

AMERICAN ACADEMY  
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# Age-Related Macular Degeneration Preferred Practice Pattern®

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We would like to acknowledge the role of Andre Ambrus, MLIS, in the initial revisions of the Retina/Vitreous PPPs and the first meeting of the Retina/Vitreous PPP Committee.

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# RETINA/VITREOUS PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Retina/Vitreous Preferred Practice Pattern Committee** members wrote the Age-Related Macular Degeneration Preferred Practice Pattern (PPP) guidelines. The Retina/Vitreous PPP Committee members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

## **Retina/Vitreous Preferred Practice Pattern Committee 2023–2024**

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*We thank our partners, the Cochrane Eyes and Vision US Satellite (CEV@US), for identifying reliable systematic reviews that we cite and discuss in support of the PPP recommendations.*

The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2024. The document was edited in response to the discussion and comments.

## **Preferred Practice Patterns Committee 2024**

David K. Wallace, MD, MPH, Chair  
 Christina J. Flaxel, MD  
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 Deborah S. Jacobs, MD  
 Francis S. Mah, MD  
 Kevin M. Miller, MD  
 Thomas A. Oetting, MD  
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The Age-Related Macular Degeneration PPP was sent for review in July 2024 to improve the quality of the guideline, to gather feedback on the draft recommendations and to assess feasibility for and applicability to the target audience, including assessing the facilitators and barriers to implementing recommendations (e.g., U.S. ophthalmologists and other important groups, including patients, other physicians, international ophthalmologists, research organizations, ophthalmological organizations, and experts in the field). The PPP was sent for review to the following patient organizations to solicit the views and preferences of patients and the public: Consumers United for Evidence-Based Healthcare, American Foundation for the Blind, Foundation Fighting Blindness, Lighthouse Guild, National Federation of the Blind, and Prevent Blindness. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Retina/Vitreous PPP Committee reviewed these comments and determined revisions to the document.

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American Uveitis Society\*  
Association for Research in Vision and Ophthalmology  
Association of University Professors in Ophthalmology  
Canadian Ophthalmological Society  
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This guideline will be formally re-evaluated and updated on a 5-year cycle in 2029. A Summary Benchmark is a resource to facilitate application of the guideline and to provide criteria that could be used to measure the application of recommendations, which will be available to all at [www.ao.org/ppp](http://www.ao.org/ppp).

# FINANCIAL DISCLOSURES

There is no external funding, including industry/commercial support, for the development of this PPP or for the distribution of the guidelines. The Academy has fully funded the development of this PPP, and the views or interests of the Academy have not influenced the final recommendations which are based on evidence from systematic reviews. All those individuals significantly involved in the guideline development process, including Retina/Vitreous PPP Committee members, PPP Committee members, Secretary for Quality of Care, and Academy staff, have declared competing/financial interests through a financial interest disclosure process as well as an assessment of the Open Payments website (available at <https://openpaymentsdata.cms.gov/>). The interests of the Retina/Vitreous PPP Committee members are provided at the beginning of each meeting and those with competing interests in a guideline topic do not participate in voting on areas of disagreement. In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at <https://cmss.org/code-for-interactions-with-companies/>), relevant relationships with industry are listed. As per CMSS code, direct financial relationships with companies do not include food and beverage, research funds paid to the institution and relationships outside of the topic of the PPP. The Academy has Relationship with Industry Procedures to comply with the Code (available at [www.aao.org/about-preferred-practice-patterns](http://www.aao.org/about-preferred-practice-patterns)). A majority (71%) of the members of the Retina/Vitreous PPP Committee 2023–2024 had no financial relationship to disclose.

## Retina/Vitreous Preferred Practice Pattern Committee 2023–2024

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2024 are available online at [www.aao.org/ppp](http://www.aao.org/ppp).

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## OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern guidelines that **identify characteristics and components of quality eye care**. Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern guidelines are based on the best available scientific data as interpreted by committees of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the committees have to rely on their collective judgment and evaluation of available evidence.

**These documents provide guidance for the pattern of practice, not for the care of a particular individual.** While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

**Preferred Practice Pattern guidelines are not medical standards to be adhered to in all individual situations.** The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern guidelines are reviewed by their parent committee annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the approved by date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at [www.aao.org/about-preferred-practice-patterns](http://www.aao.org/about-preferred-practice-patterns)) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Age-Related Macular Degeneration PPP are ophthalmologists.



## METHODS AND KEY TO RATINGS

Preferred Practice Pattern<sup>®</sup> guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network<sup>1</sup> (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation<sup>2</sup> (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.<sup>3</sup>

- ◆ All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- ◆ To rate individual studies, a scale based on SIGN<sup>1</sup> is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- ◆ Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE<sup>2</sup> as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- ◆ Key recommendations for care are defined by GRADE<sup>2</sup> as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- ◆ The Highlighted Findings and Recommendations for Care section lists points determined by the Retina/Vitreous PPP Committee to be of particular importance to vision and quality of life outcomes.
- ◆ Recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- ◆ Literature searches to update the PPP were undertaken on March 6, 2023, January 23, 2024, and August 7, 2024 in PubMed. Complete details of the literature searches are available online at [www.aao.org/ppp](http://www.aao.org/ppp).
- ◆ Relevant systematic reviews were identified by the Cochrane Eys and Vision US Satellite (CEV@US). These systematic reviews were screened by the committee and rated using the system described above by the committee methodologist.

- ◆ Recommendations are based on systematic reviews, as per the Institute of Medicine (Clinical Practice Guidelines We Can Trust, 2011). In formulating the recommendations, the health benefits, side effects/harms/risks, and the balance of benefits and risks are reviewed and considered. Final decisions are arrived at through informal consensus techniques. If there are areas of disagreement, a vote will be conducted among the members of the Retina/Vitreous PPP Committee. If there are individuals with direct financial relationships in the area of disagreement, these individuals will refrain from the vote.

## HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

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Although an estimated 80% of patients with age-related macular degeneration (AMD) have non-neovascular or atrophic AMD, the neovascular form is responsible for most of the severe vision loss associated with AMD.

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Risk factors for the development of advanced AMD include smoking, increasing age, northern European ancestry, and genetic factors. Cigarette smoking has been identified as the primary modifiable risk factor in numerous studies on advanced AMD. It is strongly recommended to advise patients with AMD or those at risk for AMD to stop smoking. Routine genetic testing is not currently recommended.

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In light of all of the available information on aspirin use and AMD, the current preferred practice for patients who have been instructed by their physician that long-term aspirin is appropriate and beneficial is to continue with aspirin therapy as prescribed.

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There is no evidence-based treatment for early AMD.

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According to the Age-Related Eye Disease Study (AREDS2), antioxidant vitamin and mineral supplementation should be considered in patients with intermediate AMD or geographic atrophy (GA) in one or both eyes and other advanced AMD in one eye. There is no evidence to support the use of these supplements for patients who have less than intermediate AMD and no evidence of any prophylactic value for family members without signs of AMD. A Mediterranean diet is associated with a reduced risk of developing AMD and of existing AMD becoming worse.

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Early detection and prompt treatment of active neovascular AMD improves visual outcomes. Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents, which may or may not target other factors such as placental growth factor or angiopoietin-2, is the most effective way to manage neovascular AMD and is the first-line treatment. Symptoms suggestive of post-injection endophthalmitis or retinal detachment require prompt evaluation.

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The choice of biologic product (reference, biosimilar, or interchangeable) should be that of the treating ophthalmologist and the patient whenever possible.

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# INTRODUCTION

## DISEASE DEFINITION

Age-related macular degeneration (AMD) is a spectrum of disorders of the macula characterized by one or more of the following:

- ◆ Presence of at least medium-size drusen ( $\geq 63 \mu\text{m}$  in diameter)
- ◆ Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- ◆ Presence of any of the following features: GA of the RPE, choroidal neovascularization ([CNV] exudative, wet), reticular pseudodrusen, or retinal angiomatous proliferation

This Preferred Practice Pattern uses the classification of the Age-Related Eye Disease Study (AREDS) and the Beckman Initiative for Macular Research Classification<sup>4</sup> to define the early and intermediate stages of AMD. The AREDS was a prospective, multicenter, randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors for age-related cataract and AMD. The effects of antioxidant vitamins and minerals on these two ocular conditions were studied.

The classification of AMD from the AREDS is as follows:<sup>5</sup>

- ◆ *No AMD* (AREDS category 1) represented the control group; it is characterized by no or few small drusen, also known as drupelets (small drusen  $\leq 63$  microns).<sup>4</sup>
- ◆ *Early AMD* (AREDS category 2) is characterized by a combination of multiple small drusen, few intermediate drusen ( $> 63$ – $124 \mu\text{m}$  in diameter), or mild RPE abnormalities.
- ◆ *Intermediate AMD* (AREDS category 3) is characterized by either of the following features:
  - ◆ Numerous medium drusen
  - ◆ At least one large druse ( $\geq 125 \mu\text{m}$  in diameter)
- ◆ *Advanced AMD* (AREDS category 4) is characterized by one or more of the following (in the absence of other causes) in one eye:
  - ◆ GA of the RPE two subtypes: fovea-involving and not involving fovea<sup>6</sup>
  - ◆ Macular neovascularization (MNV) historically referred to as CNV and includes the following:<sup>7</sup>
    - Type 1 MNV: a neovascular complex located in the sub-RPE space originating from the choroid through a defect in Bruch's membrane
    - Polypoidal choroidal vasculopathy (PCV) lesions, similar to Type 1 MNV, characterized by branching vascular networks with dilated vascular elements (historically referred to as polyps)
    - Type 2 MNV: a neovascular complex located in the subretinal space above the RPE originating from the choroid
    - Type 3 MNV: pathologic angiogenesis originating from the deep retinal capillary plexus and extending to the outer retina (historically referred to as retinal angiomatous proliferation)

Macular neovascularization can lead to the following:

- Serous detachment of the neurosensory retina or RPE
- Hard exudates (a secondary phenomenon resulting from chronic vascular leakage)
- Hemorrhage
- Intraretinal fluid
- Subretinal and sub-RPE fibrovascular proliferation
- Subretinal fibrosis (formerly known as disciform scar)

See Glossary for definitions of important terms. Clinical details are available in standard texts.<sup>8,9</sup>

## PATIENT POPULATION

Patients are typically aged 50 years or older, with or without visual symptoms. Clinicians should consider the possibility of hereditary macular dystrophies in patients under 50 years of age who have clinical features that resemble AMD.

## CLINICAL OBJECTIVES

- ◆ Educate physicians on how to identify patients at risk of vision loss related to AMD
- ◆ Educate physicians on how to counsel patients and families about the disease, risk factors, and preventive measures
- ◆ Minimize or reverse visual loss and functional impairment in these patients through appropriate detection, self-assessment, treatment, and follow-up examinations

# BACKGROUND

## INCIDENCE AND PREVALENCE

Age-related macular degeneration is a leading cause of severe, irreversible vision impairment in developed countries.<sup>10-15</sup> In 2019, there were an estimated 20 million individuals in the United States with AMD; of these, 18.34 million had early stages of AMD and 1.49 million had late stages of AMD.<sup>16</sup> A previous estimate in 2004 found an estimated 1.75 million people aged 40 years or older in the United States have advanced AMD, either neovascular AMD or GA in at least one eye; 7.3 million were considered to have high-risk features such as large drusen ( $\geq 125 \mu\text{m}$  in diameter) in one or both eyes.<sup>14, 17</sup> Although relatively few cases of advanced AMD occur between the ages of 40 and 50, detection of earlier AMD stages, which are precursors of more advanced AMD, are not uncommon occurrences during this decade. Aging is the greatest risk factor; therefore, the prevalence of AMD in the United States is anticipated to increase to 22 million by the year 2050, whereas the global prevalence is expected to increase to 288 million by the year 2040.<sup>18</sup> Overall, AMD is responsible for an estimated 46% of cases of severe visual loss (visual acuity [VA] 20/200 or worse) in people over age 40 in the United States.<sup>15</sup> Age-related macular degeneration is a disease spectrum that has early and late stages. Although an estimated 80% of patients with AMD have non-neovascular or atrophic AMD,<sup>11</sup> the neovascular form is responsible for nearly 90% of the severe VA loss (20/200 or worse) from AMD because of its natural history.<sup>19, 20</sup>

Although the prevalence, incidence, and progression of AMD and most associated features (e.g., large drusen) increase with age, the prevalence of AMD also varies by race and ethnicity.<sup>15, 21-23</sup> In the Beaver Dam Eye Study, consisting of primarily a Caucasian population base, the prevalence of any AMD (referred to as age-related maculopathy) was less than 10% in people aged 43 to 54 years yet more than tripled for people aged 75 to 85 years.<sup>10</sup> The Beaver Dam Eye Study demonstrated that the development of any AMD over a 10-year period was 4.2% for people 43 to 54 years old and 46% for those 75 and older.<sup>24</sup> The Beaver Dam Eye Study has identified that soft, indistinct drusen and pigmentary abnormalities also increase in frequency with increasing age and are strongly predictive of progression to more advanced AMD. In the Los Angeles Latino Eye Study, prevalence of advanced AMD increased from 0% in individuals 40 to 49 years old to 8.5% in those 80 years old and older.<sup>25</sup> The Proyecto Vision Evaluation and Research study of Hispanic participants in Arizona found that the prevalence of advanced AMD increased from 0.1% in persons 50 to 59 years old to 4.3% in those 80 and older.<sup>26</sup>

Observations from the Barbados Eye Study,<sup>27</sup> the Baltimore Eye Study,<sup>28</sup> and the Macular Photocoagulation Study (MPS)<sup>29</sup> suggest that late stages of AMD are more common among Caucasian individuals. Findings from the Multi-ethnic Study of Atherosclerosis also suggest that neovascular AMD may be more common in Caucasian individuals than in African American individuals.<sup>22</sup> In Asian populations, there are racial variations in the prevalence of early and late AMD, and Caucasian and Asian populations are at higher risk than Hispanic and African individuals.<sup>30-35</sup> A meta-analysis and systematic review reported a higher prevalence of AMD in

European individuals than in Asian or African individuals, with no difference in prevalence between Asian and African individuals.<sup>18</sup>

## RISK FACTORS

The main unmodifiable risk factors for the development of advanced AMD are increasing age, Northern European ancestry, and genetic factors. Although a number of modifiable risk factors have been investigated, cigarette smoking is the main one that has been consistently identified in numerous studies.<sup>36-45</sup> Importantly, it is essential to recognize that the associations found in observational studies that analyze risk factors should not be interpreted as cause and effect. Such associations may not necessarily translate into treatment recommendations, as multiple confounding variables may not be accounted for in the studies.

