong comparator.
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755. Sinha G, Gupta S, Temkar S, et al. IOP agreement between I-Care TA01 rebound tonometer and the Goldmann applanation tonometer in eyes with and without glaucoma. Int Ophthalmol. 2015;35(1):89-93. doi: 10.1007/s10792-014-0026-6. PMID: 25510295. Excluded for wrong study design for key question.
756. Sinha S, Lee D, Kolomeyer NN, et al. Fixed combination netarsudil-latanoprost for the treatment of glaucoma and ocular hypertension. Expert Opin Pharmacother. 2019:1-7. doi: 10.1080/14656566.2019.1685499. PMID: 31663782. Excluded for wrong intervention.
757. Skalicky SE, McAlinden C, Khatib T, et al. Activity limitation in glaucoma: objective assessment by the Cambridge Glaucoma Visual Function Test. Invest Ophthalmol Vis Sci. 2016;57(14):6158-66. doi: 10.1167/iovs.16-19458. PMID: 27835712. Excluded for wrong study design for key question.
758. Smith CA, West ME, Sharpe GP, et al. Asymmetry analysis of macular optical coherence tomography angiography in patients with glaucoma and healthy subjects. Br J Ophthalmol. 2020;104(12):1724-9. doi: 10.1136/bjophthalmol-2019-315592. PMID: 32107207. Excluded for wrong study design for key question.
759. Smith J. Argon laser trabeculoplasty: comparison of bichromatic and monochromatic wavelengths. Ophthalmology. 1984;91(4):355-60. PMID: 6371649. Excluded for wrong comparator.
760. Solish AM, DeLucca PT, Cassel DA, et al. Dorzolamide/timolol fixed combination versus concomitant administration of brimonidine and timolol in patients with elevated intraocular pressure: a 3-month comparison of efficacy, tolerability, and patient-reported measures. J Glaucoma. 2004;13(2):149-57. doi: 10.1097/00061198-200404000-00012. PMID: 15097262. Excluded for wrong comparator.
761. Sommer A, Pollack I, Maumenee AE. Optic disc parameters and onset of glaucomatous field loss. II. Static screening criteria. Arch Ophthalmol. 1979;97(8):1449-54. doi: 10.1001/archopht.1979.01020020111003. PMID: 464867. Excluded for wrong study design for key question.
762. Son J, Shin JY, Kim HD, et al. Development and validation of deep learning models for screening multiple abnormal findings in retinal fundus images. Ophthalmology. 2020;127(1):85-94. doi: 10.1016/j.ophtha.2019.05.029. PMID: 31281057. Excluded for wrong population.
763. Song H. Effect of latanoprost on intraocular pressure, central corneal thickness and endothelial cell density of angle-closure glaucoma [Article in Chinese]. Int J Ophthalmol. 2010;10:2385-6. Excluded for not English language.
764. Song J, Lee PP, Epstein DL, et al. High failure rate associated with 180 degrees selective laser trabeculoplasty. J Glaucoma. 2005;14(5):400-8. PMID: 16148590. Excluded for wrong study design for key question.
765. Song YJ, Kim YW, Park KH, et al. Comparison of glaucoma patients referred by glaucoma screening versus referral from primary eye clinic. PLoS One. 2019;14(1):e0210582. doi: 10.1371/journal.pone.0210582. PMID: 30629694. Excluded for wrong study design for key question.
766. Soorya M, Issac A, Dutta MK. An automated and robust image processing algorithm for glaucoma diagnosis from fundus images using novel blood vessel tracking and bend point detection. Int J Med Inform. 2018;110:52-70. doi: 10.1016/j.ijmedinf.2017.11.015. PMID: 29331255. Excluded for not a study.

Appendix A5. Excluded Studies

767. Spaide T, Wu Y, Yanagihara RT, et al. Using deep learning to automate goldmann applanation tonometry readings. Ophthalmology. 2020;127(11):1498-506. doi: 10.1016/j.ophtha.2020.04.033. PMID: 32344074. Excluded for wrong comparator.
768. Sperduto RD, Hiller R, Podgor MJ, et al. Comparability of ophthalmic diagnoses by clinical and reading center examiners in the visual acuity impairment survey pilot study. Am J Epidemiol. 1986;124(6):994-1003. doi: 10.1093/oxfordjournals.aje.a114489. PMID: 3776982. Excluded for wrong outcome.
769. Sponsel W. Timolol vs pilocarpine in open angle glaucoma: the observation of significant differences in visual field response in patients with clinically equivalent IOP control. Chibret International Journal of Ophthalmology. 1987;5(3):50-6. Excluded for wrong comparator.
770. Spry PG, Hussin HM, Sparrow JM. Clinical evaluation of frequency doubling technology perimetry using the humphrey matrix 24-2 threshold strategy. Br J Ophthalmol. 2005;89(8):1031-5. PMID: 16024860. Excluded for wrong intervention.
771. Sreelatha OK, Ramesh SV. Teleophthalmology: improving patient outcomes? Clin Ophthalmol. 2016;10:285-95. doi: 10.2147/opth.S80487. PMID: 26929592. Excluded for not a study.
772. Staffieri SE, Ruddle JB, Kearns LS, et al. Telemedicine model to prevent blindness from familial glaucoma. Clin Exp Ophthalmol. 2011;39(8):760-5. doi: 10.1111/j.1442-9071.2011.02556.x. PMID: 21749595. Excluded for wrong study design for key question.
773. Stagg BC, Medeiros FA. A comparison of OCT parameters in identifying glaucoma damage in eyes suspected of having glaucoma. Ophthalmol Glaucoma. 2020;3(2):90-6. doi: 10.1016/j.ogla.2019.11.004. PMID: 32632407. Excluded for results not usable or not fully reported.
774. Stoor K, Karvonen E, Ohtonen P, et al. Icare versus Goldmann in a randomised middle-aged population: the influence of central corneal thickness and refractive errors. Eur J Ophthalmol. 2020:1120672120921380. doi: 10.1177/1120672120921380. PMID: 32517497. Excluded for results not usable or not fully reported.
775. Stoutenbeek R, Heeg GP, Jansonius NM. Frequency doubling perimetry screening mode compared to the full-threshold mode. Ophthalmic Physiol Opt. 2004;24(6):493-7. doi: 10.1111/j.1475-1313.2004.00223.x. PMID: 15491476. Excluded for wrong study design for key question.
776. Strouthidis NG, Chandrasekharan G, Diamond JP, et al. Teleglaucoma: ready to go? Br J Ophthalmol. 2014;98(12):1605-11. doi: 10.1136/bjophthalmol-2013-304133. PMID: 24723617. Excluded for not a study.
777. Su D, Greenberg A, Simonson JL, et al. Efficacy of the amsler grid test in evaluating glaucomatous central visual field defects. Ophthalmology. 2016;123(4):737-43. doi: 10.1016/j.ophtha.2015.12.003. PMID: 26783097. Excluded for wrong study design for key question.
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Appendix A5. Excluded Studies

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Appendix A5. Excluded Studies

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805. Thompson AC, Jammal AA, Berchuck SI, et al. Assessment of a segmentation-free deep learning algorithm for diagnosing glaucoma from optical coherence tomography scans. JAMA Ophthalmol. 2020;138(4):333-9. doi: 10.1001/jamaophthalmol.2019.5983. PMID: 32053142. Excluded for wrong study design for key question.
806. Thompson AC, Jammal AA, Medeiros FA. A deep learning algorithm to quantify neuroretinal rim loss from optic disc photographs. Am J Ophthalmol. 2019;201:9-18. doi: 10.1016/j.ajo.2019.01.011. PMID: 30689990. Excluded for wrong study design for key question.
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837. Wang M, Lu AT, Varma R, et al. Combining information from 3 anatomic regions in the diagnosis of glaucoma with time-domain optical coherence tomography. J Glaucoma. 2014;23(3):129-35. doi: 10.1097/IJG.0b013e318264b941. PMID: 22828002. Excluded for wrong study design for key question.

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841. Watson PG, Barnett MF, Parker V, et al. A 7 year prospective comparative study of three topical beta blockers in the management of primary open angle glaucoma. Br J Ophthalmol. 2001;85(8):962-8. doi: 10.1136/bjo.85.8.962. PMID: 11466256. Excluded for wrong comparator.
842. Weih LM, Nanjan M, McCarty CA, et al. Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. Ophthalmology. 2001;108(11):1966-72. doi: 10.1016/s0161-6420(01)00799-0. PMID: 11713063. Excluded for wrong population.
843. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901-11. doi: 10.1001/jama.2014.3192. PMID: 24825645. Excluded for not a study.
844. Weinreb RN, Bacharach J, Fechtner RD, et al. 24-hour intraocular pressure control with fixed-dose combination brinzolamide 1%/brimonidine 0.2%: a multicenter, randomized trial. Ophthalmology. 2019;126(8):1095-104. doi: 10.1016/j.ophtha.2018.10.040. PMID: 30403988. Excluded for wrong intervention.
845. Weinreb RN, Garway-Heath D, Leung C, et al. Diagnosis of primary open angle glaucoma: WGA consensus series-10: Kugler Publications; 2017. Excluded for wrong population.
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848. Whitson JT, Realini T, Nguyen QH, et al. Six-month results from a phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. Clin Ophthalmol. 2013;7:1053-60. doi: 10.2147/OPTH.S46881. PMID: 23766627. Excluded for wrong comparator.
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850. Wilson MR, Coleman AL, Yu F, et al. Functional status and well-being in patients with glaucoma as measured by the Medical Outcomes Study Short Form-36 questionnaire. Ophthalmology. 1998;105(11):2112-6. doi: 10.1016/s0161-6420(98)91135-6. PMID: 9818614. Excluded for wrong study design for key question.
851. Wolfs RC, Ramrattan RS, Hofman A, et al. Cup-to-disc ratio: ophthalmoscopy versus automated measurement in a general population: the Rotterdam Study. Ophthalmology. 1999;106(8):1597-601. doi: 10.1016/s0161-6420(99)90458-x. PMID: 10442909. Excluded for results not usable or not fully reported.
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853. Wollstein G, Ishikawa H, Wang J, et al. Comparison of three optical coherence tomography scanning areas for detection of glaucomatous damage. Am J Ophthalmol. 2005;139(1):39-43. doi: 10.1016/j.ajo.2004.08.036. PMID: 15652826. Excluded for wrong study design for key question.
854. Wong MO, Lee JW, Choy BN, et al. Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma. Surv Ophthalmol. 2015;60(1):36-50. doi: 10.1016/j.survophthal.2014.06.006. PMID: 25113610. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
855. Wong MOM, Lai IS, Chan PP, et al. Efficacy and safety of selective laser trabeculoplasty and pattern scanning laser trabeculoplasty: a randomised clinical trial. Br J Ophthalmol. 2021;105(4):514-20. doi: 10.1136/bjophthalmol-2020-316178. PMID: 32606078. Excluded for wrong comparator.

Appendix A5. Excluded Studies

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857. Wormald R, Wilkins MR, Bunce C. Post-operative 5-fluorouracil for glaucoma surgery. Cochrane Database Syst Rev. 2000 (2). Excluded for wrong intervention.
858. Wright DM, Konstantakopoulou E, Montesano G, et al. Visual field outcomes from the multicenter, randomized controlled laser in glaucoma and ocular hypertension trial. Ophthalmology. 2020;127(10):1313-21. doi: 10.1016/j.ophtha.2020.03.029. PMID: 32402553. Excluded for wrong outcome.
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860. Wu XS, Xu L, Jonas JB, et al. Agreement between spectral domain optical coherence tomography and retinal nerve fiber layer photography in Chinese. J Glaucoma. 2012;21(4):228-33. doi: 10.1097/IJG.0b013e3182070cc6. PMID: 21654514. Excluded for wrong study design for key question.
861. Wu Z, Medeiros FA, Weinreb RN, et al. Specificity of various cluster criteria used for the detection of glaucomatous visual field abnormalities. Br J Ophthalmol. 2020;104(6):822-6. doi: 10.1136/bjophthalmol-2019-314593. PMID: 31530565. Excluded for wrong study design for key question.
862. Wu Z, Vianna JR, Reis ASC, et al. Qualitative evaluation of neuroretinal rim and retinal nerve fibre layer on optical coherence tomography to detect glaucomatous damage. Br J Ophthalmol. 2020;104(7):980-4. doi: 10.1136/bjophthalmol-2019-314611. PMID: 31662310. Excluded for wrong study design for key question.
863. Xiao D, Vignarajan J, Chen T, et al. Content design and system implementation of a teleophthalmology system for eye disease diagnosis and treatment and its preliminary practice in Guangdong, China. Telemed J E Health. 2017;23(12):964-75. doi: 10.1089/tmj.2016.0266. PMID: 28586267. Excluded for not a study.
864. Xing Y, Jiang FG, Li T. Fixed combination of latanoprost and timolol vs the individual components for primary open angle glaucoma and ocular hypertension: a systematic review and meta-analysis. Int J Ophthalmol. 2014;7(5):879-90. doi: 10.3980/j.issn.2222-3959.2014.05.26. PMID: 25349811. Excluded for wrong comparator.
865. Xu L, Asaoka R, Murata H, et al. Improving visual field trend analysis with OCT and deeply regularized latent-space linear regression. Ophthalmol Glaucoma. 2021;4(1):78-88. doi: 10.1016/j.ogla.2020.08.002. PMID: 32791238. Excluded for wrong intervention.
866. Xu L, Wang X, Wu M. Topical medication instillation techniques for glaucoma. Cochrane Database Syst Rev. 2017;2:CD010520. doi: 10.1002/14651858.CD010520.pub2. PMID: 28218404. Excluded for wrong outcome.
867. Xu Y, Xu D, Lin S, et al. Sliding window and regression based cup detection in digital fundus images for glaucoma diagnosis. Med Image Comput Comput Assist Interv. 2011;14(Pt 3):1-8. PMID: 22003677. Excluded for results not usable or not fully reported.
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Appendix A5. Excluded Studies

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Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
    - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
    - For cohort studies: consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially,

but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as: uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Internet Citation: *Appendix VI. Criteria for Assessing Internal Validity of Individual Studies*. U.S. Preventive Services Task Force. July 2017. https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies

Appendix A7. Expert Reviewers of the Draft Report

- April Maa, MD, Emory University School of Medicine, Emory Eye Center; Atlanta VA Medical Center
- Nancy Weintraub, MD, David Geffen School of Medicine at University of California at Los Angeles
- Jennifer Evans, PhD, MSc, London School of Hygiene and Tropical Medicine
- Centers for Disease Control and Prevention representatives
- One undisclosed reviewer

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix B Table 1. Trial of Glaucoma Screening

Author, year	Study design	Country	Setting	N	Duration of follow-up	Inclusion criteria	Baseline population	Baseline vision parameters
Swamy 2009[132], Cumming 2007[72]	RCT	Australia	Subjects were encouraged to come to the hospital-based study clinic or to the optomestris's own practice, but they also had the option of a home visit by the study optometrist	Randomized: 616 people (309 intervention, 307 control) Received intervention: 300 vs. NA Attrition: 35 vs. 49 Analysis: 274 vs. 258	1 year	Those >70 years recruited mainly from people attending outpatient aged care services; also advertisements Living independently in the community and no cataract surgery or new spectacle prescription in the previous 3 months Recruited August 2002 to July 2004	A vs. B Mean age: 81 vs. 80 years % female: 67% vs. 68% Race/ethnicity: NR Need help with ADLs: 27% vs. 36% Falls in the past year: 46% vs. 45% Number of medications, >4: 47% vs. 56%	A vs. B VFQ-25: 84.7 vs. 86.2 Self-reported vision, good: 50% vs. 50% Eye disease history: age-related maculopathy 10% vs. 10%, cataract 63% vs. 62%, diabetic retinopathy 1% vs. 1%, glaucoma 14% vs. 14% Cataract surgery: 41% vs. 37% No glasses: 2% vs. 3% Intervention group: Mean presenting binocular VA: 0.22 logMAR, mean Snellen equivalent of 6/9 Cataract: 62%

Appendix B Table 1. Trial of Glaucoma Screening

Author, year	Intervention (Ns)	Screener	Screening tools used and definitions	Results	Quality
Swamy 2009[132], Cumming 2007[72]	A. Comprehensive vision and eye examination, including referal to opthalmologist or public hospital eye clinic and/or occupational therapist for home modifications, mobility training, or canes (n=309) B. No vision assessment or intervention/usual care (n= 307) Intervention group, types of treatments received: Judged to need treatment: 48.7% (146/300) New glasses: 30% Referral to opthalmologist for glaucoma 5.5%, cataract surgery 4.9%, age-related maculopathy 1.6%, other 1% Referred to occupational therapist 7.7%	Optometrist	ETDRS chart for VA measured as total number of letters read correctly, converted to logMAR; if no letters read, counting fingers CSV-1000E chart for contrast sensitivity Humphrery automated visual field unit with FDT for visual fields Perkins applanation tonometer for IOP Slit -lamp biomicroscopy and direct ophthalmoscopy for exam exams	A vs. B Mean (logMAR) distance VA (n=503): 0.27 vs. 0.25, p=0.32 Mean (logMAR) near VA (n=499): -0.01 vs. -0.03, p=0.26 NEI-VFQ-25: mean composite score: 84.3 vs. 86.4, p=0.49 <u>Results from Cumming study</u>: Falls, ≥1 fall: 65% (201/309) vs. 50% (153/307), relative risk 1.31 (95% CI 1.13 to 1.50) Falls, ≥2 falls: 38% (117/309) vs. 31% (94/307), relative risk 1.24 (95% CI 0.99 to 1.54) Falls, in total: 758 vs. 516, fall incidence rate ratio: 1.57 (95% CI 1.20 to 2.05), p=0.001 Fractures: 10% (31/309) vs. 5.7% (18/307), RR 1.74 (95% CI 0.97 to 3.11), p=0.06	Good

Abbreviations: ADL = activity of daily life; CI = confidence interval; CSV-1000E = contrast sensitivity testing instrument; ETDRS = Early Treatment Diabetic Retinopathy Study; FDT = frequency doubling technology; IOP = intraocular pressure; logMAR = logarithmic minimum angle of resolution; NR = not relevant; RCT = randomized controlled trial; RR = relative risk; VA = visual acuity; VFQ-25 = visual function questionnaire 25-item.

Appendix B Table 2. Trial of Glaucoma Screening, Quality Assessment

Study, year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Blinding: outcome assessors or data analysts	Intention-to-treat analysis	Reporting of attrition, contamination, etc.	Differential loss to followup or overall high loss to followup	Appropriate analysis including cluster correlation	Funding source	Quality
Swamy 2009[132], Cumming 2007[72]	Yes	Yes	Control group more likely to report using >4 medications, needing help to do basic ADLs, and use of a walking aid	Yes	Yes	No for Swamy Yes for Cumming	Yes	No No (11% vs. 16%)	NA	National Health and Medical Research Council of Australia	Good

Abbreviations: ADL = activity of daily life; NA = not applicable.

