

Screening for Glaucoma in Adults

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Two 2013 systematic reviews to inform the US Preventive Services Task Force (USPSTF) found insufficient evidence to assess benefits and harms of screening for primary open-angle glaucoma (OAG) in adults.

OBJECTIVE To update the 2013 reviews on screening for glaucoma, to inform the USPSTF.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (to February 2021); surveillance through January 21, 2022.

STUDY SELECTION Randomized clinical trials (RCTs) of screening, referral, and treatment; and studies of screening test diagnostic accuracy.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data and a second checked accuracy. Two investigators independently assessed study quality.

RESULTS Eighty-three studies (N = 75 887) were included (30 trials and 53 diagnostic accuracy studies). One RCT (n = 616) found screening of frail elderly persons associated with no difference in vision outcomes vs no screening but with significantly greater falls risk (relative risk [RR], 1.31 [95% CI, 1.13-1.50]). No study evaluated referral to an eye health professional. For glaucoma diagnosis, spectral domain optical coherence tomography (providing high-resolution cross-sectional imaging; 15 studies, n = 4242) was associated with sensitivity of 0.79 (95% CI, 0.75-0.83) and specificity of 0.92 (95% CI, 0.87-0.96) and the Humphrey Visual Field Analyzer (for perimetry, or measurement of visual fields; 6 studies, n = 11 244) with sensitivity of 0.87 (95% CI, 0.69-0.95) and specificity 0.82 (95% CI, 0.66-0.92); tonometry (for measurement of intraocular pressure; 13 studies, n = 32 892) had low sensitivity (0.48 [95% CI, 0.31-0.66]). Medical therapy for ocular hypertension and untreated glaucoma was significantly associated with decreased intraocular pressure and decreased likelihood of glaucoma progression (7 trials, n = 3771; RR, 0.68 [95% CI, 0.49-0.96]; absolute risk difference -4.2%) vs placebo, but 1 trial (n = 461) found no differences in visual acuity, quality of life, or function. Selective laser trabeculoplasty and medical therapy had similar outcomes (4 trials, n = 957).

CONCLUSIONS AND RELEVANCE This review found limited direct evidence on glaucoma screening, showing no association with benefits. Screening tests can identify persons with glaucoma and treatment was associated with a lower risk of glaucoma progression, but evidence of improvement in visual outcomes, quality of life, and function remains lacking.

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Glaucoma is the second leading cause of irreversible blindness in the US and the leading cause in Black and Latino persons,^{1,2} and earlier stages can also affect quality of life and function.³ In 2011, an estimated 2.71 million persons had open-angle glaucoma (OAG); this number was projected to reach 4.3 million in 2025.⁴

In 2013, the US Preventive Services Task Force (USPSTF) concluded that evidence was insufficient to assess benefits and harms of screening for primary OAG in adults (I statement). Two 2013 reviews⁵⁻⁷ conducted to inform the USPSTF found no direct evidence on benefits of screening and inadequate evidence on the effects of treatment on impaired vision or quality of life, although treatment was associated with reduced intraocular pressure (IOP) and reduced progression of visual field deficits. This report was conducted to update the 2013 reviews, to inform the USPSTF for an updated recommendation.

Methods

Scope of the Review

Detailed methods and additional study details, including the diagnostic accuracy of screening tests with limited evidence (swept-source optical coherence tomography [OCT], optic disc photography, ophthalmoscopy/biomechanics/stereoscopy, pachymetry, afferent papillary defect, and a telemedicine screening intervention), are available in the full evidence report.⁸ Figure 1 shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from January 2011 to February 9, 2021 (eMethods 1 in the Supplement). Searches were supplemented by reference list review of relevant studies; studies from the prior USPSTF reviews⁵⁻⁷ that met inclusion criteria were carried forward. 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 study¹⁰ comparing glaucoma screening with no screening was identified during surveillance but was not eligible for inclusion owing to observational design and serious methodological limitations (control group was nonparticipants/nonresponders, and the study did not control for potential confounders).

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria (eMethods 2 in the Supplement). The population for screening was adults 40 years or older without known OAG; for treatment, patients had OAG or glaucoma suspect.

Screening tests were a complete eye examination or various components, and imaging tests; this article focuses on spectral-domain OCT (provides high-resolution cross-sectional imaging of ocular structures including the retina and optic nerve, the princi-

pal sites of glaucomatous changes), visual field testing (to assess whether there are deficits in the field of vision; in glaucoma, peripheral vision is typically lost before central vision), and tonometry (to measure intraocular pressure). For treatment, this article focuses on first-line medical treatments (prostaglandin analogues, β -blockers, α -2 agonists, and carbonic anhydrase inhibitors) vs placebo, selective laser trabeculoplasty (SLT) vs first-line medical treatments or no treatment, and recently approved medications vs first-line medications. 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. Randomized clinical trials of screening and treatment and cohort and cross-sectional studies on screening test diagnostic accuracy were included; diagnostic accuracy studies that used a case-control design were excluded, due to potential spectrum bias.¹¹ Inclusion was restricted to English-language articles, and studies published only as abstracts were excluded.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions, analysis, follow-up, and results from each study. A second investigator reviewed abstracted data for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria (eMethods 3 in the Supplement) developed by the USPSTF.⁹ Disagreements were resolved by consensus. In accordance with the USPSTF Procedure Manual, studies rated poor quality because of critical methodological limitations were excluded.