### Smoking, Hypertension, and Cardiovascular Disease

Smoking significantly increases the risk of AMD and there appears to be a dose-response relationship, because the odds ratio increases with an increased number of pack-year exposure.<sup>38, 46</sup> Smoking cessation is associated with a reduced risk of AMD progression; the risk of developing AMD in individuals who have not smoked for more than 20 years is comparable to the risk in nonsmokers.<sup>38</sup> Thus, smoking cessation is strongly recommended when advising patients, as it represents a key and important modifiable risk factor. A number of case-control and population-based studies have examined the relationship between AMD, hypertension, and other cardiovascular diseases, and they have shown conflicting results.<sup>21, 47-53</sup> Passive smoking exposure was associated with an increased risk of AMD (odds ratio 1.87%; 95% confidence interval [CI], 1.03–3.40) in nonsmokers.<sup>38</sup>

### Levels of Antioxidants

Additional risk factors may include low systemic levels of antioxidants. Data from observational studies have been inconsistent in identifying low levels of plasma and dietary antioxidants of vitamins C and E, carotenoids (e.g., lutein, zeaxanthin), and zinc as risk factors for AMD.<sup>54-60</sup> The original AREDS results demonstrated a beneficial effect for the use of high-dose oral antioxidant vitamins (vitamins C, E, beta-carotene) and zinc supplementation in reducing progression of intermediate AMD or advanced AMD in the fellow eye to advanced AMD by 25%.<sup>61</sup> However, additional vitamin E supplementation above the AREDS levels should be avoided.<sup>62</sup> Results of AREDS2 support the removal of beta-carotene (found in the original AREDS supplements) and the addition of lutein/zeaxanthin in the AREDS2 supplements.<sup>63</sup> Furthermore, elimination of the beta-carotene component may reduce the competitive absorption of the lutein/zeaxanthin. Importantly, removal of beta-carotene may eliminate the increased incidence of lung cancer associated with the use of supplemental beta-carotene.<sup>64</sup> Finally, AREDS2 demonstrated that there was no effect on the progression of AMD by either reducing the zinc dose (from 80 mg to 25 mg) or adding an omega-3 polyunsaturated fatty acid supplement (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]).<sup>64</sup> A Cochrane systematic review concluded that taking antioxidant vitamins plus zinc probably slows the progression to late AMD and vision loss (moderate-certainty evidence). This review also concluded that supplements containing only lutein and zeaxanthin may have little or no effect on the progression of AMD.<sup>65</sup>

### Diet

Several studies have also identified an association between dietary fat and advanced AMD.<sup>39, 66-72</sup> Similar to the reports on risk factors for cardiovascular disease, a number of reports from population-based studies have demonstrated that a reduced risk of AMD is associated with higher dietary intake of foods rich in omega-3 long-chain polyunsaturated fatty acids, such as fish.<sup>39, 70, 71, 73, 74</sup> In a nested cohort study from the original AREDS population of 1837 patients who were at moderate risk for progression, participants who reported the highest omega-3 intake (note that this was not in the form of a supplement) were 30% less likely to develop

advanced AMD after 12 years.<sup>71</sup> These dietary long-chain fatty acids are thought to decrease inflammatory mediators via immunomodulation, thus decreasing disease progression to advanced AMD.<sup>71</sup> An increased risk of AMD was found in individuals who had a higher intake of saturated fats and cholesterol and in those with a higher body mass index.<sup>43</sup> Despite this dietary association, AREDS2 failed to demonstrate a benefit from the use of DHA and EPA as oral supplements at the doses tested; both are omega-3 poly-unsaturated fatty acids.<sup>64</sup> The EYE-RISK consortium published their evaluation of the pooled data from the Rotterdam Study-1 and the Alienor Study populations, which included more than 4000 participants with mean follow-up of 9.9 years and 4.1 years, respectively, and adherence to Mediterranean diet was associated with a 41% reduced risk of advanced AMD. The Mediterranean diet includes a diet rich in fruits, vegetables, legumes, and fish.<sup>75, 76</sup> Follow-up of the AREDS1 and AREDS2 cohorts found that closer adherence to a Mediterranean-type diet was associated with reduced risk of progression to large drusen and late AMD.<sup>77</sup> A post hoc analysis of AREDS2 found that slower GA enlargement was associated with a Mediterranean type diet.<sup>78</sup>

## Aspirin

Observational studies have indicated a possible link between aspirin use and AMD. The Beaver Dam Eye Study reported two times the incidence of late macular degeneration in patients who used aspirin at least twice weekly for 10 years compared with those who used no aspirin.<sup>79, 80</sup> Other studies have shown a potential protective effect of aspirin against the development of AMD.<sup>81</sup> In a meta-analysis of 10 studies, the use of aspirin was not associated with an increased risk of AMD,<sup>82</sup> but another meta-analysis of 16 studies identified an association with aspirin in a subgroup of studies with long-term follow-up.<sup>83</sup> In light of all of the available information on aspirin use and AMD, the current preferred practice for patients who have been instructed by their physician to use aspirin is to continue their aspirin therapy as prescribed.<sup>84, 85</sup>

## Genetic Factors

Molecular genetic studies and epidemiologic studies have determined some of the genetic factors in AMD.<sup>86-92</sup> Several studies published in 2005 identified a strong association of the complement factor H (CFH) Y402H polymorphism with a higher risk of AMD.<sup>93-98</sup> The CFH gene product is involved in regulation of the complement system through binding to factor C3b. This specific complement factor represents a key regulator of the innate rather than the adaptive immune system. An alteration of regulation that occurs from modification at the C3b site leads to a defective regulation of the alternative complement pathway and results in an up-regulation of inflammation to host cells that are mediated by the membrane attack complex. Patients who are homozygous for the Y402H risk allele of CFH possess a 7.4-fold increased risk of AMD. The CFH gene is located on chromosome 1, in a region linked to AMD in multiple family studies.<sup>93</sup> Studies report an association of a CFH variant (homozygous individuals) with other factors for the risk of progression to advanced AMD compared with noncarriers who lack these determinants.<sup>99, 100</sup> Other factors associated with abnormal complement variants and AMD progression include an elevated erythrocyte sedimentation rate, an elevated serum C-reactive protein, and smoking. Such findings support the combined pathogenic mechanisms for AMD progression that include an interplay of environmental factors, heredity, and inflammation.

Strong linkage disequilibrium has been shown across the ARMS2-HTRA1 region, and these two genes are also strongly associated with AMD.<sup>101-103</sup> The exact mechanism that explains this association has not been clearly determined.<sup>104</sup> Other proposed genetic variants associated with AMD include a variant in the hepatic lipase (LIPC) gene<sup>105</sup> and the rs3775291 variant in the toll-like receptor 3 (TLR3) gene.<sup>106, 107</sup> A number of other genes have also been identified as well as several other rare variants of genes.<sup>108</sup> A combination of genes and other risk factors may dispose an individual to varying AMD risks more than any one variant taken in isolation.<sup>109</sup> A genome-wide association study has identified 19 loci ( $P < 5 \times 10^{-8}$ ), seven of which are newly described.<sup>110</sup>

Age-related macular degeneration has a complex genetic background with similar phenotypes. Many genetic associations have been identified—some are protective,<sup>111</sup> some are associated

with disease progression, and others have been reported yet not confirmed and require further investigation.

In 2013, several authors proposed that genetic selection of subjects who would most benefit from nutritional supplementation should be used to guide therapy based on a post hoc analysis of a subset of the AREDS population. Thus, the authors recommend using a personalized genetic testing approach to guide therapy in AMD.<sup>112, 113</sup> However, an analysis of the AREDS population that included an additional 526 AREDS subjects concluded that genetic testing does not provide benefits in managing nutritional supplements in this population.<sup>114-116</sup> Statistical experts found errors in the data used to support an association and bias in the analyses used to support genetic testing. They concluded that there was no evidence to support the need for genotyping to guide recommendations for use of supplements containing antioxidants and zinc in AMD.<sup>117</sup>

A prospective, multicenter study looked at genome-wide associations with treatment outcomes in a cohort of 465 patients with exudative AMD who were initiating ranibizumab therapy.<sup>118</sup> Although there was no association of any single-nucleotide polymorphism with 12-month treatment outcomes (i.e., achieving a dry macula, requiring additional treatment, and VA change), the authors found preliminary evidence of a predictive association of the ARMS/HTRA1 polymorphism with the need for additional treatment. They postulated that testing for this polymorphism might be able to predict the frequency of injection after initial ranibizumab therapy. However, a systematic review published in 2015 looked at the association between anti-VEGF response and variations in AMD-associated genes; it concluded that genetic background may influence an individual's response to treatment, however further studies are needed to better understand the contribution of various genes to treatment response.<sup>119, 120</sup>

Currently, only post hoc analysis data are available, and results are conflicting.<sup>121</sup> One or more prospective clinical trials will need to demonstrate the value of genetic testing in AMD. Thus, the routine use of genetic testing is not supported by the existing literature and is not recommended at this time.<sup>122</sup> Other variants are being studied, but there is insufficient evidence to make recommendations at this time.<sup>123, 124</sup>

## Other Risk Factors

An increased waist/hip ratio for men has been associated with an increase in the risk of both early and late AMD.<sup>125</sup> Markers of inflammation, such as C-reactive protein, may be associated with a higher risk of AMD progression.<sup>126-128</sup> Other possible factors that have been considered in various studies, with inconclusive findings, include hormonal status,<sup>129-133</sup> sunlight exposure,<sup>134-136</sup> alcohol use,<sup>137-139</sup> and vitamins B and D status.<sup>140, 141</sup> A Cochrane systematic review in 2016 concluded that there was insufficient evidence to define a role of statins in the onset or progression of AMD.<sup>142</sup>

## NATURAL HISTORY

### Normal Aging Changes

Normal age-related changes develop in the macula that are distinct from AMD. A 2013 study reported that the presence of small drusen measuring 63 microns or less, referred to as drupelets, and the absence of RPE pigmentary abnormalities are consistent with normal aging in patients over 55 years of age and do not carry an increased risk of vision loss due to AMD.<sup>4</sup> However, patients with normal aging changes can develop AMD over time.

### Early Age-Related Macular Degeneration

As defined by the AREDS, early AMD (category 2) is characterized by small drusen (< 63  $\mu\text{m}$  in diameter), few medium drusen (63–125  $\mu\text{m}$  in diameter), and/or minimally detected or no pigment epithelial abnormalities in the macula. Patients in this category have a low risk of



progressing to advanced AMD after 5 years in either eye.<sup>5</sup> The AREDS study group published a report based on 10-year follow-up data obtained from approximately 85% of the originally enrolled patients.<sup>143</sup> In the group with a combination of small drusen or no drusen at baseline, approximately 15% developed large drusen at 10 years.<sup>143</sup>

## Intermediate Age-Related Macular Degeneration

Intermediate AMD (category 3) is a more critical distinction clinically because it places the individual at risk for progression to more advanced AMD. It has been defined by the AREDS as having extensive medium drusen (63–124  $\mu\text{m}$  in diameter) or one or more large drusen ( $\geq 125 \mu\text{m}$  in diameter) in one or both eyes. The progression to advanced AMD at 5 years in this group is approximately 18% according to the original AREDS. However, for patients with large drusen in one eye, the rate of development of advanced AMD at 5 years is 6.3%, whereas the rate for patients with multiple bilateral large drusen increases to 26% at 5 years.<sup>5</sup> <sup>144</sup> In the 10-year follow-up study of the AREDS, 37% of patients developed large drusen when medium drusen were present at baseline in one eye, and 71% developed large drusen when medium drusen were present in both eyes at baseline.<sup>143</sup> When medium drusen were present at baseline, 14% progressed to advanced AMD at 10 years.

In 2005, a simplified severity scale was developed for assessing AMD risk progression that is based on two primary ophthalmoscopic features: one or more large drusen ( $\geq 125 \mu\text{m}$  in diameter) and the presence of pigmentary changes.<sup>145</sup> Individuals with two affected eyes could then be given a five-step grading score of 0–4 (based on one point for each factor being present in each eye). The following scores enable the clinician to communicate with the patient about the approximate 5-year risk for developing advanced AMD: four factors, 45%; three factors, 26%; two factors, 9%; one factor, 4%; and zero factors, 0.5%. The approximate 10-year risks were 71%, 53%, 28%, 8%, and 1.5%, respectively.<sup>143</sup>

For patients without large drusen, the presence of intermediate drusen in both eyes is considered to represent one risk factor using this severity scale. Advanced AMD in one eye is counted as two risk factors. Often, the eye contralateral to the eye with advanced AMD has large drusen and RPE pigmentary disturbances and therefore has four risk factors, the highest risk-level for progression of all patients with AMD (45% by 5 years and 71% by 10 years). Interestingly, an online AMD risk calculator that includes phenotype (simplified severity scale score described above) and demographic information (age, smoking, and family history of AMD) had excellent calibration and overall performance, whereas the addition of specific genetic analysis added little to the 9- to 10-year trend for the development of advanced AMD.<sup>146</sup>

Reticular pseudodrusen (also referred to as subretinal drusenoid deposits) may be under-recognized.<sup>143</sup> They are best imaged using fundus autofluorescence, infrared reflectance, and/or spectral-domain optical coherence tomography (SD-OCT), and they appear to represent a meaningful risk factor associated with progression to GA.<sup>147-156</sup> (See Glossary.) In 2024, the AREDS and AREDS2 research groups defined an updated simplified severity scale with two modifications: including noncentral geographic atrophy in the advanced AMD outcome (rather than as a risk factor), and incorporating the presence of reticular pseudodrusen (see Table 1). In patients without reticular pseudodrusen at baseline, the 5-year rates of progression to advanced AMD remained similar to those of the original simplified severity scale. However, in patients with reticular pseudodrusen at baseline, the 5-year progression rates increased to 72%, 59%, 29%, 8%, and 3% for patients with four, three, two, one, and zero risk factors, respectively.<sup>157</sup>

**TABLE 1 APPROXIMATE RISK FOR PROGRESSION OF AGE-RELATED MACULAR DEGENERATION\***

Number of Risk Factors**	5-Year Risk of Progression to Advanced AMD: Patients Without Reticular Pseudodrusen	5-Year Risk of Progression to Advanced AMD: Patients with Reticular Pseudodrusen
0	0.3%	3%
1	4%	8%
2	12%	29%
3	27%	59%
4	50%	72%

\*Based on AREDS 2024 updated simplified severity scale.<sup>157</sup>

\*\*Risk factors included one or more large drusen ( $\geq 125 \mu\text{m}$  in diameter) and the presence of pigmentary changes.

## Advanced Age-Related Macular Degeneration

Advanced AMD is defined in the AREDS as either neovascular AMD or GA involving the center of the macula. Eyes classified as category 4 were required to have no advanced AMD in the study eye and the fellow eye had to have VA less than 20/32 as a result of AMD abnormalities.<sup>5</sup> In the AREDS, the risk of progression for patients with advanced AMD in one eye to an advanced stage in the fellow eye ranged from 35% to 50% at 5 years, depending largely on the phenotype in the better eye.<sup>145</sup> In the Beaver Dam Eye Study, approximately 22% of the fellow eyes of such patients developed neovascular changes or GA involving the fovea over 5 years.<sup>158</sup> In the Submacular Surgery Trial, these findings were also confirmed and further emphasize the value of the simple risk scale.<sup>159</sup> In 2013, the Beckman Initiative for Macular Research Classification Committee classified advanced AMD as either neovascular AMD and/or any GA whether the macula is affected or not.<sup>4</sup>

### Geographic Atrophy

The phenotype of GA, the advanced form of non-neovascular AMD, will have one or more zones of well-demarcated RPE and/or choriocapillaris atrophy. Drusen and other pigmentary abnormalities may surround the atrophic areas. Severe VA loss occurs more slowly in patients with GA than in patients with neovascular AMD. Geographic atrophy involving the foveal center causes approximately 10% of all AMD-related visual loss of 20/200 or worse.<sup>160</sup> The presence of GA in the central 1-mm zone of the macula correlates with reduced VA, whereas total geographic atrophy area correlates poorly to VA.<sup>161</sup> Eyes with GA outside the fovea maintain relatively good VA, yet patients' quality of life can be affected because the inner left subfield is associated with reading and the inner lower subfield is associated with distance vision activities.<sup>160, 162</sup> Several different studies have published GA growth rates that range from 1.28 to 2.6 mm<sup>2</sup> per year.<sup>163-173</sup> In the Proxima A and B studies, conversion to GA or CNV in the fellow eye was reported in 30% and 6.7% of patients, respectively, at 12 months with GA or CNV in one eye.<sup>165</sup>

Growth rates of multifocal areas of GA increase over time faster than monofocal areas of GA.<sup>167, 173</sup> Extrafoveal lesions increase at a faster rate compared to foveal lesions.<sup>173</sup> Larger areas of GA have greater rates of enlargement compared with smaller areas of GA.<sup>171</sup> In cases of bilateral GA, the enlargement rates of the two eyes have high concordance.<sup>170, 171</sup> Neovascular AMD also may occur in eyes with GA.<sup>150</sup>

### Neovascular Age-Related Macular Degeneration

Historically, neovascular AMD was characterized by means of fluorescein angiography as either classic, occult, predominantly classic, minimally classic, or mixed lesions. Serous and/or hemorrhagic detachment of the neurosensory retina or the RPE, and/or various stages of an elevated, fibrovascular disciform scar, may also occur.