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Screening Test	Reference Standard	Setting Country	Screener	Age of Enrollees	N (subjects)
Aptel, 2010[55]	SD-OCT	Based on visual fields and optic nerve appearance	University glaucoma center in France	NR	62	120
Arnould, 2020[56]	SD-OCT	Based on optic disc photographs	Population study, France (Bordeau, Dijon, Montpellier)	Trained technicians	82	1153
Aksoy, 2020[54]	SD-OCT	Based on visual fields, optic disc appearance, IOP, and gonioscopy	Clinic in Turkey	Experience physician	58.8	200
Azuara-Blanco, 2016[59] Banister, 2016[61] Virgili, 2018[137]	SD-OCT	Comprehensive clinical exam by ophthalmologist with glaucoma expertise (biomicroscopy with SAP)	5 NHS hospital eye services in the United Kingdom; referred by optometrists with glaucoma-related finding	Imaging technician	60.5 (13.8)	943
Bagga, 2006[60]	Tonometry Pachymetry	Based on optic nerve appearance (with normal SAP)	University hospital, United States	NR	58	47
Blumberg, 2016[64]	SD-OCT Visual fields Disc photographs	Consensus of 3/4 glaucoma specialist based on OCT, disc photographs, and SAP	Based on photograph of optic disc, all eyes were abnormal or suspicious by referring glaucoma specialist	Unclear	57.8	50
Bonomi, 2001[65]	Tonometry	Based on visual fields, optic disc evaluation, IOP and gonioscopy	The entire population over 40 years in the Egna-Neumarkt area of Italy	Trained opthalmological specialists	40-49: 24.1% 50-59: 28.5% 60-69: 28.5% 70-79: 14.6% ≥80: 4.4%	4297
Casado, 2019[67]	SD-OCT	Visual Field Defects	Ophthalmology department of hospital in Spain	Single, well-trained ophthalmologist	64.2 (12.9)	161
Chan, 2017[68]	Tonometry	Based on VA, tonometry, HRT, GDx VCC, HFA, fundus photos	EPIC-Norfolk cohort from Norfolk, United Kingdom area	Abnormal findings resulted in definitive ey exam by consult ophthalmologist with special interest in glaucoma	68.7 (range 48-92)	8623
Charalel, 2014[69]	Relative Afferent Pupillary Defect	Glaucoma diagnosis from medical chart	Clinic in United States	Medical student	59.5	107
Choudhari, 2013[70]	Tonometry	Based on VA, pachyometry, biomicroscopy, gonioscopy	Population study of rural and urban residents of south India	2 glaucoma specialists and 2 optometrists	52	6310
Cifuentes-Canorea, 2018[71]	SD-OCT	Based on IOP, SAP, appearance of optic nerve head	Glaucoma department at San Carlos Univerwity Hospital in Brazil	Experienced operator performed OCT	72.4	193
Dabasia, 2015[73]	SD-OCT	Based on HFA, bimicroscopy, IOP, gonioscopy, fundus photography	University-based eye clinic in London, United Kingdom	Experienced technician	Median: 68	505
Danesh-Meyer, 2006[74]	Visual fields Clinical exam	Based on slit lamp exam, gonioscopy, funduscopy, SAP	University glaucoma specialty clinic in New Zealand	Sterophotographs of optic disc examined by two glaucoma specialists	58	110
Deshpande, 2019[76]	SD-OCT	Based on VA, refraction, slit-lamp exam, indirect ophthalmoscopy, IOP, gonioscopy, HFA, OCT	Hospital-based tertiary care center in central India	NR	56.8	201

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Screening Test	Reference Standard	Setting Country	Screener	Age of Enrollees	N (subjects)
Deshpande, 2019[75]	SD-OCT	Based on slit-lamp exam, indirect ophthalmoscopy, IOP, HFA, OCT	Hospital-based tertiary care center in India	NR	Normal: 54.25 POAG: 61.22 PPG: 56.85	190
Ehrlich, 2012[77]	Tonometry	Based on clinical exam, fundus photography, HRT II, visual fields	Private ophthalmology office in United States	NR	64.3	614
Field, 2016[79]	SD-OCT	Based on optic disc appearance and visual fields	Subjects part of SIG study in United States	NR	62.8	120
Francis, 2011[80] Varma, 2004[16]	Visual fields Tonometry Pacymetry Disc photographs	Based on optic disc photographs, visual fields, gonioscopy	Population-based study, Los Angeles, United States. Exams conducted in field clinics and homes	Ophthalmic technicians and ophthalmologists	54.9	6082
Garas, 2011[81]	SD-OCT	Based on slit-lamp exam, optic nerve head photography, visual fields, IOP	Glaucoma center in Hungary	Trained PhD student	57.7	286
Hammond, 1979[84]	Tonometry Opthalmoscopy	Based on visual field, IOP, CDR	Eye clinic of large hospital in United States	Nurses skilled in ophthalmoscopy and tonometry	NR	219
Hark, 2019[86] Hark, 2019[85]	Telemedicine: Disc photographs Tonometry	Based on slit-lamp exam, IOP, gonioscopy, CCT, VA, visual fields, fundus photography	7 primary care practices and 4 federally qualified health centers using telemedicine in the United States; results sent to Wills Eye Telemedicine Department	1 ocular technician	58.8 (10.4)	902
Hong, 2007[88]	Visual fields	Based on visual fields and optic disc appearance	South Korea	Glaucoma specialist	38.2	120
Ivers, 2001[89]	Visual fields	Based on visual fields and optic disc photographs	Population study in urban area west of Sydney, Australia	NR	NR	3654
Kaushik, 2011[97]	SD-OCT	Based on clinical exam including tonometry, biomicroscopy, gonioscopy, optic disc photos, visual fields	India	NR	Healthy: 50.8 Glaucoma suspect: 54.6 Glaucoma: 59.7	123
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc appearance	India	NR	47	275
Karvonen, 2020[93]	SD-OCT	Based on optic nerve head photographs, RNFL photographs and visual fields	Population study - Northern Finland Birth Cohort	NR	45 to 49	3039
Katz, 1993[95] Tielsch 1991[133]	Visual fields	Abnormal initial screen resulted in referral to ophthalmologist who diagnosed glaucoma based on visual fields and optic nerve characteristics	Population study in United States	NR for initial screening; glaucoma specialists for diagnosis	≥40	5308

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Screening Test	Reference Standard	Setting Country	Screener	Age of Enrollees	N (subjects)
Kiddee, 2013[99]	SD-OCT	Based on visual fields, optic disc appearance, and IOP	University in Thailand	Experienced opthalmic photographer	18 to 80 (enrollment criteria)	131
Kim, 2012[100]	SD-OCT	Based on visual fields and optic nerve head appearance	Hospital glaucoma clinic in South Korea	NR	55.1	106
Koh, 2018[101]	SD-OCT	Based on visual fields, optic nerve features of glaucoma and RNFL defects	Population study at Singapore Eye Research Institute	Trained optometrists	61.4	1061
Kozobolis, 2000[102]	Tonometry	Based on visual fields in patients who were glaucoma suspects on initial screening (IOP, fundus exam)	Mobile ophthamological unit in 18 villages in Crete; exam done in hospital	Ophthalmologist	40-49: 3.0% 50-59: 16.4% 60-69: 31.9% 70-79: 38.3% 80+: 10.5%	1107
Lee, 2017[105]	SS-OCT	Based on visual field, optic disc photographs	Hospital glaucoma clinic, South Korea	NR	57.2	184 eyes
Lee, 2018[106]	SD-OCT SS-OCT	Based on optic nerve head appearance and visual fields	Hospital glaucoma clinic, South Korea	Experienced technician	54	149
Lee, 2016[104]	SD-OCT SS-OCT	Based on optic nerve appearance and visual fields	University hospital clinic, South Korea	NR	60.2	120
Leibowitz, 1980[107]	Tonometry Opthalmoscopy	Based on visual fields	Population-study Frammingham Eye Study, United States	Ophthalmologist	<65: 53% 65-74: 33% 75+: 15%	2631
Liu, 2011[108]	Visual fields	Based on OCT Cirrus HD RNFL	University Eye Center in Hong Kong	NR	54.1	132
Maa, 2014[109]	Telemedicine: Tonometry Pachymetry VA Patient history	Findings from face-to-face exam to include fundus photographs	Veterans Health Administration in United States	Ophthalmic technician	NR	52
Maa, 2019[110] Maa, 2020[111]	Clinical examTechnology-based exam with SD-OCT	Findings from face-to-face exam without knowledge of OCT or fundus photographs; OCT interpreters diagnosed glaucoma without then with OCT results	Veterans Health Administration in United States	Ophthalmic technician	60	256
Marraffa, 1989[112]	Visual fields	Based on IOP, optic disc study, visual field, and evidence from followup	Hospital clinic in Italy	NR	54.3	104
Morejon, 2019[116]	SD-OCT	Based on optic nerve appearance and visual field	Glaucoma unit of Eye Institutute in Spain	Glaucoma expert ophthalmologist	58.7	161 (306 eyes)
Mundorf, 1989[117]	Visual fields Questionnaire	Based on appearance of optic disk, visual fields with or without increase in IOP	Free glaucoma detection program through university ophthalmology department in United States	NR	69	145
Park, 2013[120]	SD-OCT	Based on visual fields, optic nerve head appearance	Hospital, South Korea	NR	47.8	318

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Screening Test	Reference Standard	Setting Country	Screener	Age of Enrollees	N (subjects)
Pazos, 2017[53]	SD-OCT	Based on visual fields, IOP, and optic disc appearance	Multicenter, Spain	NR	66	80
Rao, 2015[122]	SD-OCT Visual fields	Based on optic disc photographs	Tertiary eye care facility, India	2 glaucoma experts for optic disc photography	56	175 (280 eyes)
Schweitzer, 2016[128]	SD-OCT	Based on optic disc photographs, visual fields, gonioscopy, slit-lamp exam, and IOP	Population-based study in France	NR	82.2	624
Sarigul Sezenoz, 2020[125]	SD-OCT	Based on visual fields, optic disc appearance, gonioscopy	Hospital outpatient clinic in Turkey	Experienced technician	66.1	95
Soh, 2020[130]	Stereoscopy	Based on visual fields, optic photos, HRT, OCT	Population-based study in Singapore	Trained optometrist for refraction	40-49: 25.4% 50-59: 31.9% 60-69: 25.3% ≥ 70: 17.4%	9673
Sung, 2009[131]	SD-OCT	Based on visual fields, optic disc appearance, and IOP	Glaucoma clinic in South Korea	Well-trained techniclan	52.7	163
Vernon, 1990[135]	Tonometry	Based on IOP, visual fields, optic disc appearance	Hospital glaucoma clinic in United Kingdom	Nonophthalmology-trained staff	Over 49 years: 100%	874
Vidas, 2017[136]	SD-OCT	Based on visual fields and optic disc appearance	Hospital ophthalmology department, Croatia	NR	56.6	81
Wahl, 2016[138]	Tonometry Disc photographs	Based on IOP, visual field (FDT), and appearance of optic nerve head	Industry employees in Germany	Assistance staff working in occupational health departments	40-49: 59.4% 50-59: 39.0% 60-65: 1.6%	4167
Xu, 2017[144]	SD-OCT	Based on appearance of optic disc, visual fields, and IOP	University ophthalmic center in China	NR	46.1	703

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Baseline population	Baseline vision parameters, proportion with visual conditions	Prevalence of glaucoma	Quality
Aptel, 2010[55]	Female: 62.7%	Glaucoma vs. Glaucoma suspect vs. Healthy: Mean deviation (SD): -9.88 (6.93) vs. -1.73 (2.16) vs. -0.73 (1.56) Mean pattern (SD): 4.42 (4.85) vs. 2.06 (0.54) vs. 1.24 (1.28)	Glaucoma: 33% Suspected glaucoma: 33%	Fair
Arnould, 2020[56]	Female: 62.7%	Glaucoma vs. Healthy: Mean deviation (SD): -0.97 (2.08) vs. 0.15 (2.09)	7.70%	Good
Aksoy, 2020[54]	Female: 51%	POAG vs. OH vs. Healthy: Mean deviation (SD): -2.25 (1.37) vs. 0.42 (1.25) vs. 0.05 (1.32)	32.00%	Fair
Azuara-Blanco, 2016[59] Banister, 2016[61] Virgili, 2018[137]	Female: 51.1% White British: 89.2%	Mean (SD) IOP mmHg: 19.6 (5.7) right; 19.9 (5.6) left Cataract: 8.3% right; 7.4% left AMD: 0.7% right; 1.2% left	17%	Good
Bagga, 2006[60]	Female: 72.3% White: 87.2% Black: 6.4% Hispanic: 4.3%	Glaucoma vs. Healthy: Mean IOP (SD): 17.0 (4.0) vs. 15.0 (3.0)	53.20%	Fair
Blumberg, 2016[64]	NR	Glaucoma vs. Glaucoma suspects: Mean deviation (SD): -2.5 (1.9) vs. -0.7 (1.9) Mean pattern (SD): 3.7 (2.2) vs. 1.7 (0.5)	67%	Fair
Bonomi, 2001[65]	Female: 56.2%	Mean (SD) IOP mmHg: 15.5 (2.8)	1.4% POAG; 0.6% normal tension glaucoma	Fair
Casado, 2019[67]	Female: 44.1%	IOP (SD) mmHg: 14.6 (2.3)	NR	Fair
Chan, 2017[68]	Female: 55% White: 99.4%	Mean (SD) IOP mmHg: 16.3 (3.6)	4.20%	Fair
Charalel, 2014[69]	Female: 52.3%	Prior cataract surgery: 37.4%	61.70%	Fair
Choudhari, 2013[70]	Female: 50% Rural: 48%	Mean (SD) IOP mmHg intereye difference: 0.015 (2.3)	3.40%	Fair
Cifuentes-Canorea, 2018[71]	Female: 44%	OHT vs. Early POAG vs. moderate to advanced POAG: Mean deviation (SD): 0.51 (1.15) vs. -4.00 (1.0) vs. -9.35 (2.88)	38.30%	Fair
Dabasia, 2015[73]	Female: 59% White: 88% South Asian: 8%	Moderate or advanced AMD: 9.5% Clinically significant cataract: 10.7%	5.1% glaucoma; 6.4% glaucoma suspects	Good
Danesh-Meyer, 2006[74]	Female: 51.8%	Mean deviation (SD): -4.95 (5)	40.9% glaucoma; 20.9% glaucoma suspect	Fair
Deshpande, 2019[76]	Female: 49.8%	NR	36.8% glaucoma; 63.2% glaucoma suspect	Fair
Deshpande, 2019[75]	Female: Normal: 50.39% POAG: 39.29% PPG: 52.86%	NR	Prevalence of glaucomatous eyes (not individuals) POAG: 41.5% (140/337 eyes) PPG: 20.8% (70/337)	Fair

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Baseline population	Baseline vision parameters, proportion with visual conditions	Prevalence of glaucoma	Quality
Ehrlich, 2012[77]	Female: 58% Asian: 19% White: 22% Mixed: 55% Black: 4%	High tension glaucoma vs. normal tension glaucoma vs. healthy: Mean IOP (SD): 26.5 (5.5) vs. 14.4 (3.4) vs. 14.0 (3.0)	41.90%	Fair
Field, 2016[79]	Female: 51% White: 48% Black: 13% Hispanic: 9.5% Asian: 3%	POAG vs. Healthy: Mean deviation (SD) OD: -8.69 (8.07) vs. -0.95 (2.09) Mean deviation (SD) OS: -11.10 (8.60) vs. -1.83 (2.49) Mean deviation asymmetry (SD): 6.80 (6.10) vs. 1.23 (1.04)	52.40%	Fair
Francis, 2011[80] Varma, 2004[16]	Female: 58% Hispanic: 100%	Glaucoma vs. OHT: Mean IOP (SD): 17.3 (5.4) vs. 22.8 (8.1)	3.6% to 4.4% based on how glaucoma determined (optic nerve, visual fields, or both)	Good
Garas, 2011[81]	Female: 55.9% White: 100%	NR	54.90%	Fair
Hammond, 1979[84]	NR	NR	Tonometry: 3.0% CDR: 3.7%	Fair
Hark, 2019[86] Hark, 2019[85]	Female: 61.0% Black: 61.7% White: 17.1% Hispanic: 13.9% Asian/ Hawaiian/ Pacific Islander: 5.6% Diabetic: 58.5% HTN: 67.8%	IOP≥ 30 mmHg: 1.7%	Glaucoma: 4.2% Glaucoma suspect: 17.6%	Fair
Hong, 2007[88]	Female: 55%	Mean deviation (dB): -1.91 Mean PSD (dB): 2.56	60%	Fair
Ivers, 2001[89]	NR	NR	2.40%	Fair
Kaushik, 2011[97]	NR	NR	18.70%	Fair
Kaushik, 2018[96]	NR	Glaucoma vs. glaucoma suspect vs. OHT vs. healthy: Mean deviation (SD): -5.17 (2.69) vs. -2.27 (1.93) vs. -1.45 (0.88) vs. -1.61 (1.63) IOP (SD): 18.04 (5.49(vs. 14.38 (2.82) vs. 25.04 (3.77) vs. 14.06 (1.98)	Glaucoma: 17.1% Glaucoma suspect: 38.5% OHT: 16%	Fair
Karvonen, 2020[93]	NR	NR	1.10%	Fair
Katz, 1993[95] Tielsch 1991[133]	White: 54.9% Black: 45.1%	NR	NR	Poor
Kiddee, 2013[99]	NR	Glaucoma vs. glaucoma suspect vs. healthy: Mean deviation: p<0.001	Glaucoma: 36.6% Glaucoma suspect: 36.6%	Fair
Kim, 2012[100]	Female: 53.8%	Glaucoma vs. Healthy:Mean deviation (SD): -7.61 (8.83) vs. -0.87 (1.39)Mean pattern (SD): 6.93 (4.10) vs. 1.41 (0.32)	73.60%	Fair
Koh, 2018[101]	Female: 45.8%	Glaucoma vs. non-glaucoma: Mean IOP (SD): 15.4 (3.7) vs. 14.2 (2.9) Mean deviation (SD): -8.95 (6.85) vs. -1.32 (2.56)	5.70%	Fair

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Baseline population	Baseline vision parameters, proportion with visual conditions	Prevalence of glaucoma	Quality
Kozobolis, 2000[102]	Female: 58.2%	Mean IOP (SD): right eye for men 16.46, 16.16 (3.16) for women; left eye 16.43 (3.88) for men, 16.05 (2.69) for women	2.80%	Fair
Lee, 2017[105]	NR	Early glaucoma vs. preperimetric glaucoma vs. Healthy Eyes: Mean deviation (SD): -2.39 (1.98) vs. 0.14 (1.29) vs. 0.13 (1.39) IOP (SD): 13.03 (2.63) vs. 12.55 (2.23) vs. 12.94 (2.21)	Early glaucomatous eyes: 40.2% Preperimetric glaucomatous eyes: 23.4%	Fair
Lee, 2018[106]	Female: 58%	Early glaucoma vs. Preperimetric glaucoma vs. Healthy: Mean IOP (SD): 13.07 (2.67) vs. 12.54 (2.32) vs. 12.83 (2.35) Mean deviation (SD): -2.41 (1.96) vs. 0.22 (1.31) vs. 0.05 (1.33) Mean pattern (SD): 4.25 (2.65) vs. 1.77 (0.44) vs. 1.66 (0.42)	38.90%	Fair
Lee, 2016[104]	Female: 55.8%	Mean deviation: -5.45 vs. -0.35	50.00%	Fair
Leibowitz, 1980[107]	Female: 58%	Mean IOP mmHg: 16.5	1.9% OAG Questionable OAG: 7.9%	Fair
Liu, 2011[108]	Female: NR	Glaucoma vs. Healthy, SAP: Mean deviation (SD): -8.13 (7.65) vs. -0.48 (1.03) Mean pattern (SD): 6.13 (4.46) vs. 1.46 (0.30)	72%	Fair
Maa, 2014[109]	NR	Cataract: 3.8% Macular degeneration: 3.8%	26.90%	Fair
Maa, 2019[111] Maa, 2020[110]	Female: 13.3% White: 38.3% Black: 61.3%	Eye trauma: 27.6%Family history of eye diagnosis or blindness: 25.2%	Glaucoma and glaucoma suspect: 26.6%	Good
Marraffa, 1989[112]	Female: 56.7%	IOP ≥ 21 mmHg with suspicious optic disc or both	Glaucoma eyes: 76.9%	Fair
Morejon, 2019[116]	Female: 55%	NR	Glaucoma eyes: 33%; Glaucoma suspect eyes: 33%	Fair
Mundorf, 1989[117]	Female: 72% White: 81% Black: 19%	Glaucoma vs. Glaucoma suspect vs. Healthy: Abnormal IOP: 20% vs. 7% vs. 2% Abnormal visual fields: 90% vs. 36% vs. 29%	Glaucoma: 6.9%; Glaucoma suspect: 9.7%	Fair
Park, 2013[120]	Female: 48%	Preperimetric vs. Perimetric vs. Control: Mean deviation (SD): -0.79 (1.07) vs. -7.28 (2.71) vs. 00.23 (0.52)	PPG: 27.6% Perimetric glaucoma: 45.9%	Fair
Pazos, 2017[53]	Female: 54%	Early Glaucoma vs. Healthy: Mean deviation (SD): -2.26 (1.82) vs. -0.04 (1.41)	Early glaucoma: 50%	Fair
Rao, 2015[122]	NR	Glaucoma vs. Healthy: Mean deviation (95% CI): -5.49 (-10.29 to -3.00) vs. -2.07 (-3.36 to -0.93)	Glaucomatous eyes: 64% Prevalence in study participants: NR	Good
Schweitzer, 2016[128]	Female: 66.4%	Mean IOP (SD): 14.34 (2.52)	7.10%	Fair
Sarigul Sezenoz, 2020[125]	NR	Early glaucoma vs. preperimetric glaucoma vs. ocular hypertension vs. healthy: Mean deviation (SD): -8.27 (9.78) vs. -1.62 (1.65) vs. -0.57 (1.02) vs. 0.14 (5.9) IOP: 17.96 (3.31) vs. 17.64 (2.84) vs. 20.72 (2.27) vs. 18.0 (2.83)	Early glaucoma: 32.6% PPG: 29.5%	Fair
Soh, 2020[130]	Female: 50.7% Chinese: 33.6% Indian: 33.6% Malay: 32.8%	NR	Glaucoma: 3.0%	Fair
Sung, 2009[131]	Female: 46% Asian: 100%	Glaucoma vs. glaucoma suspect vs. healthy:Mean deviation (SD): -5.91 (5.68) vs. -0.85 (1.48) vs. -0.67 (1.48)	Glaucoma: 33.7%Glaucoma suspect: 29.4%	Fair

Appendix B Table 3. Diagnostic Accuracy of Glaucoma Screening Tests, Study Characteristics

Study, Year	Baseline population	Baseline vision parameters, proportion with visual conditions	Prevalence of glaucoma	Quality
Vernon, 1990[135]	Female: 57%	Mean IOP (SD): 14.96 (3.29)	Glaucoma + ocular HTN requring treatment: 2.7%	Fair
Vidas, 2017[136]	Female: 64.2%	Moderate to advanced POAG vs. Early POAG vs. OHT vs. Healthy: Mean deviation (SD): 12.90 (6.12) vs. 3.15 (1.46) vs. 0.62 (0.99) vs. 0.40 (0.71)	Moderate-Advanced + Early glaucoma: 39.5%	Fair
Wahl, 2016[138]	Female: 22.9%	NR	Glaucoma suspects 2.7%	Fair
Xu, 2017[144]	Female: 43.0%	NR	Glaucoma: 52.2%	Fair

Abbreviations: AMD = age-related macular degeneration; CCT = Clear Chart 2; CDR = cup to disc ratio; dB= decibel; EPIC = European Prospective Investigation of Cancer; FDT = frequency doubling technology; GDx VCC = scanning laser polarimetry; HD = high-definition; HFA = Humphrey Visual Field Analyzer; HRT = scanning laser ophthalmoscopy; HTN = hypertension; IOP = intraocular pressure; mm Hg = millimeters mercury; NHS = United Kingdom National Health Service; NR = not reported; OCT = optical coherence tomography; OD = right eye; OHT = ocular hypertension; OS = left eye; POAG = primary open angle glaucoma; PPG = preperimetric glaucoma; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; SAP = standard automated perimetry; SD = standard deviation; SD-OCT = spectral domain optical coherence tomography; SIG = SD-OCT in Glaucoma study; SS-OCT = swept source optical coherence tomography; VA = visual acuity.

