JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Impaired Visual Acuity in Older Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Roger Chou, MD; Christina Bougatsos, MPH; Rebecca Jungbauer, DrPH; Sara Grusing, MPH; Ian Blazina, MPH; Shelley Selph, MD, MPH; Daniel E. Jonas, MD, MPH; Shandiz Tehrani, MD, PhD

IMPORTANCE A 2016 review for the US Preventive Services Task Force (USPSTF) found that effective treatments are available for refractive errors, cataracts, and wet (advanced neovascular) or dry (atrophic) age-related macular degeneration (AMD), but there were no differences between visual screening vs no screening on visual acuity or other outcomes.

OBJECTIVE To update the 2016 review on screening for impaired visual acuity in older adults, 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 and controlled observational studies on screening, vascular endothelial growth factor (VEGF) inhibitors (wet AMD), and antioxidant vitamins and minerals (dry AMD); studies on screening diagnostic accuracy.

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

RESULTS Twenty-five studies (N = 33 586) were included (13 trials, 11 diagnostic accuracy studies, and 1 systematic review [19 trials]). Four trials (n = 4819) found no significant differences between screening vs no screening in visual acuity or other outcomes. Visual acuity tests (3 studies; n = 6493) and screening question (3 studies; n = 5203) were associated with suboptimal diagnostic accuracy. For wet AMD, 4 trials (n = 2086) found VEGF inhibitors significantly associated with greater likelihood of 15 or more letters visual acuity gain (risk ratio [RR], 2.92 [95% CI, 1.20-7.12]; I^2 = 76%; absolute risk difference [ARD], 10%) and less than 15 letters visual acuity loss (RR, 1.46 [95% CI, 1.22-1.75]; I^2 = 80%; ARD, 27%) vs sham treatment, with no increased risk of serious harms. For dry AMD, a systematic review (19 trials) found antioxidant multivitamins significantly associated with decreased risk of progression to late AMD (3 trials, n = 2445; odds ratio [OR], 0.72 [95% CI, 0.58-0.90]) and 3 lines or more visual acuity loss (1 trial, n = 1791; OR, 0.77 [95% CI, 0.62-0.96]) vs placebo. Zinc was significantly associated with increased risk of genitourinary events and beta carotene with increased risk of lung cancer in former smokers; other serious harms were infrequent.

CONCLUSIONS AND RELEVANCE This review found that effective treatments are available for common causes of impaired visual acuity in older adults. However, direct evidence found no significant association between vision screening vs no screening in primary care and improved visual outcomes.

Editorial
Multimedia
Related article and JAMA Patient Page
Supplemental content
Related articles at jamanetworkopen.com jamaophthalmology.com

Author Affiliations: Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland (Chou, Bougatsos, Jungbauer, Grusing, Blazina, Selph); Department of Family Medicine, Oregon Health & Science University; Portland (Selph); Department of Internal Medicine, The Ohio State University, Columbus (Jonas); RTI International, University of North Carolina at Chapel Hill Evidence-based Practice Center (Jonas); Casey Eye Institute, Department of Ophthalmology, Oregon Health & Science University; Portland (Tehrani).

Corresponding Author: Roger Chou, MD, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Mail Code: BICC, Portland, OR 97239 (chour@ohsu.edu).

JAMA. doi:10.1001/jama.2022.6381
Published online May 24, 2022.

Impaired visual acuity is common in older adults. In 2017, an estimated 53 million US adults older than 65 years were at high risk for serious vision loss, which can result in disability, loss of productivity, and reduced quality of life.[1] Rates of severe vision loss are predicted to double or triple as the number of older adults increases.[1-3]

In 2016, the US Preventive Services Task Force (USPSTF) concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for impaired visual acuity in older (≥65 years) adults (I statement).[4] Although a 2016 USPSTF review found that screening can identify persons with impaired visual acuity and that effective treatments are available for common causes of impaired visual acuity such as refractive error, cataracts, and wet (advanced neovascular [caused by leakage of abnormal blood vessels under the macula]) or dry (atrophic [caused by thinning of the macula]) age-related macular degeneration (AMD), direct evidence found no differences between vision screening in older adults in primary care settings vs no screening in visual acuity or other clinical outcomes.[5,6] This report was conducted to update the 2016 review on screening for impaired visual acuity in older adults, to inform the USPSTF for an updated recommendation.

Methods

Scope of the Review

Detailed methods and additional study details are available in the full evidence report.[7] **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 2015 to February 9, 2021 (eMethods 1 in the Supplement). Searches were supplemented by reference list review of relevant studies; studies from the prior USPSTF review[5,6] 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.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria (eMethods 2 in the Supplement). The population was older adults (65 years or older). Screening was performed with vision tests or questionnaires in primary care settings or were feasible for primary care (did not require eye specialty training or equipment) and compared against no screening. Treatment focused on benefits and harms of wet AMD (intravitreal vascular endothelial growth factor [VEGF] inhibitors) and dry AMD (vitamins and antioxidants). The USPSTF previously determined that treatments for refractive errors and cataracts are effective, and this was not rereviewed.[6,9] Treatment was compared against placebo or sham; in addition, newer VEGF inhibitors (aflibercept and brolucizumab-dbll) were compared against older VEGF inhibitors because of the lack of placebo-controlled trials. Outcomes were visual acuity, vision-related quality of life; functional capacity; and harms (including falls and fractures and other treatment-related harms). An updated version[10] of a systematic review[11] on treatment for dry AMD used in the prior USPSTF review was included. Otherwise this report used primary studies. 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.[8] Discrepancies were resolved by consensus. In accordance with the USPSTF Procedure Manual,[8] 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, reporting bias, and applicability, using the approach described in the USPSTF Procedure Manual.[8] No new evidence suitable for meta-analysis was identified for this review, owing to small numbers of studies and heterogeneity in populations, interventions, and outcomes. However, a random-effects meta-analysis conducted for the prior USPSTF review[6] on the effects of VEGF inhibitors remained relevant and was carried forward in this review.

Results

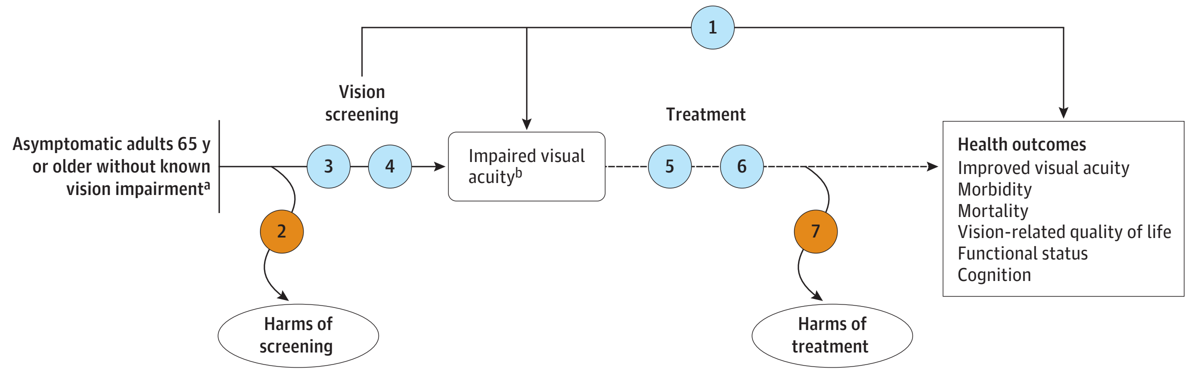
Across all KQs, 25 studies (reported in 51 publications, total N = 33 586 participants) were included (13 randomized clinical trials (RCTs), 11 diagnostic accuracy studies, and 1 systematic review) (**Figure 2**).[12-62] Sixteen studies[12, 14, 21, 23, 24, 27, 34, 35, 39, 42, 44, 46, 47, 52, 53, 58, 61] were carried forward from the 2016 USPSTF review,[5,6] 8 studies[17,19,20,29,33,41,43,57,61,62] were new, and an updated Cochrane systematic review[10] included 19 studies (the previous Cochrane review[11] included 13).[15, 16, 18, 22, 25, 26, 28, 30-32, 36, 37, 40, 49, 54-56, 59, 60]

Screening

Key Question 1. What are the effects of vision screening in asymptomatic older adults vs no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?

