SOMATO PUBLICATIONS ISSN: XXXX-XXXX

Annals of Ophthalmology and Eye Disorders

Review Article

optical coherence tomography in the Management of age-related macular degeneration among elderly patients with vision loss

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Received: 20 August 2019; Accepted: 10 November 2019; Published: 3 February 2020.

Citation of this article: Greco D, Romano C, Colombo E (2020) optical coherence tomography in the Management of age-related macular degeneration among elderly patients with vision loss. Ann Ophthalmol Eye Disord, 2(1): 01-06. DOI: 10.5281/zenodo.22811919

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Abstract

Background: Age-related macular degeneration is a leading cause of irreversible vision loss among elderly patients, and optical coherence tomography is now the reference standard for diagnosing and monitoring its neovascular and atrophic forms [1,6].

Objective: This review synthesizes evidence on OCT-based classification of AMD, its role guiding anti-VEGF treat-and-extend regimens, and its relationship to low-vision rehabilitation needs of elderly patients with persistent vision loss.

Methods: We synthesized pivotal anti-VEGF trials, OCT classification reports, treat-and-extend comparative studies, epidemiological cohorts, and low-vision rehabilitation outcome studies addressing OCT-guided AMD management.

Findings: OCT biomarkers including subretinal and intraretinal fluid and pigment epithelial detachment drive anti-VEGF re-treatment decisions [14]; OCT-guided treat-and-extend regimens achieve outcomes comparable to monthly dosing with fewer injections [25,26,27]. Many elderly patients retain disabling vision loss despite treatment, for whom low-vision rehabilitation yields significant functional gains [30].

Conclusions: OCT is now the structural backbone of AMD management in elderly patients, and pairing OCT-guided anti-VEGF dosing with timely low-vision rehabilitation referral represents the current standard of care [10,1].

Keywords: optical coherence tomography; age-related macular degeneration; anti-VEGF therapy; treat-and-extend; low-vision rehabilitation

1. Introduction

Age-related macular degeneration is now the leading cause of irreversible central vision loss in older adults in high-income countries, and its global burden is projected to keep rising simply because the population at risk is aging faster than any preventive intervention can offset [1,2]. A meaningful minority of adults over 75 show early disease on fundoscopy, and a smaller but clinically important fraction progress to the neovascular or atrophic late stages that threaten reading and face-recognition vision [3,4]. Because the two late phenotypes -- neovascular AMD and geographic atrophy -- have such different natural histories and treatment options, accurate, repeatable structural imaging has become the backbone of everyday clinical decision-making rather than a research adjunct.

Optical coherence tomography supplied exactly that capability. First described as a cross-sectional retinal imaging technique in 1991 [5], OCT was applied to AMD within a few years, when Hee and colleagues showed it could resolve subretinal fluid, pigment epithelial detachment, and the reflective signature of neovascular membranes at a resolution no other instrument could match [6]. Three decades later, spectral-domain and swept-source OCT are the reference standard for diagnosing, staging, and monitoring both forms of late AMD, and OCT angiography has added a dye-free view of the neovascular complex itself [7]. Comprehensive reviews of AMD, including de Jong's synthesis and the Lancet seminar by Mitchell and colleagues, both place OCT-based monitoring at the center of contemporary practice [8,9]. This review synthesizes what the literature has established about OCT's role in managing AMD in elderly patients with vision loss: how OCT biomarkers guide anti-VEGF treat-and-extend regimens, how OCT-based classification standardizes atrophy monitoring, and how imaging findings intersect with low-vision rehabilitation needs.

2. Methods

We synthesized the peer-reviewed literature on OCT-guided AMD management, drawing on pivotal anti-VEGF randomized trials (MARINA, ANCHOR, CATT, VIEW, PIER, TREX-AMD, TREND, and FLUID), OCT validation and consensus-nomenclature papers, population-based epidemiological cohorts, and low-vision rehabilitation outcome studies identified from consensus statements and reading-center working groups across the retina literature. Emphasis was placed on OCT-defined structural biomarkers, visual acuity outcomes under differing dosing intervals, and rehabilitation outcomes, rather than an exhaustive systematic search of every retinal-imaging publication.