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Aksoy, 2020[54]	SD-OCT	Based on visual fields, optic disc appearance, IOP, and gonioscopy	Spectralis	Mean RNFL thickness (IT)	0.8881	NR	NR	NR
Aksoy, 2020[54]	SD-OCT	Based on visual fields, optic disc appearance, IOP, and gonioscopy	Spectralis	Mean GCC (OT)	0.8712	NR	NR	NR
Aptel, 2010[55]	SD-OCT	Based on visual fields and optic nerve appearance	Cirrus	Mean RNFL Thickness	NR	NR	NR	NR
Aptel, 2010[55]	SD-OCT	Based on visual fields and optic nerve appearance	Cirrus	Mean RNFL Thickness	NR	NR	NR	NR
Arnould, 2020[56]	SD-OCT	Based on optic disc photographs	Spectralis	Mean RNFL thickness	0.809	0.7273	0.8907	NR
Azuara-Blanco, 2016 Banister, 2016 Virgili, 2018	SD-OCT	Comprehensive clinical exam by ophthalmologist with glaucoma expertise (biomicroscopy with SAP)	Spectralis	Mean RNFL thickness; cutoff outside normal limits	0.769	0.692	0.834	NR
Bagga, 2006[60]	Tonometry	Based on optic nerve appearance with normal SAP	Goldmann	IOP	NR	NR	NR	NR
Bagga, 2006[60]	Pachymetry	Based on optic nerve appearance with normal SAP	NR	CCT	NR	NR	NR	NR
Blumberg, 2016[64]	SD-OCT	Consensus of 3/4 glaucoma specialist based on OCT, disc photographs, and SAP	3D OCT 2000	RNFL thickness NOS; cutoff NR	0.81	0.68	0.95	NR
Blumberg, 2016[64]	Photographs	Based on visual fields, optic disc evaluation, IOP and gonioscopy	Nidek 3-Dx mydriatic fundus camera	Normal/Abnormal	0.64	0.47	0.81	NR
Blumberg, 2016[64]	Visual field	Based on visual fields, optic disc evaluation, IOP and gonioscopy	HFA	Normal/Abnormal	0.64	0.47	0.81	NR
Bonomi, 2001[65]	Tonometry	Based on visual fields, optic disc evaluation, IOP and gonioscopy	Goldmann	IOP 21-22 mmHg	0.801	NR	NR	NR
Casado, 2019[67]	SD-OCT	Based on visual fields	Spectralis	Mean RNFL thickness	NR	NR	NR	NR
Casado, 2019[67]	SD-OCT	Based on visual fields	Spectralis	GCL map deviation	NR	NR	NR	NR
Chan, 2017[68]	Tonometry	Based on VA, tonometry, HRT, GDx VCC, HFA, fundus photos	Noncontact tonometry (AT555 or ORA)	20 mmHg	0.363	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Chan, 2017[68]	Tonometry	Based on VA, tonometry, HRT, GDx VCC, HFA, fundus photos	Noncontact tonometry (AT555 or ORA)	21 mmHg	0.3	NR	NR	NR
Chan, 2017[68]	Tonometry	Based on VA, tonometry, HRT, GDx VCC, HFA, fundus photos	Noncontact tonometry (AT555 or ORA)	22 mmHg	0.254	NR	NR	NR
Charalel, 2014[69]	Afferent Pupillary Defect	Medical record diagnosis of glaucoma	Swinging flashlight	Normal/Abnormal	0.69	0.5	0.83	NR
Choudhari, 2013[70]	Tonometry	Based on VA, pachyometry, biomicroscopy, gonioscopy	IOP asymmetry, Goldmann	>2 mmHg intereye difference	0.26	NR	NR	NR
Choudhari, 2013[70]	Tonometry	Based on VA, pachyometry, biomicroscopy, gonioscopy	IOP asymmetry, Goldmann	>3 mmHg intereye difference	0.2	NR	NR	NR
Choudhari, 2013[70]	Tonometry	Based on VA, pachyometry, biomicroscopy, gonioscopy	IOP asymmetry, Goldmann	>4 mmHg intereye difference	0.16	NR	NR	NR
Choudhari, 2013[70]	Tonometry	Based on VA, pachyometry, biomicroscopy, gonioscopy	IOP asymmetry, Goldmann	>5 mmHg intereye difference	0.1	NR	NR	NR
Cifuentes-Canorea, 2018[71]	SD-OCT	Based on IOP, SAP, appearance of optic nerve head	Spectralis	mRNFL2 cutoff 34.5 (best combination of sensitivity/specificity)	0.81	NR	NR	NR
Cifuentes-Canorea, 2018[71]	SD-OCT	Based on IOP, SAP, appearance of optic nerve head	Spectralis	GCLT2 cutoff 32.55 (best combinaiton of sensitivity/specificity)	0.762	NR	NR	NR
Dabasia, 2015[73]	SD-OCT	Based on HFA, bimicroscopy, IOP, gonioscopy, fundus photography	iVue (compact RTVue)	GCC abnormal if falling outside the 99% normal limit based on manufacturers' normal database	0.615	0.425	0.776	NR
Dabasia, 2015[73]	SD-OCT	Based on HFA, bimicroscopy, IOP, gonioscopy, fundus photography	iVue (compact RTVue)	RNFL abnormal if falling outside the 99% normal limit based on manufacturers' normal database	0.692	0.50.0	0.835	NR
Dabasia, 2015[73]	Tonometry	Based on HFA, bimicroscopy, IOP,	Goldman	IOP >21 mmHg	0.192	0.085	0.379	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
		gonioscopy, fundus photography						
Danesh-Meyer, 2006[74]	Visual fields	Based on slit lamp exam, gonioscopy, funduscopy, SAP	HFA	Mean deviation	NR	NR	NR	NR
Danesh-Meyer, 2006[74]	Visual fields	Based on slit lamp exam, gonioscopy, funduscopy, SAP	HFA	Pattern SD	NR	NR	NR	NR
Danesh-Meyer, 2006[74]	Clinical Exam	Based on slit lamp exam, gonioscopy, funduscopy, SAP	Fundus exam	CDR	NR	NR	NR	NR
Deshpande, 2019[76]	SD-OCT	Based on VA, refraction, slit-lamp exam, indirect ophthalmoscopy, IOP, gonioscopy, HFA, OCT	Cirrus	GCC cutoff 0.07	0.7703	0.6579	0.8601	NR
Deshpande, 2019[76]	SD-OCT	Based on VA, refraction, slit-lamp exam, indirect ophthalmoscopy, IOP, gonioscopy, HFA, OCT	Cirrus	Optic nerve head & RNFL cutoff -0.24	0.8514	0.7496	0.923	NR
Deshpande, 2019[76]	SD-OCT	Based on VA, refraction, slit-lamp exam, indirect ophthalmoscopy, IOP, gonioscopy, HFA, OCT	Cirrus	GCC + Optic nerve head & RNFL cutoff 0.1	0.9054	0.8148	0.9611	NR
Deshpande, 2019[75]	SD-OCT	Based on slit-lamp exam, indirect ophthalmoscopy, IOP, HFA, OCT	Cirrus	GPL-IPL	NR	NR	NR	NR
Deshpande, 2019[75]	SD-OCT	Based on slit-lamp exam, indirect ophthalmoscopy, IOP, HFA, OCT	Cirrus	GCC Inferior Temporal cutoff 0.7339	0.8143	NR	NR	NR
Deshpande, 2019[75]	SD-OCT	Based on slit-lamp exam, indirect ophthalmoscopy, IOP, HFA, OCT	Cirrus	Average RNFL thickness	NR	NR	NR	NR
Deshpande, 2019[75]	SD-OCT	Based on slit-lamp exam, indirect ophthalmoscopy, IOP, HFA, OCT	Cirrus	RNFL Inferior cutoff 0.9819	0.8785	NR	NR	NR
Ehrlich, 2012[77]	Tonometry	Based on clinical exam, fundus photography, HRT II, visual fields	Goldmann	IOP >20.9	0.59	NR	NR	NR
Field, 2016[79]	SD-OCT	Based on optic disc appearance and visual fields	Spectralis	RNFL intereye asymmetry >5µm	0.758	NR	NR	0.082
Field, 2016[79]	SD-OCT	Based on optic disc appearance and visual fields	Spectralis	RNFL intereye asymmetry >6µm	0.742	NR	NR	0.083