Four fair-quality RCTs[19,23,34,46,47,61] (in 6 publications; n = 4819) compared vision screening in primary care–applicable settings vs no screening, usual care, or delayed screening (eTable 1 in the Supplement; all were included in the 2016 USPSTF review except for 1 small (n = 188) trial.[19] The duration of follow-up ranged from 6 months to 5 years. Screening methods varied: a brief screening questionnaire plus the Glasgow visual acuity chart followed by pinhole testing for persons with visual acuity worse than 6/18 (20/60)[23]; assessment of difficulty in recognizing a face,

Figure 1. Analytic Framework and Key Questions: Screening for Impaired Visual Acuity in Older Adults



Key questions

1. What are the effects of vision screening in asymptomatic older adults vs no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?
2. What are the harms of vision screening in asymptomatic older adults vs no screening?
3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or age-related macular degeneration?
4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or age-related macular degeneration?
5. What are the effects of treatment for wet or dry age-related macular degeneration vs placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?
6. What are the effects of newer (aflibercept or brolucizumab-dbll) vs older vascular endothelial growth factor inhibitors for wet age-related macular degeneration on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?
7. What are the harms of treatment for early impaired visual acuity due to wet or dry age-related macular degeneration?

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.[8] Subpopulations of interest include those defined by age, sex, race and ethnicity, setting (eg, rural or urban), functional and cognitive status, etc.

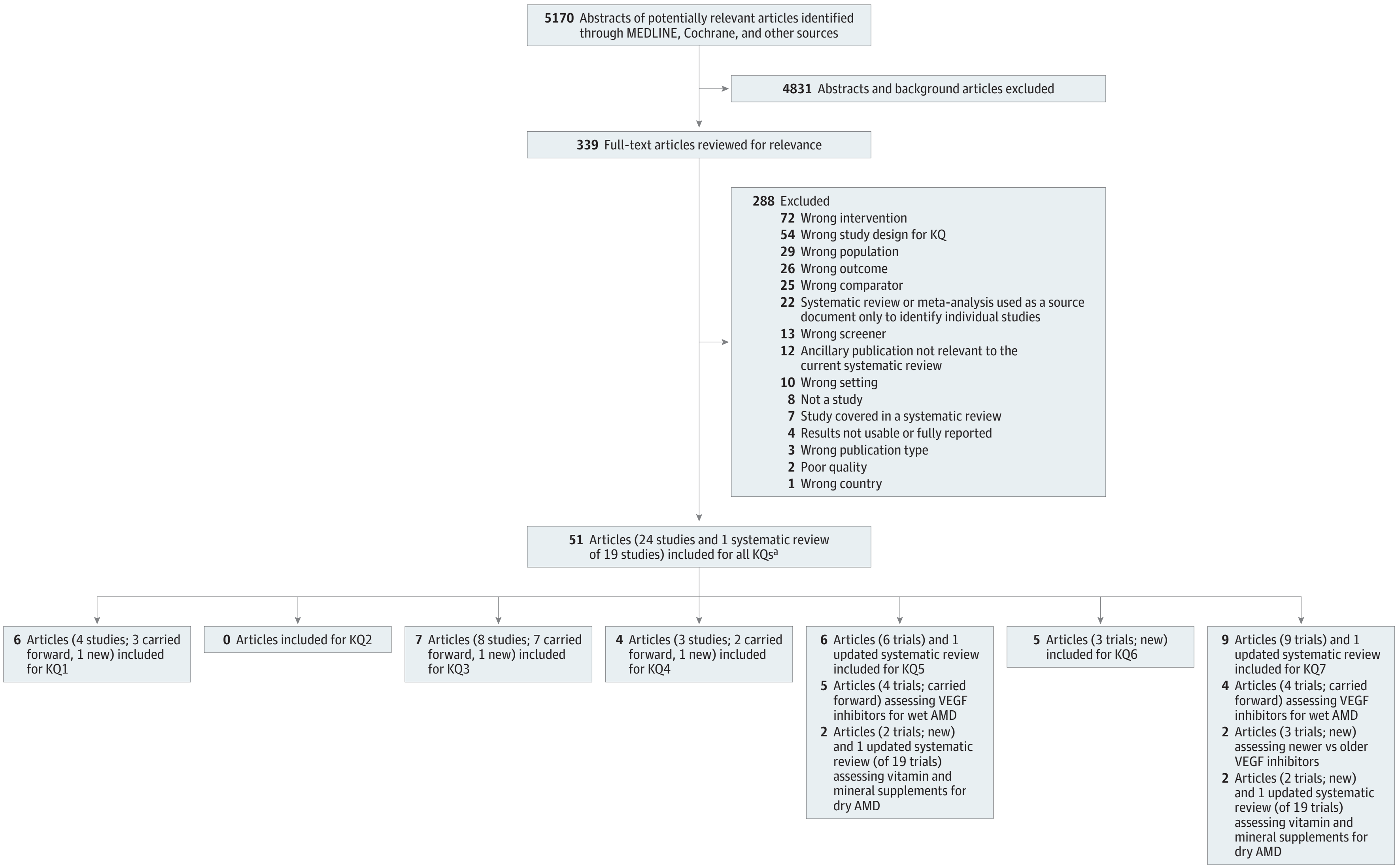
[a] Asymptomatic individuals defined as those without known impaired visual acuity (based on current corrected vision) who have not sought care for evaluation of vision problems.

[b] Conditions of interest include impaired visual acuity due to uncorrected refractive errors, cataracts, and age-related macular degeneration.

reading normal letters in a newspaper, or both, along with Snellen visual acuity eye chart[46,47]; a screening question and clinical summary followed by the Snellen eye chart[34]; and an Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart, measurement of binocular near vision and visual field testing, along with screening questions.[19] Three of the trials were conducted in community or general practice settings, and screening was conducted by general practitioners, office staff, or trained nurses. The additional trial[19] was conducted in a geriatric day hospital, although screening could be done via home visit if needed. Screening was conducted by study investigators (geriatric medicine or eye specialist) or an orthoptist, but the study was considered primary care–applicable because the screening methods consisted of visual acuity testing, binocular near vision, and visual field confrontation testing. Methodological limitations included unclear allocation concealment and blinding methods and high loss to follow-up (eTable 2 in the Supplement).