In the MPS, classification of neovascular AMD with CNV was based on fluorescein angiography. Classic CNV (Gass Type 2 membrane)<sup>174-177</sup> is defined as a well-demarcated hyperfluorescence in the early phase of the angiogram, with progressive leakage of dye into the overlying subneurosensory retinal space during the late phases of the angiogram. Occult CNV (Gass Type 1 membrane)<sup>174-177</sup> is characterized by either a fibrovascular pigment epithelial detachment (PED) or late leakage of undetermined source. A fibrovascular PED is an irregular elevation of the RPE that has accompanying stippled hetero-fluorescence or even hypofluorescence early in the angiogram, with progressive late leakage in the later stages of the angiogram.

Other clinical subtypes or features of neovascular AMD may include idiopathic PCV,<sup>178, 179</sup> which should be suspected in patients with orange polypoid lesions and especially in African or Asian individuals. The lesions are often located in the peripapillary region, but may also present in the central macula or the macular arcades initially as large hemorrhagic retinal PED, lipid exudation, and subretinal fluid. An indocyanine green (ICG) angiogram is often useful in confirming the diagnosis. Multicolor fundus imaging and optical coherence tomography (OCT) can be used to detect some PCV cases as well.<sup>180</sup>

Optical coherence tomography and OCT angiography allow histology level three-dimensional descriptions of the three types of MNV and atrophic AMD.<sup>7</sup> Classification of atrophic AMD based on OCT has led to four proposed histology level categories: complete RPE and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy, and incomplete outer retinal atrophy. Longitudinal studies are needed to validate the proposed OCT classifications.<sup>181</sup>

## RATIONALE FOR TREATMENT

Randomized, controlled clinical trials support the use of antioxidant supplementation for slowing the progression to later stages of AMD; intravitreal injection of complement factor inhibitor to decrease the rate of GA growth; and intravitreal injection of anti-VEGF agents, photodynamic therapy (PDT), and laser photocoagulation surgery to treat neovascular AMD. Thermal laser photocoagulation surgery is rarely used in clinical practice and is not recommended for subfoveal MNV.<sup>182</sup>

## TREATMENT MODALITIES

### Early Age-Related Macular Degeneration

The use of the combination of antioxidant vitamins and minerals did not reduce the progression of early AMD to the intermediate stage of AMD, and there was insufficient power to determine the effects of the combination treatment on the progression to more advanced AMD. Therefore, there is no evidence to support the use of these supplements for patients who have less than intermediate AMD. In early AMD (AREDS category 2), only 1.3% of participants progressed to advanced AMD in 5 years. A meta-analysis in 2012 that looked at the evidence about whether taking an antioxidant vitamin or mineral supplement prevents the development of AMD concluded that there was accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD.<sup>183</sup> There is no evidence-based treatment for early AMD.

### Intermediate Age-Related Macular Degeneration

The original AREDS used a factorial design whereby 4757 participants were randomized to antioxidant vitamins, zinc, a combination of antioxidant vitamins and minerals (zinc and copper), or a placebo, and were followed for a mean of 6 years.<sup>5</sup> Of these, 3640 participants were enrolled in the study for AMD. In the AREDS, daily doses of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide, to reduce the risk of zinc-induced copper deficiency anemia) were evaluated. In

the AREDS2, the replacement of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg) was explored, along with a lower dose (25 mg) of zinc oxide (see Table 2).

**TABLE 2 ANTIOXIDANT VITAMIN AND MINERAL SUPPLEMENTS USED IN THE AREDS2**

Supplement	Daily Dose*
Vitamin C	500 mg
Vitamin E	400 IU
Lutein/zeaxanthin	10 mg/2 mg
Zinc oxide	80 mg or 25 mg
Cupric oxide	2 mg

AREDS2 = Age-Related Eye Disease Study 2.

SOURCE: Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report number 4. *JAMA Ophthalmol.* 2013;131(7):843-850.

\* These doses are not those listed on the commercially available vitamin/mineral supplements because of a change in labeling rules by the U.S. Food and Drug Administration that specifies that the doses must reflect the amounts available at the end of the shelf life.

The AREDS2 study was a multicenter, randomized, double-masked, placebo-controlled phase 3 clinical trial that used a 2 x 2 factorial study design.<sup>64</sup> The study enrolled 4203 participants with either bilateral large drusen or large drusen in one eye and advanced disease in the fellow eye. This population represented a high-risk group for progression to more advanced stages as identified in the original AREDS.<sup>184</sup> Participants were randomized to receive either supplemental lutein and zeaxanthin, supplemental omega-3, or the original formulation. A secondary randomization to four variations included elimination of beta-carotene, lower zinc levels (25 mg), or both. The results of the AREDS2 support the recommendation for substitution of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg).

In the original AREDS and in AREDS2, participants who benefited from antioxidant vitamin and mineral supplementation were those who had either intermediate AMD or advanced AMD in one eye. For participants with extensive intermediate (i.e., medium-sized) drusen in one or both eyes, one or more large drusen in at least one eye, non-subfoveal GA in one eye, or advanced AMD (i.e., subfoveal GA or CNV) in one eye, the rate of development of advanced AMD at 5 years was reduced by 25% in the participants using the combination treatment of antioxidant vitamins with zinc and copper. The risk of losing vision of 3 or more lines (doubling of the visual angle) was reduced by 19% with this combination treatment. Although zinc alone or antioxidants alone reduced progression, the therapy that resulted in a statistically significant reduction in both the development of advanced AMD and vision loss was the combination treatment of antioxidant vitamins and minerals (Table 3).

**TABLE 3 SUMMARY OF RESULTS OF THE ORIGINAL AREDS FOR DEVELOPING ADVANCED AGE-RELATED MACULAR DEGENERATION AND VISION LOSS**

	Antioxidants Plus Zinc	Zinc Alone	Antioxidants Alone
Reduction of the relative risk of developing advanced AMD	25%	21%	17%
Reduction of the relative risk of vision loss (3 or more lines)	19%	11%	10%

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study.

SOURCE: 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 number 8. *Arch Ophthalmol.* 2001;119(10):1417-1436.

A meta-analysis in 2017 concluded that individuals with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation.<sup>185</sup> This finding is drawn from one large trial conducted in a relatively well-nourished American population. The generalizability of these findings to other populations is not known. Although generally regarded as safe, vitamin supplements may have side effects.<sup>65</sup> A second meta-analysis was published concluding that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. The same probably applies to vitamin C and the multivitamin (Centrum Silver) investigated in the one trial reported to date.<sup>185</sup> There is no evidence with respect to other antioxidant supplements, such as lutein and zeaxanthin.<sup>185</sup> A meta-analysis of the adverse effects of nutritional supplementation reported that there is an increased risk of death from vitamin A, beta-carotene, and vitamin E supplements (16%, 7%, 4%, respectively), but not from vitamin C supplements.<sup>186</sup> Other investigators have raised concerns about the methodology for this meta-analysis. There is potential bias in the analyses owing to the omission of clinical trials that had no deaths and the lack of biological plausibility in the authors' interpretation of the results of the subgroup analyses.<sup>187-189</sup> Also, a number of studies in the meta-analysis used antioxidant dosages much higher than those used in the AREDS and did not find an adverse association of high-dose antioxidant supplementation.<sup>190</sup> Of great concern, two studies reported an increased mortality among patients who were heavy smokers and were also taking beta-carotene supplements to prevent lung cancer.<sup>191, 192</sup>

The AREDS2 study results demonstrated that in patients at high risk for progression there was no statistically significant difference associated with supplementation with the original AREDS formula versus each of the other modifications on AMD progression. As mentioned earlier, the addition of omega-3 supplementation (DHA and EPA) had no further benefit. This result was also suggested by a meta-analysis in 2008.<sup>74</sup> Subgroup analysis indicated that for those in the lowest quartile for lutein and zeaxanthin intake, supplemental lutein and zeaxanthin was protective (95% CI, 0.59–0.94;  $P = 0.01$ ). The authors concluded from all available evidence that lutein and zeaxanthin represent an appropriate substitute for beta-carotene in the supplement.<sup>64</sup> Finally, there was no demonstrated detrimental effect of lowering the zinc levels (25 mg) on progression to advanced disease.<sup>64</sup> A meta-analysis in 2013 did show that zinc supplementation alone may not be sufficient to produce clinically meaningful changes in VA.<sup>193</sup> A post hoc analysis of the AREDS and AREDS2 studies in 2023 evaluated 1602 eyes with GA across the two studies and found that oral micronutrient supplementation slowed GA progression toward the central macula, likely by augmenting the natural phenomenon of foveal sparing.<sup>194</sup>

Other treatment modalities are being investigated. LIGHTSITE I and II and a Cochrane review in 2021 did not show a benefit of photobiomodulation,<sup>195-197</sup> but a follow-up study, LIGHTSITE III in 2024, showed that photobiomodulation appears to decrease the onset of new GA ( $P = 0.02$ ).<sup>197, 198</sup> (*I-, Insufficient quality*) In 2024, the U.S. Food and Drug Administration (FDA) approved a device for multiwavelength photobiomodulation (Valeda® Light Delivery System, LumiThera Inc., Poulsbo, WA) treatment of patients with non-neovascular AMD.<sup>199</sup>

## Non-Neovascular Age-Related Macular Degeneration with Geographic Atrophy

In 2023, two therapies for non-neovascular AMD with GA were shown to reduce GA growth and received regulatory approval. The first was pegcetacoplan 15 mg/0.1ml (SYFOVRE®, Apellis Pharmaceuticals, Waltham, MA), which blocks the C3 and C3b proteins of the complement-mediated immune system. In two phase 3 studies, OAKS and DERBY, 1258 study participants with either foveal-involving or foveal-sparing GA were randomly assigned to receive pegcetacoplan monthly, every other month (EOM) or sham.<sup>200</sup> In OAKS, the primary endpoint at 12 months was met with monthly pegcetacoplan reducing GA growth by 21% compared with sham and EOM pegcetacoplan reducing GA growth by 16%. At 24 months, monthly pegcetacoplan and EOM pegcetacoplan reduced the GA growth rate by 22% and 18% compared with sham, respectively. In DERBY, at 12 months the primary endpoint was

not met with reduced growth rates of 12% in the monthly arm and 11% in the EOM arm compared with sham. At 24 months, the growth rates of GA were significantly reduced by 19% in the monthly arm and 16% in the EOM arm compared with sham. Non-subfoveal GA had greater GA growth reductions compared with foveal GA lesions. Subgroup analysis of the eyes with non-foveal-involving GA showed reduced growth rates by 26% in the monthly arm and 23% in the EOM arm compared with sham. In both trials, there was no difference in either treatment arm versus sham for functional testing, including best corrected VA (BCVA), mesopic microperimetry, and reading speed. Treatment arms were associated with higher rates of developing exudative AMD. In OAKS, at 24 months development of new onset exudative AMD was 11%, 8%, and 2% in the monthly, EOM, and sham group, respectively. In DERBY, at 24 months development of new onset exudative AMD was 13%, 6%, and 4% in the monthly, EOM, and sham group, respectively. In combined OAKS and DERBY, there were four cases of endophthalmitis (0.03% per injection at 24 months) and three serious adverse events of ischemic optic neuropathy. At 24 months, there was no difference in BCVA, reading performance, or microperimetry.<sup>200</sup>

Postmarketing surveillance revealed retinal vasculitis occurred at a rate of 0.01% per injection and appears to occur more commonly following the first injection at a rate of 1/4000 first injections.<sup>201, 202</sup> Pegcetacoplan was found to have a 2.1% to 3.8% rate of intraocular inflammation (not counting endophthalmitis).<sup>201</sup>

The second approved treatment was an avacincaptad pegol intravitreal solution 2 mg (Izervay™, Astellas Pharma US, Northbrook IL), a PEGylated, stabilized aptamer that targets C5. GATHER2 was a phase 3 clinical trial with 448 study participants with foveal-sparing GA.<sup>203</sup> Study participants were randomized to either monthly treatment or sham. At 12 months, square-root-transformed GA area growth rate was reduced by 14% in treated eyes versus sham. There was no difference in treatment group versus sham for functional tests of BCVA and low luminance BCVA. Exudative MNV developed in 7% in eyes treated with avacincaptad pegol compared with a rate of 4% in the sham group. There were no cases of endophthalmitis, intraocular inflammation, or ischemic optic neuropathy over 12 months. Avacincaptad pegol monthly treatment led to a 14% reduction in the mean rate of GA area growth at 24 months. For patients treated monthly in the first 12 months, followed by EOM for months 13 to 24, there was a 19% reduction in mean GA growth rate at month 24. Rates of MNV were 7% in the treatment group compared with 4% in the sham group. Rates of exudative MNV were 5% in the treated group and 3% in the sham group. In a post hoc analysis, avacincaptad pegol delayed the risk of progression to persistent vision loss (i.e.,  $\geq 10$ -BCVA letter loss,  $\geq 15$ -BCVA letter loss, and  $\geq 20$ -BCVA letter loss or BCVA loss to a level below driving eligibility threshold) versus sham over 12 months.<sup>204</sup>

There was no benefit for BCVA in the clinical trials for either pegcetacoplan or avacincaptad pegol, although the post hoc analysis for avacincaptad pegol suggested a possible slowing of progression to persistent vision loss. Because of the risk of exudative AMD, patients should be monitored and treated if needed. Pegcetacoplan and avacincaptad pegol are both relatively new medications for which long-term, real-world data are lacking. The physician should discuss the use of these medications with the patient, based on individual circumstances, including documented treatment benefits and risks.

## Exudative Neovascular Age-Related Macular Degeneration

Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD, and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain VA.<sup>205</sup> (*I++*, *Good quality*, *Strong recommendation*) (See Appendix 3.) Anti-VEGF therapies are discussed below. Adverse events for all anti-VEGF agents include rare risks of arterial thromboembolic events, endophthalmitis, and elevated intraocular pressure.<sup>206-217</sup>

## Aflibercept

Aflibercept is a pan VEGF-A, VEGF-B, and placental growth factor blocker approved by the FDA,<sup>213</sup> and the 2-mg dose has been documented to be of similar efficacy to ranibizumab in the head-to-head phase-3 VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.<sup>218</sup> In these pivotal studies, the 2-mg dose of aflibercept was administered by intravitreal injection every 4 weeks and every 8 weeks after three monthly loading doses. In the first year, both study arms were similar to 0.5-mg ranibizumab dosed every 4 weeks. Aflibercept 2 mg was well tolerated and had a safety profile comparable to ranibizumab and other anti-VEGF agents.

The phase 3 PULSAR study evaluated a higher dose of aflibercept, 8 mg, compared with aflibercept 2 mg. The 48-week results showed that after three monthly loading doses, aflibercept 8 mg showed achieved noninferior VA gains at 12-week and 16-week treatment intervals compared with aflibercept 2 mg at 8-week treatment intervals. Even though eyes were treated at extended intervals, all eyes were followed monthly and treatment intervals were reduced in the aflibercept 8-mg groups if BCVA was reduced by 5 letters, if the central retinal thickness increased by 25 microns, or if new foveal hemorrhage or neovascularization developed. At 48 weeks, 79% of eyes maintained 12-week dosing intervals and 77% maintained 16-week dosing intervals. The proportion of patients without fluid in the center subfield at week 16 was greater in the aflibercept 8-mg group (63%) compared with the aflibercept 2-mg group (52%), which was maintained through week 48. The mean change from baseline in central retinal thickness was numerically greater in the aflibercept 8-mg groups at 48 weeks (-141.9  $\mu\text{m}$  for aflibercept 8-mg every 12 weeks, -147.1  $\mu\text{m}$  for aflibercept 8-mg every 16 weeks, and -126.3  $\mu\text{m}$  for aflibercept 2-mg every 8 weeks). The safety profile of aflibercept 8 mg was found to be similar to that of aflibercept 2 mg. The second year of the study will demonstrate if safety and efficacy outcomes are maintained for eyes treated every 12 weeks and 16 weeks.<sup>219</sup>

## Bevacizumab

Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF. It is FDA approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer. Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab.<sup>220, 221</sup> Because preliminary reports appeared favorable, ophthalmologists began using intravitreal bevacizumab off-label to treat MNV. Comparative trials and uncontrolled case series reported improvements in VA and decreased retinal thickness by OCT following intravitreal bevacizumab treatment.<sup>222-228</sup> Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.<sup>229</sup>

## Brolucizumab

Brolucizumab 6 mg is a single-chain variable fragment (the smallest functional portion of an antibody) that binds VEGF-A and was approved by the FDA for the treatment of neovascular AMD.<sup>214</sup> Results from the HAWK and HARRIER phase 3 clinical trials showed that brolucizumab achieved its primary endpoint of noninferiority of BCVA change compared with aflibercept at week 48. Patients treated with brolucizumab achieved superior reductions in central subfield thickness compared with aflibercept 2 mg. Fewer patients treated with brolucizumab had subretinal fluid, inter-retinal fluid, and sub-RPE fluid.<sup>230</sup> After FDA approval, several cases of occlusive retinal vasculitis occurred after intravitreal brolucizumab injection.<sup>231</sup> A phase 3a study of brolucizumab every 4 weeks for patients with recalcitrant neovascular AMD found noninferior efficacy and a greater proportion of fluid-free eyes at week 104 for brolucizumab compared with aflibercept 2 mg. However, the incidence of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, was 11.5% for brolucizumab and 6.1% for aflibercept.<sup>232</sup> Brolucizumab is approved for use every 8 to 12 weeks after the loading period, and more frequent administration should be avoided.