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Francis, 2011[80] Varma, 2004[16]	Tonometry	Based on optic disc photographs, visual fields, gonioscopy	Goldmann	IOP ≥21 mmHg	0.24	0.18	0.3	NR
Francis, 2011[80] Varma, 2004[16]	Biomicroscopy	Based on optic disc photographs, visual fields, gonioscopy	78-D lens, CDR	Vertical CDR ≥0.8	0.6	0.54	0.67	NR
Francis, 2011[80] Varma, 2004[16]	Visual field	Based on optic disc photographs, visual fields, gonioscopy	HFA	Expert reading Glaucomatous/ Nonglaucomatous	0.8	0.75	0.85	NR
Francis, 2011[80] Varma, 2004[16]	Visual field	Based on optic disc photographs, visual fields, gonioscopy	HFA	Mean Deviation <5%	0.88	0.84	0.92	NR
Francis, 2011[80] Varma, 2004[16]	Visual field	Based on optic disc photographs, visual fields, gonioscopy	HFA	Pattern SD ≥5%	0.76	0.71	0.82	NR
Francis, 2011[80] Varma, 2004[16]	Pachymetry	Based on optic disc photographs, visual fields, gonioscopy	Ultrasonic corneal pachymeter	CCT ≤504 µm	0.16	0.11	0.21	NR
Garas, 2011[81]	SD-OCT	Based on slit-lamp exam, optic nerve head photography, visual fields, IOP	RTVue-100	RNFL overall average borderline <5% and ≥1% probability of glaucoma; outside normal limits probability <1%	0.694	0.602	0.773	NR
Garas, 2011[81]	SD-OCT	Based on slit-lamp exam, optic nerve head photography, visual fields, IOP	RTVue-100	GCC overall average borderline <5% and ≥1% probability of glaucoma; outside normal limits probability <1%	0.573	0.47	0.67	NR
Garas, 2011[81]	SD-OCT	Based on slit-lamp exam, optic nerve head photography, visual fields, IOP	RTVue-100	CDR normal/abnormal	0.841	0.769	0.893	NR
Hammond, 1979[84]	Tonometry	Based on visual field, IOP, CDR	Schiotz tonometer	IOP >22.6 mmHg	0.2857	0.1128	0.5218	NR
Hark, 2019[86] Hark, 2019[85]	Tonometry	Based on slit-lamp exam, IOP, gonioscopy, CCT, VA, visual fields, fundus photography	Rebound tonometer TA0li (Icare)	IOP ≥22 mmHg	0.37	0.22	0.54	NR
Hong, 2007[88]	Visual field	Based on visual fields and optic disc appearance	HFA	Patern deviation plot <5%	1	0.95	1	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Ivers, 2001[89]	Tonometry	Based on visual fields and optic disc photographs	Goldmann	IOP > 22 mmHg	NR	NR	NR	NR
Ivers, 2001[89]	Visual field	Based on visual fields and optic disc photographs	Glacaumatous defects matched optic disc changes	IOP	NR	NR	NR	NR
Karvonen, 2020[93]	SD-OCT	Based on optic nerve head photographs, RNFL photographs and visual fields	Cirrus	RNFL results outside 99 percentile for normal	0.53	0.36	0.69	NR
Karvonen, 2020[93]	SD-OCT	Based on optic nerve head photographs, RNFL photographs and visual fields	Cirrus	GCL-IPL outside 99 percentile for normal	0.5	0.34	0.66	NR
Karvonen, 2020[93]	SD-OCT	Based on optic nerve head photographs, RNFL photographs and visual fields	Cirrus	RNFL results outside 95 percentile for normal	NR	NR	NR	NR
Karvonen, 2020[93]	SD-OCT	Based on optic nerve head photographs, RNFL photographs and visual fields	Cirrus	GCL-IPL outside 95 percentile for normal	NR	NR	NR	NR
Karvonen, 2020[93]	Tonometry	Based on optic nerve head photographs, RNFL photographs and visual fields	Goldmann	IOP >25 mmHg	0.07	0.01	0.19	NR
Katz, 1993[95] Tielsch 1991[133]	Visual field	Abnormal initial screen resulted in referral to ophthalmologist who diagnosed glaucoma based on visual fields and optic nerve characteristics	HFA	≥17 defects or ≥8 defects per quadrant or both	0.836	NR	NR	NR
Katz, 1993[95] Tielsch 1991[133]	Tonometry	Abnormal initial screen resulted in referral to ophthalmologist who diagnosed glaucoma based on visual fields and optic nerve characteristics	Device NR	IOP >21 mmHg	0.39	0.32	0.47	NR
Kaushik, 2011[97]	SD-OCT	Based on clinical exam including tonometry, biomicroscopy,	Cirrus	Mean RNFL thickness	NR	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
		gonioscopy, optic disc photos, visual fields						
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean GC-IPL	NR	NR	NR	NR
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean GC-IPL	NR	NR	NR	NR
Kaushik, 2018[96]	SD-OCT	Based on visual fields and optic disc photographs	Cirrus	Mean GC-IPL	NR	NR	NR	NR
Kiddee, 2013[99]	SD-OCT	Based on visual fields, optic disc appearance, and IOP	Cirrus	Mean RNFL thickness (peripapular)	0.8958	NR	NR	NR
Kiddee, 2013[99]	SD-OCT	Based on visual fields, optic disc appearance, and IOP	Cirrus	Mean RNFL thickness (peripapular)	0.84	NR	NR	NR
Kim, 2012[100]	SD-OCT	Based on visual fields and optic nerve head appearance	Cirrus	RNFL thickness NOS	NR	NR	NR	NR
Kim, 2012[100]	SD-OCT	Based on visual fields and optic nerve head appearance	Cirrus	Mean CDR	NR	NR	NR	NR
Koh, 2018[101]	SD-OCT	Based on visual fields, optic nerve features of glaucoma and RNFL defects	Cirrus	Average GCL-IPL thickness	NR	NR	NR	NR
Kozobolis, 2000[102]	Tonometry	Based on visual fields in patients who were glaucoma suspects on initial screening (IOP, fundus exam)	Goldmann	IOP ≥21 mmHg	0.7179	0.5513	0.85	NR
Lee, 2017[105]	SS-OCT	Based on visual fields, optic disc photographs	OCT-1 (DRI)	Mean RNFL thickness	Preperimetric Glaucoma vs. healthy: 0.93	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Lee, 2017[105]	SS-OCT	Based on visual fields, optic disc photographs	OCT-1 (DRI)	GC-IPL <5% (yellow)	Preperimetric Glaucoma vs. healthy: 0.651	NR	NR	NR
Lee, 2017[105]	SS-OCT	Based on visual fields, optic disc photographs	OCT-1 (DRI)	Mean RNFL thickness	Perimetric vs. healthy: 0.973	NR	NR	NR
Lee, 2017[105]	SS-OCT	Based on visual fields, optic disc photographs	OCT-1 (DRI)	GC-IPL <5% (yellow)	Perimetric vs. healthy: 0.797	NR	NR	NR
Lee, 2018[106]	SS-OCT	Based on optic nerve head appearance and visual fields	OCT-1 (DRI)	Mean RNFL thickness	NR	NR	NR	NR
Lee, 2018[106]	SS-OCT	Based on optic nerve head appearance and visual fields	OCT-1 (DRI)	Mean RNFL thickness	NR	NR	NR	NR
Lee, 2018[106]	SD-OCT	Based on optic nerve head appearance and visual fields	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Lee, 2018[106]	SD-OCT	Based on optic nerve head appearance and visual fields	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Lee, 2016[104]	SD-OCT	Based on optic nerve appearance and visual fields	Spectralis	Outer inferior RNFL; cutoff 36 µm	0.817	NR	NR	NR
Lee, 2016[104]	SD-OCT	Based on optic nerve appearance and visual fields	Spectralis	Outer temperop GCL-IPL; cutoff 63 µm	0.75	NR	NR	NR
Leibowitz, 1980[107]	IOP	Based on visual fields	Applanation tonometry most; Schiotz tonometry some	IOP> 21 mmHg	0.1	0.03	0.22	NR
Leibowitz, 1980[107]	Disc photos	Based on visual fields	14D Nikon lens	CDR >0.4 µm	0.18	0.09	0.31	NR
Liu, 2011[108]	Visual field	Based on OCT HD (Cirrus) RNFL	SAP using HFA II	RNFL thickness outside 95th or 99th percentile for normal limits	0.684	0.585	0.769	NR
Maa, 2014[109]	Telemedicine	Findings from face-to-face exam to include fundus photographs	Telemedicine VA, IOP, central corneal thickness, and history	Questionnaire, distance auto refraction, VA, IOP with Tono-Pen, pupil checked for reactivity, chamber depth, afferent	0.64	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
				papillary defect, fundus photos				
Maa, 2019[111] Maa, 2020[110]	Telemedicine	Findings from face-to-face exam without knowledge of OCT or fundus photographs; OCT interpreters diagnosed glaucoma without then with OCT results	Telemedicine VA, pupil exam, anterior chamber depth, fundus photographs, OCT, and history	Ocular, medical, social, family history, distance auto refraction, VA, IOP with Tono-Pen, CCT, pupil checked for reactivity, chamber depth, fundus photos	0.74	0.61	0.84	NR
Marraffa, 1989[112]	Visual field	Based on IOP, optic disc study, visual field, and evidence from followup	Armaly full field Humphrey 630	1 absolute defect associated with 1 relative defect or 3 adjacent relative defects or 4 nonadjacent relative defects or nasal step	0.642	NR	NR	NR
Morejon, 2019[116]	SD-OCT	Based on optic nerve appearance and visual fields	3D OCT-2000	RNFL thickness NOS	NR	NR	NR	NR
Morejon, 2019[116]	SD-OCT	Based on optic nerve appearance and visual fields	3D OCT-2000	RNFL thickness NOS	NR	NR	NR	NR
Morejon, 2019[116]	SD-OCT	Based on optic nerve appearance and visual fields	3D OCT-2000	RNFL thickness NOS	NR	NR	NR	NR
Mundorf, 1989[117]	Questionnaire	Based on appearance of optic disk, visual fields with or without increase in IOP	Questionnaire	Risk factors for glaucoma with ≥6 a positive screen	0.81	NR	NR	NR
Mundorf, 1989[117]	Visual field	Based on appearance of optic disk, visual fields with or without increase in IOP	HFA	Normal/Abnormal	0.9	NR	NR	NR
Mundorf, 1989[117]	Visual field	Based on appearance of optic disk, visual fields with or without increase in IOP	HFA	Normal/Abnormal	0.36	NR	NR	NR
Park, 2013[120]	SD-OCT	Based on visual fields and optic nerve head appearance	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Park, 2013[120]	SD-OCT	Based on visual fields and optic nerve head appearance	Cirrus	Mean RNFL thickness	NR	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Pazos, 2017[53]	SD-OCT	Based on visual fields, IOP, and optic disc appearance	OCT-SD	pRNFL temporal/ inferior; best cutoff 123	0.925	NR	NR	NR
Pazos, 2017[53]	SD-OCT	Based on visual fields, IOP, and optic disc appearance	OCT-SD	pRNFL temporal/ inferior; best cutoff 123	0.875	NR	NR	NR
Pazos, 2017[53]	SD-OCT	Based on visual fields, IOP, and optic disc appearance	OCT-SD	mGCC outer/temporal; best cutoff 76	0.9	NR	NR	NR
Pazos, 2017[53]	SD-OCT	Based on visual fields, IOP, and optic disc appearance	OCT-SD	mGCC outer/temporal; best cutoff 76	0.65	NR	NR	NR
Rao, 2015[122]	SD-OCT	Based on optic disc photographs	RTVue	Mean RNFL thickness	0.772	0.708	0.835	NR
Rao, 2015[122]	SD-OCT	Based on optic disc photographs	RTVue	Mean GCC thickness	0.719	0.647	0.784	NR
Rao, 2015[122]	Visual field	Based on optic disc photographs	HFA	Normal/Abnormal	0.698	0.625	0.765	NR
Sarigul Sezenoz, 2020[125]	SD-OCT	Based on visual fields, optic disc appearance, gonioscopy	Heidelberg HD OCT	Mean RNFL thickness	NR	NR	NR	NR
Sarigul Sezenoz, 2020[125]	SD-OCT	Based on visual fields, optic disc appearance, gonioscopy	Heidelberg HD OCT	Mean RNFL thickness	NR	NR	NR	NR
Sarigul Sezenoz, 2020[125]	SD-OCT	Based on visual fields, optic disc appearance, gonioscopy	Heidelberg HD OCT	GCC	NR	NR	NR	NR
Sarigul Sezenoz, 2020[125]	SD-OCT	Based on visual fields, optic disc appearance, gonioscopy	Heidelberg HD OCT	GCC	NR	NR	NR	NR
Schweitzer, 2016[128]	SD-OCT	Based on optic disc photographs, visual fields, gonioscopy, slit-lamp exam, and IOP	OCT-SD	Mean RNFL thickness	0.775	0.625	0.877	NR
Soh, 2020[130]	Stereoscopy	Based on visual fields, optic disc photos, HRT, OCT measurements	CDRD	≥ 60	0.91	NR	NR	NR
Soh, 2020[130]	Stereoscopy	Based on visual fields, optic disc photos, HRT, OCT measurements	CDRD asymmetry	≥ 20, with CDRD ≥ 60	0.951	NR	NR	NR
Sung, 2009[131]	SD-OCT	Based on visual fields, optic disc appearance, and IOP	Cirrus	Mean RNFL thickness	0.636	0.495	0.759	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Screening test category	Reference standard	Screening test details	Screening test parameter	Sensitivity	Sensitivity lower bound 95% CI	Sensitivity upper bound 95% CI	Sensitivity SD
Vernon, 1990[135]	Tonometry	Based on IOP, visual fields, and optic nerve appearance	Pulsair non-contact	IOP >22 mmHg	0.917	NR	NR	NR
Vernon, 1990[135]	Optic disc	Based on IOP, visual fields, and optic nerve appearance	Ophthalmologist disc assessment	Normal/Abnormal	0.583	NR	NR	NR
Vidas, 2017[136]	SD-OCT	Based on visual fields and optic disc appearance	Copernicus HR	Mean RNFL thickness	0.7813	NR	NR	NR
Vidas, 2017[136]	SD-OCT	Based on visual fields and optic disc appearance	Copernicus HR	Mean GCC:	0.6563	NR	NR	NR
Wahl, 2016[138]	Tonometry	Based on IOP, visual field (FDT), and appearance of optic nerve head	Noncontact tonometry (AT555)	IOP >21 mmHg	0.5545	0.4608	0.6445	NR
Wahl, 2016[138]	Tonometry	Based on IOP, visual field (FDT), and appearance of optic nerve head	Noncontact tonometry (AT555)	IOP >21 mmHg	0.6154	0.3436	0.8302	NR
Xu, 2017[144]	SD-OCT	Based on appearance of optic disc, visual fields, and IOP	Cirrus	Mean RNFL thickness	NR	NR	NR	NR
Xu, 2017[144]	SD-OCT	Based on appearance of optic disc, visual fields, and IOP	Cirrus	CDR	NR	NR	NR	NR
Xu, 2017[144]	SD-OCT	Based on appearance of optic disc, visual fields, and IOP	Cirrus	Macular ganglion cell-inter plexifor layer mean	NR	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Specificity	Specificity lower bound 95% CI	Specificity upper bound 95% CI	Specificity SD	AUROC	AUROC upper bound 95% CI	AUROC lower bound 95% CI	AUROC SD
Aksoy, 2020[54]	0.8	NR	NR	NR	0.782	0.704	0.86	NR
Aksoy, 2020[54]	0.8	NR	NR	NR	0.793	0.705	0.87	NR
Aptel, 2010[55]	NR	NR	NR	NR	0.948 (SE 0.038)	NR	NR	NR
Aptel, 2010[55]	NR	NR	NR	NR	0.888 (SE 0.072)	NR	NR	NR
Arnould, 2020[56]	0.8714	0.8504	0.8924	NR	0.901	0.867	0.935	NR
Azuara-Blanco, 2016[59] Banister, 2016[61] Virgili, 2018[137]	0.785	0.754	0.814	NR	NR	NR	NR	NR
Bagga, 2006[60]	NR	NR	NR	NR	0.66 (SE 0.08)	NR	NR	NR
Bagga, 2006[60]	NR	NR	NR	NR	0.55 (SE 0.08)	NR	NR	NR
Blumberg, 2016[64]	0.87	0.69	1	NR	0.99	0.96	1	NR
Blumberg, 2016[64]	0.73	0.51	0.96	NR	0.85	0.73	0.96	NR
Blumberg, 2016[64]	0.73	0.51	0.96	NR	0.86	0.76	0.96	NR
Bonomi, 2001-28217[65]	0.978	NR	NR	NR		NR	NR	NR
Casado, 2019[67]	NR	NR	NR	NR	0.832	NR	NR	NR
Casado, 2019[67]	NR	NR	NR	NR	0.708	NR	NR	NR
Chan, 2017[68]	0.81	NR	NR	NR	NR	NR	NR	NR
Chan, 2017[68]	0.869	NR	NR	NR	NR	NR	NR	NR
Chan, 2017[68]	0.912	NR	NR	NR	NR	NR	NR	NR
Charalel, 2014[69]	0.89	0.72	0.96	NR	NR	NR	NR	NR
Choudhari, 2013[70]	0.85	NR	NR	NR	NR	NR	NR	NR
Choudhari, 2013[70]	0.92	NR	NR	NR	NR	NR	NR	NR
Choudhari, 2013[70]	0.96	NR	NR	NR	NR	NR	NR	NR
Choudhari, 2013[70]	0.98	NR	NR	NR	NR	NR	NR	NR
Cifuentes-Canorea, 2018[71]	0.594	NR	NR	NR	NR	NR	NR	NR
Cifuentes-Canorea, 2018[71]	0.719	NR	NR	NR	NR	NR	NR	NR
Dabasia, 2015[73]	0.934	0.908	0.953	NR	NR	NR	NR	NR
Dabasia, 2015[73]	0.945	0.921	0.963	NR	NR	NR	NR	NR
Dabasia, 2015[73]	0.889	0.858	0.914	NR	NR	NR	NR	NR
Danesh-Meyer, 2006[74]	NR	NR	NR	NR	0.78	0.72	0.91	NR
Danesh-Meyer, 2006[74]	NR	NR	NR	NR	0.8	0.7	0.93	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Specificity	Specificity lower bound 95% CI	Specificity upper bound 95% CI	Specificity SD	AUROC	AUROC upper bound 95% CI	AUROC lower bound 95% CI	AUROC SD
Danesh-Meyer, 2006[74]	NR	NR	NR	NR	0.81	0.61	0.93	NR
Deshpande, 2019[76]	0.7559	0.6718	0.8277	NR	0.81	0.75	0.87	NR
Deshpande, 2019[76]	0.8425	0.7673	0.9011	NR	0.9	0.86	0.95	NR
Deshpande, 2019[76]	0.8031	0.7233	0.8684	NR	0.92	0.89	0.96	NR
Deshpande, 2019[75]	NR	NR	NR	NR	0.83	0.781	0.879	NR
Deshpande, 2019[75]	0.77.96	NR	NR	NR	0.865	0.82	0.91	NR
Deshpande, 2019[75]	NR	NR	NR	NR	0.923	0.892	0.953	NR
Deshpande, 2019[75]	0.8426	NR	NR	NR	0.922	0.89	0.954	NR
Ehrlich, 2012[77]	0.9	NR	NR	NR	0.78	NR	NR	NR
Field, 2016[79]	0.85	NR	NR	0.068	NR	NR	NR	NR
Field, 2016[79]	0.9	NR	NR	0.057	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.97	0.97	0.97	NR	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.98	0.975	0.982	NR	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.89	0.88	0.9	NR	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.64	0.63	0.65	NR	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.78	0.77	0.79	NR	NR	NR	NR	NR
Francis, 2011[80] Varma, 2004[16]	0.98	0.98	0.99	NR	NR	NR	NR	NR
Garas, 2011[81]	100	0.96	100	NR	NR	NR	NR	NR
Garas, 2011[81]	0.989	0.941	0.998	NR	NR	NR	NR	NR
Garas, 2011[81]	0.72	0.603	0.814	NR	NR	NR	NR	NR
Hammond, 1979[84]	1	0.9793	1	NR	NR	NR	NR	NR
Hark, 2019[86] Hark, 2019[85]	0.83	0.8	0.85	NR	NR	NR	NR	NR
Hong, 2007[88]	0.971	0.8	0.976	NR	NR	NR	NR	NR
Ivers, 2001	NR	NR	NR	NR	0.67	NR	NR	NR
Ivers, 2001[89]	NR	NR	NR	NR	0.87	NR	NR	NR
Karvonen, 2020[93]	0.95	0.95	0.96	NR	0.76	NR	NR	NR
Karvonen, 2020[93]	0.92	0.92	0.93	NR	0.73	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Specificity	Specificity lower bound 95% CI	Specificity upper bound 95% CI	Specificity SD	AUROC	AUROC upper bound 95% CI	AUROC lower bound 95% CI	AUROC SD
Karvonen, 2020[93]	NR	NR	NR	NR	0.78	0.7	0.86	NR
Karvonen, 2020[93]	NR	NR	NR	NR	0.68	0.58	0.78	NR
Karvonen, 2020[93]	0.99	0.99	0.99	NR	0.59	NR	NR	NR
Katz, 1993[95] Tielsch 1991[133]	0.749	NR	NR	NR	NR	NR	NR	NR
Katz, 1993 [95] Tielsch 1991[133]	0.87	0.86	0.88	NR	NR	NR	NR	NR
Kaushik, 2011[97]	NR	NR	NR	NR	0.906	NR	NR	0.051 (SE)
Kaushik, 2018[96]	NR	NR	NR	NR	OHT vs. Healthy: 0.643	0.535	0.751	NR
Kaushik, 2018[96]	NR	NR	NR	NR	Suspicious disc vs. Healthy: 0.64	0.556	0.724	NR
Kaushik, 2018[96]	NR	NR	NR	NR	Early glaucoma vs. Healthy: 0.951	0.908	0.993	NR
Kaushik, 2018[96]	NR	NR	NR	NR	OHT vs. Healthy: 0.667	0.56	0.773	NR
Kaushik, 2018[96]	NR	NR	NR	NR	Suspicious disc vs. Healthy: 0.0.637	0.552	0.722	NR
Kaushik, 2018[96]	NR	NR	NR	NR	Early glaucoma vs. Healthy: 0.873	0.801	0.945	NR
Kiddee, 2013[99]	1	NR	NR	NR	Glaucoma vs. Healthy: 0.964	0..93	0.99	NR
Kiddee, 2013[99]	0.7292	NR	NR	NR	Glaucoma vs. Glaucoma suspect: 0.833	0.73	0.94	NR
Kim, 2012[100]	NR	NR	NR	NR	NR	0.944	0.9222	NR
Kim, 2012[100]	NR	NR	NR	NR	NR	0.787	0.715	NR
Koh, 2018[101]	NR	NR	NR	NR	NR	0.87	0.81	NR
Kozobolis, 2000[102]	0.9316	0.9148	0.946	NR	NR	NR	NR	NR
Lee, 2017[105]	0.94	NR	NR	NR	0.716	0.619	0.8	NR
Lee, 2017[105]	0.985	NR	NR	NR	GC-IPL (IT): 0.809	0.722	0.878	NR
Lee, 2017[105]	0.94	NR	NR	NR	0.853	782	0.908	NR
Lee, 2017[105]	0.985	NR	NR	NR	GC-IPL (IT): 0.865	0.797	0.917	NR
Lee, 2018[106]	NR	NR	NR	NR	0.851	0.755	0.947	NR
Lee, 2018[106]	NR	NR	NR	NR	0.979	0.956	1	NR
Lee, 2018[106]	NR	NR	NR	NR	0.818	0.715	0.921	NR
Lee, 2018[106]	NR	NR	NR	NR	0.951	0.906	0.996	NR
Lee, 2016[104]	0.817	NR	NR	NR	0.859	0.792	0.925	NR
Lee, 2016[104]	0.9	NR	NR	NR	0.894	0.839	0.95	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Specificity	Specificity lower bound 95% CI	Specificity upper bound 95% CI	Specificity SD	AUROC	AUROC upper bound 95% CI	AUROC lower bound 95% CI	AUROC SD
Leibowitz, 1980[107]	0.97	0.96	0.97	NR	NR	NR	NR	NR
Leibowitz, 1980[107]	0.93	0.92	0.94	NR	NR	NR	NR	NR
Liu, 2011[108]	1	0.906	1	NR	NR	NR	NR	NR
Maa, 2014[109]	0.95	NR	NR	NR	NR	NR	NR	NR
Maa, 2019[111] Maa, 2020[110]	0.84	0.77	0.89	NR	NR	NR	NR	NR
Marraffa, 1989[112]	0.642	NR	NR	NR	NR	NR	NR	NR
Morejon, 2019[116]	NR	NR	NR	NR	0.8209	NR	NR	NR
Morejon, 2019[116]	NR	NR	NR	NR	0.8942	NR	NR	NR
Morejon, 2019[116]	NR	NR	NR	NR	0.7432	NR	NR	NR
Mundorf, 1989[117]	0.29	NR	NR	NR	NR	NR	NR	NR
Mundorf, 1989[117]	0.7	NR	NR	NR	NR	NR	NR	NR
Mundorf, 1989[117]	0.66	NR	NR	NR	NR	NR	NR	NR
Park, 2013[120]	NR	NR	NR	NR	Preperimetric vs. control: 0.880	0.865	0.895	NR
Park, 2013[120]	NR	NR	NR	NR	Perimetric vs. control: 0.911	0.9	0.93	NR
Pazos, 2017[53]	0.8	NR	NR	NR	0.956	0.912	0.999	NR
Pazos, 2017[53]	0.95	NR	NR	NR	NR	NR	NR	NR
Pazos, 2017[53]	0.8	NR	NR	NR	0.94	0.893	0.986	NR
Pazos, 2017[53]	0.95	NR	NR	NR	NR	NR	NR	NR
Rao, 2015[122]	0.822	0.733	0.891	NR	NR	NR	NR	NR
Rao, 2015[122]	0.881	0.802	0.937	NR	NR	NR	NR	NR
Rao, 2015[122]	0.95	0.888	0.984	NR	NR	NR	NR	NR
Sarigul Sezenoz, 2020[125]	NR	NR	NR	NR	Early glaucoma vs. healthy: 0.84	NR	NR	NR
Sarigul Sezenoz, 2020[125]	NR	NR	NR	NR	Preperimetric glaucoma vs. healthy: 0.744	NR	NR	NR
Sarigul Sezenoz, 2020[125]	NR	NR	NR	NR	Early glaucoma vs. health: 0.876	NR	NR	NR
Sarigul Sezenoz, 2020[125]	NR	NR	NR	NR	Preperimetric glaucoma vs. healthy: 0.78	NR	NR	NR
Schweitzer, 2016[128]	0.878	0.846	0.904	NR	0.895	0.849	0.945	NR
Soh, 2020[130]	0.916	NR	NR	NR	NR	NR	NR	NR
Soh, 2020[130]	0.909	NR	NR	NR	NR	NR	NR	NR
Sung, 2009[131]	1	0.925	1	NR	NR	NR	NR	NR
Vernon, 1990[135]	0.956	NR	NR	NR	NR	NR	NR	NR
Vernon, 1990[135]	0.987	NR	NR	NR	NR	NR	NR	NR
Vidas, 2017[136]	0.9184	NR	NR	NR	0.906	NR	NR	NR
Vidas, 2017[136]	1	NR	NR	NR	0.957	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Glaucoma Screening Tests, Results

Author, year	Specificity	Specificity lower bound 95% CI	Specificity upper bound 95% CI	Specificity SD	AUROC	AUROC upper bound 95% CI	AUROC lower bound 95% CI	AUROC SD
Wahl, 2016[138]	0.9268	0.9183	0.9344	NR	NR	NR	NR	NR
Wahl, 2016[138]	0.9157	0.9069	0.9238	NR	NR	NR	NR	NR
Xu, 2017[144]	NR	NR	NR	NR	0.953	NR	NR	NR
Xu, 2017[144]	NR	NR	NR	NR	0.909	NR	NR	NR
Xu, 2017[144]	NR	NR	NR	NR	0.932	NR	NR	NR

Abbreviations: AT555 = model of auto non-contact tomometer; AUROC = area under the receiver operating characteristic curve; CCT = central corneal thickness; CDRD = cup to disc ratio; CI = confidence interval; DRI = OCT model; FDT = frequency doubling technology; GCC = gangion cell complex; GCL = ganglion cell layer; GCLT2 = ganglion cell layer group 2 parameter; GDx VCC = scanning laser polarimetry; GPL-IPL = ganglion cell layer-inner plexiform layer; HFA = Humphrey Visual Field Analyzer; HRT = scanning laser ophthalmoscopy; IOP = intraocular pressure; mGCC = macular GCC; mm Hg= millimeters mercury; mRNFL2 = macular RNFL group 2; NOS = Newcastle-Ottawa Scale; NR = not reported; OCT = optical coherence tomography; OHT = ocular hypertension; ORA = ocular response analyzer; pRNFL = peripapillary RNFL; RNFL = retinal nerve fiber layer; SAP = standard automated perimetry; SD = standard deviation; SD-OCT = spectral domain optical coherence tomography; SE = standard error; SS-OCT = swept source optical coherence tomography; VA = visual acuity.