3. Epidemiology of AMD and Vision Loss in the Elderly

Age is the dominant risk factor for every stage of AMD. The Beaver Dam Eye Study's fifteen-year incidence data showed late AMD rising sharply beyond age 75 [4], and Friedman and colleagues, pooling US surveys, estimated that neovascular AMD and geographic atrophy together affected well over a million Americans, concentrated overwhelmingly in the 80-and-older band, confirming AMD as the leading cause of legal blindness among white Americans [3]. Wong and colleagues' global meta-analysis projected the worldwide burden climbing from roughly 196 million in 2020 to nearly 288 million by 2040, driven almost entirely by population aging [1], and Rein and colleagues' US forecast reached a similar conclusion even after modeling anti-VEGF uptake [2]. Elderly AMD patients also frequently carry comorbid cataract, cognitive impairment, or mobility limitations that make monthly injection visits burdensome, in exactly the age group that most needs preserved central vision and is least able to tolerate an inefficient monitoring schedule.

4. OCT-Based Classification and Monitoring of AMD

Standardized OCT nomenclature has been essential to

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making imaging findings comparable across clinics and trials. Ferris and colleagues' clinical classification scheme divided AMD into no apparent aging changes, early, intermediate, and late disease, anchoring the late category on neovascular AMD or geographic atrophy detected by multimodal imaging including OCT [10]. Staurenghi and colleagues' IN*OCT consensus supplied a common vocabulary for retinal layers and features on spectral-domain OCT, making trial endpoints and reading-center adjudication reproducible [11]. The Classification of Atrophy Report 3 by Sadda and colleagues defined OCT-based criteria for retinal pigment epithelium and outer retinal atrophy now used across geographic-atrophy trials [12], and Spaide and colleagues' CONAN consensus did analogous work for neovascular AMD reporting [13].

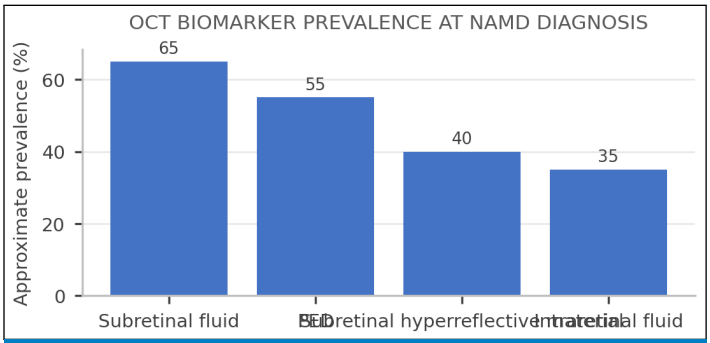


Figure 1: Approximate prevalence of principal OCT biomarkers at diagnosis of treatment-naive neovascular age-related macular degeneration, drawn from OCT morphology and biomarker literature underlying current anti-VEGF treatment decisions [7,15,14].

At the level of individual patients, OCT biomarkers now drive most treatment decisions in neovascular AMD. Intraretinal fluid, subretinal fluid, pigment epithelial detachment, and subretinal hyperreflective material each carry distinct prognostic weight, and Waldstein and colleagues' post hoc analysis found that morphologic parameters, particularly the presence and location of retinal fluid, predicted visual acuity outcomes more reliably than clinical variables alone [14]. Figure 1 summarizes the approximate prevalence of principal OCT biomarkers at diagnosis of treatment-naive neovascular AMD, a pattern that now informs how clinicians triage new patients into urgent versus routine anti-VEGF pathways [7,15]. Geographic atrophy monitoring relies on a distinct OCT signature: progressive loss of the ellipsoid zone, external limiting membrane, and retinal pigment epithelium, tracked as lesion area expands, as Holz and colleagues characterized in detail [16].