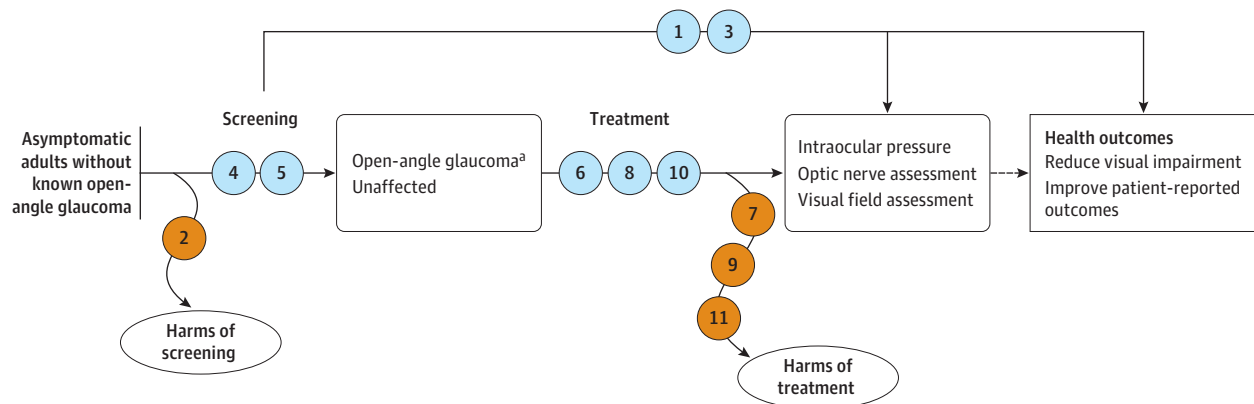
Data Synthesis

For all KQs, the overall strength of evidence was rated "high," "moderate," "low," or "insufficient" based on study limitations, consistency, precision of estimates, reporting bias, and applicability, using the approach described in the USPSTF Procedure Manual.⁹

Meta-analysis was conducted to summarize effects of treatments and diagnostic accuracy of screening tests. Details of the meta-analytic methods are provided in eMethods 4 in the Supplement. Briefly, for treatment, a random-effects profile likelihood model was used to pool studies of first-line treatment vs 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 on difference in mean IOP. Analyses were stratified by medication type, and prespecified study-level subgroup analyses were conducted on glaucoma status (OAG, ocular hypertension, or mixed), quality, baseline IOP, and duration of follow-up. For diagnostic accuracy, a bivariate logistic random-effects model was used to summarize sensitivity and specificity of screening tests for glaucoma simultaneously, while incorporating the correlation between sensitivity and specificity. Stratified analyses were conducted based on control type (healthy eye, glaucoma suspect, or ocular hypertension) and study quality.

All meta-analyses were conducted using Stata/SE version 14.2 or 16.1 (StataCorp). Statistical heterogeneity was assessed using the I^2 statistic.¹² Two-sided tests with P values $<.05$ were considered statistically significant.

Figure 1. Analytic Framework and Key Questions: Screening for Glaucoma in Adults



Key questions

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

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that

immediately follows an intermediate outcome. For additional information see the USPSTF Procedure Manual.⁹ Subpopulations of interest include those defined by age, sex, race and ethnicity, and setting (eg, rural or urban).

^a Includes patients with suspected open-angle glaucoma.

Results

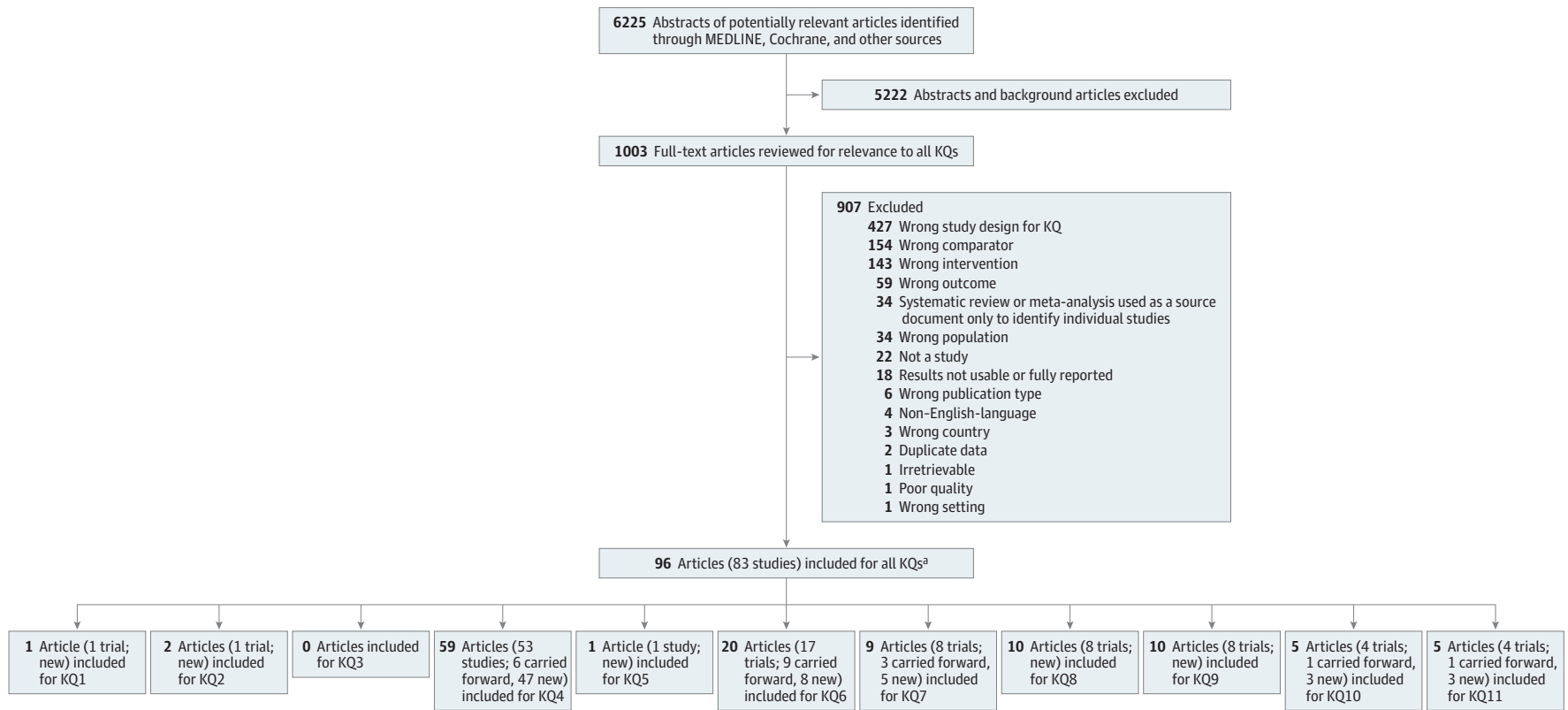
Across all key questions, 83 studies (reported in 96 publications, total 75 887 participants) were included (30 trials and 53 diagnostic accuracy studies) (Figure 2).¹³⁻¹⁰⁸ Sixteen studies were carried forward from the 2013 reviews, and 67 studies were new.