Appendix B Table 5. Diagnostic Accuracy of Glaucoma Screening Tests, Quality Assessment

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid inappropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?
Aptel, 2010[55]	Unclear	Yes	Yes	Unclear	Unclear
Arnould, 2020[56]	Yes	Yes	Yes	Yes	Yes
Aksoy, 2020[54]	Yes	Yes	Yes	Yes	Yes
Azuara-Blanco, 2016[59] Banister, 2016[61] Virgili, 2018[137]	Yes	Yes	Yes	Unclear	Unclear
Bagga, 2006[60]	Unclear	Yes	Yes	Unclear	Unclear
Blumberg, 2016[64]	Unclear-part of cohort study but study not cited	Yes	Yes	No as index test part of reference standard; 1 specialist was referring physician and not masked	Unclear
Bonomi, 2001[65]	Yes	Yes	Yes	Unclear	Unclear
Casado, 2019[67]	Unclear	Yes	Yes	Unclear	Unclear
Chan, 2017[68]	Unclear-participants from a multi-cohort study	Yes	Yes	Yes	Unclear but range of thresholds used
Charalel, 2014[69]	Unclear	Yes	Yes	Yes	NA
Choudhari, 2013[70]	Yes	Yes	Yes	Unclear	Unclear but range of thresholds used
Cifuentes-Canorea, 2018[71]	Yes	Yes	Yes	Unclear	Unclear
Dabasia, 2015[73]	Yes	Yes	Yes	Yes	Yes
Danesh-Meyer, 2006[74]	Yes	Yes	Yes	Yes	Unclear
Deshpande, 2019[76]	Yes	Yes	Yes	Unclear	Unclear
Deshpande, 2019[75]	Unclear	Yes	Yes	Unclear	Unclear
Ehrlich, 2012[77]	Yes	Yes	Yes	Unclear	Unclear
Field, 2016[79]	Unclear	Unclear	Yes	Unclear	Unclear
Francis, 2011[80]	No-population study	Yes	Yes	Yes	Yes
Garas, 2011[81]	Yes	Yes	Yes	Unclear	Unclear
Hammond, 1979[84]	Unclear	Yes	Yes	Unclear	Unclear
Hark, 2019[86] Hark, 2019[85]	No	Yes	Yes	Unclear	Unclear
Ivers, 2001[89]	Yes	Yes	Yes	Unclear	Unclear
Karvonen, 2020[93]	Yes	Yes	Yes	Unclear	Unclear
Katz, 1993[95] Tielsch 1991[133]	Yes	Yes	No; excluded 33 nonWhite, nonBlack subjects due to small numbers	Unclear	Unclear
Kaushik, 2011[97]	Unclear	Yes	Yes	Unclear	Unclear
Kaushik, 2018[96]	Unclear	Yes	Yes	Yes	Yes

Appendix B Table 5. Diagnostic Accuracy of Glaucoma Screening Tests, Quality Assessment

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid inappropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?
Kiddee, 2013[99]	Unclear	Yes	Yes	Unclear	Yes
Kim, 2012[100]	Yes	Yes	Yes	Unclear	Unclear
Koh, 2018[101]	Yes	Yes	Yes	Unclear	Unclear
Kozobolis, 2000[102]	Yes	Yes	Yes	Unclear	Unclear
Lee, 2017[105]	Unclear	Yes	Yes	Yes	Unclear
Lee, 2018[106]	Unclear	Yes	Yes	Yes	Unclear
Leibowitz, 1980[107]	Unclear	Yes	Yes	Unclear	Unclear
Liu, 2011[108]	Yes	Yes	Yes	Yes	Unclear
Maa, 2014[109]	Yes	Yes	Yes	Yes	Unclear
Maa, 2019[111] Maa, 2020[110]	Unclear but probably yes	Yes	Yes	Yes	Unclear
Marraffa, 1989[112]	Unclear	Yes	Yes	Unclear	Unclear
Morejon, 2019[116]	Unclear	Yes	Yes	Yes	Unclear
Mundorf, 1989[117]	No	Yes	Yes	Unclear	Unclear
Park, 2013[120]	Yes	Yes	Yes	Unclear	Unclear
Pazos, 2017[53]	Yes	Yes	Yes	Yes	Unclear
Rao, 2015[122]	Yes	Yes	Yes	Yes	Yes
Sarigul Sezenoz, 2020[125]	Unclear	Yes	Yes	Unclear	Yes
Schweitzer, 2016[128]	Unclear	Yes	Yes	Unclear	Unclear
Soh, 2020[130]	Yes	Yes	Yes	Unclear	Yes
Sung, 2009[131]	Yes	Yes	Yes	Unclear	Unclear
Vernon, 1990[135]	Unclear	Yes	Yes	Yes	Unclear
Vidas, 2017[136]	Yes	Yes	Yes	Yes	Yes
Wahl, 2016[138]	Unclear	Yes	Yes	Unclear	Unclear
Xu, 2017[144]	Yes	Yes	Yes	Unclear	Unclear

Appendix B Table 5. Diagnostic Accuracy of Glaucoma Screening Tests, Quality Assessment

Author, year	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index text?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard?	Flow and timing: Did all patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Aptel, 2010[55]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Arnould, 2020[56]	Yes	Unclear	Unclear	Yes	Yes	Yes except for missing or unusable scans	Good
Aksoy, 2020[54]	Yes	Unclear	Unclear	Yes	Yes	Unclear	Fair
Azuara-Blanco, 2016[59] Banister, 2016[61] Virgili, 2018[137]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bagga, 2006[60]	Possibliy (based on one test result)	Unclear	Unclear	Yes	Yes	Yes	Fair
Blumberg, 2016[64]	Yes	No as index test part of reference standard; 1 specialist was referring physician and not masked	Unclear	Yes	Yes	No-agreement not reached on 4 eyes which were then excluded	Fair
Bonomi, 2001[65]	Yes	No as index test part of reference standard	Unclear	Yes	Yes	Yes	Fair
Casado, 2019[67]	Reference standard was visual fleid defects alone so potentially not	Unclear	Yes	Yes	Yes	Yes	Fair
Chan, 2017[68]	Yes	No as index test part of reference standard	Unclear	Yes	Yes	Yes	Fair
Charalel, 2014[69]	Yes	Unclear	Unclear	Yes	Unclear	Yes	Fair
Choudhari, 2013[70]	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Cifuentes-Canorea, 2018[71]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Dabasia, 2015[73]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Danesh-Meyer, 2006[74]	Yes	Yes	Unclear	Yes	Yes	Yes	Fair
Deshpande, 2019[76]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Deshpande, 2019[75]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Ehrlich, 2012[77]	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Field, 2016[79]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Francis, 2011[80]	Yes	Yes	Yes	Yes	Yes	No, 7.6% only had home interview	Good
Garas, 2011[81]	Yes	Unclear	Yes	Yes	Yes	Yes	Fair

Appendix B Table 5. Diagnostic Accuracy of Glaucoma Screening Tests, Quality Assessment

Author, year	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index text?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard?	Flow and timing: Did all patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Hammond, 1979[84]	Yes	Unclear	Unclear	Yes	Yes	No, some only received one of the screening tests	Fair
Hark, 2019[86] Hark, 2019[85]	Yes	No	No. Interval between telemedicine screening and follow-up differed based on screening findings	Yes	Yes	Yes	Fair
Ivers, 2001[89]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Karvonen, 2020[93]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Katz, 1993[95] Tielsch 1991[133]	Yes	Unclear	Unclear	Yes	Yes	No	Fair
Kaushik, 2011[97]	Yes	Yes	Unclear	Yes	Yes	Yes except for those with unusable scans	Fair
Kaushik, 2018[96]	Yes	Yes	Unclear	Yes	Yes	Unclear	Fair
Kiddee, 2013[99]	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
Kim, 2012[100]	Yes	Yes for peripapillary atrophy	Yes	Yes	Yes	Yes	Fair
Koh, 2018[101]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Kozobolis, 2000[102]	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Lee, 2017[105]	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
Lee, 2018[106]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Leibowitz, 1980[107]	Yes	Unclear	Unclear	No, only those with abnormal initial screening	Yes among those who received it	Yes for those with positive screen	Fair
Liu, 2011[108]	Unclear as reference standard based on only one measure (RNFL thickness)	Yes	Yes	Yes	Yes	Yes	Fair
Maa, 2014[109]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Maa, 2019[111] Maa, 2020[110]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Marraffa, 1989[112]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Morejon, 2019[116]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Mundorf, 1989[117]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Park, 2013[120]	Yes	Unclear	Yes	Yes	Yes	Yes except for those with unusable scans	Fair
Pazos, 2017[53]	Yes	Unclear	Yes	Yes	Yes	Yes	Fair

Appendix B Table 5. Diagnostic Accuracy of Glaucoma Screening Tests, Quality Assessment

Author, year	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index text?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard?	Flow and timing: Did all patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Rao, 2015[122]	Yes	Unclear	Yes	Yes	Yes	Yes except for those with unusable scans	Good
Sarigul Sezenoz, 2020[125]	Yes	Unclear	Unclear	Yes	Yes	Unclear	Fair
Schweitzer, 2016[128]	Yes	Yes	Unclear	Yes	Yes	Yes	Fair
Soh, 2020[130]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Sung, 2009[131]	Yes	Unclear	Unclear	Yes	Yes	Yes except for those with unusable scans	Fair
Vernon, 1990[135]	Yes	Yes-disc evaluation	Unclear	Yes	Yes	Yes	Fair
Vidas, 2017[136]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Wahl, 2016[138]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Xu, 2017[144]	Yes	Yes-disc evaluation	Yes	Yes	Yes	Yes	Fair

Abbreviations: NA = not applicable; RNFL = retinal nerve fiber layer.

Appendix B Table 6. Diagnostic Accuracy of Glaucoma Screening Instrument, Study Characteristics

Study, year	Screening test	Reference standard	Setting country	Screener	Age of enrollees	N (subjects)	Baseline population	Baseline vision parameters, proportion with visual conditions	Prevalence of glaucoma	Quality
Mundorf, 1989[117]	Questionnaire	Based on appearance of optic disk, visual fields with or without increase in IOP	Free glaucoma detection program through university ophthalmology department in the United States	NR	69	145	Female: 72% White: 81% Black: 19%	Glaucoma vs. Glaucoma suspect vs. Healthy: Abnormal IOP: 20% vs. 7% vs. 2% Abnormal visual fields: 90% vs. 36% vs. 29%	Glaucoma: 6.9%; Glaucoma suspect: 9.7%	Fair

Abbreviations: IOP = intraocular pressure; NR = not reported.

Appendix B Table 7. Diagnostic Accuracy of Glaucoma Screening Instrument, Results

Author, year	Screening test	Screening test details	Reference standard	Sensitivity	Specificity
Mundorf, 1989[117]	Questionnaire	Weighted screening questionnaire for identifying persons with glaucoma Highest weights were assigned for taking steroid medication and having a previous glaucoma diagnosis; less highly weighted risk factors were previous eye injury or stroke, age, race, prior eye surgery, high blood pressure, being nearsighted, and family history of diabetes or glaucoma	Based on appearance of optic disk, visual fields with or without increase in IOP	0.20, 95% CI 0.03 to 0.56 2/10	0.96, 95% CI 0.91 to 0.99 116/121

Abbreviations: CI = confidence interval; IOP = intraocular pressure.

Appendix B Table 8. Diagnostic Accuracy of Screening Instrument, Quality Assessment

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid inappropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?
Mundorf, 1989[117]	No	Yes	Yes	Unclear	Unclear

Appendix B Table 8. Diagnostic Accuracy of Screening Instrument, Quality Assessment

Author, year	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index text?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard?	Flow and timing: Did all patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Mundorf, 1989[117]	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Bensinger, 1985[62]	RCT	United States Single center	IOP 23 or higher with simple OHT or OAG Criteria for diagnosis: IOP (method NR), Goldmann perimetry, gonioscopy	Randomized: 42 Analyzed: 42 Attrition: 43% vs. 46% vs. 87%	A: Levobunolol 0.5% twice daily (n=14) B: Levobunolol 1.0% twice daily (n=13) C: Placebo (n=15)	A vs. B vs. C Age: 57 vs. 61 vs. 59 years Female sex: 44% vs. 36% vs. 38% NonWhite: 19% vs. 7% vs. 0% OAG: 32% vs. 43% vs. 44% OHT: 68% vs. 57% vs. 56% IOP: 27.3 (3.9) vs. 27.2 (3.1) vs. 27.3 (3.5)	3 months
Bergstrand, 2002[63]	RCT	Sweden Single center	Previously untreated OAG Criteria for diagnosis: visual fields (Humphrey or SITA; ONH damage (ophthalmoscopy); and gonioscopy	Randomized: 47 Analyzed: 45 Attrition: 2/47	A: Dorzolamide, dose NR, three times daily (n=23) B: Placebo (n=22)	A vs. B Age: 72 vs. 74 years Female sex: NR Race/ethnicity: NR Pretreatment IOP: 22.5 (5.3) vs. 20.6 (4.8) OAG: 100%	1.5 months
Epstein, 1989[78]*	RCT	United States Single center	Open-angle glaucoma suspects, treatment naïve, IOP 22-28, normal visual field, no progressive retinopathy Excluded: Pregnant women Criteria for diagnosis: Goldmann perimetry, Shiotz tonography, stereoscopic disc photographs, Goldmann applanation tonometry, gonioscopy	Randomized: 109 Analyzed: 107 Attrition: 39/107 (26 failures and 23 lost to followup)	A: Timolol 0.5% twice daily (n=53) B: Placebo (n=54)	A vs. B Age: 60 (11) vs. 59 (12) Female sex: 53% vs. 59% Black: 6% vs. 15% Family history of glaucoma: 21% vs. 35% Baseline IOP: 24.0 (1.3) vs. 23.9 (1.6)	A vs. B Mean followup: 56 vs. 51 months
Garway-Heath, 2015[35] UKGTS (Vision outcomes)	RCT	United Kingdom 10 centers	Newly diagnosed, untreated open-angle glaucoma Criteria for diagnosis: visual field assessment, ONH damage (confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT); and gonioscopy	Randomized: 516Analyzed: 461 Attrition: 55/516	A: Latanaprost 0.005% once daily (n=231)B: Placebo (n=230)	A vs, B Age: 66 (10) vs. 65 (11) years Female sex: 48% vs. 46% Race/ethnicity: 89% white, 7% Black, 3% Asian, <1% other, 1% unknown vs. 91% White, 4% Black, 4% Asian, <1% other, <1% unknown BCVA: 0.95 (0.24) vs. 0.94 (0.22)IOP: 20.1 (4.8) vs. 19.6 (4.6)	24 months
Jones, 2019[90] UKGTS (QoL outcomes)	RCT	United Kingdom 10 centers	Newly diagnosed, untreated open-angle glaucoma Criteria for diagnosis: visual field assessment, ONH damage (confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT); and gonioscopy	Randomized: 516 Analyzed: 350 Attrition: 166/516	A: Latanaprost 0.005% once daily (n=231) B: Placebo (n=230)	A vs, B Age: 66 (10) vs. 65 (11) years Female sex: 48% vs. 46% Race/ethnicity: 89% White, 7% Black, 3% Asian, <1% other, 1% unknown vs. 91% White, 4% Black, 4% Asian, <1% other, <1% unknown BCVA: 0.95 (0.24) vs. 0.94 (0.22) IOP: 20.1 (4.8) vs. 19.6 (4.6)	24 months

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Heijl, 2000[87]*	RCT	SwedenSingle center	IOP 22-35 mm Hg, normal visual fields, and at least one risk factor (suspicious disc, family history of glaucoma, diabetes, pseudoexfoliation); or an IOP 27-35 without risk factors Criteria for diagnosis: Goldmann tonometry, Goldmann perimetry, Competer perimetry, optic disc photography, gonioscopy	Randomized: 90 Analyzed: 90 Attrition: 4 lost to followup	A: Timolol 0.5% twice daily (n=46)B: Placebo (n=44)	A vs. B Age: 63 vs. 62 yearsFemale sex: 57% vs. 59% Race: NR IOP: 27.1 vs. 26.2	120 months
Kamal, 2003[92]*	RCT	United Kingdom Single center	Age >35 years, IOP 22-35, visual acuity 6/12 or better, normal visual field Criteria for diagnosis: Goldmann tonometry, Humphrey 24-2, gonioscopy	Randomized: 356 Analyzed: 356 Attrition: 28% (101/356)	A: Betaxolol twice daily (dose NR) (n=182) B: Placebo (n=168)	A vs. B Age: 66.2 (10.9) vs. 65.2 (10.5) years Female sex: 39% vs. 34% Race: NR Mean IOP: 26.2 (2.3) vs. 25.7 (2.4); p<0.01	60 months
Kass, 1989[94]*	RCT	United StatesSingle center	IOP >24 but <35, normal visual fieldsCriteria for diagnosis: tonometry (equipment NR), Goldmann perimetry, fundus photography	Randomized: 62Analyzed: 35Attrition: 27/62 (44%)	A: Timolol 0.5% (n=62 eyes)B: Placebo (n=62 eyes)Fellow eye comparator	Mean age: 58 Female sex: 61% Black: 40% IOP: 26.4 (4.4) vs. 26.6 (4.5) [Timolol eye vs. Placebo eye]	Mean 56.1 months
Kass, 2002[21]*; Gordon, 1999[83]	RCT	United States 22 centers	Age 40-80 years, IOP 24-32 in one eye and 21-32 in the other eye, open angles, normal visual field, and normal optic discs Criteria for diagnosis: normal visual fields as assessed by Visual Field Reading Center, normal discs as assessed by Optic Disc Reading Center (Equipment NR)	Randomized: 1,636 Analyzed: 1.636 Attrition: 14% (228/1636)	A: Drug treatment targeting IOP of 24 mm Hg or less or a 20% reduction in IOP (n=817) B: No treatment (n=819)	Mean age: 55 years (NR by group) A vs. B Female sex: 56% vs. 58% Race: 71% White, 25% Black, 3% Hispanic vs. 69% White, 25% Black, 4% Hispanic Mean IOP: 24.9 vs. 24.9 mm Hg	Mean 76.5 months

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Miglior, 2002[114] (baseline); Miglior 2005[114]* (results) EGPS	RCT	Multinational 18 centers	Age ≥30 years, IOP (22–29 mm Hg), two normal and reliable visual fields (on the basis of mean defect and corrected pattern standard deviation/corrected loss of variance ofstandard 30/II Humphrey or Octopus perimetry), and normal optic disc Criteria for diagnosis: Goldmann applanation tonometry (performed between 8:00 and 11:00 AM), complete ophthalmologic examination, automated static perimetry, and color slide stereo-photography of the optic disc	Randomized: 1,077 Analyzed: 1,077 Attrition: 29% (310/1,077)	A; Dorzolamide 2% three times daily (n=536) B: Placebo (n=541)	A vs. B Age: 56.4 (10.3) vs. 57.6 (10.3) years Female sex: 57% vs. 52% Race: 99% vs. 100% White IOP, left eye: 23.6 (1.6) vs. 23.7 (1.7) IOP, right eye: 23.5 (1.5) vs. 23.7 (1.7)	Mean 55.3 months
Ravalico, 1994[123]	RCT	Italy Single center	20/20 visual acuity, IOP 22-30 mm Hg, CDR <0.5, normal visual field indices, normal ERG Exclude: family history of glaucoma, diabetes Criteria for diagnosis: Goldmann tonometry, HFA, disc photography, gonioscopy	Randomized: 26 Analyzed: 26 at 6 months, 42 of 48 eyes at 12 months, 19 eyes at 24 months	A: Levobunolol 0.5% twice daily (n=12) B: No treatment (n=14)	A vs. B Age: 64.8 (10.1) vs. 57.5 (11.7) years Female sex: NR Race: NR Mean IOP: 24.1 (2.1) vs. 23.7 (1.4) mm Hg	24 months

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Sall, 2000[124]	RCT	United States Multicenter	Adults 21 years of age or older, of any race and either gender, diagnosedwith open-angle glaucoma, pseudoexfoliative or pigmentary glaucoma, or OHT Criteria for diagnosis: Goldmann tonometry and HFA, gonioscopy	Randomized: NR Analyzed: 463 (ITT), 409 (per protocol) Attrition: 35/463	A: Brinzolamide 1.0% twice daily (n=134) B: Brinzolamide 1.0% three times daily (n=133) C: Dorzolamide 2.0% three times daily (n=131) D: Placebo (n=65)	A vs. B vs. C vs. D Age: 60.9 (13.7) vs. 63.8 (12.1) vs. 64.0 (13.3) vs. 62.8 (12.5) years Female sex: 52% vs. 62% vs. 53% vs. 46% Race: 80% White, 11% Black, 1% Asian, 11% other vs. 74% White, 11% Black, 0% Asian, 15% other vs. 75% White, 5% Black, 1% Asian, 18% other vs. 73% White, 11% Black, 0% Asian, 16% other OHT: 21% vs. 27% vs. 23% vs. 20% POAG: 78% vs. 69% vs. 76% vs. 79% Pigmentary dispersion glaucoma: 1% vs. 3% vs. 0% vs. 2% Pseudoexfoliative glaucoma: 0% vs. 1% vs. 1% vs. 0% Baseline IOP, 8am: 26.6 (2.3) vs. 26.9 (2.8) vs. 26.2 (2.0) vs. 26.2 (2.1) Baseline IOP, 10am: 25.1 (2.7) vs. 25.6 (3.1) vs. 25.0 (2.6) vs. 25.1 (2.6) Baseline IOP, 6pm: 24.6 (2.2) vs. 24.7 (2.8) vs. 24.3 (2.5) vs. 24.7 (2.8)	3 months
Schulzer, 1991[126]*	RCT	Canada Single center	Age 45-70 years, untreated IOP ≥22 mm Hg, previous normal visual fields, and no obvious signs of glaucomatous disc changes Criteria for diagnosis: visual acuity, slit-lamp examination, ophthalmoscopy, color-stereo photography, and three examinations on automatic perimeters	Randomized: 143 Analyzed: 137 Attrition: 36/143	A: Timolol 0.25% twice daily for 1 month, followed by timolol 0.5% twice daily for 1 month, then continued on concentration with best response (n=70) B: No treatment (n=73)	A vs. B Age: 59.3 (9.2) vs. 61.3 (11.6) Female sex: 53% vs. 58% Race: NR Baseline IOP: 26.1 (3.2) vs. 26.3 (3.5)	72 months