None of the trials, including the trials added for this update, found beneficial effects of screening on visual acuity, likelihood of vision disorders, or vision-related functional impairment or quality of life (**Table 1**). In the largest (n = 3249) trial, universal vision screening identified about 10 times as many patients with impaired visual acuity and correctable impairment compared with targeted screening, but there was no significant difference in the likelihood of visual acuity worse than 20/60 at 3- to 5-year follow-up (relative risk [RR], 1.07 [95% CI, 0.84-1.36]).[23] Another large (n = 1121) trial found no significant difference between immediate vs delayed screening in the likelihood of visual disorders at 2 years (51% [95% CI, 45%-58%] vs 47% [95% CI, 42%-52%]; $P = .68$).[46,47] Potential reasons for lack of screening benefit may include attrition (24% to nearly 60% in the larger trials at 2 to 5 years),[23,46,47] similar frequency of vision disorder detection and treatment in the screening and control groups,[34] use of a suboptimal method (a question) for initial screening,[34] low uptake of recommended

Figure 2. Literature Search Flow Diagram: Screening for Impaired Visual Acuity in Older Adults



AMD indicates Age-Related Macular Degeneration; AREDS, Age-Related Eye Disease Study; KQ, key question; VEGF, vascular endothelial growth factor.

[a] Number of articles includes the studies in the systematic review. The number of included studies does not sum to the number shown because some studies are included for more than 1 KQ.

Table 1. Screening Trials

Source	Intervention	Screening tools	Results
Eekhof et al,[46,47] 2000 From prior report	A. Vision screening (n = 576) B. Delayed screening (n = 545)	Validated diagnostic tests: Assessment of difficulty in recognizing a face at 4 m and/or reading normal letters in a newspaper, and/or impaired vision with both eyes by Snellen eye chart or not being able to read normal newspaper letters at 25 cm distance Vision was measured with glasses usually worn	A vs B: Vision disorder detected: 49% (95% CI, 43% to 54%) vs NR Visual disorder in second year: 51% (95% CI, 45%-58%) vs 47% (42%-52%); *P* = .68
Moore et al,[34] 1997 From prior report	A: Vision screening, coupled with clinical summaries (n = 112) B: Usual care (n = 149)	Question, "Do you have difficulty driving or watching television or reading or doing any of your daily activities because of your eyesight (even while wearing glasses)?" followed by Snellen eye chart if affirmative	A vs B: Vision problem detected: 20% vs 19%; *P* = .84 Improvement in vision at 6 mo: 20% (20/99) vs 24% (31/131); RR, 0.85 (95% CI, 0.52-1.40)
MRC Trial Smeeth et al,[23] 2003 From prior report	A: Universal screening (brief health assessment plus detailed health assessment, latter of which included measurement of VA [n = 1565]) B: Targeted screening (brief health assessment [n = 1684, 120 of which had a detailed assessment due to severity of problems, although 150 were eligible])	Detailed health assessment: VA measured using Glasgow acuity eye chart (Snellen equivalent provided in results), and pinhole testing if VA worse than 6/18 in either eye; referral to ophthalmologist when appropriate Brief health assessment: Covered all areas specified in the general practitioner contract, including a question about difficulty seeing, but did not include measurement of VA; those with a specified range and level of problems were eligible to have a detailed assessment Reporting difficulty seeing was not on its own sufficient to lead to a detailed assessment	A vs B, found to have VA worse than 6/18 (20/60) in either eye: 29% (451/1565) vs 3.1% (53/1684) Eligible for referral to ophthalmologist: 14% 220/1565) vs 1.7% (29/1684) Eligible for referral to optician: 5% (79/1565) vs 0.4% (8/1684) At follow-up: VA worse than 6/18 (20/60) in either eye at 3 y: 37% (307/829) vs 35% (339/978); RR, 1.07 (95% CI, 0.84-1.36) VA worse than 6/18 binocular vision: 14% (114/817) vs 17% (160/962); RR, 0.84 (95% CI, 0.64-1.10) VA worse than 6/12 in either eye: 59% (486/829) vs 60% (584/978); RR, 0.98 (95% CI, 0.82-1.17) VA worse than 6/12 binocular vision: 31% (256/817) vs 37% (351/962); RR, 0.86 (95% CI, 0.65-1.13) NEI-VFQ mean composite score (scale 0-100; higher score = better quality of life): 86.0 vs 85.6; mean difference, 0.4 (95% CI, −1.7 to 2.5)
ACCS Tay et al,[19] 2006 New	Routine aged care assessment and interview using a standardized questionnaire, plus A: Vision screening (n = 96) B: No vision screening (n = 92)	LogMAR chart for presenting VA for distance (with glasses, if worn) using letters read correctly using ETDRS-Fast protocol Binocular near vision and visual field using confrontation method Self-report questions: Did you notice any deterioration in one or both eyes? Are you able to recognize a friend across the street? Can you read the ordinary print in the newspaper reasonably well, with or without glasses?	A vs B: Mean VA: 39 letters vs 35 letters; *P* = .25 Bilateral visual impairment: 35% vs 47%; *P* = .17

Abbreviations: ACCS, Aged Care Client pilot Study; ETDRS, Early Treatment Diabetic Retinopathy Study; LogMAR, logarithmic minimum angle of resolution; MRC, Medical Research Counsel; NEI-VFQ, National Eye Institute Visual Function Questionnaire; NR, not reported; RR, relative risk; VA, visual acuity.

follow-up or interventions,[23,47] or high rates of antecedent eye professional care.[19]

Key Question 2. What are the harms of vision screening in asymptomatic older adults vs no screening?

No screening study reported harms.

Key Question 3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?

Eight fair-quality studies (n = 7398) examined the accuracy of screening tests for impaired visual acuity due to visual conditions such as cataracts, refractive error, and AMD in older adults (eTables 3-4 in the Supplement). Seven (reported in 6 publications)[12,14,21,35,39,58] were in the prior USPSTF review[6] and 1 study (n = 104)[57] was added. Screening was conducted using an eye chart (Snellen or logarithm of the minimum angle of resolution [logMAR], 3 studies),[12,14,58] a computerized tool based on 4 tests of vision function (2 studies),[39] the Minimum Data Set Vision Patterns section score (1 study),[21] geriatrician examination (1 study),[35] the Amsler grid (a grid of horizontal and vertical lines used for central visual field monitoring) (1 study),[58] or a mobile application.[57] Methodological limitations included failure to apply the reference standard in all patients, interpretation of the reference standard not independent from screening test results, and thresholds for a positive screening test result not prespecified (eTable 5 in the Supplement).

Three studies (n = 6493) evaluated screening visual acuity tests compared with a complete ophthalmologist examination. Based on a visual acuity threshold on screening of less than 20/30 or less than

20/40, sensitivity ranged from 0.27 to 0.75 and specificity from 0.51 to 0.87. One study each found low accuracy of a computer-based screening tool or the Minimum Data Set MDS Vision Patterns section score.[21,39] One study (n = 50) in the prior USPSTF review found a geriatrician examination had sensitivity of 1.0 (95% CI, 0.69-1.0) for cataract and 0.80 (95% CI, 0.28-0.99) for AMD compared with ophthalmologist examnation, with no false-positive results, but estimates were imprecise.[35] One new study found visual acuity screening using a mobile application associated with sensitivity of 0.98 (95% CI, 0.91-1.00) and specificity of 0.94 (95% CI, 0.82-0.99) for identifying visual acuity 20/40 or less compared with a visual acuity chart.[57]

Key Question 4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?

Two studies[42,46,47] (n = 1121 and n = 3997) included in the prior USPSTF review and 1 new study[33] (n = 85), all fair quality, found that screening questions were not accurate for identifying older persons with impaired visual acuity compared with an eye chart; all studies reported low sensitivity, low specificity, or both (eTables 6-8 in the Supplement). Sensitivities ranged from 0.17 to 0.81 and specificities from 0.19 to 0.84. Questions included asking about trouble recognizing faces, reading the newspaper, or seeing.