Screening

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?

One trial (n = 616) of frail elderly persons, not included in the 2013 reviews, found no significant difference between vision screening vs no screening in distance visual acuity (mean logarithm of the

Figure 2. Literature Search Flow Diagram: Screening for Glaucoma in Adults



H2H indicates head to head; KQ, key question; PCTs, placebo-controlled trials; SLT, selective laser trabeculoplasty.

^a The number of included studies does not sum to the number shown because some studies are included for more than 1 KQ.

minimum angle of resolution [logMAR], 0.27 vs 0.25; $P = .32$), near visual acuity (mean logMAR, -0.01 vs -0.03 ; $P = .26$) or vision-related quality of life after 1 year (eTables 1-2 in the Supplement).⁹⁵ Screening was conducted by an optometrist and included components for identifying glaucoma (IOP, direct ophthalmoscopy, and visual field); interventions for screen-positive persons included referral for eye care, occupational therapy, or both. Seventy-two percent of control patients had visited an eye care professional in the last year, which could have attenuated potential screening benefits.

Key Question 2. What are the harms of screening for OAG vs no screening?

The trial described in KQ1 found screening associated with significant increased risk for falls vs no screening (incidence rate ratio, 1.57 [95% CI, 1.20-2.05]; risk of 1 or more falls, 65% vs 50%; relative risk [RR], 1.31 [95% CI, 1.13-1.50]). Screening was associated with increased risk for fractures that was not statistically significant (RR, 1.74 [95% CI, 0.97-3.11]). In the trial, 46% of patients had fallen in the past year.⁹⁵

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 study addressed this KQ.

Key Question 4. What is the accuracy of screening for diagnosis of OAG?

Fifty-three studies evaluated the diagnostic accuracy of screening tests (reported in 59 publications, $n = 65\,464$) (eTables 3-4 in the Supplement).^{13-15, 18-20, 23, 24, 26-30, 32-36, 38-40, 45-47, 49, 50, 54, 57-59, 61-64, 66-74, 78, 79, 82, 83, 85, 88, 91, 93, 94, 96, 98-102, 108} Most studies evaluated spectral-domain OCT (29 studies, $n = 11\,434$), tonometry (17 studies, $n = 49\,742$), and visual field assessment (10 studies, $n = 11\,633$). No study evaluated the diagnostic accuracy of a comprehensive ophthalmological examination. Seven studies were rated good quality,^{15, 18, 32, 39, 71, 73, 85} and the remainder were rated fair quality (eTable 5 in the Supplement). Methodological limitations in the fair-quality studies included nonindependent evaluation of the reference standard from the screening test and uncertain interval between index and reference tests.

Spectral-domain OCT using retinal nerve fiber layer thickness was associated with a pooled sensitivity of 0.79 (95% CI, 0.75-0.83) and specificity of 0.92 (95% CI, 0.87-0.96) for identifying glaucomatous eyes, based on 15 studies ($n = 4242$) (eFigure 1 in the Supplement); the pooled area under the receiver operating characteristic curve was 0.90 (95% CI, 0.86-0.93), based on 16 studies ($n = 4060$). Findings were similar for spectral-domain OCT using ganglion cell complex thickness (pooled sensitivity, 0.74 [95% CI, 0.68-0.80] and specificity, 0.91 [95% CI, 0.80-0.96] based on 9 studies [$n = 1522$] [eFigure 2 in the Supplement]; pooled area under the receiver operating characteristic curve, 0.88 [95% CI, 0.84-0.92], based on 6 studies [$n = 765$]). The Humphrey Visual Field Analyzer was associated with a pooled sensitivity of 0.87 (95% CI, 0.69-0.95) and specificity of 0.82 (95% CI, 0.66-0.92), based on 6 studies ($n = 11\,244$) (eFigure 3 in the Supplement). Tonometry for measurement of intraocular pressure was associated with a pooled sensitivity of 0.48 (95% CI, 0.31-0.66) and specificity of 0.94 (95% CI, 0.90-0.96), based on 13 studies ($n = 32\,892$) (eFigure 4 in the Supplement). Findings for diagnostic accuracy were consistent in analyses stratified by

control type (healthy eyes, glaucoma suspect, or ocular hypertension) or study quality (Table 1 and Table 2).