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Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Schwartz, 1995[127]*	RCT	United States Single center	Patients with ocular pressures greater than or equal to 21 mm Hg and less than 35 mm Hg with normal visual fields Criteria for diagnosis: Goldmann perimetry, Goldmann tonometry, disc photographs	Randomized: 37 Analyzed: 37 Loss to followup: 16% (6/37; 3 in each group)	A: Timolol 0.5% twice daily (n=17) B: Placebo (n=20)	A vs. B Age: 60.3 (3.7) vs. 60.0 (2.9) years Female sex: 50% vs. 47% Race: 82% White, 18% Black vs. 100% White Visual acuity: 0.96 (0.06) vs. 0.96 (0.07) Refractive error: -0.51 (0.60) vs. -0.12 (0.43) IOP, left eye: 23.1 (0.6) vs. 23.7 (0.8) IOP, right eye: 22.4 (1.0) vs. 23.4 (1.0)	18 months
Toris, 1999[134]	RCT	United States Single center	Diagnosis of OHT for at least 6 months, open angle grade 3-4, IOP 20-40 mm Hg without ocular medication, inter-eye IOP difference <3 mm Hg, no prior surgery or laser therapy Criteria for diagnosis: “complete exam”	Randomized: 30 eyes Analyzed: 28 eyes Withdrawn: 2	A. Brimonidine 0.2% every 12 hours for 29 days B. Placebo Fellow eye comparator	Age: 53.6 (12.4) years Female: 75% Race: 68% White, 29% Black, 4% Asian Baseline mean IOP: 22.1 (2.1) treatment eye vs. 22.4 (2.5) contralateral eye Prior ocular therapy (betaxolol or timolol): 29%	29 days

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Wilkerson, 1993[142]	RCT	United States Three centers	Patients ages 35-85 years diagnosed with OAG or OHT with IOP >22 mm Hg and visual acuity 20/100 or better, no concurrent ocular therapy or prior surgery Criteria for diagnosis: ultrasound pachymeter (DGH Technology Ine, Frazer, Pa) and wide field scanning corneal microscope (Product Research Organization Ine, Tustin, Calif) at Duke University, Durham, NC; Corneal-Scan modelCS 1000 (Storz, St Louis, Mo) and Koan clinical specular microscope model CSP 580 (Keeler, Broomall, Pa) at Franklin Eye Consultants, Southfield, Mich; and ultrasound pachymeter model 2000 (DGH Technology Ine, Frazer, Pa) and Prototype of Alcon Surgical Wide Field Specular Microscope (Alcon, Fort Worth, Texas) at Cornell University, New York, NY.	Randomized: 48 Analyzed: 43 Withdrawn: 5	A. Dorzolamide 2% every 8 hours for 29 days (n=26) B. Placebo (n=17) Worse eye comparator	Age: 65 (female) and 59.9 (male) years Female sex: 52% Race: 85% White, 15% nonWhite Prior ocular hypotensive therapy: 69% Baseline IOP, dorzolamide vs. placebo: 27.1 (4.1) vs. 27.1 (3.0)	29 days

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/ Study Participants, including vision parameters	Duration of Follow-up
Wishart, 1992[143]*	RCT	United Kingdom Single center	IOP 21 mm Hg or greater with normal visual fields and optic discs Criteria for diagnosis: PPPT on all patients. If the test was positive, Mapstone believed an angle-closing mechanism had been identified, even in an eye with an apparently open angle, and the eye would undergo a peripheral iridectomy. If the PPPT was negative in both eyes, and the patient had OHT, the patient was invited to take part in the OHT study in which one eye was randomly assigned to treatment with topical timolol 0.5% twice daily, with no treatment to fellow eye which would act as a control.	Randomized: 35 Analyzed: 33 Attrition: 2/35	A; Timolol 0.5% twice daily (n=35) B: No treatment (n=35)* *Fellow eyes of same individuals	Age: 63 years Female sex: 59% Race/ethnicity: NR IOP: 24.9 (2.4); 24.5 (SD NR) in treated eye and 25.3 (SD NR) in untreated eye	48 months

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Bensinger, 1985[62]	NR	A vs. B vs. C IOP change, 3 months: -10.0 (3.2) vs. -10.6 (2.9) vs. -3.3 (1.1); A vs. C and B vs. C, p<0.05 Overall mean change during study: -9.0 vs. -9.1 vs. -0.5, p<0.05 Discontinued due to failure to control IOP: 14% (2/14) vs. 8% (1/13) vs. 33% (5/15)	NR	A vs. B vs. C Withdrawal due to AEs: 0% vs. 0% vs. 0%	Allergan	Fair
Bergstrand, 2002[63]	NR	A vs. B On-treatment IOP: 17.7 (5.3) vs. 18.8 (4.9); difference -1.0 (p=0.50); change from baseline, -4.7 (2.9) vs. -1.8 (3.0), difference -2.9, p=0.002	NR	NR	Malmo University Hospital, Merck	Fair
Epstein, 1989[78]*	Visual field progression: Definite glaucomatous field loss (a nasal step >8°; paracentral scotoma >5° (in largest diameter) out to 1-2-e; peripheral constriction of the outermost isopter >10°, central constriction of baseline isopter (used to define central 30°), by ≥10°) on the Goldmann or Octopus perimeter) confirmed by a second visual field on the Goldmann or Octopus perimeter 1 month after the first abnormal field	A vs. B Univariate ITT survival analysis: p=0.07 Visual field progression (ITT): 7.5% (4/53) vs. 16.7% (9/54); RR 0.45 (95% CI 0.15 to 1.38), adjusted RR 0.25 (95% CI 0.09 to 0.70) Visual field progression (per-protocol): 12% (4/33) vs. 36% (9/25); RR 0.33 (95% CI 0.12 to 0.97), adjusted RR 0.38 (95% CI 0.16 to 0.89)	NR	A vs. B Withdrawal due to AEs: 19% (10/53) vs. 0% (0/54); RR 21.39 (1.29 to 356.02)	National Eye Instiute; Merck	Fair
Garway-Heath, 2015[35] UKGTS (Vision outcomes)	Progression of visual field defects: Using HFA, at least three test locations showing significant deterioration at the p<0·05 level in three consecutive 30–2 visual fields—to at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields	A vs. B Progression of visual field defects, 24 months: 15% (35/231) vs. 26% (59/230) Time to first deterioration: adjusted HR 0.44 (95% CI 0.28 to 0.69) Significant treatment differences also at 12 months (HR 0.47; 95% CI 0.23 to 0.95) and 18 months (HR 0.44; 95% CI 0.26 to 0.71) Primary endpoint*, imputed analysis: HR 0.43 (0.26 to 0.69) Mean IOP reduction from baseline, 24 months: 4.0 (3.4) vs. 1.3 (3.6) mm LOCF-adjusted mean IOP reduction from baseline, 24 months: 3.8 (4.0) vs. 0.9 (3.8) mm	NR	A vs. B AEs: 93 vs. 99 Any AE: 22% (50/231) vs. 21% (48/230) Serious AEs: 4% (9/231) vs. 4% (9/230) Withdrawal due to AEs: 3% (7/231) vs. 0% (0/230)	Moorfield's Eye Hospital	Good

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Jones, 2019[90] UKGTS (QoL outcomes)	NR	NR	A vs. B EQ-5D: 1.7 (15.4) vs. 1.7 (10.6); MD 0.0, p=0.98 EQ-5D VAS: 2.1 (12.5) vs. 1.9 (12.0); MD 0.2, p=0.88 SF-36: 4.8 (19.8) vs. 5.0 (22.5); MD 0.2, p=0.94 GQL-15: 2.7 (7.7) vs. 3.2 (11.7); MD 0.5, p=0.66 GAL-9: 3.0 (8.5) vs. 3.2 (12.8); MD 0.2, p=0.87 Overall patient-reported outcomes: MD -0.23 (1.9) vs. 0.14 (2.0), p=0.07	NR	Moorfield's Eye Hospital	Good
Heijl, 2000[87]*	Glaucomatous field loss: Repeated abnormal field testing on field chart, confirmed with detailed Goldmann perimetry (no specific threshold used)	A vs. B Glaucomatous field loss, 5 years: 11% (5/46) vs. 18% (8/44); RR 0.60 (95% CI 0.21 to 1.69) Glaucomatous field loss, 10 years: 15% (7/46) vs. 34% (15/44); RR 0.45 (95% CI 0.20 to 0.99) [Study reported p=0.07] Mean IOP reduction: 6.7 vs. 1.0 mm Hg; p<0.001	NR	NR	Merck, Sharp, Dohme, Jarnhardt Foundation, Malmo University Hospital	Fair
Kamal, 2003[92]*	Progression to glaucomatous visual field loss: Change from initial AGIS score of 0 to an AGIS score ≥1 on three consecutive reliable visual fields, with at least on eof the locations consistently below the threshold for normality	A vs. B Post-treatment IOP: 21.6 (2.9) vs. 23.7 (2.9); p<0.001 Mean IOP decrease: 4.7 (2.8) vs. 1.9 (2.6) mm Hg; MD 2.3 mm Hg, p<0.001 Progression to glaucomatous visual field loss, 3 years: 5% (6/121) vs. 3.7% (5/134)* Progression to glaucomatous visual field loss, 60 months: 14.9% (18/121) vs. 11.4% (15/134) *Percentages don't correspond to total sample or completers	NR	NR	Guide Dogs for the Blind Association, Moorfields Eye Hospital, Alcon	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Kass, 1989[94]*	Glaucomatous field changes: Using Goldmann perimetry, kinetic visual field defects (a paracentral scotoma 3° wide and 0.5 log units deep; a nasal step 10° wide to two or more isopters; a temporal wedge defect 10° wide to two or more isopters; an enlargement of the blind spot 45° above or below the horizontal; or an arcuate scotoma or automated threshold perimetry visual field defects (four or more contiguous points depressed by 5 dB or more). Field changes had to be reproducible, defined as defects in the same area of the field on three consecutive tests.	A vs. B IOP, MD during study: 2.3 (2.6), P<0.001 IOP, end of treatment: 21.6 (3.7) vs. 23.8 (4.0), P<0.001 [35 patients analyzed at end of treatment] Glaucomatous field changes: 6.5% (4/62) vs. 16.1% (10/62), P=0.039	NR	NR	Merck	Fair
Kass, 2002[21]*; Gordon, 1999[83]	Progression of visual field defects: Utilizing HFA, abnormal visual field defined as p<0.05 for the corrected pattern standard deviation or if the glaucoma hemifield test results outside normal limits according to StatPac2 statistical software on 3 consectuvie tests with the same type, location and index of abnormality. Progression of optic disc changes: Generalized or localized thinning of the neuroretinal rim compared with baseline stereoscopic optic disc photographs	A vs. B IOP, followup average: 19.3 (2.2) vs. 23.9 (2.9) IOP, reduction from baseline: -22.5% (9.9%) vs. -4.0% (11.6%) Progression of visual field defects or optic disc changes for any reason: 9.9% (81/817) vs. 16.7% (137/819); RR 0.59 (95% CI 0.46 to 0.77) Progression of visual field defects or optic disc changes due to POAG: 4.4% (36/817) vs. 10.9% (89/819); RR 0.41 (95% CI 0.28 to 0.59)	NR	A vs. B Ocular symptoms: 57% vs. 47% Serious psychiatric AEs: 1.5% (12/800) vs. 0.5% (4/802); p=0.05 Serious genitourinary AEs: 5.5% (44/800) vs. 3.4% (27/802); p=0.04	National Eye Institute, National Institutes of Health	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Miglior, 2002[115] (baseline); Miglior 2005[114]* (results)EGPS	Visual field defect change: Using HFA, three or more horizontally or vertically adjacent points that differ ≥5 db from baseline; two or more horizontally or vertically adjacent points that differ ≥10 db from baseline, or difference of ≥10 db across nasal horizontal meridaian at ≥2 adjacent pointsOptic disc change: Visually recognizable (stereo photograph) narrowing of the neuroretinal rim ara (localized or diffuse) not attributable to photographic artifacts	A vs. B IOP, mean across visits: 19.3 vs. 20.4 mm Hg; p<0.001 IOP, 6 months: 20.0 (2.7) vs. 21.3 (3.0) IOP, 12 months: 19.7 (2.9) vs. 21.0 (3.4) IOP, 54 months: 17.9 (3.1) vs. 19.1 (3.6) IOP, 60 months: 18.2 (3.5) vs. 19.1 (3.7) IOP, mean reduction from baseline to 6 months: 14.5% vs. 9.3%; p<0.001 IOP, mean reduction from baseline to 5 years: 22.1% vs. 18.7%; p<0.001 IOP, mean reduction at 6 months, LOCF: 13.1% vs. 8.6%; p<0.001 IOP, mean reduction at 5 years, LOCF: 17.9% vs. 13.7%; p<0.001 Visual field defect or optic disc change: 8.6% (46/536) vs. 11.1% (60/541) Safety endpoint (IOP>35 mm Hg): 0.2% (1/536) vs. 2.2% (12/541)	NR	A vs. B Any AE: 21.7% (116/536) vs. 9.4% (51/541); RR 2.30 (95% CI 1.69 to 3.12) Serious AEs: 3.4% vs. 4.5% Ocular AEs related to study drug: 22.8% vs. 6.5%	The European Commission, Brussels, Belgium, and Merck & Co.	Good
Radius, 1983[121]	NR	A vs. B IOP, 6 weeks: 25.7 (0.8) vs. 27.0 (0.5); mean reduction from baseline, -5.5 (0.5) vs. -1.6 (0.5), p<0.05 [Unclear whether SD or SE]	NR	NR	Alcon Research	Fair
Ravalico, 1994[123]	NR	A vs. B IOP, 6 months: 15.4 (2.3) vs. 23.1 (1.8); p<0.001 IOP, 12 months: 16.1 (4.1) vs. 22.8 (2.6); p<0.001 IOP, 18 months: 16.2 (3.7) vs. 22.8 (1.9); p<0.001 IOP, 24 months: 15.3 (1.9) vs. 23.2 (1.1); p<0.001	NR	NR	NR	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Sall, 2000[124]	NR	A vs. B vs. C vs. D Response to treatment (IOP reduction >5 mm Hg) or well controlled (IOP <22 mm Hg), 1 month: 60% vs. 65% vs. 71% vs. 33% Response to treatment (IOP reduction >5 mm Hg) or well controlled (IOP <22 mm Hg), 2 months: 62% vs. 70% vs. 74% vs. 42% Response to treatment (IOP reduction >5 mm Hg) or well controlled (IOP <22 mm Hg), 3 months: 63% vs. 73% vs. 74% vs. 53% Mean IOP, 3 months: 22.5 (4.0) vs. 23.7 (3.9)	NR	A vs. B vs. C vs. D Blurred vision: 3% (4/134) vs. 4.5% (6/133) vs. 0.8% (1/131) vs. 1.5% (1/65) Discomfort: 3% (4/134) vs. 3% (4/133) vs. 12% (16/131) vs. 1.5% (1/65) Any AE: NR by group Serious AEs: None reported Withdrawal due to AEs: NR	Alcon Research	Fair
Schulzer, 1991[126]*	Glaucomatous visual field defects: Repeated finding on Peritest of any two adjacent points with a depression of 6 dBs or more, any single isolated point with a depression of 10 dBs in the central 30°, any point immediately above or below the nasal horizontal with a depression of 0.6 dB or more, any point within 5° of fixation with a depression of 0.4 dBs or more, and adjacent peripheral points depressed 10 dBs or more, providing this was not part of a generalized depression; confirmed on Octopus or Humphrey perimetry Disc change: Change from baseline in disc appearance on optic disc photography Disc hemorrhage: Presence of hemorrhage	A vs. B Mean IOP during study: 21.8 (3.2) vs. 26.3 (4.3); p<0.001 Mean survival before endpoint: 2061 vs. 1942 days; p=NS Glaucomatous visual field defects: 21% (15/70) vs. 18% (13/73) Disc changes: 3% (2/70) vs. 8% (6/73)Disc hemorrhage: 9% (6/70) vs. 4% (3/73) Glaucomatous progression: 29% (20/70) vs. 30% (22/73); RR 0.95 (95% CI 0.57 to 1.58)	NR	NR	Merck Sharp & Dohme Laboratoriesand Medical Research Council of Canada	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Schwartz, 1995[127]*	NR	A vs. B IOP, left eye, 0-9 months: 18.2 (0.8) vs. 23.9 (0.8) IOP, right eye, 0-9 months: 18.7 (0.8) vs. 23.7 (0.9) IOP, left eye, 9-15 months: 18.5 (0.6) vs. 23.3 (0.7) IOP, right eye, 9-15 months: 18.2 (0.5) vs. 23.7 (0.9) IOP, left eye, 15-24 months: 19.7 (0.6) vs. 22.0 (0.6) IOP, right eye, 15-24 months: 19.3 (0.6) vs. 23.2 (0.8) *Average for periods 1, 2, and 3 for the right eye minus baseline, tirnolol compared to placebo p < 0.001; left eye minus baseline, timolol compare to placebo p < 0.001	NR	A vs. B Withdrawal due to AEs: 29% (5/17) vs. 15% (3/20); RR 1.96 (95% CI 0.55 to 7.03)	Merck and Company, Inc., Medical and Scientific Affairs, Human Health Division, Clinical Development, West Point, Pennsylvania and the National Institutes of Health	Good
Toris, 1999[134]	NR	A vs. B Mean IOP reduction (SEM): 5 (0.7) vs 2.7 (0.5) Percent reduction from baseline: 24% vs. 15% p>0.001 vs. baseline for A, p<0.001 A vs. B **Text p.10 says p<0.01 A vs. B, figure 1 legend says p<0.001*	NR	Withdrawal: 2 due to scheduling conflicts	NR	Fair

Appendix B Table 9. Placebo-Controlled Trials of Glaucoma Medical Treatments

Author, Year Study	Definition for progression	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Wilkerson, 1993[142]	NR	A vs. B, analyses per protocol Mean IOP (at morning trough, 8 am): 23.5 (4.6) vs. 26.4 (3.1) Percent change in mean IOP: -13.3% (11.5) vs. -2.3% (8.0), p<0.01	NR	Withdrawal: 2 dorzolamide and 2 placebo discontinued due to AE not associated with the drug or administration; 1 placebo due to entry criterion violation Drug-related AE: 1 vs. 1 (1 patient each group with transient burning and blurred vision) Punctate epithelial erosions (predominantly on diurnal curve days): 29% vs. 40% Non-drug related AE: 3 vs. 3 (1 dorzolamide patient each with dizziness, herpes labialis, and a serious hypertensive episode; 1 placebo patient each with lid edema and corneal epithelial defects, light-headedness, and exacerbation of asthma)	NR; 5 report no financial interest in dorzo, 3 authors work for Merck	Fair
Wishart, 1992[143]*	NR	A vs. BIOP, 48 months: 21.4; MD, -1.1, p>0.1 vs. 22.1; MD 0.4, p>0.1 (n=7)	NR	NR	NR	Fair

Abbreviations: AE = adverse event; AGIS = Advanced Glaucoma Intervention Study; BVCA = best corrected visual acuity; dB= decibel; EGPS = European Glaucoma Prevention Study; EQ-5D = EuroQol-5D instrument; ERG = electroretinogram; GAL-9 = Glaucoma Activity Limitation questionnaire; GQL-15 = Glaucoma Quality of Life 15-item Questionnaire; HR = hazard ratio; IOP = intraocular pressure; ITT = intention to treat; LOCF = last observation carried forward; MD = mean difference; mmHG = millimeters mercury; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; PPPT = pilocarpine phenylephrine provocative test; QoL = quality of life; RCT = randomized controlled trial, RR = relative risk; SD = standard deviation; SE = standard error; SEM = standard error of the mean; UKGTS = The United Kingdom Glaucoma Treatment Study; VAS = visual analogue scale.