5. Anti-VEGF Treat-and-Extend Regimens Guided by OCT

The randomized trials that established anti-VEGF therapy as the standard of care for neovascular AMD were built on fixed monthly or bimonthly dosing, setting the benchmark against which every OCT-guided regimen has since been measured. Rosenfeld and colleagues' MARINA trial showed that monthly ranibizumab produced a mean gain of roughly 7 letters at 12 months against a loss of over 10 letters with sham treatment [17], and Brown and colleagues' companion ANCHOR trial found an even larger gain, on the order of 11 letters, against photodynamic therapy [18]. Regillo and colleagues' PIER study showed that fixed quarterly dosing after loading failed to sustain gains, an early signal that extended intervals without imaging-based triggers could under-treat active disease [19]. Heier and colleagues' VIEW 1 and VIEW 2 trials showed that aflibercept every eight weeks was non-inferior to monthly ranibizumab [20]. Table 1 summarizes outcomes across these trials together with the comparative CATT program.

Table 1: Visual acuity outcomes at approximately 12 months across pivotal fixed-dosing and comparative anti-VEGF trials in neovascular AMD [17,18,20,21,19].

Trial	Agent(s) / regimen	Duration	Mean VA change
[17]	Ranibizumab monthly vs sham	12 months	Approximately +7 letters vs -10 letters
[18]	Ranibizumab monthly vs photodynamic therapy	12 months	Approximately +11 letters vs -10 letters
[20]	Aflibercept every 8 weeks vs ranibizumab monthly	12 months	Non-inferior, approximately +8 letters both arms

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Trial	Agent(s) / regimen	Duration	Mean VA change
[21]	Ranibizumab / bevacizumab, monthly vs OCT-guided as-needed	12 months	Approximately +8.5/+8.0 monthly vs +6.8/+5.9 as-needed
[19]	Ranibizumab fixed quarterly dosing after loading	12 months	Gains not sustained without imaging-triggered dosing

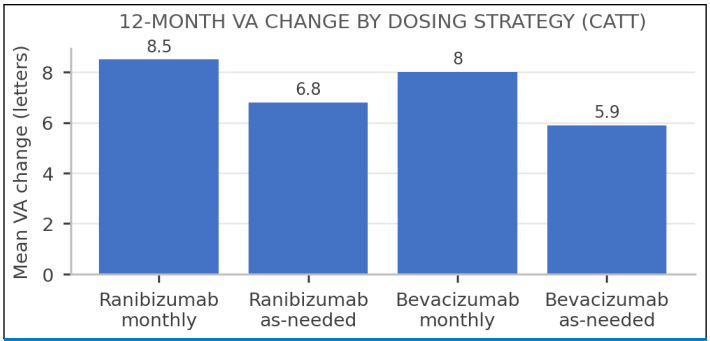


Figure 2: Approximate mean visual acuity change at 12 months under monthly versus OCT-guided as-needed ranibizumab and bevacizumab dosing in the CATT program [21,22].

Monthly fixed dosing imposes a visit burden that is particularly hard for elderly patients to sustain over years, and OCT-guided treat-and-extend regimens were designed to solve exactly that problem. The CATT Research Group found both ranibizumab and bevacizumab effective under monthly and OCT-triggered as-needed dosing, with as-needed regimens producing slightly smaller but still meaningful gains [21,22], and the UK IVAN trial reached a concordant conclusion [23]. Freund and colleagues' consensus review formalized the concept itself: after loading, the interval is lengthened while OCT shows no recurrent fluid, and shortened once fluid reappears [24]. Wykoff and colleagues' TREX-AMD and Schmidt-Erfurth and colleagues' TREND trial both showed that OCT-guided treat-and-extend achieved outcomes similar to monthly dosing while reducing injections needed [25,26]. Guymer and colleagues' FLUID study showed that tolerating a small amount of persistent subretinal fluid did not compromise outcomes and allowed longer extension [27]. Figure 2 illustrates the approximate one-year visual acuity change under these strategies.