## Faricimab-svoa

Faricimab-svoa, a humanized bispecific monoclonal antibody for intravitreal use that acts through dual inhibition of both angiopoietin-2 and VEGF-A, was approved by the FDA for the treatment of patients with neovascular AMD.<sup>215, 233</sup> Angiopoietin-2 is a growth factor belonging to the angiopoietin/TIE (tyrosine kinase with Ig and EGF homology domains) signaling pathway. The TENAYA and LUCERNE studies showed that patients receiving faricimab for neovascular AMD dosed up to every 16 weeks showed noninferior VA gains compared with patients receiving aflibercept 2 mg every 8 weeks.<sup>234</sup> Through week 60 of the study, fixed dosing intervals of 8 weeks, 12 weeks, or 16 weeks were maintained in the faricimab group following assessment of disease activity criteria at weeks 20 and 24. After week 60, a personalized treatment interval regimen was used. Approximately 80% of eyes could be dosed every 12 weeks or more, and 45% could be dosed every 16 weeks in year 1 and increased to 63% in year 2. Through year 2, the median number of injections in the faricimab group was 10, compared with 15 for aflibercept. In the personalized treatment interval phase (after week 60), the median number of injections in the faricimab group was 3 and in the aflibercept group it was 6.<sup>234</sup> Comparable reductions in central subfield thickness were observed in the faricimab and aflibercept groups through year 2. There were no new safety signals, and adverse events were comparable to aflibercept 2 mg. A faricimab single-dose prefilled syringe was FDA approved in 2024.<sup>215</sup>

The TRUCKEE study is an ongoing multicenter retrospective review of eyes treated with faricimab for neovascular AMD. Six-month results included 376 eyes, 337 of which had been previously treated with other anti-VEGF agents with an average of 31.1 prior injections. After one and three injections of faricimab, both treatment-naïve and previously treated eyes demonstrated maintained or improved BCVA. A significant reduction in mean central subfield thickness was observed in treatment-naïve and previously treated eyes after one injection and in previously treated eyes after three injections.<sup>235</sup>

## Ranibizumab

Ranibizumab 0.5-mg was approved by the FDA for the treatment of all subtypes of neovascular AMD, based on results from three double-masked, randomized controlled trials.<sup>217, 236, 237</sup> (See Table 4.) Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of all isoforms of human VEGF-A. Ranibizumab was well tolerated in randomized controlled trials with a safety profile similar to that of other anti-VEGF agents.

The FDA approved ranibizumab 100 mg/ml for use with an ocular implant that continuously releases the medication over 6 months.<sup>216</sup> The implant is surgically inserted into the eye in the operating room and can be refilled every 6 months with an office procedure. The Archway phase 3 study showed that patients receiving the ranibizumab implant had VA gains equivalent to patients receiving monthly ranibizumab injections.<sup>238, 239</sup> Approximately 98% of patients could receive continuous treatment for 6 months before requiring a refill or supplemental ranibizumab.<sup>239</sup> Importantly, after using the implant, there was a 2% risk of endophthalmitis in clinical trials (a rate three times higher than monthly intravitreal injections of ranibizumab). Other risks included vitreous hemorrhage, rhegmatogenous retinal detachment, implant dislocation, septum dislodgement, conjunctival erosion, conjunctival retraction, and conjunctival blebs. In 2022, the implant was voluntarily recalled due to concerns about septum dislodgment. The implant was re-introduced to the market in 2024.

## Other Studies

The Comparison of AMD Treatment Trials (CATT) study was a multicenter clinical trial that compared the safety and efficacy of bevacizumab with ranibizumab and an individualized dosing regimen (as needed, or PRN) with monthly injections. At 1 year,



the CATT study found that ranibizumab and bevacizumab had comparable VA improvements for monthly dosing.<sup>225</sup> Ranibizumab PRN had similar VA improvements compared with a fixed schedule of monthly injections. Further follow-up at 2 years showed that the two drugs remained comparable in both efficacy and safety, but the PRN arms for both drugs did not perform as well in terms of maintaining the visual gains at the end of year 1 compared with the two monthly arms, especially in the bevacizumab PRN group.<sup>240</sup> The CATT 5-year follow-up study demonstrated that vision gains during the first 2 years were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti-VEGF therapy as a major long-term therapeutic advance for neovascular AMD.<sup>241</sup> Similar results were seen in the 2-year Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial conducted in the United Kingdom.<sup>242, 243</sup> Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.<sup>241</sup> A meta-analysis in 2018 of more than 8000 eyes comparing aflibercept 2 mg, bevacizumab, and ranibizumab concluded that bevacizumab and ranibizumab had equivalent efficacy for BCVA, whereas ranibizumab had greater reduction in central macular thickness, and aflibercept and ranibizumab had comparable efficacy for BCVA and central macular thickness.<sup>244</sup> A review in 2015 also elicited similar results.<sup>245</sup> The systemic safety data in the CATT and IVAN studies are inconclusive and two Cochrane systematic reviews have also concluded that if a difference in safety between these anti-VEGF drugs exists, it is minimal.<sup>246, 247</sup> (*I+, Good quality, Strong recommendation*) A real-world analysis of 13,859 patients found that all three agents improved VA similarly over 1 year.<sup>248</sup>

Randomized clinical trials have been performed to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT, following the publication of results from uncontrolled case series.<sup>249-252</sup> However, the data do not currently support the use of combination therapy with corticosteroids, especially given the long-term side effects of glaucoma and cataract that are associated with corticosteroid use.

The DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone) did not show a significant benefit of adding PDT to anti-VEGF therapy in new-onset neovascular AMD.<sup>253, 254</sup> However, the EVEREST study demonstrated that fewer anti-VEGF injections were needed in combination therapy compared with anti-VEGF monotherapy in eyes with the PCV variant of neovascular AMD.<sup>255</sup> A 2017 meta-analysis and systematic review also concluded that treatment of PCV by PDT combined with ranibizumab is valuable in improving VA and maintaining long-term efficacy but recommended further study.<sup>256, 257</sup> A randomized trial of 310 subjects has shown aflibercept to treat PCV effectively in 85% of patients; 15% required PDT for control.<sup>257</sup> A 2018 meta-analysis of 16 studies compared 587 patients in the monotherapy group with various anti-VEGF agents against 673 patients in the combination group and found no statistically significant difference between groups in mean BCVA, the proportion of patients who gained 15 or more letters, or central retinal thickness at the end of the study.<sup>258</sup> However, combination therapy did require fewer anti-VEGF injections, as noted in other studies with reduced-fluence PDT, demonstrating this reduction in the number of injections at a statistically significant level as opposed to the standard fluence group.<sup>258</sup> Although current practice patterns support anti-VEGF monotherapy for exudative neovascular AMD, verteporfin PDT remains approved for the treatment of subfoveal lesions and can be used in certain situations.

Table 4 summarizes the findings from randomized controlled trials of verteporfin PDT and VEGF inhibitors for the treatment of subfoveal CNV.

A randomized, double-masked, sham controlled, multicenter clinical trial in the United Kingdom investigated the use of 16-Gray stereotactic radiation therapy (SRT) combined with PRN ranibizumab for patients with chronic active neovascular AMD. At 2 years, a mean of 10.7 (standard deviation [SD] 6.3) injections were administered in the SRT group, and 13.3 (SD 5.8) injections were administered in patients who had received a sham radiation procedure. The SRT group achieved noninferior change in VA compared with the sham group. Rates of adverse events were generally similar between the groups.

However, microvascular abnormalities were detected in 35% of the SRT group and 12% of the sham group on reading center assessment of multimodal imaging. Further study is needed to determine the long-term safety and efficacy of SRT and the effects of SRT combined with other anti-VEGF agents.<sup>259</sup>

## Biosimilars

As defined by the FDA, biosimilars are large complex molecules produced by living organisms that are similar to an existing molecule.<sup>260</sup> To approve a biosimilar, the FDA compares the purity, molecular structure, and bioactivity of the biosimilar to the existing molecule. The FDA also examines comparative clinical studies to ensure that there are “no clinically meaningful differences between the proposed biosimilar product (also called biosimilar) and the reference product in terms of safety, purity, or potency (safety and effectiveness).”<sup>261</sup> This abbreviated approval process means that the usual process of clinical trials that involve human subjects to determine safety and efficacy of a reference molecule is not needed.

A randomized clinical equivalence trial found that a proposed ranibizumab biosimilar product met efficacy for mean changes of BCVA at 8 weeks and OCT central subfield thickness at week 4. Safety and immunogenicity profiles were reported to be similar.<sup>262</sup> Post hoc analysis revealed no evidence of immunogenicity affecting clinical efficacy, safety, or penetrating keratoplasty profiles.<sup>263</sup> There are several biosimilar ranibizumab molecules approved by the FDA and others are available in numerous other countries.<sup>264</sup> A study compared ranibizumab 0.5 mg to FYB201 and found it biosimilar in terms of clinical efficacy and safety.<sup>265</sup> There are no prospective long-term clinical data comparing ranibizumab biosimilars to ranibizumab.

In 2021, the FDA approved the first biosimilar for the treatment of retinal disease, ranibizumab-nuna 0.5-mg dosage (Byooviz™, Samsung Bioepis, Incheon, South Korea and Biogen Inc., Cambridge MA), based on ranibizumab as the reference molecule for the retinal indication that ranibizumab-nuna is interchangeable with ranibizumab for treating neovascular AMD.<sup>206</sup> A study found that there was equivalence in primary efficacy at 1 year.<sup>266</sup>

In 2022, the FDA approved ranibizumab-eqrn 0.5-mg dosage (Cimerli®, Coherus Biosciences, Redwood City, CA), based on ranibizumab as the reference molecule for the retinal indications that ranibizumab-eqrn is interchangeable with ranibizumab for patients with neovascular AMD.<sup>207</sup> A 2023 systematic review of ranibizumab biosimilars found that they had similar outcomes for treatment of patients with neovascular AMD.<sup>267</sup> (*I+*, *Moderate quality*)

In 2024, the FDA approved five biosimilars to aflibercept 2 mg as of November 2024: Aflibercept-jbvf (Yesafili™, Biocon Biologics, Bridgewater, NJ),<sup>208</sup> aflibercept-yszy (Opviz™, Samsung Bioepis, Incheon, South Korea, and Biogen Inc, Cambridge MA),<sup>209</sup> aflibercept-mrbb (Ahzantive®, Formycon AG, Martinsried/Planegg, Germany),<sup>210</sup> aflibercept-abzv (Enzeevu™, Sandoz, Inc., Princeton, NJ), and aflibercept-ayyh (Pavblu™, Amgen, Inc., Thousand Oaks, CA).<sup>211, 268</sup> All are injected intravitreally as a 2-mg solution, and the adverse events appear comparable to aflibercept. The recommended dose for all five agents is 2 mg every 4 weeks for the first 12 weeks, followed by 2 mg every 8 weeks. When used, the choice of biologic product (reference, biosimilar, or interchangeable) should be that of the treating ophthalmologist and the patient because patients may respond more favorably to one biologic over another.<sup>269</sup>

**TABLE 4** EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
TAP (2001; verteporfin PDT) <sup>270</sup>	609	Mean age 75 years; BCVA 20/40 to 20/200; classic CNV or occult CNV if >50% of total lesion size	Following first treatment, retreatment was considered every 3 months per FA findings through 21 months of follow-up	47% 41% <sup>†</sup>	8%	62% 69% <sup>†</sup>	4%	2
ANCHOR (2006; ranibizumab) <sup>237</sup>	423	Mean age 77 years; BCVA 20/40 to 20/320; total lesion size ≤5400 μm; no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment; predominantly classic CNV lesions	Monthly ranibizumab injections for 2 years  Verteporfin PDT on day 0 and then PRN following FA at months 3, 6, 9, or 12	10% (0.5 mg)  66%	41% (0.5 mg)  6%	N/A (All patients received treatment)		2
MARINA (2006; ranibizumab) <sup>236</sup>	716	Mean age 77 years; BCVA 20/40 to 20/320; primary or recurrent CNV; minimally classic or occult with no classic CNV lesions; presumed recent progression of disease	Monthly ranibizumab injections for 2 years	10% (0.5 mg)	33% (0.5 mg)	47%	4%	2
VISION (2006; pegaptanib sodium) <sup>271</sup>	590	Age ≥50 years; BCVA 20/40 to 20/320; subfoveal CNV with total lesion size ≤12 disc areas; IOP ≤23 mmHg	Injection every 6 weeks for 54 weeks (9 total treatments); then re-randomized and injection every 6 weeks through week 96 (8 total treatments)	45%	10%	59%	4%	2

**TABLE 4 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION**

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
CATT (2011; bevacizumab vs ranibizumab) <sup>225</sup>	1208	Mean age 79 years; BCVA 20/25 to 20/320; untreated, active CNV, with CNV, fluid, or hemorrhage under the fovea	Ranibizumab 0.5 mg every 4 weeks	6%	34%	NA (All patients received treatment)	1	
			Bevacizumab 1.25 mg every 4 weeks	6%	31%			
			Ranibizumab 0.5 mg PRN	5%	25%			
			Bevacizumab 1.25 mg PRN	9%	28%			
VIEW 1 and 2 (2012; aflibercept 2 mg) <sup>218</sup>	2419	Mean age 76 years; BCVA 20/40 to 20/320; primary, active subfoveal (or juxtafoveal) CNV, with the total CNV area (classic plus occult CNV) ≥50% of total lesion size; any lesion subtype	Aflibercept 0.5 mg every 4 weeks	4%	30%	NA (All patients received treatment)		1
			Aflibercept 2 mg every 4 weeks	5%	34%			
			Aflibercept 2 mg every 4 weeks x 3, then every 8 weeks	4%	31%			
			Aflibercept 2 mg every 4 weeks x 3, then every 8 weeks	6%	33%			
HAWK (2020; brolucizumab) <sup>272</sup>	1082	Mean age 77 years; baseline BCVA ETDRS letters = 61, 58% occult lesion, 33% predominantly classic, total lesion area by FFA = 4.5 mm, 69% with subretinal fluid, 54% with intraretinal fluid, 44% with sub-RPE fluid, 14% with subretinal hemorrhage, 2% with intraretinal hemorrhage	Ranibizumab 0.5 mg every 4 weeks			NA (All patients received treatment)		1 (48 weeks)
			Brolucizumab 3 mg	6%	25%			
			Brolucizumab 6 mg	6%	34%			
			Aflibercept 2 mg	6%	25%			