Treatment

Key Question 5. What are the effects of treatment for wet or dry AMD vs placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

VEGF Inhibitors for Wet AMD

Four good-quality RCTs (n = 2086; reported in 5 publications), all included in the prior USPSTF review, evaluated intravitreal injection with VEGF inhibitors vs sham injection.[24,27,44,52,53] At 1 year, intravitreal VEGF inhibitors were significantly associated with greater likelihood vs sham of 15 letters or more of visual acuity gain (RR, 2.92 95% CI, 1.20-7.12], I^2 = 76%; absolute risk difference [ARD], 10%); less than 15 letters of visual acuity loss (RR, 1.46 [95% CI, 1.22-1.75]; I^2 = 80%; ARD, 27%); and having vision 20/200 or better (RR, 1.47 [95% CI, 1.30-1.66]; I^2 = 42%; ARD, 24%) (eFigures 1-3 and eTables 9-10 in the Supplement).[24,27,44] In 1 trial,[52] VEGF inhibitors were significantly associated with better vision-related function and quality-of-life measures vs sham injection at 1 and 2 years. Differences on the National Eye Institute–Vision Function Questionnaire 25 (NEI-VFQ) composite and subscales were about 8 points on a 0 to 100 scale, or above the proposed threshold for a clinically important difference (4 to 6 points).[63]

Antioxidant Vitamins and Minerals for Dry AMD

The large (n = 3640), good-quality Age-Related Eye Disease Study[59] (AREDS), included in prior USPSTF reviews,[5,6] remains the key trial on treatment for dry AMD (eTables 11-12 in the Supplement). At 6.3 years, it found an antioxidant plus zinc combination significantly associated with decreased risk of progression to advanced AMD vs placebo (odds ratio [OR], 0.72 [99% CI, 0.52-0.98]).[59] In patients with more advanced (category 3 or 4) AMD, antioxidants plus zinc were significantly associated with decreased risk of visual acuity loss of 15 lines or more on the ETDRS (OR, 0.73 [99% CI, 0.54-0.99]). Ten-year results[64] were consistent with 6.3-year results.

An updated (2017) Cochrane systematic review[10] included 19 trials[15,16,18,22,25,26,28,30-32,36,37,40,49,54-56,59,60] (n = 11 162; 13 trials in the prior [2012] version[11]) of antioxidant multivitamins, zinc, lutein and zeaxanthin, or vitamin E for dry AMD; results were heavily influenced by AREDS (eTables 13-14 in the Supplement). Besides AREDS, the systematic review included the large (n = 4203) AREDS2 trial,[51,60] which evaluated the AREDS formulation or a variation of it (elimination of beta carotene, lowering of zinc dose, or both), and the Vitamin E, Cataract, and Age-related Maculopathy (VECAT) study (n = 1193).[18] In the other trials, sample sizes ranged from 14 to 433. The review found antioxidant multivitamins significantly associated with decreased risk of progression to late AMD (3 trials, n = 2445; OR, 0.72 [95% CI, 0.58-0.90]; 73% of patients from AREDS) and 3 lines or more visual acuity loss (1 trial [AREDS], n = 1791; OR, 0.77 [95% CI, 0.62-0.96]) vs placebo. Zinc was significantly associated with decreased risk of progression to late AMD vs placebo (3 trials, n = 3790; OR, 0.83 [95% CI, 0.70-0.98]; 96% of patients from AREDS) and decreased risk of 3 lines or more of visual acuity loss that was of borderline statistical significance (2 trials, n = 3791; RR, 0.87 [95% CI, 0.75-1.00]; 96% of patients from AREDS). Lutein and zeaxanthin or vitamin E were associated with little or no effect on risk of AMD progression. Data on effects of multivitamins on vision-related function were limited, with most trials showing no statistically significant differences.[18,25,28,65] AREDS found no differences between antioxidants, zinc, both, or placebo in measures of cognition at 6.9 years.[13]

Two additional fair-quality trials not included in the systematic review[20,29] evaluated an antioxidant combination or α-lipoic acid, but were small (n = 80 and 100) with imprecise estimates, and did not affect the findings of the systematic review (eTables 15-16 in the Supplement).

Key Question 6. What are the effects of newer (aflibercept or brolucizumab-dbll) vs older VEGF inhibitors for wet AMD on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

Three new good-quality trials (n = 2738; reported in 5 publications) compared aflibercept vs the older VEGF inhibitor ranibizumab (eTables 9-10 in the Supplement).[17,41,43,45,62] The duration of follow-up ranged from 1 year to 4 years. Aflibercept was noninferior to ranibizumab in likelihood of less than 15 ETDRS letters of visual acuity loss or 15 letters or more of visual acuity gain, and 2 trials (n = 2457) found similar improvements in vison-related function. No trial compared brolucizumab-dbll vs an older VEGF inhibitor.

Key Question 7. What are the harms of treatment for early impaired visual acuity due to wet or dry AMD?

VEGF Inhibitors for Wet AMD

There were no significant differences between VEGF inhibitors vs sham treatment in likelihood of withdrawal due to adverse events (eTables 9-10 in the Supplement). Evidence on the effects of VEGF inhibitors on other harms was limited.[6] Serious ocular harms were infrequent, and incidence of endophthalmitis (2 trials, n = 1924; RR, 5.49 [95% CI, 0.30-99] and RR, 8.33 [95% CI, 0.50-140]), ocular hemorrhage (1 trial, n = 184; RR, 0.52 [95% CI, 0.08-3.61]), and retinal detachment (2 trials, n = 1924; RR, 0.17 [95% CI, 0.01-4.07], and RR, 3.67 [95% CI, 0.20-65]) were similar in VEGF and sham treatment groups.[6,24,27,44] The studies were not sufficiently powered to assess rates of cardiovascular events or other serious adverse events, although no statistically significant differences were reported.[24,27,44,66]

Newer vs Older VEGF Inhibitors for Wet AMD

Three trials (n = 2738; reported in 2 publications) found that serious ocular adverse events and cardiovascular events were infrequent and occurred in similar proportions of patients randomized to aflibercept or ranibizumab (eTables 9-10 in the Supplement).[43,62]

Antioxidant Vitamins and Minerals for Dry AMD

AREDS found zinc use associated with increased risk of hospitalization due to genitourinary causes vs nonuse (7.5% vs 4.9%; RR, 1.47 [95% CI, 1.19-1.80])[38] and antioxidant use significantly associated with increased risk of yellow skin vs nonuse (8.3% vs 6.0%; RR, 1.38 [95% CI, 1.09-1.75]).[59] No active treatment in AREDS (antioxidants, zinc, or both) was associated with increased risk of other serious adverse events, which were uncommon (eTable 17 in the Supplement). In AREDS2, there were no differences between AREDS formulation variations and risk of serious adverse events.[60] However, in an analysis in which current smokers were excluded, the AREDS formulation with beta carotene was significantly associated with increased risk of lung cancer vs without beta carotene (2.0% vs 0.9%, $P = .04$). Almost all (91%) of the lung cancers occurred in former smokers.

VECAT (n = 1193), the largest trial other than AREDS and AREDS2, reported no serious adverse events with vitamin E or placebo, and no differences in risk of withdrawal due to adverse events or specific adverse events.[18] Evidence on harms from other trials was limited because of suboptimal reporting and imprecision but did not indicate increased risk of serious adverse events or withdrawal due to adverse events.