Key Question 5. What is the accuracy of instruments for identifying patients at higher risk of OAG?

One fair-quality cross-sectional study ($n = 145$) not included in the 2013 reviews found a questionnaire associated with low sensitivity (0.20 [95% CI, 0.03-0.56]) but high specificity (0.96 [95% CI, 0.91-0.99]) for identifying persons with glaucoma (eTables 6-8 in the Supplement).⁷⁹

Treatment

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?

Seventeen trials ($n = 4665$) evaluated medical treatments for OAG vs placebo or no treatment.^{56, 86, 89, 107} Nine trials^{37, 48, 53, 55, 56, 76, 89, 90, 107} were in the 2013 review⁶ and 8 trials^{21, 22, 41, 84, 86, 87, 97, 106} were added (eTable 9 in the Supplement).^{21, 22, 41, 84, 86, 87, 97, 106} Two trials enrolled patients with untreated, newly diagnosed OAG,^{22, 41} 3 trials enrolled mixed populations (OAG or ocular hypertension,^{21, 87, 106} and 12 trials enrolled patients with ocular hypertension. Mean baseline IOP ranged from 19.6 to 27.3 mm Hg (≥ 22 mm Hg in all trials except for the trials of patients with early untreated OAG^{22, 41}). Ten trials evaluated a β -blocker, 5 trials a carbonic anhydrase inhibitor, 1 trial a prostaglandin analogue, and 1 trial an α agonist.⁹⁷ One trial allowed various topical therapies, with a target IOP of 24 mm Hg or less or 20% or greater IOP reduction.⁵⁶ The duration of follow-up ranged from 1.5 months^{22, 84} to 120 months⁴⁸ (>1 year in 10 trials). Four trials were rated good quality^{41, 53, 77, 90} and 12 fair quality^{21, 37, 48, 55, 56, 84, 86, 87, 89, 97, 106, 107} (eTable 10 in the Supplement). Methodological limitations in the fair-quality trials included unclear reporting of randomization, allocation concealment, and blinding methods; and high attrition in some studies.

Treatment was significantly associated with greater reduction in IOP vs placebo or no treatment (16 trials, $n = 3706$; mean difference, -3.14 mm Hg [95% CI, -4.19 to -2.08]; $I^2 = 95\%$) (eFigure 5 in the Supplement). There was a subgroup difference by drug class ($P < .001$), although estimates favored treatment for all drug classes. The mean difference in IOP ranged from -3.75 mm Hg (95% CI, -5.43 to -2.06 ; $I^2 = 92\%$) for β -blockers (9 trials, $n = 455$) to -1.20 mm Hg (95% CI, -2.30 to -0.61) for carbonic anhydrase inhibitors (4 trials, $n = 1635$). Treatment with topical therapy also significantly decreased risk of glaucoma progression (defined as progression of visual field defects,^{37, 41} progression of visual field defects or optic disc change,^{56, 76, 77} or progression to glaucoma diagnosis among patients with ocular hypertension^{48, 53, 89}) vs placebo or no treatment (7 trials, $n = 3771$; RR, 0.68 [95% CI, 0.49-0.96], $I^2 = 53\%$; absolute risk difference (ARD), -4.8% [95% CI, -8.5% to -1.0%]) (eFigure 6 in the Supplement). There was no subgroup difference based on drug class. For both outcomes, findings consistently favored treatment in analyses stratified according to baseline status (OAG, ocular hypertension, or mixed), baseline IOP, or study quality, although some subgroup differences were present (Table 3).

One trial ($n = 461$), the UK Glaucoma Treatment Study (UKGTS) found no differences between latanoprost vs placebo in visual acuity (logMAR, -0.01 vs -0.02 ; $P = .9$) or general or vision-related quality of life at 24 months.^{41, 51}