**TABLE 4** EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
HARRIER (2020; brolucizumab) <sup>272</sup>	743	Mean age 75 years; baseline BCVA ETDRS letters = 61, 20/40, 20.80 Snellen VA = 60%, 50% occult lesion, 41% predominantly classic, total lesion area by FFA = 2.8 mm, 70% with subretinal fluid, 39% with intraretinal fluid, 34% with sub-RPE fluid, 3% with subretinal hemorrhage, 23% with intraretinal hemorrhage	Brolucizumab 6 mg Aflibercept 2 mg	4% 5%	29% 30%	NA (All patients received treatment)		1 (48 weeks)
Archway (2022; ranibizumab implant) <sup>238, 239</sup>	418	Mean age 75 years; baseline BCVA 74 ETDRS letters; patients had received mean of 5.0 prior anti-VEGF injections	Ranibizumab implant with refill exchange every 24 weeks Ranibizumab 0.5 mg every 4 weeks	Noninferior to monthly ranibizumab per mean change in BCVA	Not assessed			<1 (40 weeks)
LUCERNE (2024; faricimab) <sup>234</sup>	658	Mean age 76 years; baseline BCVA ETDRS letters = 59, 20/40; 20.80 Snellen VA = 55%, 61 % subfoveal CNV, 24% juxtafoveal CNV, 13% extrafoveal CNV, 47% occult lesion, 31% classic, total lesion area by FFA = 4.5 mm	Faricimab 6 mg up to 16 weeks after initial dosing Aflibercept 2 mg every 8 weeks	22% 7%	21% 9%	NA (All patients received treatment)		2
PULSAR (2024; aflibercept 8 mg) <sup>219</sup>	1009	Mean age 75 years; baseline BCVA 59 ETDRS letters, 21% predominantly classic, 18% minimally classic, 57% occult only.	Aflibercept 8 mg 12-week regimen Aflibercept 8 mg 16-week regimen	Noninferior to 2-mg aflibercept Noninferior to 2-mg aflibercept		NA (All patients received treatment)		1

**TABLE 4** EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes		Untreated Eyes		Years after Enrollment
				Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*	
TENAYA (2024; faricimab) <sup>234</sup>	671	Mean age 76 years; baseline BCVA ETDRS letters = 61, 20/40; 20.80 Snellen VA = 60%, 58 % subfoveal CNV, 26% juxtafoveal CNV, 14% extrafoveal CNV, 52% occult lesion, 23% classic, total lesion area by FFA = 4.6 mm	Faricimab 6 mg up to 16 weeks after initial dosing  Aflibercept 2 mg every 8 weeks	17%  11%	23%  8%	NA (All patients received treatment)		2

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; FA = fluorescein angiography; FFA = fundus fluorescein angiography; CATT = Comparison of Age-Related Macular Degeneration Treatment Trials; IOP = intraocular pressure; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; NA = not applicable; PDT = photodynamic therapy; PRN = as needed; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF Inhibition Study in Ocular Neovascularization.

\* Defined as doubling of the visual angle.

<sup>†</sup> Pegaptanib sodium injection was administered to patients who were allowed both prior and on-study PDT.

<sup>‡</sup> Predominantly classic.

## Extrafoveal Choroidal Neovascularization

There still remains a role for laser photocoagulation surgery in eyes with extrafoveal and peripapillary CNV lesions as defined by the MPS.<sup>174, 273</sup> Although photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years, recurrence or persistence occurs in approximately 50% of cases, thus reducing this benefit over the subsequent 3 years of follow-up.<sup>174</sup> After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to VA loss of 30 or more letters when compared with 62% of untreated eyes.<sup>174</sup> The historical data are important to recognize in current practice patterns, because none of the anti-VEGF or PDT trials included extrafoveal lesions. Practitioners have extrapolated data from the dramatic improvements seen in the treatment of subfoveal lesions and applied it to extrafoveal lesions. The current trend is to use anti-VEGF agents in preference to laser photocoagulation surgery.

Current therapies that have insufficient data to demonstrate clinical efficacy for treatment of CNV lesions include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, currently, these therapies have not proven to be beneficial.

The risk for progression of AMD and the treatments by severity level are shown in Table 5 according to the stage of AMD.

**TABLE 5 RISK FOR PROGRESSION OF AGE-RELATED MACULAR DEGENERATION AND TREATMENTS BY SEVERITY LEVEL**

Stage of AMD	Risk of Progression to Advanced AMD (approximately)*	Treatment Options
No drusen (AREDS category 1)	5-year risk 0.5%, 10-year risk 1.5%	None
Early AMD (AREDS category 2)	5-year risk 4%, 10-year risk 8%	None
Intermediate AMD (AREDS category 3) Without pigment OU	5-year risk 9%, 10-year risk 28%	AREDS2 antioxidant supplements**
Advanced AMD – GA (AREDS category 4)	5-year risk 45%, 10-year risk 71%	Consider intravitreal medication
Advanced AMD – MNV (AREDS category 4)	5-year risk 45%, 10-year risk 71%	Anti-VEGF intravitreal injections may be recommended
Extrafoveal Choroidal Neovascularization in AMD (AREDS category 4)	5-year risk 45%, 10-year risk 71%	Anti-VEGF intravitreal injections or laser surgery may be recommended

AMD = Age-Related Macular Degeneration; Anti-VEGF = Anti-vascular endothelial growth factor; GA = geographic atrophy; MNV = macular neovascularization.

\*The risk of progression to advanced AMD is based on the simplified severity scale and based on the AREDS cohort aged 55 to 80 years of age.<sup>143</sup>

\*\*The AREDS design included participants ages 55–80 years old.<sup>61</sup>

# CARE PROCESS

## PATIENT OUTCOME CRITERIA

Patient outcome criteria are to reverse or minimize visual loss and improve visual function.

## DIAGNOSIS

The initial evaluation of a patient with signs and symptoms suggestive of AMD includes all features of the comprehensive adult medical eye evaluation,<sup>274</sup> with particular attention to those aspects relevant to AMD.

### History

An initial history should consider the following elements:

- ◆ Symptoms<sup>275</sup>
  - ◆ Metamorphopsia
  - ◆ Decreased vision
  - ◆ Scotoma
  - ◆ Photopsia
  - ◆ Difficulties in dark adaptation
- ◆ Medication and nutritional supplement use
- ◆ Ocular history<sup>13, 276, 277</sup>
- ◆ Medical history<sup>13, 276, 277</sup> (including any hypersensitivity reactions<sup>278, 279</sup>)
- ◆ Family history, especially family history of AMD<sup>89, 280</sup>
- ◆ Social history, especially a quantitative smoking history<sup>38-42</sup>

### Examination

- ◆ Comprehensive eye examination
- ◆ Amsler grid
- ◆ Stereoscopic biomicroscopic examination of the macula

Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical signs of MNV. These include small areas of hemorrhage, hard exudates, subretinal fluid, macular edema, subretinal fibrosis, or pigment epithelial elevation.

## Diagnostic Tests

### Optical Coherence Tomography

Optical coherence tomography is important in diagnosing and managing AMD, particularly with respect to determining the presence of subretinal and intraretinal fluid and in documenting the degree of retinal thickening.<sup>281</sup> Optical coherence tomography defines the cross-sectional architecture of the retina, which is not possible with any other imaging technology. It may reveal the presence of fluid that is not apparent on biomicroscopy alone. It also helps in evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately.<sup>282-285</sup> Newer-generation OCT modalities, including SD-OCT and swept-source (SS) OCT, are preferred technologies. Advances in OCT have increased the image resolution and enhanced our ability to detect structural changes of the retina and choroid.<sup>286-289</sup> The implementation of newer technologies, such as SS-OCT, is evolving at this time.<sup>287-289</sup>



## Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality that provides evaluation of the retinal and choroidal vasculature; it is becoming more commonly applied in the evaluation and management of AMD, but it has not replaced other angiographic methods.<sup>290</sup> Sensitivity and specificity for MNV detection with en face OCTA combined with cross-sectional OCTA approaches the gold standard of specificity and sensitivity of fluorescein angiography with OCT, and it is better than en face OCTA alone.<sup>291</sup> A meta-analysis of OCTA for detection of MNV revealed a sensitivity of 0.87 and specificity of 0.97.<sup>290</sup> Structural OCT alone has excellent sensitivity for MNV detection. False positives from the structural OCT can be mitigated with the addition of flow information with OCTA.<sup>291</sup> Optical coherence tomography angiography may detect subclinical MNV, which needs close monitoring and not treatment.<sup>236, 290, 292, 293</sup>

## Fluorescein Angiography

Intravenous fundus fluorescein angiography may be indicated<sup>174, 176, 177</sup> when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, macular edema, subretinal blood, hard exudates, or subretinal fibrosis, or the OCT shows evidence of fluid. Fluorescein angiography is also warranted as follows:

- ◆ To detect the presence of and determine the extent, type, size, and location of MNV. If verteporfin PDT or laser photocoagulation surgery is being considered, the angiogram is used as a guide to direct treatment. The role and indications for fluorescein angiography are evolving as continued advances in OCT occur.
- ◆ To detect persistent or recurrent MNV or other retinal diseases following treatment.
- ◆ To assist in determining the cause of visual loss that is not explained by the clinical examination.

If MNV is suspected on the basis of new symptoms or ocular findings, fluorescein angiography should be performed and interpreted expeditiously by an individual experienced in managing patients with neovascular AMD.<sup>174, 176, 177</sup>

When fluorescein angiography is performed, the physician must be aware of potential risks associated with this procedure:<sup>294, 295</sup> tissue infiltration (if the drug extravasates the vein), pain, and allergic reactions. Even death from anaphylaxis has been reported (approximately 1 in 200,000 patients). Each angiographic facility should have a care plan in place for an emergency situation as well as a clear protocol to minimize the risks and to manage complications. Of note, fluorescein crosses the placenta and it is present in breastmilk for 72 hours.<sup>296, 297</sup>

## Fundus Photography

Color fundus photographs may be obtained when angiography is performed, because they are useful in finding landmarks, evaluating serous detachments of the neurosensory retina and RPE, and determining the etiology of blocked fluorescence. Fundus photographs may also be used as a baseline reference for selected patients with advanced non-neovascular AMD and for follow-up of treated patients.

## Fundus Autofluorescence

Fundus autofluorescence is helpful to demonstrate areas of GA and monitor their progression. Some patterns of autofluorescence may predict faster rates of GA.<sup>298</sup> Also, fundus autofluorescence may be used to quantify lipofuscin in the RPE.<sup>298</sup>

## Indocyanine Green Angiography

Indocyanine green angiography allows visualization of the choroidal circulation. The value of this test in evaluating and treating AMD has been debated.<sup>299</sup> Indocyanine green angiography has been shown to be useful in evaluating specific forms of AMD, such as PED, poorly defined MNV, occult MNV, and lesions including retinal angiomatous proliferation or idiopathic PCV.<sup>300, 301</sup> The PCV form of neovascular AMD may be more easily identified when ICG is used, particularly in patients of African or Asian descent.<sup>14, 302</sup> When ICG angiography is performed, the physician must be aware of potential risks associated with this procedure: severe medical complications, allergic reactions, and even death.<sup>303</sup> Indocyanine green does not cross the placenta and is generally safe in pregnancy.

## Other Tests

Several other tests including microperimetry<sup>304</sup> (to measure macular sensitivity), and adaptive optics (to identify individual rods and cones)<sup>305</sup> have been used to evaluate patients with AMD; however, their specific role in clinical practice has yet to be specifically defined. Artificial intelligence is being evaluated as an adjunct in clinical practice to monitor and predict disease progression in AMD.<sup>306-308</sup>

## MANAGEMENT

Consequences of untreated neovascular AMD include a substantial economic burden on patients, their family, and society. Anti-VEGF agents are cost-effective for the management of neovascular AMD, and the choice of which agent to use should be individually tailored based on discussion between the patient and physician. Early detection and treatment of AMD to arrest the deterioration in vision may help preserve patients' quality of life and independence. Management options for AMD include observation, antioxidant vitamin and mineral supplements, intravitreal injection of anti-VEGF agents, PDT, and laser photocoagulation surgery. Several new treatments such as stem cells and gene therapy are currently under investigation.<sup>309-311</sup>

Patients who are currently smoking should be advised to stop.<sup>312, 313</sup> Studies have found that the physician's advice to stop smoking is a helpful motivator for patients who are attempting to quit<sup>313</sup> and is associated with increased long-term smoking abstinence rates.<sup>314</sup> An important component of care for a patient with AMD is referral for vision rehabilitation as well as continued follow-up for general eye care.

## Monitoring and Early Detection

Patients with early AMD and/or a family history of AMD should be encouraged to assess their own VA using monocular vision testing (i.e., Amsler grid or electronic home monitoring<sup>315, 316</sup>) and have scheduled dilated eye examinations for detecting the intermediate stage of AMD. Treatment with antioxidants and minerals as described previously in the original AREDS and AREDS2 trials should be considered for patients who have progressed to intermediate or advanced AMD in at least one eye.

Patients with a high-risk AMD phenotype are at increased risk of progression to advanced AMD and should be educated about methods of detecting new symptoms of MNV, including self-monitoring. They should also be educated about the need for promptly reporting new symptoms to an ophthalmologist who can confirm if the new symptoms are from MNV and who can begin any necessary treatment.

Follow-up examinations of patients at increased risk of progression to advanced AMD may enable (1) early detection of asymptomatic and treatable neovascular lesions that could improve or preserve VA, (2) education about the possible benefit of AREDS2-based nutritional supplements, and (3) reinforcement of the need for self-monitoring and prompt evaluation with the onset of new symptoms. Patients who check monocular near vision (reading/Amsler grid/Amsler-grid equivalent) may be more likely to become aware of subtle visual symptoms

due to MNV, increasing the likelihood of detecting MNV at an early stage which, on average, yields better long-term visual outcomes with treatment compared with neovascular disease detected at a more advanced stage.

Electronic monitoring devices are now available to aid in the detection of neovascularization at an early stage. Such devices use hyperacuity perimetry (or vernier acuity) to create a quantified central visual map of metamorphopsia.<sup>317</sup> Further studies of a variety of such devices are ongoing.<sup>317-319</sup>

## Indications for Treatment for Macular Neovascularization

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 6. The criteria for treatment of AMD and the techniques of therapy are described in the anti-VEGF agent, MPS, and AREDS literature. Anti-VEGF agent product labeling and other literature discuss techniques of intravitreal injection.<sup>278, 279, 320-322</sup>

As is the case with most clinical trials, these treatment trials do not provide clear guidance for the management of all patients encountered in clinical practice. The first major prospective randomized anti-VEGF treatment trials (Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD [ANCHOR], Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA], VIEW, CATT, IVAN, and HARBOR) used either a fixed continuous treatment regimen (approximately every 4 or 8 weeks) or an individualized discontinuous treatment regimen (as-needed or PRN treatment).<sup>218, 225, 236, 237, 240, 242, 243, 323</sup> Choice of the treatment strategy to use should be individually tailored based on discussion between the patient and physician.