Discussion

This report evaluated evidence regarding screening for impaired visual acuity in older adults; the findings are summarized in **Table 2**. As in the prior review for the USPSTF, direct evidence on screening older adults for impaired visual acuity in primary care settings vs no screening, delayed screening, or usual care found no benefits on vision-related or other outcomes.[19,23,34,47,61] Potential reasons for lack of benefit in the screening trials may include high attrition, use of suboptimal screening interventions, low uptake of recommended interventions, or high rates of antecedent eye professional care. Recent reviews of vision screening in older adults in broader (eg, community and home-based) settings[67,68] also found no differences between screening vs no screening in vision or vision-related outcomes, even though they included a number of trials that did not meet inclusion criteria for this report because they did not evaluate the vision screening component separately or screening was conducted by an eye specialist and was not primary care feasible.

Conclusions regarding the suboptimal diagnostic accuracy of vision screening tests for identifying conditions associated with impaired visual acuity in primary care settings are also unchanged from the prior review for the USPSTF. No screening question is comparable in accuracy to tests of visual acuity for identifying impaired visual acuity,[42,46,69-71] and visual acuity testing with a chart is inaccurate for identifying visual conditions identified on a comprehensive ophthalmological examination. However, it is not known whether identification of cataracts or AMD prior to the development of impaired visual acuity is associated with improved clinical outcomes compared with identification after the development of mildly impaired visual acuity. Data on other screening tests was limited or indicated suboptimal performance.[21,39,57] There remains insufficient evidence to assess the accuracy or utility of pinhole testing, the Amsler grid, visual acuity tests other than the Snellen or ETDRS, physical examination, or funduscopic examination performed in primary care settings.

As in the prior review for the USPSTF, strong evidence supports the effectiveness of treatments for common causes of impaired visual acuity. The USPSTF previously determined that a very high proportion of patients experience favorable vision-related outcomes and improvement in vision-related quality of life following treatment for impaired visual acuity due to refractive error and cataracts; therefore, this evidence was not rereviewed for this update.[72] For dry AMD, evidence showing the effectiveness of antioxidant vitamins and minerals for slowing progression of disease or improving visual acuity remains largely based on the large AREDS trials, which included extended (10-year) follow-up.[49,59,73] Based on AREDS2 and other evidence[74] indicating an association between use of beta carotene and increased risk of lung cancer in smokers, recommendations[75] for current and former smokers are to avoid the AREDS formula with beta carotene, using lutein and zeaxanthin in its place. For wet AMD, this update focused on VEGF inhibitors, which are first-line treatment in most patients. As in the prior review for the USPSTF, VEGF inhibitors were associated with improvement in visual acuity–related outcomes, with a relatively low incidence of serious harms, although data on effects on vision-related quality of life or function are limited and inconclusive. One area of concern with VEGF inhibitors has been a potential association with increased risk of cardiovascular events.[76] Although randomized trials of VEGF inhibitors for AMD did not report increased risk of cardiovascular events, they were not designed to evaluate these outcomes and the number of events were small. Although new sham-controlled trials of VEGF inhibitors were not identified, head-to-head trials[43,77] of the recently approved US Food and Drug Administration (FDA)–approved VEGF inhibitor aflibercept vs an older VEGF inhibitor indicated similar effects on visual acuity–related outcomes and no difference in serious harms. No trial of the recently FDA-approved VEGF inhibitor brolucizumab-dbll met inclusion criteria. However, in May 2021, several ongoing brolucizumab-dbll trials were discontinued because of higher rates of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion.[78]

Limitations

This evidence review has several limitations. First, a previously published systematic review[10] on antioxidant multivitamins and minerals for dry AMD was used. The reliability of systematic reviews depends on how well they are designed and conducted. Therefore, the systematic review was required to meet a quality threshold based on predefined criteria,[79] and data abstraction and quality assessment of included trials was independently verified. Second, evidence on effectiveness of treatment for dry AMD relied heavily on results of a single trial—the large, well-conducted AREDS trial.[59]

Table 2. Summary of Evidence

Studies	Summary of findings	Evidence consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of screening					
4 Trials (3 in prior USPSTF review, 1 new) (4819 observations)	Four trials of screening vs no screening, usual care, or delayed screening in older adults found no difference on vision or other clinical outcomes in older adults	Consistent Reasonably precise	All studies rated fair quality Interventions and comparators differed across studies Adherence to recommended follow-up and interventions was low in some trials Attrition high in some trials Reporting bias not detected	Moderate for no benefit	Screening tests feasible for primary care Studies conducted in the US, Europe, and Australia Screening conducted in community or general practice settings or a geriatric day hospital Screening conducted by general practitioners, office staff, or trained nurses; vision screening was conducted as part of a multicomponent health screen
KQ2: Harms of screening					
No studies	No included trials reported harms of screening	NA	NA	Insufficient	NA
KQ3: Diagnostic accuracy of screening tests					
8 Cross-sectional studies (7 in prior USPSTF review, 1 new) (7398 observations)	Visual acuity tests (3 studies) were associated with poor diagnostic accuracy for identifying visual conditions compared with a complete examination by an ophthalmologist; evidence on other screening tests was limited	Consistent Precise	All studies rated fair quality Variability in screening tests and testing thresholds; test threshold not specified in some studies Clinical relevance of visual conditions identified on ophthalmological examination but not associated with impaired visual acuity unclear Some screening tests have not been validated Reporting bias not detected	Moderate	Screening tests were feasible for primary care Studies conducted in the US, UK, and Australia Variability in screening settings (primary care clinics, general eye clinics, hospitals, community day centers, and nursing homes); screener-trained research staff or unclear in some studies
KQ4: Diagnostic accuracy of screening instruments					
3 Cross-sectional studies (2 in prior USPSTF review, 1 new) (5203 observations)	Three studies found that a screening question was not accurate for identifying older persons with impaired visual acuity compared with a visual acuity chart	Consistent Reasonably precise	All studies rated fair quality Screening question varied across studies Reporting bias not detected	Moderate	Screening questions were highly feasible for primary care Studies conducted in the US and Europe
KQ5: Benefits of treatment for AMD vs placebo/no treatment					
VEGF inhibitors for wet AMD: 4 Trials (all in prior USPSTF review) (2086 observations)	Four trials of VEGF inhibitors were associated with greater likelihood of >15 letters (3 lines) of visual acuity gain (RR, 2.92 [95% CI, 1.20-7.12]; I^2 = 76%; ARD, 10%), <15 letters (3 lines) of visual acuity loss (RR, 1.46 [95% CI, 1.22-1.75]; I^2 = 80%; ARD, 27%), and having vision 20/200 or better (RR, 1.47 [95% CI, 1.30-1.66]; I^2 = 42%; ARD, 24%) at 1 y vs sham injection In 1 trial, VEGF inhibitors were associated with better vision-related function and quality-of-life measures vs sham injection at 1 and 2 y; the mean difference was above the threshold for a minimum clinically important difference	Consistent (statistical heterogeneity present in pooled analyses, but inconsistency was in magnitude of effect, not direction of effect) Precise	Data on function or quality of life limited to 1 trial Studies not designed to evaluate mortality or other health outcomes Reporting bias not detected	Moderate for benefit	VEGF inhibitors are considered first-line therapy in the US Baseline visual acuity 20/80 in 3 studies and ranged from 20/40 to 20/200 in 1 study Studies conducted in the US in 2 trials, and the others had various sites (US, Canada, Europe, Israel, Australia, South America)

(continued)

Table 2. Summary of Evidence (continued)