6. Low-Vision Rehabilitation for Persistent Vision Loss

Even with prompt OCT-guided anti-VEGF therapy, a substantial fraction of elderly patients retain meaningful central vision loss, either because disease was already advanced at first treatment, geographic atrophy has no comparably effective pharmacologic therapy, or gains plateau below the level needed for unaided reading. Nutritional supplementation has some role in slowing progression -- the Age-Related Eye Disease Study and its follow-up established that high-dose antioxidant and zinc supplementation, and later a lutein and zeaxanthin-based regimen, modestly reduced progression to late AMD in selected intermediate-risk patients [28,29] -- but it does not restore vision already lost, which is where rehabilitation becomes essential. Stelmack and colleagues' Veterans Affairs Low Vision Intervention Trial found that structured rehabilitation produced significant improvements in patient-reported visual function versus usual care, particularly in reading and mobility, in a cohort dominated by AMD [30]. Owsley and colleagues' national survey found substantial variability in access to low-vision services across the United States, a gap that matters because delayed referral leaves patients without adaptive strategies while adjusting to a new deficit [31]. Mangione and colleagues' National Eye Institute Visual Function Questionnaire, validated originally in AMD and cataract cohorts, remains the standard instrument for quantifying the impact rehabilitation programs aim to improve [32].

7. Discussion

Two threads run through the literature synthesized here. First, OCT's role in AMD has moved from a diagnostic curiosity to the organizing structure of clinical decision-making: consensus nomenclature and classification systems built directly on OCT findings now define disease activity, progression, and treatment

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response across the field [10,11,12,13]. The treat-and-extend paradigm that dominates real-world neovascular AMD management exists specifically because OCT allows fluid-based titration of dosing frequency, and randomized evidence consistently shows OCT-guided extension preserves most of the benefit of monthly dosing while reducing the burden that is disproportionately difficult for elderly patients to sustain [25,26,27,24].

Second, imaging-guided treatment does not eliminate the need for low-vision rehabilitation. Geographic atrophy has lacked an anti-VEGF-equivalent disease-modifying therapy, and even successfully treated neovascular AMD frequently leaves residual central scotomas. The rehabilitation literature, though smaller in volume, establishes that structured low-vision intervention meaningfully improves functional outcomes and should be a standard companion to OCT-guided pharmacotherapy [30,32], a need that will only grow as the population most affected by AMD continues to age [1,2].

Limitations are worth naming: most treat-and-extend trials enroll selected, healthier populations, so their benefits may understate the burden faced by the frailest elderly patients least likely to be enrolled, and low-vision rehabilitation outcome studies remain fewer and smaller than the pharmacologic trials that dominate the retina literature.

8. Conclusion

Optical coherence tomography has become the structural backbone of age-related macular degeneration management in elderly patients, standardizing disease classification, driving OCT-guided treat-and-extend anti-VEGF regimens that reduce treatment burden without sacrificing visual outcomes, and defining the atrophy progression that current pharmacotherapy cannot yet halt [10,25,26,16]. Because a meaningful fraction of elderly patients retain disabling central vision loss despite optimal OCT-guided treatment, effective AMD management in this population depends equally on timely referral to low-vision rehabilitation, a component of care supported by solid if smaller-scale evidence and one that the epidemiological trajectory of this disease makes only more urgent going forward [30,1].

9. Acknowledgements and Declarations

Acknowledgements: The authors thank the retina imaging and low-vision rehabilitation staff at their affiliated institutions for their clinical insight during the preparation of this review. **Funding:** This work received no dedicated external funding. **Conflict of Interest:** The authors declare no conflicts of interest relevant to this work. **Author Contributions:** All authors contributed to the conception, literature synthesis, drafting, and critical revision of this manuscript, and approved the final version submitted for publication. **Ethics Statement:** This article is a narrative literature review and did not involve new patient data collection; no institutional ethics approval was required. **Data Availability:** No new datasets were generated during this review; all data discussed are available in the cited original publications.