The PRN regimens using ranibizumab appear to have efficacy and safety comparable to fixed monthly regimens over 1 year of treatment, but they do not maintain the initial visual gains with longer follow-up.<sup>240, 241</sup> Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens and other PRN anti-VEGF regimens.<sup>240</sup> Vision gains during the first 2 years of the CATT clinical trials were not maintained at the 5-year follow-up visit, but 50% of the patients maintained a VA of 20/40.<sup>241</sup> A continuous, variable dosing regimen that attempts to individualize therapy, commonly referred to as treat-and-extend, is frequently used in clinical practice as an alternative to the two treatment approaches above.<sup>324-327</sup> Prospective studies such as Lucentis Compared to Avastin Study (LUCAS) have shown similar efficacy between monthly and treat-and-extend for bevacizumab and ranibizumab.<sup>328</sup>

Personalized treatment interval dosing regimens, which are based on treat-and-extend and use prespecified criteria, maintain visual and anatomic improvements while allowing for extended dosing intervals in clinical studies evaluating faricimab and aflibercept 8 mg.<sup>219, 233</sup>

Subretinal hemorrhages are relatively common in neovascular AMD. Small subretinal hemorrhages are a sign of active MNV or PCV and may be managed with anti-VEGF therapy. For the management of larger submacular hemorrhages, the Submacular Surgery Trial study was inconclusive.<sup>159</sup> Pneumatic displacement procedures, the use of tissue plasminogen activator (tPA), and/or pars plana vitrectomy have been proposed. The data on management of these larger hemorrhages are inadequate to make a recommendation at this time.<sup>329</sup>

TABLE 6 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations	
Non-neovascular AMD		Intervals	Testing
Observation with no medical or surgical therapies <sup>5, 158, 330</sup>	Early AMD (AREDS category 2)	Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	Fundus photos, fluorescein angiography, OCT, or OCTA as appropriate <sup>5</sup>
	Advanced AMD with bilateral subfoveal GA or disciform scars	Return examination at 6–24 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	Fundus photos, fluorescein angiography, OCT, or OCTA as appropriate <sup>5</sup>
Medical therapy	Some patients with GA (with or without subfoveal involvement)	Pegcetacoplan every 25 to 60 days <sup>200</sup>	<p>OCT, fundus autofluorescence, fluorescein angiography, OCT, or OCTA as appropriate:</p> <ul style="list-style-type: none"> <li>• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters.</li> <li>• Patients should be instructed to promptly report symptoms suggestive of macular CNV, including decreased vision, distortion, loss of vision.</li> <li>• Patients without subfoveal atrophy should be monitored for monocular near vision (reading/Amsler grid).</li> </ul>
		Avacincaptad pegol every 28 days for 12 months <sup>331</sup>	<p>OCT, fundus autofluorescence, fluorescein angiography, OCT, or OCTA as appropriate:</p> <ul style="list-style-type: none"> <li>• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters.</li> <li>• Patients should be instructed to promptly report symptoms suggestive of macula CNV, including decreased vision, distortion, loss of vision.</li> </ul>

TABLE 6 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations	
		<ul style="list-style-type: none"> <li>Patients without subfoveal atrophy should be monitored for monocular near vision (reading/Amsler grid).</li> </ul>	
Antioxidant vitamin and mineral supplements as recommended in the original AREDS and AREDS2 reports <sup>5, 63</sup>	<ul style="list-style-type: none"> <li>Intermediate AMD (AREDS category 3)</li> <li>Advanced AMD in one eye (AREDS category 4)</li> </ul>	Return examination at 6-18 months if asymptomatic or prompt examination for new symptoms suggestive of CNV	<ul style="list-style-type: none"> <li>Monitoring of monocular near vision (reading/Amsler grid)</li> <li>Fundus photography and/or fundus autofluorescence as appropriate</li> <li>Fluorescein angiography and/or OCT for suspicion of CNV</li> </ul>
<b>Neovascular AMD</b>			
Aflibercept intravitreal injection 2 mg and 8 mg as described in published reports <sup>218</sup>	CNV	<ul style="list-style-type: none"> <li>Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters.</li> <li>Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>A 2-mg maintenance treatment regimen of every 8 weeks has been shown to have results comparable to every 4 weeks in the first year of therapy.</li> <li>The 8-mg recommended dose is every 4 weeks (monthly) for the first 3 months, followed by 8 mg every 8 to 16 weeks, but subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>	
Bevacizumab intravitreal injection 1.25 mg as described in published reports <sup>223-228, 240, 242, 321, 325</sup>	CNV	<ul style="list-style-type: none"> <li>Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.</li> <li>Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>	
The ophthalmologist should provide appropriate informed consent with respect to the off-label status <sup>229</sup>			

**TABLE 6 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION**

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Brolucizumab intravitreal injection 6 mg as described in FDA labeling <sup>272</sup>	CNV	<ul style="list-style-type: none"> <li>• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.</li> <li>• Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on clinical findings and judgment of the treating ophthalmologist.</li> <li>• The recommended dose is every 4 weeks (monthly) for the first 3 doses, followed by 6 mg every 8 to 12 weeks, but subsequent treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>• Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>
Faricimab 6 mg <sup>215</sup>	CNV	<ul style="list-style-type: none"> <li>• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.</li> <li>• Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on clinical findings and judgment of the treating ophthalmologist.</li> <li>• The recommended dose is every 4 weeks (monthly) for the first 4 doses, followed by administration every 4 to 16 weeks, but subsequent treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>• Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>
Ranibizumab intravitreal injection 0.5 mg as recommended in literature <sup>225, 236, 237, 240, 242, 279, 323, 324, 326, 327</sup>	CNV	<ul style="list-style-type: none"> <li>• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.</li> <li>• Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>• Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>

**TABLE 6 TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR AGE-RELATED MACULAR DEGENERATION**

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Ranibizumab implant	CNV	<ul style="list-style-type: none"> <li>Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.</li> <li>Patients should return for examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist.</li> <li>Monocular near vision (reading/Amsler grid) should be monitored.</li> <li>Patients with an implant placed surgically and filled during surgery should follow postoperative instructions.</li> <li>The implant can be refilled every 6 months with rescue ranibizumab 2 mg given per clinical judgment between implant refills.</li> </ul>
<b>Less Commonly Used Treatments for Neovascular AMD</b>		
PDT with verteporfin as recommended in the TAP and VIP reports <sup>270, 332-334*</sup>	<ul style="list-style-type: none"> <li>CNV, new or recurrent, where the classic component is &gt;50% of the lesion and the entire lesion is ≤5400 μm in greatest linear diameter</li> <li>Occult CNV may be considered for PDT with vision &lt;20/50 or if the CNV is &lt;4 MPS disc areas in size when the vision is &gt;20/50.</li> <li>Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases.</li> </ul>	<ul style="list-style-type: none"> <li>Patients should return for examination approximately every 3 months until stable, with retreatments as indicated.</li> <li>Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>
Thermal laser photocoagulation surgery as recommended in the MPS reports is rarely used <sup>174, 177, 330</sup>	<ul style="list-style-type: none"> <li>May be considered for extrafoveal CNV, new or recurrent</li> <li>May be considered for juxtapapillary CNV</li> </ul>	<ul style="list-style-type: none"> <li>Patients should return for examination with fluorescein angiography approximately 2–4 weeks after treatment, and then at 4–6 weeks and thereafter depending on the clinical and angiographic findings, with retreatments as indicated.</li> <li>Monocular near vision (reading/Amsler grid) should be monitored.</li> </ul>

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy.

\* Contraindicated in patients with porphyria or known allergy.

## Complications of Treatment

Possible complications of the four main modalities of treatment for AMD are listed below. Retinal pigment epithelium tears (tears) may occur with or without these treatment modalities, yet this is not a contraindication to continued anti-VEGF therapy.

### Intravitreal Pharmacotherapy

All anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events (ATEs) and increased intraocular pressure, although the results of clinical trials studying these risks remain inconclusive.<sup>205, 246, 247, 335-338</sup> A 2021 systematic review and meta-analysis found that intravitreal anti-VEGF agent use did not increase major cardiovascular events, but there were increased nonocular hemorrhages in patients with AMD.<sup>337</sup> (*I+*, *Moderate quality*) Another systematic review with meta-analyses concluded that anti-VEGF treatment intensity had no significant influence on mortality.<sup>338</sup> (*I+*, *Moderate quality*) A review of the literature concluded that anti-VEGF therapy is safe and effective for neovascular AMD.<sup>339</sup> The risks of intravitreal anti-VEGF agents in pregnant or lactating women have not been studied.<sup>340, 341</sup> Intravitreal pharmacotherapy can result in endophthalmitis, noninfectious inflammation, retinal tear, or detachment. Intravitreal anti-VEGF agents are discussed below.

#### *Aflibercept 2 mg*

Endophthalmitis had a cumulative incidence of 1.0% or less over 1 year in VIEW studies.<sup>218</sup> The incidence of reported thromboembolic events in neovascular AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with aflibercept 2 mg compared with 1.5% (9 out of 595) in patients treated with ranibizumab. Through 96 weeks, the incidence was 3.3% (60 out of 1824) in the aflibercept 2-mg group compared with 3.2% (19 out of 595) in the ranibizumab group.<sup>213</sup> Serious adverse reactions related to the injection procedure have occurred in less than 0.1% of intravitreal injections with aflibercept 2 mg, including endophthalmitis and retinal detachment. The most common adverse reactions ( $\geq 5\%$ ) reported in patients receiving aflibercept 2 mg were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. At 1 year, there were no statistically significant differences in rates of serious systemic adverse events such as death, arteriothrombotic events, or venous thrombotic events between ranibizumab and aflibercept.<sup>218, 342</sup> Aflibercept was found to have a 0% to 0.16% rate of intraocular inflammation (not counting endophthalmitis).<sup>343</sup>

#### *Aflibercept 8 mg*

The safety profile for aflibercept 8 mg was similar to aflibercept 2 mg at 48 weeks. The incidence of reported thromboembolic events from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with aflibercept 8 mg.<sup>219</sup> The most common adverse reactions ( $\geq 3\%$ ) reported in patients treated with aflibercept 8 mg were cataract, conjunctival hemorrhage, increased intraocular pressure, ocular discomfort/eye pain/eye irritation, blurred vision, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.<sup>213</sup>

#### *Bevacizumab*

Reported safety data are limited by relatively short and variable follow-up periods and by differences in reporting criteria.<sup>344, 345</sup> Reported ocular adverse events include bacterial endophthalmitis (0.16%) per injection, tractional retinal detachments (0.16%), uveitis (0.09%), rhegmatogenous retinal detachment (0.02%), and vitreous hemorrhage (0.16%).<sup>321, 346</sup> Bevacizumab was found to have a 0.081% to 0.10% rate of intraocular inflammation (not counting endophthalmitis).<sup>343</sup>

At 1 year, the CATT study had no statistically significant differences in rates of death, arteriothrombotic events, or venous thrombotic events for the two drugs, but there was



limited statistical power. There was a higher rate of serious systemic events (e.g., arteriothrombotic events, venous thrombosis, or gastrointestinal disorders such as hemorrhage) among patients treated with bevacizumab compared with ranibizumab (24% vs. 19%;  $P = 0.04$ ), and this statistically significant difference was persistent at 2 years of follow-up.<sup>225, 240</sup> The IVAN trial showed greater serum VEGF suppression with bevacizumab but did not show any statistically significant difference in serious systemic adverse events.<sup>242</sup>

#### *Brolucizumab*

Although HAWK and HARRIER found a 2.1% incidence of retinal vasculitis with retinal vascular occlusion, postmarketing surveillance revealed a higher incidence of intraocular inflammation.<sup>230, 347</sup>

Arterial thromboembolic events occurred in 1.1% and 1.4% of the patients in the 3-mg and 6-mg study groups of HAWK study, respectively, and in 1.6% of the brolucizumab patients in HARRIER study. Among them, four patients in the 3-mg group and six patients in the 6-mg group had retinal artery occlusion and all of them had cardiovascular comorbidities such as hypertension or cardiac arrhythmias. The other mentioned adverse effects in the study were retinal hemorrhage, cataract, dry eye, eye pain, posterior capsule opacification, increased intraocular pressure, blepharitis, retinal pigment epithelial tear, punctate keratitis, corneal abrasion, conjunctivitis, and macular fibrosis.<sup>230</sup>

#### *Faricimab*

The incidence of reported ATEs during the first year was 1% (7 out of 664) in patients treated with faricimab compared with 1% (6 out of 662) in patients treated with aflibercept. The risk of endophthalmitis was less than 1%.<sup>235</sup> Recently, case reports of intraocular inflammation (excluding endophthalmitis) with faricimab were as high as 2% and retinal vasculitis with or without occlusion were 0.17 per 10,000 injections (vasculitis) and 0.06 per 10,000 for occlusive vasculitis.<sup>348</sup>

#### *Ranibizumab*

The incidence of endophthalmitis was cumulative 1.0% or less over 2 years in the MARINA study and less than 1.0% over 1 year in ANCHOR study. There was a per injection rate of endophthalmitis of 0.05% in MARINA.<sup>236</sup> Retinal detachment or traumatic injury to the lens occurred in less than 0.1% of treated cases during the first year of treatment.<sup>236, 237</sup> Ranibizumab was found to have a 0.081% to 0.10% rate of intraocular inflammation (not counting endophthalmitis).

#### *Ranibizumab Ocular Implant*

The ranibizumab implant has been associated with a threefold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. Many of these events were associated with conjunctival retractions or erosions. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one episode of endophthalmitis. Patients had a 5.2% risk of vitreous hemorrhage, which resolved spontaneously.<sup>349</sup>

#### *Biosimilars*

Ophthalmic biosimilars require one comparative trial of 9 months or more for AMD demonstrating safety and efficacy compared with the reference product.<sup>269</sup> They have no clinically meaningful differences from the reference product except in inactive components, or excipients, which can have implications for safety.<sup>269</sup> Ranibizumab-nuna and ranibizumab-eqrn were found to have comparable safety profiles to that of ranibizumab in randomized phase 3 clinical trials.<sup>265, 266</sup> Similarly, aflibercept-yszy

demonstrated a similar safety profile to that of aflibercept 2 mg in a randomized phase 3 study.<sup>350</sup>

### Verteporfin Photodynamic Therapy

Possible complications of verteporfin photodynamic therapy include the following:

- ◆ A severe decrease in central vision occurred within 1 week following treatment in 1% to 4% of patients, which may be permanent<sup>270, 332, 333</sup>
- ◆ Infusion site extravasation
- ◆ Idiosyncratic back pain during infusion of the drug (1%–2% of patients)<sup>270, 332, 333</sup>
- ◆ Photosensitivity reaction (<3% of patients).<sup>270, 332, 333</sup> The stated, current recommendations are to avoid direct sunlight for the first 5 days after a treatment.

Verteporfin is contraindicated in patients with porphyria or a known allergy or sensitivity to the drug. Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breastfeeding, or of pediatric age, because these patients were not studied in published reports.<sup>351</sup>

### Thermal Laser Photocoagulation Surgery

Possible complications of the thermal laser surgery modality include the following:

- ◆ Severe vision loss following treatment, which may be permanent
  - ◆ Rupture of Bruch's membrane with subretinal or vitreous hemorrhage
- Thermal laser is no longer recommended for subfoveal MNV.

### Antioxidant Vitamin and Mineral Supplements

Possible complications of high-dose beta-carotene are as follows:

- ◆ Self-reported yellowing of the skin (8.3% in the antioxidant arm compared with 6.0% in the no antioxidant arm;  $P = 0.008$ )<sup>5</sup>
- ◆ Increased risk of developing lung cancer in current smokers (an excess cumulative incidence of lung cancer was observed after 18 months and increased progressively thereafter, resulting in an 18% difference in incidence by the end of the study (95% CI, 3%–36%;  $P = 0.01$ ) between the patients who received beta-carotene and those who did not.<sup>191</sup> The active treatment group had a relative risk of lung cancer of 1.28 (95% CI, 1.04–1.57;  $P = 0.02$ ) compared with the placebo group.<sup>192</sup>

Possible complications of high-dose zinc supplements include the following:

- ◆ Increased risk of hospitalizations for genitourinary causes (i.e., unspecified urinary tract infection and prostatic hyperplasia in men and stress incontinence in women) were 7.5% in those treated with zinc compared with 4.9% in those not treated with 80 mg of zinc;  $P = 0.001$ .<sup>5</sup> In the AREDS2, there was no significant difference in AMD progression between 80 mg and 25 mg of zinc.
- ◆ Copper-deficiency anemia (concomitant administration of copper is necessary according to the AREDS and AREDS2)

When considering long-term supplementation, some people may have reason to avoid one or more of the supplements evaluated in the original AREDS or AREDS2. Because of the potential adverse effects, such as increased rate of genitourinary conditions that may require hospitalizations, the high doses of antioxidant vitamins and minerals recommended by the original AREDS and AREDS2 should be reviewed by the patient's primary care physician.

## Follow-up Evaluation

A history and examination are the recommended elements of the follow-up visits, and the recommended follow-up intervals are listed in Table 6.