Studies	Summary of findings	Evidence consistency and precision	Other limitations	Strength of evidence	Applicability
Vitamin and mineral supplements for dry AMD: 1 Systematic review of 19 trials (n = 11 162) and 2 additional trial (180 observations) The prior USPSTF review included a prior version of the systematic review with 13 trials	Antioxidant multivitamins associated with decreased risk of progression to late AMD (3 trials, n = 2445; OR, 0.72 [95% CI, 0.58-0.90]) and >3 lines visual acuity loss (1 trial, n = 1791; OR, 0.77 [95% CI, 0.62-0.96]) vs placebo Zinc was associated with decreased risk of progression to late AMD vs placebo (3 trials, n = 3790; OR, 0.83 [95% CI, 0.70-0.98]; 96% of patients from AREDS) and decreased risk of visual acuity loss >3 lines that was of borderline statistical significance (2 trials, n = 3791; RR, 0.87 [95% CI, 0.75-1.00])	Consistent Precise	Findings primarily based on 1 study (AREDS) Heterogeneity in the interventions assessed	Moderate for benefit	AREDS was conducted in the US and the AREDS and AREDS2 formulations are widely used in clinical practice Baseline visual acuity was 20/32 or better in AREDS ≈75% of patients in AREDS had mild to moderate AMD at baseline
KQ6: Benefits of newer (aflibercept or brolucizumab-dbll) vs older VEGF inhibitors for AMD					
3 Trials (all new) (2738 observations)	Aflibercept was noninferior to ranibizumab in likelihood of <15 ETDRS letters of visual acuity loss (3 trials) and >15 letters of visual acuity gain (3 trials) and was similar to ranibizumab for vison-related function (2 trials)	Consistent Reasonably precise	No trial of brolucizumab-dbll met inclusion criteria Trials not designed to assess mortality or other health outcomes Reporting bias not detected	Moderate for similar benefit	Aflibercept was FDA approved for AMD in 2011 and with a longer dosing schedule in 2018 One trial was conducted in Australia and the others had various sites (US, Canada, international)
KQ7: Harms of treatment for AMD					
VEGF inhibitors for wet AMD: VEGF vs sham: 4 trials (all in prior USPSTF review) (2086 observations) Newer vs older VEGF inhibitors: 3 trials (all new) (2738 observations)	No differences between VEGF inhibitors vs sham injection in likelihood of withdrawal due to adverse events, cardiovascular events, or serious ocular adverse events Three trials found that serious ocular adverse events were infrequent and occurred in similar proportions of patients randomized to either aflibercept or ranibizumab	Consistent Imprecise	Trials not powered for serious cardiovascular or ocular adverse events Reporting bias not detected	Moderate for no harm	VEGF inhibitors vs sham: VEGF inhibitors are considered first-line therapy in the US Baseline visual acuity 20/80 in 3 studies and ranged from 20/40 to 20/200 in 1 study Studies were conducted in the US in 2 trials, and the others had various sites (US, Canada, Europe, Israel, Australia, South America) Newer vs older VEGF inhibitors: Aflibercept was FDA approved for AMD in 2011 and with a longer dosing schedule in 2018 One trial was conducted in Australia, and the others had various sites (US, Canada, international)
Vitamin and mineral supplements for dry AMD: 1 Systematic review of 19 trials (n = 11 162) and 2 additional trials (180 observations) The prior USPSTF review included a prior version of the systematic review with 13 trials	The AREDS trial found zinc use associated with increased risk for hospitalization due to genitourinary causes vs nonuse (7.5% vs 4.9%; RR, 1.47 [95% CI, 1.19-1.80]) and antioxidant use associated with increased risk of yellow skin compared with nonuse (8.3% vs 6.0%; RR, 1.38 [95% CI, 1.09-1.75]) The AREDS2 trial found the AREDS formulation with beta carotene associated with increased risk of lung cancer vs the AREDS formulation without beta carotene (2.0% vs 0.9%, *P* = .04); almost all (91%) of the lung cancers in this analysis occurred in former smokers (current smokers were excluded from the analysis) Evidence on harms of antioxidant vitamins and minerals for dry AMD was otherwise limited but did not indicate increased risk of serious adverse events or withdrawal due to adverse events	Consistent Precise for the AREDS formulation but imprecise for other antioxidant multivitamins and minerals	Trials not designed to evaluate harms, and reporting of harms from some trials was suboptimal	Moderate for harm (for AREDS formulation)	AREDS was conducted in the US and the AREDS and AREDS2 formulations are widely used in clinical practice Baseline visual acuity was 20/32 or better in AREDS ≈75% of patients in AREDS had mild to moderate AMD at baseline

Abbreviations: AMD, age-related macular degeneration; ARD, absolute risk difference; AREDS, Age-Related Eye Disease Studies; ETDRS, Early Treatment Diabetic Retinopathy Study; FDA, US Food and Drug Administration; KQ, key question; NA, not applicable; OR, odds ratio; RR, risk ratio; USPSTF, US Preventive Services Task Force; VEGF, vascular endothelial growth factor.

Third, 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. Fourth, there were too few randomized trials to perform formal assessments for publication bias with graphical or statistical methods for small sample effects. However, unpublished trials likely to affect findings were not identified. Fifth, there was statistical heterogeneity in some pooled analyses of VEGF inhibitors vs sham. However, inconsistency was in the magnitude of benefit, not direction of effect, which consistently favored VEGF inhibitors. In addition, because of anticipated heterogeneity, a random-effects model was used for pooling. Sixth, trials of screening vs no screening had methodological limitations, including high attrition and use of a suboptimal screening test. In some trials, low uptake of recommended interventions or a high rate of eye specialist care prior to screening could have attenuated potential benefits. In addition, the screening trials were published between 1997 and 2006, potentially reducing applicability to current clinical practice.

Conclusions

This review found that effective treatments are available for common causes of impaired visual acuity in older adults. However, direct evidence found no significant association between vision screening vs no screening in primary care and improved visual outcomes.

ARTICLE INFORMATION

Accepted for Publication: April 5, 2022.

Published Online: May 24, 2022. doi:10.1001/jama.2022.6381

Author Contributions: Dr Chou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.
Concept and design: Chou, Jonas.
Acquisition, analysis, or interpretation of data: Chou, Bougatsos, Jungbauer, Grusing, Blazina, Selph, Tehrani.
Drafting of the manuscript: Chou, Bougatsos, Jungbauer, Grusing, Blazina.
Critical revision of the manuscript for important intellectual content: Chou, Blazina, Selph, Jonas, Tehrani.
Statistical analysis: Chou, Blazina.
Obtained funding: Chou, Bougatsos, Jonas.
Administrative, technical, or material support: Bougatsos, Jungbauer, Grusing, Blazina, Jonas, Tehrani.
Supervision: Chou, Bougatsos, Jonas, Tehrani.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under contract HHSA-290-2015-00011-I, Task Order 75Q80119F32015, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We thank the following individuals for their contributions to this project: Pacific Northwest Evidence-based Practice Center Librarian, Tracy Dana, MLS; Agency for Healthcare Research and Quality Medical Officer, Justin Mills, MD, MPH; as well as the US Preventive Services Task Force. We also acknowledge past and current USPSTF members who contributed to topic deliberations. The USPSTF members, external reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 4 content experts (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; and 1 nondisclosed reviewer) and federal partners representing the Centers for Disease Control and Prevention. Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence report.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

REFERENCES

1. Saydah SH, Gerzoff RB, Saaddine JB, Zhang X, Cotch MF. Eye care among US adults at high risk for vision loss in the United States in 2002 and 2017. *JAMA Ophthalmol*. 2020;138(5):479-489. doi:10.1001/jamaophthalmol.2020.0273

2. American Foundation for the Blind. Aging and vision loss fact sheet. Published 2013. Accessed October 15, 2014. https://www.afb.org/info/programs-and-services/professional-development/experts-guide/aging-and-vision-loss/1235

3. Swenor BK, Ehrlich JR. Ageing and vision loss: looking to the future. *Lancet Glob Health*. 2021;9(4):e385-e386. doi:10.1016/S2214-109X(21)00031-0

4. US Preventive Services Task Force. Screening for impaired visual acuity in older adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315(9):908-914. doi:10.1001/jama.2016.0763

5. Chou R, Dana T, Bougatsos C, Grusing S, Blazina I. Screening for impaired visual acuity in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;315(9):915-933. doi:10.1001/jama.2016.0783

6. Chou R, Dana T, Bougatsos C, et al. *Screening for Impaired Visual Acuity in Older Adults: A Systematic Review to Update the 2009 US Preventive Services Task Force Recommendation*. Agency for Healthcare Research and Quality; 2016.