*From prior report.

Appendix B Table 10. Placebo-Controlled Trials of Glaucoma Medical Treatments, Quality Assessment

Author, year	Random-ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	People analyzed in the groups in which they were randomized?	Quality
Bensinger, 1985[62]	Unclear	Unclear	Yes	Yes	Unclear; "doubled masked"	Unclear; "doubled masked"	Unclear; "doubled masked"	Yes	Yes/Yes; 43% vs. 46% vs. 87%	Yes	Fair
Bergstrand, 2002[63]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Fair
Epstein, 1989[78]	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Garway-Heath, 2015[35] UKGTS (Vision outcomes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Jones, 2019[90] UKGTS (QoL outcomes)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Heijl, 2000[87]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Fair
Kamal, 2003[92]	Yes; random numbers table	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Kass, 1990[94]	Unclear	Unclear	NA; fellow eye	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Kass, 2002[21]; Gordon, 1999[83]	Yes; central	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair
Miglior, 2002[115] (baseline); Miglior 2005[114] (results) EGPS	Yes; central	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Radius, 1983[121]	Unclear	Unclear	No; not IOP and NR for most other demographics	Yes	Unclear; "double masked"	Unclear; "double masked"	Unclear; "double masked"	No	Unclear	Yes	Fair

Appendix B Table 10. Placebo-Controlled Trials of Glaucoma Medical Treatments, Quality Assessment

Author, year	Random-ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	People analyzed in the groups in which they were randomized?	Quality
Ravalico, 1994[123]	Unclear	Unclear	Unclear; only mean age and IOP reported	Yes	Unclear	No	No	Yes	No	Yes	Fair
Sall, 2000[124]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Fair
Schulzer, 1991[126]	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	No	Yes	Fair
Schwartz, 1995[127]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes		No	Yes	Good
Wilkerson, 1993[142]	NR	NR	Reports no differences	Yes	Unclear – trial is double-masked, but no specifics reported	Unclear	Yes	Yes	No	Yes; reported analyses were per-protocol, but apparently ITT results were similar	Fair
Toris, 1999[134]	NR	NR	NA, as comparisons were eyes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Fair
Wishart, 1992[143]	NR	NR	NA; fellow eye comparison	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair

Abbreviations: EGPS = European Glaucoma Prevention Study; IOP = intraocular pressure; ITT = intention to treat; NA = not applicable; NR = not reported; QoL = quality of life; UKGTS = The United Kingdom Glaucoma Treatment Study.

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/Study Participants, including vision parameters	Duration of Follow-up
Asrani, 2019[58] MERCURY-1 3 month follow-up	RCT	United States Multi-center	Age 18 or older, diagnosis of OAG or OHT in both eyes, IOP >20 but <36 mmHg	Randomized: 718 (480 eligible) Analyzed: 718 (480 eligible) Attrition: 12.9% (93/718)	A: Netarsudil/Latanaprost FDCP (n=238; comparison NR) B: Netarsudil 0.02% (n=244) C: Latanaprost 0.005% (n=236)	B vs. C Age ≥65 years: 56% vs. 60% Female sex: 56% vs. 58% Race: 68% White, 29% Black, 3% Asian vs. 67% White, 28% Black, 4% Asian OHT: 24% vs. 24% OAG: 76% vs. 76%	3 months
Brubaker, 2020[66] MERCURY-1 12 month follow-up	RCT	United States Multi-center	Age 18 or older, diagnosis of OAG or OHT in both eyes, IOP >20 but <36 mmHg	Randomized: 718 (480 eligible) Analyzed: 718 (480 eligible) Attrition: 29% (208/718)	A: Netarsudil/Latanaprost FDCP (n=238; comparison NR) B: Netarsudil 0.02% (n=244) C: Latanaprost 0.005% (n=236)	B vs. C Age: 64.6 vs. 65.4 years Female sex: 56% vs. 58% Race: 68% White, 29% Black, 3% Asian vs. 67% White, 28% Black, 4% Asian OHT: 23% vs. 23% OAG: 77% vs. 77% Mean IOP: 23.6 vs. 23.5	12 months
Asrani, 2020[57] MERCURY-1 and MERCURY-2 pooled analysis	Preplanned pooled analysis of RCT	United States Multi-center	Age 18 or older, diagnosis of OAG or OHT in both eyes, IOP >20 but <36 mmHg	Randomized: 1,468 (985 eligible) Analyzed: 1,468 (985 eligible) Attrition: 19.6% (273/1,468)	A: Netarsudil/Latanaprost FDCP (n=483; comparison NR) B: Netarsudil 0.02% (n=499) C: Latanaprost 0.005% (n=486)	B vs. C Age: 64.6 vs. 64.9 years Female sex: 58% vs. 58% Race: 67% White, 29% Black, 3% Asian vs. 66% White, 30% Black, 3% Asian OHT: 25.1% vs. 27.6% OAG: 74.9% vs. 72.4% Mean IOP: 23.6 vs. 23.5	12 months (MERCURY-1 and safety analysis of MERCURY-2) 3 months (MERCURY-2 efficacy analysis)
Serle, 2018[129] ROCKET-1 3 month follow-up	RCT	United States Multi-center	Age 18 years or older, IOP 20-27 at first visit and 17-27 at second visit, corrected visual acuity +1.0 logMAR or better Criteria for diagnosis: dilated ophthalmoscopy and static automated visual fields, Goldmann applanation tonometry	Randomized: 411 Analyzed: 411 Attrition: NR	A: Netarsudil 0.02% four times per day B: Timolol 0.5% twice per day	A vs. B Age: 65.8 (11.7) vs. 64.2 (11.3) Female sex: 56% vs. 65% Race: 78% White, 21% Black, 1% Asian vs. 73% White, 24% Black, 2% Asian OHT: 34% vs. 35% OAG: 66% vs. 65% Mean IOP: 23.4 vs. 23.3 mm Hg	3 months

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/Study Participants, including vision parameters	Duration of Follow-up
Serle, 2018[129] ROCKET-2 (Same publication as above)	RCT	United States Multi-center	Age 18 years or older, IOP 20-27 at first visit and 17-27 at second visit, corrected visual acuity +1.0 logMAR or betterCriteria for diagnosis: dilatedophthalmoscopy and static automated visual fields, Goldmann applanation tonometry	Randomized: 756 Analyzed: 756 Attrition: 18% (46/251) vs. 40% (101/254) vs. 6% (14/251)	A: Netarsudil 0.02% four times per day B: Netarsudil 0.02% twice per day C: Timolol 0.5% twice per day	A vs. B vs. C Age: 65.3 vs. 64.1 vs. 63.0 years Female sex: 59% vs. 65% vs. 60% Race: 71% White, 28% Black, 1% Asian, 1% Native American vs. 70% White, 27% Black, 2% Asian vs. 66% White, 30% Black, 2% Asian OHT: 34% vs. 38% vs. 32% OAG: 67% vs. 62% vs. 68% Mean IOP: 22.5 vs. 22.5 vs. 22.5 mm Hg	3 months
Kahook, 2019[91] ROCKET-2 12 month follow-up	RCT	United States Multi-center	Age 18 years or older, IOP 20-27 at first visit and 17-27 at second visit, corrected visual acuity +1.0 logMAR or better Criteria for diagnosis: dilated ophthalmoscopy and static automated visual fields, Goldmann applanation tonometry	Randomized: 756 Analyzed: 756 Attrition: 42% (105/251) vs. 66% (168/254) vs. 19% (47/251)	A: Netarsudil 0.02% four times per day B: Netarsudil 0.02% twice per day C: Timolol 0.5% twice per day	A vs. B vs. C Age: 65.3 vs. 64.1 vs. 63.0 years Female sex: 59% vs. 65% vs. 60% Race: 71% White, 28% Black, 1% Asian, 1% Native American vs. 70% White, 27% Black, 2% Asian vs. 66% White, 30% Black, 2% Asian OHT: 34% vs. 38% vs. 32% OAG: 67% vs. 62% vs. 68% Mean IOP: 22.5 vs. 22.5 vs. 22.5 mm Hg	12 months
Khouri, 2019[98] ROCKET-4	RCT	United States Multi-center	Age 18 years or older, IOP 20-27 at first visit and 17-27 at second visit, corrected visual acuity +1.0 logMAR or betterCriteria for diagnosis: Goldmann applanation tonometry	Randomized: 708 Analyzed: 557 (efficacy), 708 (safety) Attrition: 31% (108/351) vs. 12% (43/357)	A: Netarsudil 0.02% four times per day B: Timolol 0.5% twice per day	A vs. B Age: 64.1 (11.6) vs. 64.5 (11.0) years Female sex: 59% vs. 66% Race/ethnicity: 74% White, 24% Black, 2% Asian vs. 77% White, 21% Black, 2% Asian OAG: 64% vs. 68% OHT: 37% vs. 32% Mean IOP, 8am: 22.4 vs. 22.4 mm Hg Mean IOP, 10am: 21.1 vs. 21.3 mm Hg Mean IOP, 4pm: 20.7 vs. 20.7 mm Hg	3 months

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/Study Participants, including vision parameters	Duration of Follow-up
Medeiros, 2016[113] LUNAR	RCT	Inter-national Multi-center	Age >18 years with a diagnosis of OAG (including pigmentary or pseudoexfoliative) or OHT in 1 or both eyes and IOP ≥26 mm Hg Criteria for diagnosis: tonometry (type NR), medical history	Randomized: 420 Analyzed: 414 (efficacy), 415 (safety) Attrition: 27/420	A: Latanaprostene bunod 0.024% four times per day B: Timolol 0.5% twice per day	A vs. B Age: 65.0 (9.7) vs. 64.1 (9.7) Female sex: 58% vs. 58% Race/ethnicity: 73% White, 25% Black, 1% Asian vs. 65% White, 34% Black, 1% Asian Baseline IOP: 26.6 (2.39) vs. 26.4 (2.30)	3 months
Weinreb, 2015[140] VOYAGER	RCT	International Multi-center	Currently treated and treatment-naivesubjects (aged ≥18 years) diagnosed with OAG (including pigmentary or pseudoexfoliative) or OHT in one or both eyes, IOP of 22–32 mm Hg, and an IOP of ≥24 mm Hg for at least two of three measurements during Visit 3 (Day 1, baseline), which occurred after a 28-day washout period in subjects previously treated with IOP-lowering medications, and BCVA +0.7 logMAR or better Criteria for diagnosis: tonometry (type NR), medical history	Randomized: 413 Analyzed: 413 Attrition: 4% (17/413)	A: Latanaprostene bunod 0.006% B: Latanaprostene bunod 0.012% C: Latanaprostene bunod 0.024% D: Latanaprostene bunod 0.04% E: Latanaprost 0.005%	A vs. B vs. C vs. D vs. E Age: 60.9 (11.4) vs. 61.6 (9.6) vs. 60.8 (11.5) vs. 60.3 (12.9) vs. 61.2 (11.9) years Female sex: 68% vs. 54% vs. 69% vs. 53% vs. 65% Race/ethnicity: 74% White, 26% Black vs. 72% White, 27% Black, 1% American Indian vs. 75% White, 25% Black vs. 69% White, 28% Black, 1% other vs. 80% White, 20% Black Mean IOP: 26.1 (1.8) vs. 26.3 (1.9) vs. 26.0 (1.7) vs. 26.0 (1.5) vs. 26.2 (1.8)	28 days

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Study Design	Country Setting	Inclusion criteria	Randomized Analyzed Attrition	Intervention	Baseline Population/Study Participants, including vision parameters	Duration of Follow-up
Weinreb, 2016[141] APOLLO	RCT	Inter-national Multi-center	Aged 18 years with a diagnosis of OAG (including pigmentary or pseudoexfoliative OAG) or OHT in 1 or both eyes. Intraocular pressure was assessed once at screening and at 8 AM, 12 PM, and 4 PM at baseline to establish eligibility and baseline values. Eligible subjects had an IOP 26 mmHg at a minimum of 1 time point, 24 mmHg at a minimum of 1 time point, and 22 mmHg at 1 time point in the same eye, and IOP 36 mmHg at all 3 measurement time points in both eyes at baseline, and BCVA +0.7 or better Criteria for diagnosis: tonometry (type NR), medical history	Randomized: 420 Analyzed: 417 (efficacy), 418 (safety) Attrition: 7% (30/420)	A: Latanaprostene bunod 0.024% fout times per day B: Timolol 0.5% twice per day	A vs. B Age: 64.7 (10.3) vs. 63.1 (11.2) years Female sex: 59% vs. 50% Race/ethnicity: 76% White, 23% Black vs. 81% White, 18% Black Mean IOP: 26.7 (2.5) vs. 26.5 (2.4)	3 months
Weinreb, 2018[139] LUNAR and APOLLO	Meta-analysis	Inter-national Multi-center	See criteria of LUNAR and APOLLO above	Randomized: 840 Analyzed: 774 Attrition: 9/840	A: Latanaprostene bunod 0.024% four times per day (n=562) B: Timolol 0.5% twice per day (n=269)	A vs. B Age: 64.9 vs. 63.7 years Female sex: 58% vs. 58% Race/ethnicity: 75% White, 24% Black, 1% Asian vs. 73% White, 26% Black, 1% Asian Mean IOP: 26.7 (2.4) vs. 26.5 (2.4) mmHg	3 months

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Asrani, 2019[58] MERCURY-1 3 month follow-up	B vs. C Mean IOP, 3 months: 18.1 vs. 17.1 mmHg Mean IOP ≤16 mmHg: 31.8% vs. 38.6% Mean 1OP ≤18mmHg: 53.5% vs. 69.1% Mean IOP reduction ≥20%: 56.1% vs. 78.0% IOP, % change from baseline: -22.8 (-24.5, -21.2) vs. -27.6 (-28.9, -26.2)	NR	B vs. C Any adverse event: 63.1% (154/244) vs. 40.7% (96/236), RR 1.55 (95% CI 1.29 to 1.86) Ocular adverse events: 60.7% (148/244) vs. 30.9% (73/236), RR 1.96 (95% CI 1.58 to 2.43) Withdrawal due to adverse events: 14.3% (35/244) vs. 0% (0/236), RR 68.68 (95% CI 4.24 to 1113.29) Serious adverse events, none considered related to treatment: 2 patients vs. 1 patient	Aerie Pharma-ceuticals	Fair
Brubaker, 2020[66] MERCURY-1 12 month follow-up	B vs. C Mean IOP, 6 weeks: 18.2 vs. 17.3; MD 1.1 (95% CI NR) Mean IOP, 12 months: 17.9 vs. 17.6; MD 0.3 (95% CI NR) Mean IOP <16 mmHg, 12 months: 36.5% (54/148) VS. 34.5% (70/203); RR 1.06 (95% CI 0.80 to 1.41) Mean IOP <18 mmHg, 12 months: 57.4% vs. 65.5%*; RR 0.73 (95% CI 0.61 to 0.88) Mean IOP reduction >20%, 12 months: 58.8% (87/148) vs. 74.4% (151/203); RR 0.79 (95% CI 0.68 to 0.92) *Results also available for <17, <15, and <14 mmHg, all differences=NS	NR	B vs. C Any adverse event: 78.2% (190/243) vs. 54.0% (128/237); RR 1.45 (95% CI 1.27 to 1.66) Ocular adverse events: 75.7% (184/243) vs. 43.0% (102/237); RR 1.76 (95% CI 1.50 to 2.07) Withdrawal due to adverse events: 21.7% (53/244) vs. 1.7% (4/236); RR 12.82 (95% CI 4.71 to 34.85)	Aerie Pharma-ceuticals	Fair
Asrani, 2020[57] MERCURY-1 and MERCURY-2 pooled analysis	B vs. C Mean IOP, month 3: 18.4 vs. 17.3 mm Hg; MD 1.1 (95% CI NR) Mean IOP <18 mm Hg: 48% vs. 63% (estimated from Figure 2a) Mean IOP reduction >20%: 52.8% (263/499) vs. 75.1% (365/486); RR 0.70 (95% CI 0.64 to 0.77)	NR	B vs. C* Any adverse event: 1190 vs. 540 events Serious adverse events: 19 vs. 19 events Ocular adverse events: 1033 vs. 336 events Withdrawal due to adverse events, 3 months: 7.6% (38/499) vs. 1.0% (5/486): RR 7.40 (95% CI 2.94 to 18.65) *All reported as number of events; pooling a 3 month duration study and a 12 month duration study	Aerie Pharma-ceuticals	Good

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Serle, 2018[129] ROCKET-1 3 month follow-up	A vs. B Mean IOP, 6 weeks, 8am: 19.4 vs. 18.2; MD 1.11 (95% CI 0.42 to 1.80) Mean IOP, 6 weeks, 10am: 18.1 vs. 17.4; MD 0.70 (95% CI 0.04 to 1.36) Mean IOP, 6 weeks, 4pm: 17.9 vs. 17.7; MD 0.15 (95% CI -0.52 to 0.83) Mean IOP, 3 months, 8am: 19.8 vs. 18.5; MD 1.33 (95% CI 0.64 to 2.03) Mean IOP, 3 months, 10am: 18.9 vs. 18.0; MD 0.96 (95% CI 0.26 to 1.66) Mean IOP, 3 months, 4pm: 18.5 vs. 17.7; MD 0.74 (95% CI 0.07 to 1.42) Mean decreases across time points, range: 3.3-5.0 (15-21% reduction) vs. 3.7-5.1 (17-22% reduction)	NR	A vs. B Ocular AEs: 77% (156/203) vs. 44% (92/208); RR 1.74 (95% CI 1.47 to 2.06) Withdrawal due to AEs: 10% (20/202) vs. 2% (4/208); RR 5.15 (95% CI 1.79 to 14.80)	Aerie Pharma-ceuticals	Fair
Serle, 2018[129] ROCKET-2 (Same publication as above)	A vs. B vs. C Mean IOP, 6 weeks, 8am: 18.0 vs. 17.6 vs 17.5; MD=NS Mean IOP, 6 weeks, 10am: 17.0 vs. 16.3 vs. 16.6; MD=NS Mean IOP, 6 weeks, 4pm: 17.0 vs. 15.8 vs. 16.6; B vs C, MD -0.85 (95% CI -1.53 to -0.17) Mean IOP, 3 months, 8am: 18.2 vs. 17.6 vs. 17.5; A vs. B, MD 0.77 (95% CI 0.03 to 1.50) Mean IOP, 3 months, 10am: 17.0 vs. 17.0 vs. 16.9; MD=NS Mean IOP, 3 months, 4pm: 17.1 vs. 16.5 vs. 17.0; MD=NS	NR	A vs. B vs. C Ocular AEs: 73% (182/251) vs. 84%(213/253) vs. 41% (102/251); A vs. C, RR 1.78 (95% CI 1.51 to 2.11); B vs. C, RR 2.07 (95% CI 1.77 to 2.43) Withdrawal due to AEs: 12% (31/251) vs. 30% (77/253) vs. 1% (2/251); A vs. B, RR 0.41 (95% CI 0.28 to 0.59); A vs. C, RR 15.5 (95% CI 3.75 to 64.07); B vs. C, RR 38.20 (95% CI 9.49 to 153.80)	Aerie Pharma-ceuticals	Fair
Kahook, 2019[91] ROCKET-2 12-month followup	A vs. B vs. C Mean IOP, 6 months, 8am: 17.9 vs. 17.7 vs. 17.9; MD=NS Mean IOP, 9 months, 8am: 18.2 vs. 17.2 vs. 17.5; MD=NS Mean IOP, 12 months, 8am: 18.8 vs. 18.0 vs. 17.6; A vs B. MD 1.25 (95% CI 0.25 to 2.26)	NR	A vs. B vs. C Ocular AEs: 83% (209/251) vs. 88% (222/253) vs. 49% (124/251); A vs. C, RR 1.69 (95% CI 1.47 to 1.93); B vs, C, RR 1.78 (95% CI 1.55 to 2.03) Withdrawal due to AEs: 28% (71/251) vs. 52% (132/254) vs. 6% (15/251); A vs. B, RR 0.54 (95% CI 0.43 to 0.68); A vs. C, RR 4.73 (95% CI 2.79 to 8.03); B vs. C, RR 8.70 (95% CI 5.24 to 14.4)	Aerie Pharma-ceuticals	Fair