10. References

1. Wong, W.L., Su, X., Li, X., Cheung, C.M.G., Klein, R., Cheng, C.Y., et al. (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040. Lancet Global Health, 2(2): e106-e116. DOI: 10.1016/S2214-109X(13)70145-1

2. Rein, D.B., Wittenborn, J.S., Zhang, X., Honeycutt, A.A., Lesesne, S.B., Saaddine, J. (2009) Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Archives of Ophthalmology, 127(4): 533-540. DOI: 10.1001/archophthalmol.2009.58

3. Friedman, D.S., O'Colmain, B.J., Munoz, B., Tomany, S.C., McCarty, C., de Jong, P.T., et al. (2004) Prevalence of age-related macular degeneration in the United States. Archives of Ophthalmology, 122(4): 564-572. DOI: 10.1001/archopht.122.4.564

© 2020 Somato Publications. All rights reserved.

4. Klein, R., Klein, B.E., Knudtson, M.D., Meuer, S.M., Swift, M., Gangnon, R.E. (2007) Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology, 114(2): 253-262. DOI: 10.1016/j.ophtha.2006.10.040

5. Huang, D., Swanson, E.A., Lin, C.P., Schuman, J.S., Stinson, W.G., Chang, W., et al. (1991) Optical coherence tomography. Science, 254(5035): 1178-1181. DOI: 10.1126/science.1957169

6. Hee, M.R., Baumal, C.R., Puliafito, C.A., Duker, J.S., Reichel, E., Wilkins, J.R., et al. (1995) Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. Ophthalmology, 102(3): 493-503. DOI: 10.1016/S0161-6420(95)30846-9

7. Schmidt-Erfurth, U., Waldstein, S.M. (2016) A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. Progress in Retinal and Eye Research, 50: 1-24. DOI: 10.1016/j.preteyeres.2015.07.007

8. de Jong, P.T.V.M. (2006) Age-related macular degeneration. New England Journal of Medicine, 355(14): 1474-1485. DOI: 10.1056/NEJMra062326

9. Mitchell, P., Liew, G., Gopinath, B., Wong, T.Y. (2018) Age-related macular degeneration. Lancet, 392(10153): 1147-1159. DOI: 10.1016/S0140-6736(18)31550-2

10. Ferris, F.L., Wilkinson, C.P., Bird, A., Chakravarthy, U., Chew, E., Csaky, K., et al. (2013) Clinical classification of age-related macular degeneration. Ophthalmology, 120(4): 844-851. DOI: 10.1016/j.ophtha.2012.10.036

11. Staurenghi, G., Sadda, S., Chakravarthy, U., Spaide, R.F. (2014) Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN*OCT consensus. Ophthalmology, 121(8): 1572-1578. DOI: 10.1016/j.ophtha.2014.02.023

12. Sadda, S.R., Guymer, R., Holz, F.G., Schmitz-Valckenberg, S., Curcio, C.A., Bird, A.C., et al. (2018) Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Report 3. Ophthalmology, 125(4): 537-548. DOI: 10.1016/j.ophtha.2017.09.028

13. Spaide, R.F., Jaffe, G.J., Sarraf, D., Freund, K.B., Sadda, S.R., Staurenghi, G., et al. (2020) Consensus nomenclature for reporting neovascular age-related macular degeneration data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. Ophthalmology, 127(5): 616-636. DOI: 10.1016/j.ophtha.2019.11.004

14. Waldstein, S.M., Wright, J., Warburton, J., Margaron, P., Simader, C., Schmidt-Erfurth, U. (2016) Predictive value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular AMD. Ophthalmology, 123(1): 60-69. DOI: 10.1016/j.ophtha.2015.09.013

15. Keane, P.A., Patel, P.J., Liakopoulos, S., Heussen, F.M., Sadda, S.R., Tufail, A. (2012) Evaluation of age-related macular degeneration with optical coherence tomography. Survey of Ophthalmology, 57(5): 389-414. DOI: 10.1016/j.survophthal.2012.01.006

16. Holz, F.G., Strauss, E.C., Schmitz-Valckenberg, S., van Lookeren Campagne, M. (2014) Geographic atrophy: clinical features and potential therapeutic approaches. Ophthalmology, 121(5): 1079-1091. DOI: 10.1016/j.ophtha.2013.11.023

17. Rosenfeld, P.J., Brown, D.M., Heier, J.S., Boyer, D.S., Kaiser, P.K., Chung, C.Y., et al. (2006) Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine, 355(14): 1419-1431. DOI: 10.1056/NEJMoa054481