7. Chou R, Selph S, Blazina I, et al. *Screening for Impaired Visual Acuity in Older Adults: A Systematic Review for the US Preventive Services Task Force. Evidence Synthesis No. 213*. Agency for Healthcare Research and Quality; 2022. AHRQ publication 21-05285-EF-1.

8. US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Published 2018. Accessed September 16, 2020. https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual

9. Chou R, Dana T, Bougatsos C. Screening older adults for impaired visual acuity: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med*. 2009;151(1):44-58. doi:10.7326/0003-4819-151-1-200907070-00008

10. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2017;7:CD000253. doi:10.1002/14651858.CD000253.pub4

11. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev*. 2012;11:CD000254. doi:10.1002/14651858

12. Ivers RQ, Optom B, Macaskill P, et al. Sensitivity and specificity of tests to detect eye disease in an older population. *Ophthalmology*. 2001;108(5):968-975. doi:10.1016/s0161-6420(00)00649-7

13. Yaffe K, Clemons TE, McBee WL, Lindblad AS; Age-Related Eye Disease Study Research Group. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology*. 2004;63(9):1705-1707. doi:10.1212/01.WNL.0000142969.19465.8F

14. Woods RL, Tregear SJ, Mitchell RA. Screening for ophthalmic disease in older subjects using visual acuity and contrast sensitivity. *Ophthalmology*. 1998;105(12):2318-2326. doi:10.1016/S0161-6420(98)91235-0

15. Weigert G, Kaya S, Pemp B, et al. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(11):8174-8178. doi:10.1167/iovs.11-7522

16. Wang H, Li R, Wang M. Effects of zinc and antioxidant on visual function of patients with age-related macular degeneration. *Zhongguo Linchuang Kangfu*. 2004;8:1290-1291.

17. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. *Ophthalmology*. 2016;123(7):1521-1529. doi:10.1016/j.ophtha.2016.03.037

18. Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil JJ. Vitamin E supplementation and macular degeneration: randomised controlled trial. *BMJ*. 2002;325(7354):11. doi:10.1136/bmj.325.7354.11

19. Tay T, Rochtchina E, Mitchell P, Lindley R, Wang JJ. Eye care service utilization in older people seeking aged care. *Clin Exp Ophthalmol*. 2006;34(2):141-145. doi:10.1111/j.1442-9071.2006.01139.x

20. Tao Y, Jiang P, Wei Y, et al. α-Lipoic acid treatment improves vision-related quality of life in patients with dry age-related macular degeneration. *Tohoku J Exp Med*. 2016;240(3):209-214. doi:10.1620/tjem.240.209

21. Swanson MW, McGwin G Jr, Elliott AF, Owsley C. The nursing home minimum data set for vision and its association with visual acuity and contrast sensitivity. *J Am Geriatr Soc*. 2009;57(3):486-491. doi:10.1111/j.1532-5415.2008.02144.x

22. Stur M, Tittl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1996;37(7):1225-1235.

23. Smeeth L, Fletcher AE, Hanciles S, Evans J, Wormald R. Screening older people for impaired vision in primary care: cluster randomised trial. *BMJ*. 2003;327(7422):1027-1031. doi:10.1136/bmj.327.7422.1027

24. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431. doi:10.1056/NEJMoa054481

25. Richer S, Stiles W, Statkute L, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry*. 2004;75(4):216-230. doi:10.1016/S1529-1839(04)70049-4

26. Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study—part 2: antioxidant intervention and conclusions. *J Am Optom Assoc*. 1996;67(1):30-49.

27. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145(2):239-248. doi:10.1016/j.ajo.2007.10.004

28. Piermarocchi S, Saviano S, Parisi V, et al; Carmis Study Group. Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. *Eur J Ophthalmol*. 2012;22(2):216-225. doi:10.5301/ejo.5000069

29. Piatti A, Croce A, Mazzacane D, et al. Effect of 2-year nutritional supplementation on progression of age-related macular degeneration. *Eur J Ophthalmol*. 2020;30(2):376-381. doi:10.1177/1120672119836007

30. Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. *Arch Ophthalmol*. 1988;106(2):192-198. doi:10.1001/archopht.1988.01060130202026

31. Newsome DA. A randomized, prospective, placebo-controlled clinical trial of a novel zinc-monocysteine compound in age-related macular degeneration. *Curr Eye Res*. 2008;33(7):591-598. doi:10.1080/02713680802178437

32. Murray IJ, Makridaki M, van der Veen RLP, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. *Invest Ophthalmol Vis Sci*. 2013;54(3):1781-1788. doi:10.1167/iovs.12-10715

33. Mueller YK, Monod S, Locatelli I, et al. Performance of a brief geriatric evaluation compared to a comprehensive geriatric assessment for detection of geriatric syndromes in family medicine: a prospective diagnostic study. *BMC Geriatr*. 2018;18(1):72. doi:10.1186/s12877-018-0761-z

34. Moore AA, Siu A, Partridge JM, et al. A randomized trial of office-based screening for common problems in older persons. *Am J Med*. 1997;102(4):371-378. doi:10.1016/s0002-9343(97)00089-2

35. McMurdo ME, Baines PS. The detection of visual disability in the elderly. *Health Bull (Edinb)*. 1988;46(6):327-329.

36. Ma L, Yan SF, Huang YM, et al. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. *Ophthalmology*. 2012;119(11):2290-2297. doi:10.1016/j.ophtha.2012.06.014

37. Kaiser HJ, Flammer J, Stümpfig D, Hendrickson P. Visaline in the treatment of age-related macular degeneration: a pilot study. *Ophthalmologica*. 1995;209(6):302-305. doi:10.1159/000310646

38. Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *J Urol*. 2007;177(2):639-643. doi:10.1016/j.juro.2006.09.047

39. Jessa Z, Evans BJW, Thomson DW. The development & evaluation of two vision screening tools for correctable visual loss in older people. *Ophthalmic Physiol Opt*. 2012;32(4):332-348. doi:10.1111/j.1475-1313.2012.00919.x

40. Holz F, Wolfensberger T, Piguet B, et al. Oral zinc-therapy in age-related macular degeneration: a double blind study. *Ger J Ophthalmol*. 1993;2(suppl):391.