### History

The follow-up history should take into account the following:

- ◆ Symptoms, including decreased vision and metamorphopsia<sup>275</sup>
- ◆ Changes in medications and nutritional supplements
- ◆ Changes in medical and ocular history<sup>13, 276, 277</sup>
- ◆ Changes in social history (smoking)<sup>38-42</sup>

### Examination

The examination on the follow-up visit should include the following:

- ◆ Visual acuity at distance with correction
- ◆ Amsler grid
- ◆ Stereoscopic biomicroscopic examination of the fundus

### Follow-up after Treatment for Neovascular Age-Related Macular Degeneration

In addition to the above recommendations, patients who have been treated with intravitreal injections, verteporfin PDT, or thermal laser photocoagulation surgery should be examined at regular intervals by means of biomicroscopy of the fundus. Optical coherence tomography,<sup>281</sup> OCTA,<sup>352-355</sup> fluorescein angiography,<sup>174, 176, 177</sup> and fundus photography may be helpful to detect signs of active exudation or disease progression and should be used when clinically indicated. In common clinical practice, OCT is a simple, noninvasive procedure that is well accepted by the patient and provides important information for the provider to manage AMD.

Initial treatment and follow-up with intravitreal anti-VEGF therapy should be at approximately 4-week intervals.<sup>206-217, 229</sup> Subsequent follow-up and treatment intervals vary depending on the clinical findings and judgment of the treating ophthalmologist. After three loading doses administered at 4-week intervals, a maintenance treatment regimen every 8 weeks with aflibercept 2 mg has been shown to have comparable efficacy to every 4 weeks of either ranibizumab and aflibercept 2 mg in the first year of therapy.<sup>218</sup> There are numerous protocols: monthly or bimonthly injections, treat-and-extend, PRN, or personalized treatment interval. There is no consensus about the ideal treatment intervals with anti-VEGF agents, and the physician can tailor treatment on an individual patient basis.

Subsequent examinations, OCT, OCTA, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist. Treated patients should be instructed to report symptoms of endophthalmitis, retinal detachment, or decreased vision, and they should be re-examined promptly.

Real-world treatment tends to fall short of clinical trial guidelines and protocols, and it results in worse outcomes. A systematic review found multiple factors contributing to nonadherence and nonpersistence in neovascular AMD treatment, including poorer vision at baseline and less than optimal treatment response.<sup>356</sup> (*II-, Moderate quality*) Another systematic review of intravitreal injection therapy found that worse vision at baseline, worsening of vision, age, and distance from a treatment center were associated with nonadherence.<sup>357</sup> (*II-, Moderate quality*) Loss to follow-up is not uncommon in patients with neovascular AMD. One study found that 1 out of 9 patients undergoing treatment with

anti-VEGF injections was lost to follow-up. Risk factors included increased age, male sex, unilateral involvement, diabetes, Medicaid insurance, and race and ethnicity.<sup>358-360</sup>

### Fellow Eyes without Macular Neovascularization

For patients with unilateral disease, the fellow eye without MNV remains at high risk of developing advanced AMD.<sup>361</sup> The risk can be lowered by as much as 36% over a 10-year period by taking the AREDS/AREDS2 supplements.<sup>5</sup> Patients should be instructed to monitor their vision and to return to the ophthalmologist periodically, even in the absence of symptoms, but promptly after the onset of any new or significant visual symptoms. Patients at exceptionally high risk (e.g., those who have advanced AMD in one eye and large drusen with RPE changes in the fellow eye) may be examined more frequently (i.e., every 6–12 months) in an effort to detect asymptomatic MNV at a treatable stage. Since some patients with AMD also have cognitive impairment, a family member or care assistant should prompt the patient to self-test. Optical coherence tomography is useful and OCTA may be useful for evaluating the status of high-risk fellow eyes.

## PROVIDER AND SETTING

Ophthalmologists, optometrists, and ancillary clinical personnel should be aware that patients with the onset of new symptoms suggestive of AMD (e.g., new visual loss, metamorphopsia, or scotoma) should be examined promptly. The ophthalmologist should perform the examination, order appropriate testing, and administer all treatment and anti-VEGF injections, and certain aspects of the testing may be conducted by other trained individuals under the ophthalmologist's supervision. The American Academy of Ophthalmology has a stated position and a policy statement on the role of the ophthalmologist in the delivery of intravitreal agents.<sup>362</sup>

## COUNSELING AND REFERRAL

All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment as appropriate for their visual and functional status. Patients can be informed that while central visual loss is common, total visual loss is extremely rare. Patients with AMD can be reassured that there is no harm in using their eyes for normal visual tasks, and they may be told that the effect of total sunlight exposure remains uncertain. Insofar as cigarette smoking is a key modifiable risk factor, smoking cessation is strongly recommended when advising patients with AMD or at risk for AMD.

The informed consent process should include a discussion of the risks and benefits of treatment and treatment alternatives. Patients should be told that these are treatments not cures for neovascular AMD and ongoing follow-up is essential to maintain the best possible vision. The off-label status of bevacizumab for neovascular AMD should be included in the discussion; information and a consent form are available from the Ophthalmic Mutual Insurance Company.<sup>229</sup>

Vision rehabilitation optimizes the patient's functional ability,<sup>363</sup> and patients with reduced visual function should be referred for vision rehabilitation and social services.<sup>364</sup> Empathic communication and questioning by the provider is helpful to elicit patient concerns. Referrals for counseling, vocational rehabilitation, and or peer support groups for patients with depression, anxiety, and loss of independence or employment should be considered.<sup>365</sup> Patients with severe visual loss related to AMD who are referred for vision rehabilitation services often have unrealistic expectations. Educating patients that the visual rehabilitation specialist helps to optimize their existing visual function rather than "helping them see better" will establish more appropriate expectations around such services. Special optical or electronic magnifying lenses, bright lights, and electronic reading aids may help patients to read more effectively but not as well as they did before the onset of AMD. An Implantable Miniature Telescope (IMT) is an FDA-approved device that may be effective for screened, phakic, motivated patients with end-stage AMD.<sup>366, 367</sup> A systematic review in 2018 found insufficient evidence on the IMT's safety and effectiveness in patients with late or advanced AMD.<sup>344</sup> (*III, Insufficient evidence*) More information on vision rehabilitation, including materials for patients, is available at [www.aao.org/low-vision-and-vision-rehab](http://www.aao.org/low-vision-and-vision-rehab).

Loss of VA increases the risk of frequent falls.<sup>368, 369</sup> Depression and visual hallucinations (Charles Bonnet syndrome) frequently accompany severe central vision loss. Patients who have Charles Bonnet syndrome and their family members should be informed that visual symptoms are not unusual and do not represent a sign of psychosis or mental deterioration. Age-related macular degeneration is associated with depression and reduced vision-related quality of life.<sup>370</sup> The ophthalmologist may inquire about symptoms of clinical depression and, when appropriate, suggest that the patient seek professional advice, as depression may exacerbate the effects of AMD.<sup>371</sup>

## SOCIOECONOMIC CONSIDERATIONS

The considerable burden of disease associated with AMD, as well as the public health benefits of prevention, are highlighted in analyses conducted by the AREDS authors. This research, published in 2003, estimated that 8 million Americans aged 55 and older are at high risk for developing advanced AMD. If these persons received AREDS-formulation supplements, it was estimated that approximately 300,000 would avoid advanced AMD and any associated vision loss over a 5-year period.<sup>372</sup> The Salisbury Eye Study reported that VA loss adversely affected activities of daily living, which subsequently increased mortality risk in older adults. Further calculations estimated that treating AMD with anti-VEGF agents saves 1 to 2 years of life.<sup>373</sup>

More cost-effectiveness studies on the use of anti-VEGF therapies have demonstrated that they are highly cost-effective over prior therapies such as PDT.<sup>374 375-378</sup> The off-label use of intravitreal bevacizumab was suggested to represent a highly cost-effective, off-label option for management of neovascular AMD compared with the higher cost of ranibizumab.<sup>377</sup> Others have investigated the cost utility of various treatments for AMD. One analysis using CATT trial data found that bevacizumab with PRN dosing offered considerably greater value than ranibizumab in the treatment of neovascular AMD among patients 80 and older.<sup>378</sup> Another analysis using CATT and MARINA data evaluated the relative 10-year cost-effectiveness of bevacizumab and ranibizumab in 65-year-old patients with neovascular AMD. This study estimated the cost utility of bevacizumab treatment (relative to no treatment) at approximately \$2,700 per quality-adjusted life year ([QALY] for monthly dosing) and \$3,300 per QALY (for PRN dosing). In contrast, the cost-effectiveness of ranibizumab was estimated as \$63,300/QALY for monthly dosing and \$18,600 per QALY for PRN dosing.<sup>375</sup> Wholesale prices of anti-VEGF medications range from \$50 to \$1,950 per dose, depending on the medication.<sup>375-378</sup> The use of personalized anti-VEGF treatment guided by OCT has resulted in savings for the U.S. government of \$9 billion and \$22 billion for patients with neovascular AMD, respectively, in a study comparing patient and Medicare savings.<sup>379</sup>

After the FDA approval of the ranibizumab ocular implant, Brown et al evaluated the cost-effectiveness of this new treatment.<sup>380</sup> They found that although the implant seemed to compare favorably at \$21,825 with two ranibizumab 100-mg/ml fills at 1 year compared with \$18,405 for 11.8 injections of ranibizumab 0.5 mg over that same time period, this benefit did not seem to extend to 5- and 12-year time points. Both treatments were cost-effective compared with no treatment, however.

One study developed a drug-pricing model using the Medicare average sales price for bevacizumab, ranibizumab, and aflibercept 2 mg, wholesale acquisition costs of currently available ranibizumab biosimilars, and postulated prices for bevacizumab and aflibercept biosimilars. Results from this model indicated increased costs from a bevacizumab biosimilar and cost reductions from ranibizumab and aflibercept biosimilars. Medicare Part B average sales prices for ranibizumab 0.3 mg, ranibizumab 0.5 mg, and aflibercept 2 mg were \$776, \$1,292, and \$1,806, respectively, as of October 2022. The respective wholesale acquisition costs for biosimilar versions of the two dosages of ranibizumab were \$816 and \$1,130 to \$1,360. The model predicted that a bevacizumab biosimilar priced at \$500 would increase Medicare Part B costs by \$457 million annually, and one priced at \$900 would increase costs by \$897 million annually. However, switching from ranibizumab and aflibercept 2 mg to their biosimilars could lead to total cost savings of \$132 million for Medicare.<sup>381</sup>

Since the FDA approved pegcetacoplan for GA, the cost-effectiveness of this new treatment was evaluated.<sup>382</sup> Based on 2022 Medicare reimbursement data, the authors of the study found that the cost of the two treatment frequencies varied. The cost per area of delaying GA for 2 years with monthly treatment was \$87,300/mm<sup>2</sup>, compared with EOM treatment, which cost \$49,200/mm<sup>2</sup>. The costs for extrafoveal GA had greater utility, with costs of \$53,900/mm<sup>2</sup> for those treated monthly compared

with \$32,100/mm<sup>2</sup> in the EOM group. Their model also predicted that 95% atrophy was delayed by 2.5 years in patients treated monthly compared with 2.1 years in the EOM group.

# APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

*Providing quality care  
is the physician's foremost ethical obligation, and is  
the basis of public trust in physicians.  
AMA Board of Trustees, 1986*

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- ◆ The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- ◆ The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- ◆ The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- ◆ Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - ◆ The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - ◆ The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - ◆ When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - ◆ The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - ◆ The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner. The ophthalmologist maintains complete and accurate medical records.

- ◆ On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- ◆ The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- ◆ The ophthalmologist and those who assist in providing care identify themselves and their profession.
- ◆ For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- ◆ Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- ◆ The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- ◆ The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- ◆ The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- ◆ The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- ◆ The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

Reviewed by: Council  
Approved by: Board of Trustees  
October 12, 1988

2<sup>nd</sup> Printing: January 1991  
3<sup>rd</sup> Printing: August 2001  
4<sup>th</sup> Printing: July 2005



## APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Age-related macular degeneration, which includes entities with the following ICD-9 and ICD-10 classifications (see Glossary):

ICD-9 CM	ICD-10 CM
Macular degeneration, dry - 362.51	Nonexudative AMD - H35.31-
Macular degeneration, wet - 362.52	Exudative AMD - H35.32-
Macular drusen - 362.57	Drusen (degenerative) of macula - H35.36-

ICD = International Classification of Diseases; CM = Clinical Modification used in the United States

- AMD = age-related macular degeneration; does not require laterality indicators
- Macular drusen; (-) = 1, right eye; 2, left eye; 3, bilateral

Additional information for ICD-10 codes:

- Certain ICD-10 CM categories have applicable 7<sup>th</sup> characters. The applicable 7<sup>th</sup> character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7<sup>th</sup> character must always be the 7<sup>th</sup> character in the data field. If a code that requires a 7<sup>th</sup> character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4<sup>th</sup> digit, 5<sup>th</sup> digit, or 6<sup>th</sup> digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

## APPENDIX 3. INTRAVITREAL AGENTS FOR THE TREATMENT OF ADVANCED AGE-RELATED MACULAR DEGENERATION

The intravitreal agents used in the treatment of advanced AMD are listed in Table A3-1.

**TABLE A3-1 INTRAVITREAL AGENTS FOR THE TREATMENT OF ADVANCED AGE-RELATED MACULAR DEGENERATION**

Generic	Brand Name	Company
Aflibercept intravitreal injection 2 mg	EYLEA®	Regeneron
Aflibercept intravitreal injection 8 mg	EYLEA® HD	Regeneron
Aflibercept-jbvf intravitreal injection 2 mg (biosimilar)	Yesafili™	Biocon Biologics
Aflibercept-yszy intravitreal injection 2 mg (biosimilar)	Opuviz™	Samsung Bioepis and Biogen MA Inc.
Aflibercept-mrbb intravitreal injection 2 mg (biosimilar)	Ahzantive®	Formycon AG
Aflibercept-abzv intravitreal injection 2 mg (biosimilar)	Enzeevu™	Sandoz Inc.
Aflibercept-ayyh intravitreal injection 2 mg (biosimilar)	Pavblu™	Amgen, Inc.
Avacincaptad pegol intravitreal injection 2 mg	Izervay™	Astellas
Bevacizumab intravitreal injection 1.25 mg	Avastin®	Genentech
Brolucizumab intravitreal injection 6 mg	Beovu®	Novartis
Faricimab-svoa intravitreal injection 6 mg	VABYSMO®	Genentech
Pegcetacoplan intravitreal injection 15 mg	SYFOVRE®	Apellis Pharmaceuticals Inc.
Ranibizumab intravitreal injection 0.5 mg	LUCENTIS®	Genentech
Ranibizumab implant	Susvimo®	Genentech
Ranibizumab-eqrn intravitreal injection 0.5 mg (biosimilar)	Cimerli™	Coherus Biosciences
Ranibizumab-nuna intravitreal injection 0.5 mg (biosimilar)	Byooviz™	Samsung Bioepis and Biogen MA Inc.

## GLOSSARY

**Advanced AMD (Advanced age-related macular degeneration):** This is the most severe form of AMD, defined as GA involving the center of the macula (fovea) or features of CNV.

**AMD (Age-related macular degeneration):** There is no universally accepted definition of this term. The condition is characterized by the presence of drusen and alterations of the RPE as well as by the fundus abnormalities associated with CNV, and it generally occurs in persons over age 65. The VA may vary from normal to severe impairment.

**Amsler grid:** This is a graph paper with a central dot for fixation. While viewing this central spot, the patient is asked to evaluate vision for the early signs of metamorphopsia by looking for any changes in the grid.

**ANCHOR Study:** Anti-VEGF antibody (ranibizumab) for the treatment of predominantly classic CNV in AMD study.

**Anti-VEGF (Anti-vascular endothelial growth factor):** Substances that inhibit the action of vascular endothelial growth factor protein.

**AREDS (Age-Related Eye Disease Study):** A prospective, multicenter, randomized clinical trial designed to assess the natural course and risk factors of age-related cataract and AMD and the effects of antioxidants and minerals on these two conditions.

**AREDS2 (Age-Related Eye Disease Study 2):** A prospective, multicenter, randomized clinical trial of 4000 participants designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and/or omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) for the treatment of AMD and cataract. All participants were offered the AREDS supplements. A secondary randomization evaluated the possibility of deleting beta-carotene and decreasing the original levels of zinc in the AREDS formulation. Follow-up occurs over 5 years.