Table 1. Diagnostic Accuracy Pooled Analyses: Sensitivity and Specificity

Pooled analysis	No. of trials	No. of participants	Sensitivity (95% CI)	Specificity (95% CI)
RNFL thickness	15	4242	0.79 (0.75-0.83)	0.92 (0.87-0.96)
Healthy-eye controls	9	2404	0.81 (0.74-0.86)	0.96 (0.89-0.99)
Glaucoma suspect controls	3	1130	Range, 0.77-0.85	Range, 0.79-0.87
Ocular hypertension + healthy controls	1	81	0.78 (0.60-0.91) ^a	0.92 (0.80-0.98) ^a
Ocular hypertension controls	2	228	0.59 (0.41-0.76)	0.81 (0.69-0.90)
Not glaucoma	1	532	0.80 (0.68-0.89)	0.96 (0.88-0.99)
Restricted-overall mean RNFL	1	532	0.77 (0.62-0.89)	0.88 (0.85-0.91)
Good quality	12	3819	0.79 (0.74-0.84)	0.90 (0.85-0.93)
Fair quality	3	2400	Range, 0.65-0.81	Range, 0.79-0.90
GCC thickness	12	1880	0.80 (0.74-0.85)	0.94 (0.88-0.97)
Healthy-eye controls	9	1522	0.74 (0.68-0.80)	0.91 (0.80-0.96)
Glaucoma suspect controls	6	1145	0.76 (0.66-0.83)	0.92 (0.86-0.96)
Ocular hypertension controls	1	201	0.77 (0.66-0.86) ^a	0.76 (0.67-0.83) ^a
Healthy-eye + ocular hypertension controls	1	95	0.75 (0.57-0.89) ^a	0.59 (0.46-0.71) ^a
Restricted-studies that used inner plexiform layer or ganglion cell layer	1	81	0.66 (0.47-0.81) ^a	1.00 (0.93-1.00) ^a
Good quality	5	998	0.73 (0.60-0.83)	0.95 (0.87-0.98)
Fair quality	1	456	0.62 (0.41-0.80) ^a	0.93 (0.91-0.96) ^a
Intraocular pressure	8	542	0.75 (0.68-0.81)	0.91 (0.78-0.97)
Healthy-eye or nonglaucoma controls	13	32892	0.48 (0.31-0.66)	0.94 (0.90-0.96)
Probable glaucoma vs not probable glaucoma	12	28726	0.47 (0.29-0.66)	0.94 (0.90-0.97)
Goldmann tonometry	1	4166	0.61 (0.56-0.67) ^a	0.92 (0.91-0.92) ^a
Other tonometry methods	4	11690	0.66 (0.36-0.87)	0.95 (0.92-0.98)
Good quality	9	21202	0.39 (0.22-0.58)	0.93 (0.87-0.97)
Fair quality	2	6587	0.24 (0.19-0.30)	0.97 (0.97-0.97)
Good quality	2	6587	0.19 (0.07-0.39)	0.89 (0.86-0.92)
Fair quality	11	26305	0.54 (0.34-0.72)	0.94 (0.89-0.97)
HFA visual fields	6	5162	0.54 (0.34-0.72)	0.94 (0.89-0.97)
Good quality	6	11244	0.87 (0.69-0.95)	0.82 (0.66-0.92)
Fair quality	2	6082	0.88 (0.83-0.92) ^a	0.64 (0.64-0.65) ^a
Fair quality	5	5162	Range, 0.65-1.00 ^b	Range, 0.64-1.00 ^b

Abbreviations: GCC, ganglion cell complex; HFA, Humphrey Field Analyzer; RNFL, retinal nerve fiber layer.
^a Estimate from a single study (not pooled).
^b Pooled estimate was not produced because the model did not converge.

Key Question 7. What are the harms of medical treatments for OAG vs placebo or no treatments?

Eight trials (in 9 publications) of medical treatments vs placebo or no treatment reported harms (eTable 9 in the Supplement).^{21,37,41,56,76,77,87,90,106} There were no statistically significant differences in risk of serious adverse events (3 trials, n = 3140; RR, 1.14 [95% CI, 0.60-1.99]; I² = 32%) (eFigure 7 in the Supplement),^{41,56,76,77} withdrawal due to adverse events (5 trials, n = 648; RR, 2.40 [95% CI, 0.71-19.32]; I² = 0%) (eFigure 8 in the Supplement),^{21,37,41,90,106} or any adverse event (2 trials, n = 1538; RR, 1.56 [95% CI, 0.59-4.03]; I² = 82%).^{41,76,77} However, estimates were imprecise and the estimate for any adverse event had substantial statistical heterogeneity. Two trials found treatment associated with increased risk of ocular adverse events (most commonly localized itching, irritation, dryness, or taste issues) vs placebo (RR, 1.21 [95% CI, 1.10-1.33] in a trial of various

treatments^{76,77} and RR, 3.52 [95% CI, 2.46-5.02]⁵⁶ in a trial of dorzolamide).

Key Question 8. What are the effects of newly US Food and Drug Administration (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?

Eight trials (n = 4113) compared latanoprostene bunod or netarsudil vs an older glaucoma medication in mixed populations of patients with OAG or ocular hypertension (eTable 11 in the Supplement).^{16,17,25,52,60,75,92,103-105} The duration of follow-up was 3 months in all trials except for 3, which had 1-month¹⁰⁴ or 12-month follow-up.^{25,52} Three trials^{16,75,105} were rated good quality and 5 trials were rated fair quality (eTable 12 in the Supplement).^{25,52,60,92,104} Methodological limitations in the fair-quality trials included unclear reporting of randomization, allocation concealment, and