41. Ho AC, Saroj N, Baker K, et al. Impact of baseline characteristics on treatment response to intravitreal aflibercept injection for wet age-related macular degeneration. *Ophthalmol Retina*. 2018;2(7):676-683. doi:10.1016/j.oret.2017.10.017

42. Hiller R, Krueger DE. Validity of a survey question as a measure of visual acuity impairment. *Am J Public Health*. 1983;73(1):93-96. doi:10.2105/AJPH.73.1.93

43. Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

44. Gragoudas ES, Adamis AP, Cunningham ET, et al. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351(27):2805-2816. doi:10.1056/NEJMoa042760

45. Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(4):372-379. doi:10.1001/jamaophthalmol.2018.6776

46. Eekhof JA, De Bock GH, Schaapveld K, et al. Screening for hearing and visual loss among elderly with questionnaires and tests: which method is the most convincing for action? *Scand J Prim Health Care*. 2000;18(4):203-207. doi:10.1080/028134300448751

47. Eekhof J, De Bock G, Schaapveld K, et al. Effects of screening for disorders among the elderly: an intervention study in general practice. *Fam Pract*. 2000;17(4):329-333. doi:10.1093/fampra/17.4.329

48. Chew EY, Sperduto RD, Milton RC, et al. Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25. *Ophthalmology*. 2009;116(2):297-303. doi:10.1016/j.ophtha.2008.09.019

49. Chew EY, Clemons TE, Agrón E, et al; Age-Related Eye Disease Study Research Group. Long-term effects of vitamins C and E, β-carotene, and zinc on age-related macular degeneration: AREDS report no. 35. *Ophthalmology*. 2013;120(8):1604-1611. doi:10.1016/j.ophtha.2013.01.021

50. Chew EY, Clemons TE, Agrón E, Launer LJ, Grodstein F, Bernstein PS; Age-Related Eye Disease Study 2 (AREDS2) Research Group. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. *JAMA*. 2015;314(8):791-801. doi:10.1001/jama.2015.9677

51. Chew EY, Clemons T, SanGiovanni JP, et al; AREDS2 Research Group. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282-2289. doi:10.1016/j.ophtha.2012.05.027

52. Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR; MARINA Study Group. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. *Arch Ophthalmol*. 2007;125(11):1460-1469. doi:10.1001/archopht.125.11.1460

53. Bressler NM, Chang TS, Varma R, et al. Driving ability reported by neovascular age-related macular degeneration patients after treatment with ranibizumab. *Ophthalmology*. 2013;120(1):160-168. doi:10.1016/j.ophtha.2012.07.027

54. Berrow EJ, Bartlett HE, Eperjesi F, Gibson JM. The effects of a lutein-based supplement on objective and subjective measures of retinal and visual function in eyes with age-related maculopathy—a randomised controlled trial. *Br J Nutr*. 2013;109(11):2008-2014. doi:10.1017/S0007114512004187

55. Beatty S, Chakravarthy U, Nolan JM, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. *Ophthalmology*. 2013;120(3):600-606. doi:10.1016/j.ophtha.2012.08.040

56. Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease:

a randomized controlled trial. *Eur J Clin Nutr*. 2007;61(9):1121-1127. doi:10.1038/sj.ejcn.1602626

57. Arora KS, Chang DS, Supakontanasan W, Lakkur M, Friedman DS. Assessment of a rapid method to determine approximate visual acuity in large surveys and other such settings. *Am J Ophthalmol*. 2014;157(6):1315-1321. doi:10.1016/j.ajo.2014.02.031

58. Ariyasu RG, Lee PP, Linton KP, LaBree LD, Azen SP, Siu AL. Sensitivity, specificity, and predictive values of screening tests for eye conditions in a clinic-based population. *Ophthalmology*. 1996;103(11):1751-1760. doi:10.1016/S0161-6420(96)30431-4

59. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417-1436. doi:10.1001/archopht.119.10.1417

60. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005-2015. doi:10.1001/jama.2013.4997

61. Jee J, Wang JJ, Rose K, Landau P, Lindley R, Mitchell P. Incorporating vision and hearing tests into aged care assessment: methods and the pilot study. *Ophthalmic Epidemiol*. 2004;11(5):427-436. doi:10.1080/09286580490888807

62. Gillies MC, Hunyor AP, Arnold JJ, et al. Macular atrophy in neovascular age-related macular degeneration: a randomized clinical trial comparing ranibizumab and aflibercept (RIVAL study). *Ophthalmology*. 2020;127(2):198-210. doi:10.1016/j.ophtha.2019.08.023

63. Clemons TE, Chew EY, Peto T, et al. Responsiveness and the minimal clinically important difference for the NEI VFQ-25 in patients with macular telangectasia type 2 (MacTel Type 2). *Invest Ophthalmol Vis Sci*. 2015;56(7):1360.

64. Chew EY, Clemons TE, Agrón E, et al; Age-Related Eye Disease Study Research Group. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132(3):272-277. doi:10.1001/jamaophthalmol.2013.6636

65. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. *Biomed Res Int*. 2015;2015(564738):564738. doi:10.1155/2015/564738

66. D'Amico DJ, Masonson HN, Patel M, et al; VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology*. 2006;113(6):992-1001. doi:10.1016/j.ophtha.2006.02.027

67. Clarke EL, Evans JR, Smeeth L. Community screening for visual impairment in older people. *Cochrane Database Syst Rev*. 2018;2:CD001054. doi:10.1002/14651858.CD001054.pub3

68. Pillay J, Freeman EE, Hodge W, et al. Screening for impaired visual acuity and vision-related functional limitations in adults 65 years and older in primary health care: systematic review. Published 2017. Accessed May 8, 2020. https://canadiantaskforce.ca/ctfphc-guidelines/overview/

69. Stone DH, Shannon DJ. Screening for impaired visual acuity in middle age in general practice. *Br Med J*. 1978;2(6141):859-861. doi:10.1136/bmj.2.6141.859

70. Chu-Ai Teh R, Lim WS, Basri R, Ismail NH. Utility of a patient-response screening question for visual impairment. *J Am Geriatr Soc*. 2006;54(2):370-372. doi:10.1111/j.1532-5415.2005.00592_4.x

71. Wang F, Tielsch JM, Ford DE, et al. Evaluation of screening schemes for eye disease in a primary care setting. *Ophthalmic Epidemiol*. 1998;5(2):69-82. doi:10.1076/opep.5.2.69.1575

72. Chou R, Dana T, Bougatsos C. *Screening for Visual Impairment in Older Adults: Systematic Review to Update the 1996 US Preventive Services Task Force Recommendation. Evidence Synthesis No. 71*. Agency for Healthcare Research and Quality; 2009. AHRQ publication 09-05135-EF-1.

73. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2008;(1):CD000253. doi:10.1002/14651858.CD000253.pub2

74. Tanvetyanon T, Bepler G. Beta-carotene in multivitamins and the possible risk of lung cancer among smokers versus former smokers: a meta-analysis and evaluation of national brands. *Cancer*. 2008;113(1):150-157. doi:10.1002/cncr.23527

75. National Eye Institute. AREDS/AREDS2 clinical trials. Published 2020. Accessed September 5, 2020. https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/about-areds-and-areds2

76. Yashkin AP, Hahn P, Sloan FA. Introducing anti-vascular endothelial growth factor therapies for AMD did not raise risk of myocardial infarction, stroke, and death. *Ophthalmology*. 2016;123(10):2225-2231. doi:10.1016/j.ophtha.2016.06.053

77. Gillies M, Arnold J, Bhandari S, et al. Ten-year treatment outcomes of neovascular age-related macular degeneration from two regions. *Am J Ophthalmol*. 2020;210(210):116-124. doi:10.1016/j.ajo.2019.10.007

78. Beovu's future: reasons for uncertainty and hope. *Review of Ophthalmology*. Published July 15, 2021. Accessed November 6, 2021. https://reviewofophthalmology.com/article/beovus-future-reasons-for-uncertainty-and-hope

79. Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. *Ann Intern Med*. 2008;148(10):776-782. doi:10.7326/0003-4819-148-10-200805200-00010