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Khouri, 2019[98] ROCKET-4	A vs. B Mean IOP reduction from baseline, week 6, 8am: -4.55 vs. -4.85 mm Hg; MD 0.25 (95% CI -0.34 to 0.83) Mean IOP reduction from baseline, week 6, 10am: -4.27 vs. -4.29 mm Hg; MD -0.22 (95% CI -0.82 to 0.37) Mean IOP reduction from baseline, week 6, 4pm: -4.09 vs. -4.01 mm Hg; MD -0.10 (95% CI -0.66 to 0.46) Mean IOP reduction from baseline, month 3, 8am: -4.52 vs. -5.17 mm Hg; MD 0.56 (95% CI -0.02 to 1.15) Mean IOP reduction from baseline,month 3, 10am: -4.10 vs. -4.56 mm Hg; MD 0.21 (95% CI -0.37 to 0.79) Mean IOP reduction from baseline, month 3, 4pm: -3.88 vs. -3.89 mm Hg; MD -0.07 (95% CI -0.68 to 0.55)	NR	A vs. B Any AE: 80% (281/351) vs. 60% (215/357); RR 1.33 (95% CI 1.20 to 1.47) Ocular AEs: 76% (267/351) vs. 50% (180/357); RR 1.51 (95% CI 1.34 to 1.70) Withdrawal due to AEs: 19.4% (68/351) vs. 2.2% (8/357); RR 8.65 (95% CI 4.22 to 17.72)	Aerie Pharma-ceuticals	Fair
Medeiros, 2016[113] LUNAR	A vs. B Mean IOP, week 6, 8am: 18.7 vs. 19.6; treatment difference -0.9 (95% CI -1.6 to -0.3), p=0.005 Mean IOP, week 6, noon: 18.0 vs. 18.9; treatment difference -0.8 (95% CI -1.5 to -0.2), p=0.007 Mean IOP, week 6, 4pm: 17.9 vs. 18.9; treatment difference -1.0 (95% CI -1.6 to -0.4), p=0.003 Mean IOP, month 3, 8am: 18.7 vs. 19.6; treatment difference -0.9 (-1.5 to -0.2), p=0.006 Mean IOP, month 3, noon: 17.9 vs. 19.2; treatment difference -1.3 (95% CI -1.9 to -0.7), p<0.001 Mean IOP, month 3, 4pm: 17.7 vs. 19.1; treatment difference -1.3 (95% CI -2.0 to -0.7), p<0.001 Proportion with ≥25% reduction in IOP at all time points: 31% vs. 18.5%; difference of proportions 12.5% (95% Ci 4.0-21.1%), p=0.007 Proportion with mean IOP ≤18 at all time points: 17.1% vs. 11.1%; p=NS	NR	A vs. B Any AE: NR Ocular AEs: 23.8% (66/277) vs. 13.3% (18/135); RR 1.79 (95% CI 1.11 to 2.88) Withdrawal due to AEs: 1.4% (4/277) vs. 0.7% (1/136); RR 1.96 (95% CI 0.22 to 17.40)	Allergan, Alcon, Bausch & Lomb, other industry	Good

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Weinreb, 2015[140] VOYAGER	A vs. B vs. C vs. D vs. E IOP, change from baseline, day 28: 7.81 vs. 8.26 vs. 9.00 vs. 8.93 vs. 7.77; C vs. E, difference 1.23 (95% CI 0.37 to 2.10), p=0.005; D vs. E, difference 1.16 (95% CI 0.29 to 2.03), p=0.009; others NS Proportion with IOP ≤18 mm Hg at each visit significantly higher with C vs. E at all visits (all p<0.046) and D vs. E at day 7 (p=0.007) and day 28 (p=0.039) [Visualized in Figure 2 without numbers] *All treatments led to significant reductions from baseline at all follow-up visits (p<0.001)	NR	A vs. B vs. C vs. D vs. E Any AE: 24% (20/82) vs. 21% (18/84) vs. 24% (20/83) vs. 28% (23/81) vs. 12% (10/82); all p=NS Withdrawal due to AEs: 4% (3/82) vs. 1% (1/84) vs. 1% (1/81) vs. 0% vs. 1% (1/82)	Bausch & Lomb	Fair
Weinreb, 2016[141] APOLLO	A vs. B Mean IOP, week 6, 8am: 18.6 vs. 19.6; treatment difference -1.0 (95% CI -0.4 to -1.7), p=0.002 Mean IOP, week 6, noon: 17.8 vs. 19.1; treatment difference -1.3 (95% CI -0.6 to -1.9), p<0.001 Mean IOP, week 6, 4pm: 17.8 vs. 19.1; treatment difference -1.3 (95% CI -0.6 to -2.0), p<0.001 Mean IOP, month 3, 8am: 18.7 vs. 19.7; treatment difference -1.0 (95% CI -0.4 to -1.7), p=0.002 Mean IOP, month 3, noon: 17.9 vs. 19.2; treatment difference -1.3 (95% CI -0.6 to -1.9), p<0.001 Mean IOP, month 3, 4pm: 17.8 vs. 19.2; treatment difference -1.3 (95% CI -0.6 to -2.0), p<0.001 IOP ≤18 mmHg at all visits: 22.9% vs. 11.3%; difference 11.6% (95% CI 4.3-18.9%), p=0.005 IOP reduction ≥25% at all visits: 34.9% vs. 19.5%; difference 15.3% (95% CI 6.6-24.0%), p=0.001	NR	A vs. B Any AE: NR Ocular AEs: 13.4% (38/283) vs. 11.9% (16/135); RR 1.13 (95% CI 0.66 to 1.96) Withdrawal due to AEs: 1.4% (4/283) vs. 3.0% (4/135); RR 0.48 (95% CI 0.12 to 1.88)	Bausch & Lomb	Good

Appendix B Table 11. Newer vs. Older Trials of Glaucoma Medical Treatments

Author, Year Study	Vision-related Outcomes	Other Outcomes	Adverse Events	Sponsor	Quality
Weinreb, 2018[139] LUNAR and APOLLO	A vs. B LSM IOP during treatment, range: 17.8-18.9 vs. 19.0-19.7 mmHg; p<0.001 at all time points; LSM difference, -1.0 (-0.5 to -1.4) at 8am, -1.3 (-0.8 to -1.7) at noon, and -1.3 (-0.9 to -1.8) at 4pm IOP ≤18 at all timepoints: 20.2% vs. 11.2%; p=0.001 IOP reduced ≥25% at all timepoints: 32.9% vs. 19.0%; p<0.001	NR	A vs. B Ocular AEs: 21.6% (175/811) vs. 12.5% (34/271); RR 1.72 (95% CI 1.22 to 2.42) Serious AEs: 0% vs. 0% Withdrawal due to AEs: 2% (16/811) vs. 2% (5/271); RR 1.07 (95% CI 0.40 to 2.89)	Bausch & Lomb	Good

Abbreviations: AE = adverse event; APOLLO = APOLLO trial; BVCA = best corrected visual acuity; CI = confidence interval; IOP = intraocular pressure; logMAR = logarithmic minimum angle of resolution; LUNAR = LUNAR study; MD = mean difference; mmHG = millimeters mercury; NR = not relevant; NS = not significant; OAG = open-angle glaucoma; OHT = ocular hypertension; RCT = randomized controlled trial; ROCKET = Rho Kinase Elevated IOP Treatment Trial; RR = relative risk; VOYAGER = VOYAGER trial.

Appendix B Table 12. Newer vs. Older Trials of Glaucoma Medical Treatments, Quality Assessment

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	People analyzed in the groups in which they were randomized?	Quality
Asrani, 2019[58] Brubaker, 2020[66] MERCURY-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12 months: Yes (40% vs. 14%)/No (29% overall)	Yes (ITT); no (safety)	Fair
Asrani, 2020[57] MERCURY-1 and MERCURY-2 pooled analysis (3 month data)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No (14% vs. 6%)/No (10% overall)	Yes	Good
Serle, 2018[129] Kahook, 2019[91] ROCKET-1	Yes; computerized	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	12 months: Yes (42% vs. 66% vs. 19% attrition)/ Yes (42% overall)	Yes	Fair
Serle, 2018[129] ROCKET-2 (Same publication as above)	Yes; computerized	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes (18% vs. 40% vs. 6%)/ No	Yes	Fair
Khouri, 2019[98] ROCKET-4	Yes; computerized	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes (31% vs. 12% attrition)/ No	Yes	Fair
Medeiros, 2016[113] LUNAR	Yes; computerized	Yes; central	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Weinreb, 2015[140] VOYAGER	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
Weinreb, 2016[141] APOLLO	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Good

Abbreviations: APOLLO = APOLLO trial; LUNAR = LUNAR study; ROCKET = Rho Kinase Elevated IOP Treatment Trial; VOYAGER = VOYAGER trial.

Appendix B Table 13. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments

Author, year study	Study design	Country setting	Inclusion criteria	Randomized analyzed attrition	Eyes or patient randomized	Intervention	Baseline population/study participants, including vision parameters
Gazzard, 2019[37,82] LiGHT	RCT	United Kingdom 6 hospitals	Age 18 years with newly diagnosed untreated OAG or OHT; for OAG, visual field loss MD not worse than -12 dB in better eye; visual acuity 6/36 or better; no prior surgery Criteria for diagnosis: (OAG) Swedish Interactive Threshold Algorithm, HFA, Glaucoma Hemifield Test; (OHT) IOP > 21 mmHg and requiring treatment as per NICE guidelines	Randomized: 718 Analyzed: 652 Attrition: 66	Randomized by individual-one or both eyes treated	A. SLT: 100 spots over 360°; if target IOP not reached, second SLT allowed (n=356) B. Medical therapy: first line prostaglandin analogues, then β blockers, then topical carbonic anhydrase inhibitors or alpha agonists (n=362)	A vs B Mean age (SD) 63.4 years (12) vs. 62.7 (11.6) Female 43.8% vs. 45.6% Caucasian 68.3% vs. 71.3% Black 21.6% vs. 19.1% Asian 6.5% vs 7.7% OAG 76.7% vs. 77.9% OHT 23.3% vs. 22.1% Family history of glaucoma 30.1% vs. 29.6% HTN 37.1% vs. 32.9% Diabetes 11.8% vs. 11.1% Mean visual acuity (SD) 0.1 (0.2) vs. 0.1 (0.1) Mean visual field deviation -3 dB (3.4) vs. -3 dB (3.6) Mean IOP 24.5 mm Hg (5.2) vs. 24.4 mm Hg (5.0) Mean EQ-5D score (SD) 0.91 (0.13) vs. 0.92 (0.13) Mean GUI score (SD) 0.89 (0.12) vs. 0.89 (0.11) Mean GSS score (SD) 81.4 (17.2) vs. 83.3 (16.6) Mean GQL-15 score (SD) 18.9 (6.6) vs. 18.7 (5.6)
Lai, 2004[103]	RCT	Hong Kong University hospital	Patients newly diagnosed with POAG or OHT, IOP >21 mmHg in both eyes without antiglaucomatous treatment Criteria for diagnosis: NR	Randomized: 32 patients (64 eyes) Analyzed: 29 patients (58 eyes) Attrition: 8 patients	Randomized by eye—two eyes per individual, one eye randomized to a treatment and the other serves as control	A. SLT: 1% apraclonidine drop, then 360° B. Latanoprost (no details given)	Mean age 51.9 years (14.7) Female 55% POAG 59% OHT 41% A vs B BCVA (range) 0-1 to 1.0 vs. 0.2 to 1.0 Mean baseline IOP (SD) 26.8 mm Hg (5.6) vs. 26.2 mm Hg (4.2)

Appendix B Table 13. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments

Author, year study	Study design	Country setting	Inclusion criteria	Randomized analyzed attrition	Eyes or patient randomized	Intervention	Baseline population/study participants, including vision parameters
Nagar, 2005[119]	RCT	England Two ophthal-mology centers	Patients with OHT or primary or secondary OAG, either newly diagnosed or controlled on medical therapy; no prior surgery Criteria for diagnosis: NR	Randomized: 167 patients (and eyes) Analyzed: 167 Attrition: None	Randomized by individual-one or both eyes treated, but only one eye entered into study	SLT: amethocaine 1%, then A. inferior 90˚ (25-30 spots, n=35) B. inferior 180˚ (48-53, n=49) C. 360˚ (93-102, n=44) D. Latanoprost 0.005% (n=39)	Mean age (range) 63 years (22-90) Female 54% Caucasian 78% African or Afro-Caribbean 22% OAG 49% OHT 51% Mean IOP (range) 29.3 mm Hg (22–50)
Nagar, 2009[118]	RCT	England One eye center	Patients age 40-80 years, with newly diagnosed OHT or POAG, diurnal intraocular pressure fluctuation of >3 mm Hg Criteria for diagnosis: NR	Randomized: 40 Analyzed: 30 Attrition: 10	Randomized by individual-one or both eyes treated, but only one eye entered into study	A. SLT: amethocaine 1%, 100 spots (n=20) B. Latanoprost 0.005% one drop nightly (n=20)	Mean age (range) 66.4 years (43 to 88) Female 48% White 100% OAG 43% OHT 57% Mean IOP A vs. B 26.1 mm Hg (4.0) vs. 22.8 mm Hg (4.5), p=0.02

Appendix B Table 13. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments

Author, year study	Duration of followup	Vision-related outcomes	Other outcomes	Adverse events	Sponsor	Quality
Gazzard, 2019[37,82] LiGHT	3 years	A vs. B Mean visual acuity (SD): 0.07 logMAR (0.18) vs. 0.08 (0.17) Mean IOP (SD): 16.6 mm Hg (3.62) vs. 16.3 (3.87) Mean visual field mean deviation (SD): -3.19 dB (3.92) vs. -3.21 dB (3.76) Eyes at target IOP: 95% (509/536 eyes) vs. 93.1% (499/526 eyes) Disease progression: 3.8% (23/329) vs. 5.8% (36/323)	A vs. B **EQ-5D, GUI, GSS, higher scores = better HrQOL; GQL-15, lower scores = better HrQoL* Mean EQ-5D scores (SD): 0.90 (0.16) vs. 0.89 (0.18) Mean Mean GUI scores (SD): 0.89 (0.13) vs. 0.89 (0.13) Mean GSS scores (SD): 83.3 (17.3) vs. 83.1 (17.7) Mean GQL-15 scores (SD): 19.8 (7.2) vs. 19.8 (7.8) Number of treatment escalations: 299 vs. 348 QALY: 2.74 (0.37) vs. 2.70 (0.42) At £20 000, 97% probability SLT more cost-effective per QALY gained (ophthalmology costs only; 68% probability non-ophthalmology costs included)	A vs. B Any AE: 73.3% (261/356) vs. 71.8% (260/362) Ocular AE (Includes ocular irritation, discomfort, dry eye, retinal haemorrhages, vision changes, flashes, floaters, conjunctivitis, blepharitis, vascular occlusions, diabetic retinopathy, macular pathology): 52% (186/356) vs. 61% (221/362) SLT-related transent AEs (discomfort, transient blurred vision, transient photophobia, hyperaemia): 34.4% (122/356) Any serious AE: 18% (64/356) vs. 18.8% (68/362) Ocular SAEs (central retinal artery occlusion, choroidal neovascularisation, epiretinal membrane, angle closure, anterior chamber surgery, corneal pathologies, trauma, and any treatment required for these pathologies): 2.2% (8/356) vs. 1.7% (6/362)	National Institute of Health Research Health Technology Assessment Panel; authors report conflicts of interest	Good
Lai, 2004[103]	Yearly for 5 years	A vs. B Mean IOP reduction (SD) at 5 years: 8.6 mm Hg (6.7) vs. 8.7 mm Hg (6.6), p>0.05 Mean number range of treatment to control IOP: 0.46 to 0.55 vs. 1.45 to 1.63, p<0.001 Failure (IOP >21 mm Hg on maximal tolerated treatment): 17% (5 eyes) vs. 28% (8 eyes)	NR	"Transient postlaser IOP spike of greater than 5 mmHg was observed in three eyes (10.3%). No persistent anterior chamber reaction beyond 1 week postlaser was recorded. No patients in group 1 had increase in trabecular meshwork pigmentation or formation of peripheral anterior synechiae as a result of the laser treatment."	NR	Fair

Appendix B Table 13. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments

Author, year study	Duration of followup	Vision-related outcomes	Other outcomes	Adverse events	Sponsor	Quality
Nagar, 2005[119]	1, 3, 6, 9, 12 months (mean 10 months)	A vs. B vs. C vs. D 20% IOP reduction vs. baseline with no additional antiglaucomatous interventions: 34% (12/35) vs. 65% (32/49) vs. 82% (36/44) vs. 90% (35/39)30% IOP reduction vs. baseline with no additional antiglaucomatous interventions: 11% (4/35) vs. 48% (21/49) vs. 59% (26/44) vs. 78% (28/39)A vs. D overall, p<0.001B vs. D overall, p<0.01C vs. D overall, p>0.05B or C vs. A, p<0.05B vs. C, p>0.05*Numbers not provided, but "mean IOP was significantly lower in eyes receiving latanoprost than 90˚SLT at 1, 6, and 12 months (p<0.02), 180˚ SLT at 1, 3, 6, and 12 months (p<0.01), and 360˚ SLT at 12 months (p<0.05)."*	Addition treatment or medication needed after last followup: 66% vs. 35% vs. 25% vs. 10% (D vs. A or B, p<0.01)	A vs. B vs. C Discomfort / pain: 6% vs. 20% vs. 39% (A vs. C, p<0.001) Uveitis: 31% vs. 41% vs. 50% IOP spike at 1 hour: 11% vs. 16% vs. 27% (A vs. C, p<0.05) No discomfort / pain, uveitis, or IOP spike reported for latanoprost	NR, but "study supported by provision of A Selectra 7000 laser by Lumenis"	Fair

Appendix B Table 13. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments

Author, year study	Duration of followup	Vision-related outcomes	Other outcomes	Adverse events	Sponsor	Quality
Nagar, 2009[118]	1 week, 1, 4-6 months	A vs. B Mean IOP reduction (SE) Week 1: 3.6 mm Hg (0.7) vs. 5.3 mm Hg (0.8) Month 1: 3.2 mm Hg (0.8) vs. 7.0 mm Hg (0.7), p<0.05 Months 4-6: 6.2 mm Hg (0.8) vs. 7.8 mm Hg (0.8) IOP control (≥20% reduction from baseline), aOR (95% CI)Week 1: 45% vs. 56%, aOR 2.20, 95% CI, 0.92 to 6.22, p>0.05 Month 1: 41% vs. 67% (n not provided), aOR 6.21, 95% CI, 1.72 to 51.1, p=0.003 Months 4-6: 75% vs. 73%, aOR 1.65, 95% CI, 0.52 to 6.07, p>0.05 IOP fluctuation success (≥50% reduction in fluctuation): 50% vs. 83%, aOR 2.25, 95% CI, 1.01 to 5.67, p=0.049 **aOR adjusted for baseline IOP* Mean IOP fluctuation, mean reduction, % reduction, vs. baseline A: 5.5 mm Hg (2.7), 2.3 mm Hg (2.4), 41%, p<0.001 B: 5.7 mm Hg (2.1), 3.7 mm Hg (2.8), 64%, p<0.001 A vs. B, 2.5 vs. 3.6 mmHg, p=0.04	NR	NR	NR, but authors report no conflicts	Fair

Abbreviations: AE = adverse event; aOR = adjusted odds ratio; BCVA = best corrected visual acuity; dB = decibel; EQ-5D = EuroQol-5D instrument; GQL-15 = Glaucoma Quality of Life-15 (higher scores represent poorer glaucoma quality of life); GSS = Glaucoma Symptom Scale (higher scores represent better outcomes); GUI = Glaucoma Utility Index (higher scores represent a higher quality of life); HrQOL = health-related quality of life; HTN = hypertension; IOP = intraocular pressure; LiGHT = Laser in Glaucoma and ocular HyperTension study; logMAR = logarithmic minimum angle of resolution; MD = mean difference; mmHG = millimeters mercury; NR = not reported; OAG = open angle glaucoma; OHT = ocular hypertension; POAG = primary open angle glaucoma; QALY = quality-adjusted life year; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SLT = selective laser trabeculoplasty.

Appendix B Table 14. Trials of Selective Laser Trabeculoplasty vs. Medical Treatments, Quality Assessment

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	People analyzed in the groups in which they were randomized?	Quality
Gazzard, 2019[37,82] LiGHT	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Good
Lai, 2004[103]	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	Unclear	Fair
Nagar, 2005[119]	Yes	Yes	Yes	Yes	Unclear	No	No	Analyzed all, but details NR	No	Unclear	Fair
Nagar, 2009[118]	Yes	Yes	No (baseline IOP)	Yes	Yes	No	No	Yes	Yes (25% overall; unclear on each arm)	Unclear	Fair

Abbreviations: IOP = intraocular pressure; LiGHT = Laser in Glaucoma and ocular HyperTension study; NR = not reported.