Table 2. Diagnostic Accuracy Pooled Analyses: AUROC

Pooled analysis	No. of trials	No. of participants	AUROC (95% CI)
RNFL thickness	16	4060	0.90 (0.86-0.93)
Healthy-eye controls	10	2262	0.92 (0.89-0.94)
Glaucoma suspect controls	4	496	0.90 (0.86-0.94)
Ocular hypertension controls	3	319	0.80 (0.71-0.89)
Glaucoma suspect + healthy-eye controls	1	91	0.91 (0.81-1.00) ^a
Glaucoma suspect + ocular hypertension controls	1	883	0.83 (0.79-0.87) ^a
Not glaucoma	1	532	0.89 (0.85-0.94) ^a
Overall mean RNFL	12	3634	0.92 (0.89-0.94)
Good quality	2	1944	0.87 (0.80-0.94)
Fair quality	14	2116	0.90 (0.86-0.94)
Ganglion cell analysis	6	765	0.88 (0.84-0.92)
Healthy-eye controls	5	564	0.87 (0.82-0.92)
Glaucoma suspect	2	354	0.84 (0.69-1.00)
Ocular hypertension	2	224	0.76 (0.70-0.82)
Restricted studies of ganglion cell complex	2	211	0.87 (0.72-1.00)
HFA visual fields			
HFA SITA-Standard 24-2			
Mean deviation	3	288	0.83 (0.70-0.97)
Pattern standard deviation	2	242	0.87 (0.76-0.99)

Abbreviations: AUROC, area under the receiver operating characteristic curve; HFA, Humphrey Field Analyzer; RNFL, retinal nerve fiber layer; SITA, Swedish Interactive Thresholding Algorithm.

^a Estimate from a single study (not pooled).

blinding of outcome assessors; some trials also had high and differential attrition.

All trials focused on IOP. In 5 trials (n = 2860), netarsudil was noninferior to or associated with similar effects on IOP vs older glaucoma medications.^{16,52,60,92} Three trials (n = 1253) found latanoprostene bunod significantly associated with greater reduction in IOP vs older glaucoma medications (mean difference, -1.0 to -1.3 mm Hg).^{103,104} The trials did not evaluate visual impairment, quality of life, or function.

Key Question 9. What are the harms of newly FDA-approved medical treatments vs older medical treatments?

The trials described in KQ8 also reported harms. Three trials (n = 1875) found netarsudil associated with increased risk of ocular adverse events vs timolol.^{52,60,92} The most commonly reported ocular adverse events were conjunctival redness or hemorrhage, corneal deposits (cornea verticillata, typically asymptomatic), blurry vision, tearing, and itching. The proportion of patients with ocular adverse events ranged from 73% to 88% with netarsudil and from 41% to 50% with timolol; RRs ranged from 1.51 to 2.07 at 3 to 12 months (ARDs ranged from 26% to 38%). One trial (n = 480) of netarsudil vs latanoprost (RR, 1.76 [95% CI, 1.50-2.07])²⁵ and 2 trials (n = 840) of latanoprostene bunod vs timolol (pooled RR, 1.72 [95% CI, 1.22-2.42])¹⁰³ also found the newer therapy significantly associated with increased risk of ocular adverse events. Netarsudil was associated with significantly increased risk of withdrawal due to adverse events vs timolol (3 trials, n = 1875; RRs ranged from 4.73 to 38.20; ARDs ranged from 8% to 34%)^{52,60,92} or latanoprost (2 trials, n = 985; RR, 7.40 [95% CI, 2.94-18.65] at 3 months¹⁶ and 1 trial, n = 480; RR, 12.82 [95% CI, 4.71-34.85] at 12 months²⁵). For latanoprostene bunod

vs latanoprost (1 trial, n = 413¹⁰⁴) or timolol (2 trials, n = 840),¹⁰³ estimates for withdrawal due to adverse events indicated no differences or were imprecise (eTable 11 in the Supplement).

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?

Four trials (in 5 publications; n = 957) evaluated SLT vs a topical prostaglandin analogue (eTables 13 and 14 in the Supplement).^{42,43,65,80,81} All trials except for 1⁶⁵ were added for this update. The largest study was the good-quality Laser in Glaucoma and Ocular Hypertension Trial (LiGHT), which enrolled 718 participants with OAG (77%) or ocular hypertension (23%) and visual acuity approximately 20/120 or better; mean baseline IOP was 24.5 mm Hg.^{42,43} LiGHT found 360° SLT and medical therapy 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 (n = 32, 40, and 167) also found SLT and medical therapy associated with similar reduction in IOP at 4 to 12 months and 5 years^{65,80,81}; the trials did not evaluate other ocular and health outcomes.

Key Question 11. What are the harms of laser trabeculoplasty for OAG vs no trabeculoplasty or medical treatment?

The LiGHT trial found no differences between SLT and medical therapy in likelihood of any adverse event (73% vs 72%), ocular adverse events (52% vs 61%), or serious ocular adverse events (2.2% vs 1.7%) (eTable 13 in the Supplement).^{42,43} Evidence on harms of SLT vs medical therapy from other trials was limited by suboptimal reporting and imprecision.^{65,80,81}