**Bevacizumab:** A full-length monoclonal antibody that binds all isoforms of VEGF and has FDA approval for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.

**CATT (Comparison of AMD Treatment Trials):** A multicenter clinical trial that compared the safety and efficacy of bevacizumab and ranibizumab and an individualized dosing regimen (PRN) to monthly injections.

**Classic choroidal neovascularization:** The angiographic findings in which the CNV is recognized in the early phase of the fluorescein angiogram as an area of bright, well-demarcated hyperfluorescence and during the late phases of the angiogram as progressive pooling of dye in the overlying subsensory retinal space. Usually considered a Gass Type 2 membrane.

**CNV (Choroidal neovascularization):** Synonymous with subretinal or choroidal neovascular membrane. These are vessels from the choriocapillaris that perforate and grow through Bruch's membrane and enter the subretinal pigment epithelial and/or subretinal spaces.

**DENALI study:** Part of the SUMMIT studies, this trial compares ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

**DERBY study:** Phase 3 clinical trial for pegcetacoplan (complement C3 inhibitor) compared with sham injections in patients with GA.

**Disc area:** As defined by the Macular Photocoagulation Study, the area of a circle with a diameter of 1.5 mm (1500 µm) equal to 1.77 square mm. The area on a photograph will vary with the type of fundus camera used.

**Disciform scar:** Subretinal fibrovascular tissue that usually becomes more fibrous within a few years and that is often the end result of CNV.

**Drusen:** Yellow lesions at the level of the basement membrane of the RPE. They are the ophthalmoscopic and histologic hallmark of AMD. They are considered to be small if they are less than 63  $\mu\text{m}$  in diameter, intermediate if they are greater than or equal to 63 and less than or equal to 125  $\mu\text{m}$ , and large when the diameter is greater than 125  $\mu\text{m}$ , and they may be considered soft if they have ill-defined edges.

**EVEREST study:** A study conducted in Asia that investigated combination PDT and anti-VEGF therapy.

**Extrafoveal choroidal neovascularization:** A choroidal neovascular membrane that comes no closer than 200  $\mu\text{m}$  from the center of the foveal avascular zone, as defined by the Macular Photocoagulation Study.

**Foveal avascular zone:** An area usually 300 to 500  $\mu\text{m}$  in diameter centered on the foveola and lacking retinal blood vessels, also known as the capillary-free zone.

**GA (Geographic atrophy):** One or several well-demarcated zones of photoreceptor, RPE, and choriocapillaris atrophy. Drusen are usually present surrounding these zones and there may be surrounding pigment clumping. This is an advanced form of AMD when the center of the fovea is involved.

**GATHER study:** Phase 3 clinical trial for avacincapad pegol (complement C5 inhibitor) compared with sham injections in patients with GA

**HARBOR study:** A 12-month dose-comparison study of 0.5 mg and 2 mg of ranibizumab. It also compared monthly to PRN treatment over 2 years.

**HARRIER study:** Phase 3 clinical trial for brolucizumab compared with aflibercept 2-mg for neovascular AMD.

**HAWK study:** Phase 3 clinical trial for brolucizumab compared with aflibercept 2-mg for neovascular AMD.

**ICD-9:** International Statistical Classification of Diseases and Related Health Problems, Ninth Edition.

**ICD-10:** International Statistical Classification of Diseases and Related Health Problems, Tenth Edition.

**ICG (Indocyanine green):** A cyanine dye that fluoresces in the near-infrared spectrum and is used in diagnostic evaluation to visualize CNV.

**IVAN trial (Inhibition of VEGF in Age-related choroidal Neovascularization):** A 2-year study conducted in the United Kingdom that compared intravitreal bevacizumab with ranibizumab dosed either on a continuous (monthly) or discontinuous (PRN) basis.

**Juxtafoveal choroidal neovascularization:** Well-demarcated CNV that is between 1  $\mu\text{m}$  and 199  $\mu\text{m}$  from the center of the foveal avascular zone but that does not reach its center, as defined by the Macular Photocoagulation Study.

**LUCAS:** Lucentis Compared to Avastin Study.

**LUCERNE:** Phase 3 clinical trial for faricimab compared with aflibercept 2-mg in patients with neovascular AMD.

**Macular translocation:** An operation designed to move the sensory retina from an area of damaged RPE to another area of more intact RPE.

**MARINA study:** Study of minimally classic/occult trial of the anti-VEGF antibody, ranibizumab, in the treatment of neovascular AMD.

**MNV:** Macular neovascularization historically referred to as CNV and includes the following

- ◆ Type 1 MNV: neovascular complex located in the sub-RPE space originating from the choroid through a defect in Bruch's membrane

- ◆ PCV: Similar to Type 1 MNV, characterized by branching vascular networks with dilated vascular elements (historically referred to as polyps)
- ◆ Type 2 MNV: neovascular complex located in the subretinal space above the RPE originating from the choroid
- ◆ Type 3 MNV: pathologic angiogenesis originating from deep retinal capillary plexus extending to the outer retina (historically referred to as retinal angiomatous proliferation)

**MONT BLANC study:** Part of the SUMMIT study, this European trial compares ranibizumab and verteporfin PDT combination treatment with ranibizumab alone.

**MPS (Macular Photocoagulation Study):** A series of prospective, randomized, multicenter, clinical trials designed to determine the efficacy of laser photocoagulation surgery in CNV caused by AMD, ocular histoplasmosis, and idiopathic causes.

**Neovascular macular degeneration:** Manifestations of CNV and/or RPE detachment associated with subretinal serous fluid, exudates, and/or blood.

**OAKS:** Phase 3 clinical trial for pegcetacoplan (complement C3 inhibitor) compared with sham in patients with GA.

**Occult choroidal neovascularization:** Angiographic findings characterized by a fibrovascular RPE detachment and/or late leakage of an undetermined source. This is also referred to as poorly defined CNV that has indistinct or poorly demarcated boundaries on fluorescein angiography. Usually considered a Gass Type 1 membrane.

**OCT (Optical coherence tomography):** A noninvasive technique to image intraocular tissues by measuring the echo time delay and intensity of back-reflected light. The resulting image provides high-resolution, cross-sectional representation of structure with near-histological detail.

**OCTA (Optical coherence tomography angiography):** A noninvasive imaging technique for the microvasculature of the retina and choroid.

**PCV (Polypoidal choroidopathy):** Characterized by multiple and recurrent serosanguineous RPE detachments, which often resemble hemorrhagic detachment in AMD. A fluorescein angiogram and ICG may be helpful in distinguishing these conditions.

**PDT (Photodynamic therapy):** A method of treating CNV in a two-part process involving systemic administration of a photosensitizing drug followed by nonthermal light application to the macular pathology.

**PED (Pigment epithelial detachment):** Accumulation of fluid (serous RPE detachment) or blood (hemorrhagic RPE detachment) beneath the RPE. Associated CNV is usually present in older patients and/or patients with drusen. Another form is the fibrovascular pigment epithelial detachment, which is a form of occult CNV.

**Pegaptanib sodium (Macugen):** A compound that binds to a specific isoform of vascular endothelial growth factor (VEGF<sub>165</sub>) and thus blocks its activity. It is administered by intravitreal injection.

**Persistent choroidal neovascularization:** Angiographically documented CNV found within 6 weeks of laser surgery, typically but not always at the site of the previously treated CNV, according to the Macular Photocoagulation Study definition.

**PGF (Placental growth factor):** A growth factor related to VEGF that may play a role in ocular angiogenesis.

**Predominantly classic lesion:** CNV in which classic CNV occupies more than 50% of the entire lesion area.

**PULSAR:** Phase 3 clinical trial for aflibercept 8 mg compared with aflibercept 2 mg for patients with neovascular AMD.

**Ranibizumab (Lucentis):** A recombinant humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment that binds to and inhibits the biologic activity of a form of VEGF-A.

**Recurrent choroidal neovascularization:** Angiographically documented CNV found more than 6 weeks after laser surgery and typically occurring on the perimeter of the previous treatment scar, as defined by the Macular Photocoagulation Study.

**Reticular pseudodrusen:** Also referred to as subretinal drusenoid deposits.

**Retinal angiomatous proliferation:** See Subretinal drusenoid deposits.

**RPE abnormalities (Retinal pigment epithelial abnormalities):** Alterations of the retinal pigment epithelium-Bruch's membrane complex that lead to an appearance of hypopigmentation and/or hyperpigmentation. Its extreme form is GA.

**Severe visual loss:** In this document, severe visual loss means quadrupling or more of the visual angle (e.g., 20/20 to 20/80 or worse, or 20/50 to 20/200 or worse).

**Subfoveal choroidal neovascularization:** Choroidal neovascularization that underlies the center of the foveal avascular zone.

**Submacular Surgery Trial:** A trial conducted in the mid-1990s, prior to the emergence of currently used therapies, that evaluated the efficacy of submacular surgery for treating complications of CNV and subretinal hemorrhage.

**Subretinal drusenoid deposits:** Characterized by proliferation of retinal capillaries in the paramacular area that may present as intraretinal, subretinal, or CNV.

**SUMMIT:** Two studies, called DENALI in North America and MONT BLANC in Europe, that compare ranibizumab and verteporfin PDT combination therapy with ranibizumab alone.

**TENAYA:** Phase 3 clinical trial for faricimab compared with aflibercept 2 mg in patients with neovascular AMD.

**VEGF (Vascular endothelial growth factor):** A significant mediator in the process of angiogenesis and increased vascular permeability and inflammation. It has been identified in neovascularization related to both diabetic retinopathy and AMD. In animal models, the introduction of VEGF has initiated the cascade of neovascularization seen in AMD. Thus, the inhibition or antagonism of the action of VEGF is a targeted area of research, with several novel therapeutic agents being developed, and in various stages of investigation and FDA approval.

**Verteporfin (Visudyne):** A drug used as a photosensitizer in conjunction with a nonthermal PDT laser.

**VIEW Study:** Phase 3 clinical trial for aflibercept 2 mg compared with ranibizumab in patients with neovascular AMD.

# LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed database were conducted on March 6, 2023; the search strategies are listed below. Specific limited update searches were conducted on January 23, 2024 and August 7, 2024. The searches had added filters for human, English-language randomized controlled trials and systematic reviews and date limiters to capture literature published since June 1, 2019. The Retina/Vitreous PPP Committee analyzed 4,228 studies of which 79 were included in the PPP. The literature searches with the disease condition and the search terms patient values and patient preferences yielded 73 studies. The literature searches for economic evaluation and treatment cost yielded 71 studies which were provided to the Retina/Vitreous PPP Committee and 1 study merited inclusion in the PPP.

**Cost Benefit:** ("Macular Degeneration/economics"[Mesh] OR ("Macular Degeneration"[Mesh] AND "Cost-Benefit Analysis"[Mesh])) NOT "Cost of Illness"[Mesh]

**Cost of Illness:** ("Macular Degeneration"[Mesh] OR macular degeneration[tiab]) AND "Cost of Illness"[Mesh]

**Diagnosis:** "Macular Degeneration/diagnosis"[Mesh]

**Epidemiology/Ethnology:** "Macular Degeneration/epidemiology"[Mesh] OR "Macular Degeneration/ethnology"[Mesh]

**Genetics:** "Macular Degeneration/genetics"[Mesh]

**Major headings:** Macular degeneration[mh] OR macular degeneration[tiab]

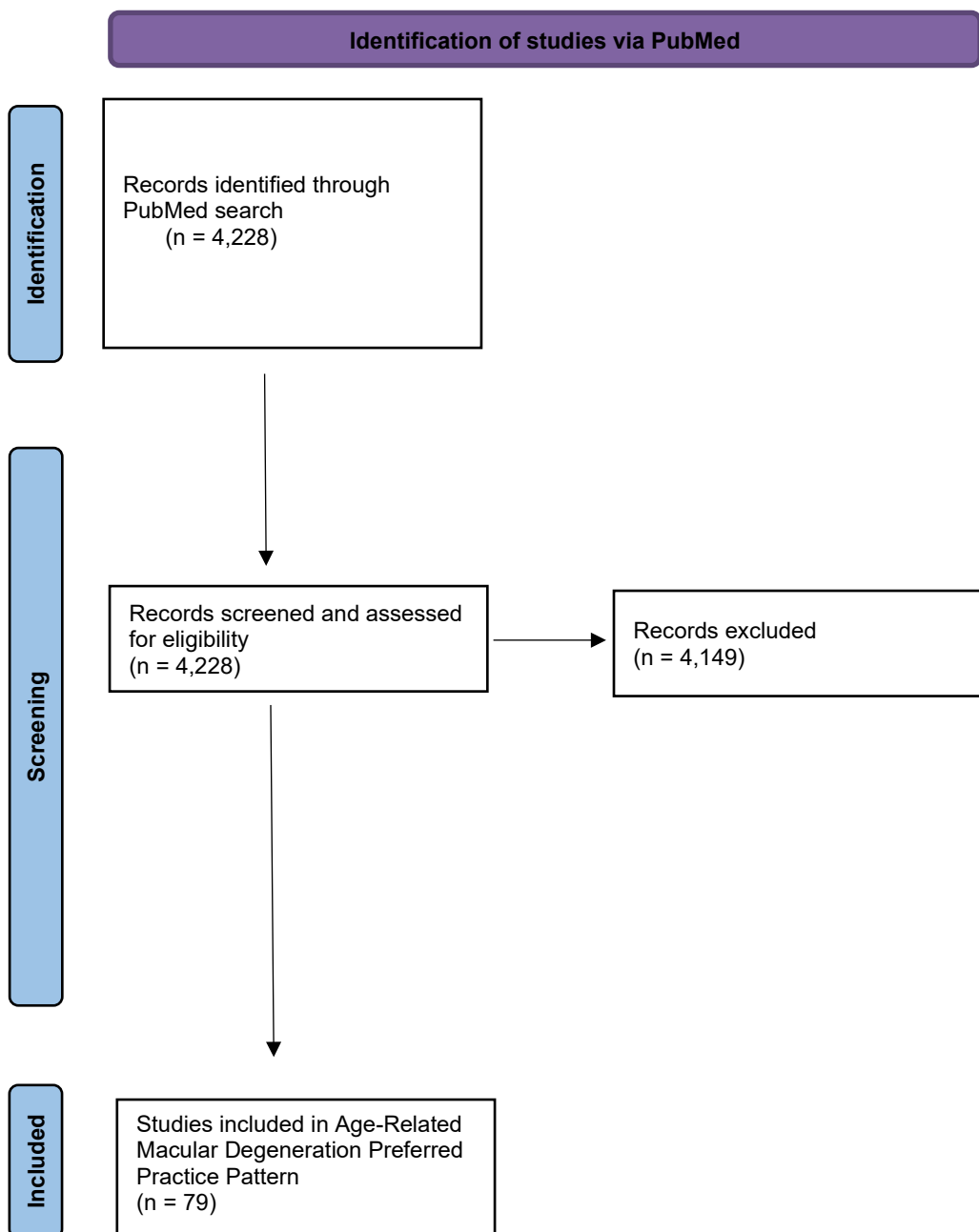
**Natural History:** ("Macular Degeneration"[Mesh] OR macular degeneration[tiab]) AND "natural history"[tiab]

**Patient Values and Preferences:** ("Macular Degeneration"[MeSH] OR "macular degeneration"[tiab]) AND ((("patient values"[tiab] OR "patient preferences"[tiab]) OR (patient[tiab] AND (values[tiab] OR preferences[tiab])))

**Quality of Life:** "Macular Degeneration/therapy"[Mesh] AND "Quality of Life"[Mesh]

**Risk Factors:** ("Macular Degeneration"[Mesh] OR macular degeneration[tiab]) AND "Risk Factors"[Mesh]

**Therapy:** "Macular Degeneration/therapy"[Mesh] OR "Macular Degeneration"[Mesh] AND ((combinations[tiab] OR combined[tiab]) OR (("Drug Therapy, Combination"[Mesh] OR "Drug Combinations"[Mesh]) OR "Combined Modality Therapy"[Mesh]))



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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