18. Brown, D.M., Kaiser, P.K., Michels, M., Soubrane, G., Heier, J.S., Kim, R.Y., et al. (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New England Journal of Medicine, 355(14): 1432-1444. DOI: 10.1056/NEJMoa062655

19. Regillo, C.D., Brown, D.M., Abraham, P., Yue, H., Ianchulev, T., Schneider, S., et al. (2008) Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular

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age-related macular degeneration: PIER Study year 1. American Journal of Ophthalmology, 145(2): 239-248. DOI: 10.1016/j.ajo.2007.10.004

20. Heier, J.S., Brown, D.M., Chong, V., Korobelnik, J.F., Kaiser, P.K., Nguyen, Q.D., et al. (2012) Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology, 119(12): 2537-2548. DOI: 10.1016/j.ophtha.2012.09.006

21. CATT Research Group, Martin, D.F., Maguire, M.G., Ying, G.S., Grunwald, J.E., Fine, S.L., et al. (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine, 364(20): 1897-1908. DOI: 10.1056/NEJMoa1102673

22. CATT Research Group, Martin, D.F., Maguire, M.G., Fine, S.L., Ying, G.S., Jaffe, G.J., et al. (2012) Ranibizumab and bevacizumab for neovascular age-related macular degeneration: two-year results. Ophthalmology, 119(7): 1388-1398. DOI: 10.1016/j.ophtha.2012.03.053

23. Chakravarthy, U., Harding, S.P., Rogers, C.A., Downes, S.M., Lotery, A.J., Wordsworth, S., et al. (2013) Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: the IVAN randomised controlled trial. Lancet, 382(9900): 1258-1267. DOI: 10.1016/S0140-6736(13)61501-9

24. Freund, K.B., Korobelnik, J.F., Devenyi, R., Framme, C., Galic, J., Herbert, E., et al. (2015) Treat-and-extend regimens with anti-VEGF agents in retinal diseases: a literature review and consensus recommendations. Retina, 35(8): 1489-1506. DOI: 10.1097/IAE.0000000000000627

25. Wykoff, C.C., Croft, D.E., Brown, D.M., Wang, R., Payne, J.F., Clark, L., et al. (2015) Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology, 122(12): 2514-2522. DOI: 10.1016/j.ophtha.2015.08.009

26. Schmidt-Erfurth, U., Fabianska, M., Waldstein, S.M. (2018) Efficacy and safety of ranibizumab 0.5 mg treat-and-extend versus monthly dosing in neovascular age-related macular degeneration: TREND study. Ophthalmology, 125(1): 57-65. DOI: 10.1016/j.ophtha.2017.07.014

27. Guymer, R.H., Markey, C.M., McAllister, I.L., Gillies, M.C., Hunyor, A.P., Arnold, J.J. (2019) Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. Ophthalmology, 126(5): 723-734. DOI: 10.1016/j.ophtha.2018.11.025

28. Age-Related Eye Disease Study Research Group (2001) 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. Archives of Ophthalmology, 119(10): 1417-1436. DOI: 10.1001/archopht.119.10.1417

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

30. Stelmack, J.A., Tang, X.C., Reda, D.J., Rinne, S., Mancil, R.M., Massof, R.W. (2008) Outcomes of the veterans affairs low vision intervention trial (LOVIT). Archives of Ophthalmology, 126(5): 608-617. DOI: 10.1001/archopht.126.5.608

31. Owsley, C., McGwin, G., Lee, D.J., Lam, B.L., Friedman, D.S., Gower, E.W., et al. (2009) Characteristics of low-vision rehabilitation services in the United States. Archives of Ophthalmology, 127(5): 681-689. DOI: 10.1001/archophthalmol.2009.55

32. Mangione, C.M., Lee, P.P., Gutierrez, P.R., Spritzer, K., Berry, S., Hays, R.D. (2001) Development of the 25-item National Eye Institute Visual Function Questionnaire. Archives of Ophthalmology, 119(7): 1050-1058. DOI: 10.1001/archopht.119.7.1050

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