Table 3. Medical Treatment vs Placebo/No Treatment, Pooled Analyses

Analysis	No. of trials	No.	Estimate, mean difference (95% CI)	I ² , %
Intraocular pressure	16	3706	-3.14 (-4.19 to -2.08)	95
Drug class ^a				
β-Blockers	9	455	-3.75 (-5.43 to -2.06)	92
Prostaglandin	1	516	-2.70 (-3.34 to -2.06)	NA
Alpha agonists	1	30	-2.30 (-3.52 to -1.08)	NA
Carbonic anhydrase inhibitors	4	1635	-1.20 (-2.30 to -0.61)	0
Mixed/various medications	1	817	-4.60 (-4.85 to -4.35)	NA
Baseline population ^a				
OHT	11	2745	-3.178 (-4.48 to -1.85)	95
Untreated OAG	2	506	-2.63 (-3.47 to -1.04)	0
Mixed status	3	455	-3.704 (-7.515 to -0.083)	83
Baseline IOP, mm Hg ^a				
<20	1	461	-2.70 (-3.34 to -2.06)	NA
≥20	15	3245	-3.17 (-4.30 to -2.03)	94
Quality ^a				
Fair	12	2555	-3.49 (-4.83 to -2.11)	94
Good	4	1151	-2.09 (-3.19 to -1.10)	74
Duration, y ^a				
<1	6	576	-2.66 (-4.52 to -0.86)	77
>1	10	3130	-3.38 (-4.75 to -2.00)	96
Progression	7	3771	RR, 0.68 (0.49 to 0.96)	53
Population ^b				
OAG	1	461	RR, 0.59 (0.41 to 0.86)	0
OHT	6	3310	RR, 0.71 (0.46 to 1.08)	57
Quality ^c				
Fair	4	1978	RR, 0.59 (0.31 to 1.20)	54
Good	3	1793	RR, 0.76 (0.52 to 1.30)	15
Progression of visual field defects	6	3679	RR, 0.73 (0.53 to 1.05)	25
Adverse effects				
Serious adverse events	3	3140	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: IOP, intraocular pressure; NA, not applicable; OAG, open-angle glaucoma; OHT, ocular hypertension; RR, risk ratio.

^a *P* < .001 for interaction.

^b *P* = .71 for interaction.

^c *P* = .36 for interaction.

Discussion

Table 4 summarizes the evidence reviewed for this update. Although 1 trial found no difference between vision screening (including components for glaucoma diagnosis) vs no screening on vision outcomes or vision-related quality of life,⁹⁵ the vision screening intervention was not specific for glaucoma, imaging was not used as part of the screening intervention, and the proportion of patients referred for glaucoma management was small. In addition, potential benefits could have been attenuated because most patients had visited an eye care professional in the prior year. Unexpectedly, the trial found screening associated with increased falls risk and potential increased fractured risk. The reason was unclear but could be due in part to evaluation of a frail elderly population at high falls risk or difficulty adapting to large corrections in vision or use of multifocal lenses. No study evaluated outcomes associated with referral to an eye health professional vs no referral.

For diagnostic accuracy, spectral-domain OCT and visual field assessment using the Humphrey Automated Field Analyzer were

associated with moderate to high accuracy for identifying glaucoma compared with a comprehensive eye examination. Although visual field assessment is generally performed in eye specialty settings, OCT could be ordered from a primary care clinic. Swept-source OCT, a newer OCT technology with increased scan speed and resolution, appears to provide improved visualization of ocular structures, but evidence on glaucoma diagnostic accuracy is currently limited.¹⁰⁹ Tonometry was associated with high specificity but low sensitivity, consistent with data indicating that a significant proportion of patients with glaucoma have normal IOP. As detailed in the full report, evidence on other screening tests, including swept-source OCT, optic disc photography, ophthalmoscopy and biomicroscopy, and pachymetry was limited.⁸ Evidence on risk instruments to identify persons with glaucoma was restricted to 1 study that showed low sensitivity⁷⁹; therefore, no well-validated risk assessment instrument is currently available.

Consistent with the 2013 review⁶ that informed the previous USPSTF recommendation on this topic, this update found first-line medical treatments associated with lower IOP; effects on mean IOP

Table 4. Summary of Evidence

Studies (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: 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) vs no screening on visual acuity (mean logMAR distance acuity, 0.27 vs 0.25; P = .32; and mean logMAR near visual acuity scores, -0.01 vs -0.03; P = .26) or vision-related quality of life (NEI-VFQ-25 mean composite scores, 84.3 vs 86.4; P = .49) after 1 y	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-fourths of control group visited 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
KQ2: 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 vs no screening (incidence rate ratio, 1.57 [95% CI, 1.20-2.05]); effects on risk of fractures was not statistically significant (RR, 1.74 [95% CI, 0.97-3.11])	Unable to assess consistency (1 study) Reasonably precise	See KQ1	Low for harm	See KQ1
KQ3: Effects of referral					
No studies	NA	NA	NA	Insufficient	NA
KQ4: 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, 0.75-0.83) and specificity, 0.92 (95% CI, 0.87-0.96) (15 studies, n = 4242); pooled AUROC, 0.90 (95% CI, 0.86-0.93) (16 studies, n = 4060) SD-OCT (GCC): Pooled sensitivity, 0.74 (95% CI, 0.68-0.80) and specificity, 0.91 (95% CI, 0.80-0.96) (9 studies, n = 1522); pooled AUROC, 0.88 (95% CI, 0.84-0.92) (6 studies, n = 765) Tonometry: Pooled sensitivity, 0.48 (95% CI, 0.31-0.66) and specificity, 0.94 (95% CI, 0.90-0.96) (13 studies, n = 32 892); AUROC ranged from 0.66 to 0.78 (3 studies, n = 4684) Visual fields (HFA): Pooled sensitivity, 0.87 (95% CI, 0.69-0.95) and specificity, 0.82 (95% CI, 0.66-0.92) (6 studies, n = 11244); pooled AUROC, 0.83 (95% CI, 0.70-0.97) (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 are 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 US, Europe, and Asia

(continued)

Table 4. Summary of Evidence (continued)

Studies (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ5: 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, 0.03-0.56]) but high specificity (0.96 [95% CI, 0.91-0.99]) 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 US; limited applicability to screening because previous glaucoma diagnosis was one of the most heavily weighted risk factors
KQ6: Effects of treatments vs placebo/no treatments					
17 Trials (9 in prior treatment CER, 8 new) (n = 4737)	IOP: Topical medical treatment associated with greater reduction in IOP vs placebo or no treatment (16 studies, n = 3706; 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 = 3771; RR, 0.68 [95% CI, 0.49-0.96]; 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 US, Europe, and Canada
KQ7: Harms of treatments vs placebo/no treatments					
8 Trials (3 in prior treatment CER, 5 new) (n = 3928)	No differences between medical therapy vs 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 vs placebo in 2 trials (RR, 1.21 [95% CI, 1.10-1.33] and RR, 3.52 [95% CI, 2.46-5.02])	Inconsistency present for withdrawal due to adverse events and any adverse events Imprecise	Harms not reported in most trials of medical therapies vs placebo or no treatment and inconsistent reporting in trials that reported harms	Low	See KQ6
KQ8: Effects of new vs older treatments					
8 Trials (KQ not addressed in the prior treatment CER) (n = 4113)	Recently approved medical therapies (netarsudil and latanoprostene bunod) were associated with similar or greater effects on IOP vs older medications	Consistent Precise	Most trials rated fair quality; duration of follow-up 3 mo in most trials (range, 1-12 mo); evidence on effects on vision, function, and quality of life NA	Moderate for similar or greater effects of new treatments	Trials conducted in multinational settings; trials enrolled mixed populations of patients with OAG or OHT
KQ9: Harms of new vs older treatments					
8 Trials (this KQ was not addressed in the prior treatment CER) (n = 4113)	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, 1.20-1.47]) vs 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 vs timolol (pooled RR, 1.72 [95% CI, 1.22-2.42])	Consistent Imprecision for some estimates	Most trials rated fair quality; duration of follow-up 3 mo in most trials (range, 1-12 mo)	Moderate	See KQ8

(continued)

Table 4. Summary of Evidence (continued)

Studies (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ10: 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 UK; patients randomized to medical therapy in LIGHT received a variety of medications to achieve a target IOP
KQ11: Harms of SLT					
4 Trials (1 in prior treatment CER and 3 new) (n = 957)	One trial (n = 718) found no differences between SLT vs medical therapy in risk of serious adverse events or any adverse event Evidence on harms from other trials of SLT vs medical therapies was limited by suboptimal reporting and imprecision	Unable to assess consistency (1 study) Reasonably precise	1	Moderate for no differences	See KQ10

Abbreviations: ARD, adjusted risk difference; AUROC, area under the receiver operating characteristic curve; CER, comparative effectiveness review; 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; NA, not available; NEI-VFQ, National Eye Institute Vision

vs placebo or no treatment generally ranged from 2 to 3 mm Hg. Medical treatments were also associated with reduced risk of glaucoma progression, based on visual field or optic disc changes. New evidence is available on effect of treatments on visual acuity and vision-related function or quality of life, most notably from the UKGTS,⁴¹ which compared latanoprost vs placebo and found no difference in visual acuity or overall or vision-related quality of life at 2 years. However, because visual acuity changes and associated effects on quality of life are a late finding of glaucoma progression, large studies with longer duration of follow-up would be necessary to adequately evaluate these outcomes. Data on harms of topical medical therapies were limited but did not indicate an increased risk of serious adverse events, although they were associated with nonserious ocular adverse events (eg, redness, irritation, itching, burning, tearing). Newly approved topical medications for glaucoma (netarsudil and latanoprost bunod) were associated with similar or greater IOP-reducing effects vs older medications but increased risk of adverse events. For SLT vs medical therapy, LIGHT found similar effects on IOP, visual acuity, visual field, and quality of life, with no differences in serious adverse events or ocular adverse events.^{42,43} Findings regarding treatment are most applicable to patients with ocular hypertension or early, untreated OAG, the populations typically enrolled in the trials.

Limitations

This evidence review has several limitations. First, there was statistical heterogeneity in pooled analyses on effects of medical therapy vs placebo or no treatment on IOP. However, inconsistency was in the magnitude but not direction of effect, which favored medical therapy across studies, and differences between drug classes in IOP-lowering effects were small (1 to 2 mm Hg). In addition, because of anticipated heterogeneity, a random-effects model was used for pooling. Second, statistical heterogeneity was also present in pooled analyses of sensitivity and specificity. However, standard bivariable methods for measuring statistical heterogeneity in studies of diagnostic accuracy do not account for the variability in sensitivity and specificity estimates related to threshold effects, and results were robust in stratified and sensitivity analyses. Third, direct evidence on benefits and harms of screening vs no screening and effects of treatment vs no treatment for ocular hypertension or early OAG on visual impairment, quality of life, and function remains very limited. Fourth, evaluations of publication bias through graphical or statistical methods were limited by small numbers of studies or statistical heterogeneity. However, this review did not identify unpublished studies likely to affect findings. Fifth, non-English-language studies were excluded, which could introduce language bias. However, no relevant non-English-language studies that appeared likely to affect conclusions were identified.

Conclusions

This review found limited direct evidence on glaucoma screening, showing no association with benefits. Screening tests can identify persons with glaucoma and treatment was associated with a lower risk of glaucoma progression, but evidence of improvement in visual outcomes, quality of life, and function remains lacking.

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