AGE-RELATED MACULAR DEGENERATION
LIMITED REVISION
As a service to its members and the public, the American Academy of Ophthalmology is developing a series of guidelines called Preferred Practice Patterns that identify characteristics and components of quality eye care. These guidelines are particularly timely and appropriate as third-party payors and government grapple with the need to maintain quality care in the face of cost-containment, and as traditional attitudes of Academy members are challenged by changing patterns of health care delivery and emerging market forces.

These Preferred Practice Patterns are neither minimal nor aspirational; they represent quality eye care commensurate with present knowledge and resources. They are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, the data are particularly persuasive (as with results of carefully conducted clinical trials) and provide clear guidance; in other instances, the panels have had to rely more heavily on their collective judgment and evaluation of available evidence. As better data become available, these guidelines will be altered as appropriate.

The Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. Innovation in medicine is essential to assure the future health of the American public. Preferred Practice Patterns are not intended to stifle such new development, but rather to provide guidelines for current, state-of-the-art eye care.

Preferred Practice Patterns 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. Depending on a host of medical and social variables, it is anticipated that it will be necessary to approach some patients' needs in different ways. The ultimate judgment regarding the propriety of the care of a particular patient must be made by the physician in light of all of the circumstances presented by the patient. Adherence to these Preferred Practice Patterns will certainly 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.

Preferred Practice Patterns are intended to serve as guides in patient care, with greatest emphasis on technical aspects of our specialty. In applying this knowledge, it is essential to recognize that true medical excellence is achieved only when skills are applied in such a manner that the patients' needs are the foremost consideration. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Patterns 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.

It is the Academy's intention to update all Preferred Practice Patterns as new knowledge dictates. To ensure all Preferred Practice Patterns are current (and, where not, no longer applicable), each is valid for 5 years from the date of issue unless superseded by a revision.
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AGE-RELATED MACULAR DEGENERATION LIMITED REVISION
INTRODUCTION

The Preferred Practice Patterns series of guidelines has been written on the basis of three principles.

- Each Preferred Practice Pattern should be clinically relevant and specific enough to provide useful information to practitioners.
- Each recommendation that is made should be given an explicit rating that shows its importance to the care process.
- Each recommendation should also be given an explicit rating that shows the strength of evidence that supports the recommendation and reflects the best evidence available.

The limited revision of this document was prompted by the introduction of photodynamic therapy for age-related macular degeneration and the results of the Age-Related Eye Disease Study. Recommendations for care are based on the results of a literature search on the subject of age-related macular degeneration, and are rated in two ways.

The Retina Panel first rated each recommendation according to its importance to the care process. This "importance to the care process" rating represents care that the panel thought would improve the quality of the patient's care in a meaningful way. The ratings of importance are divided into three levels.

- Level A, defined as most important
- Level B, defined as moderately important
- Level C, defined as relevant but not critical

The panel also rated each recommendation on the strength of evidence in the available literature to support the recommendation made. The "ratings of strength of evidence" are also divided into three levels.

- Level I includes evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial. It could include meta-analyses of randomized controlled trials.
- Level II includes evidence obtained from the following:
  - Well-designed controlled trials without randomization
  - Well-designed cohort or case-control analytic studies, preferably from more than one center
  - Multiple-time series with or without the intervention
- Level III includes evidence obtained from one of the following:
  - Descriptive studies
  - Case reports
  - Reports of expert committees/organization
  - Expert opinion (e.g., PPP panel consensus)

The evidence is that which supports the value of the recommendation as something that should be performed to improve the quality of care. The panel believes that it is important to make available the strength of the evidence underlying the recommendation. In this
way, readers can appreciate the degree of importance the panel attached to each recommendation and they can understand what type of evidence supports the recommendation.

The ratings of importance and the ratings of strength of evidence are given in parentheses after each recommendation. For instance, "[A: II]" indicates a recommendation with high importance to clinical care [A], supported by sufficiently rigorous published evidence, though not by a randomized controlled trial [II].

The sections entitled "Orientation" and "Background" do not include recommendations; rather they are designed to educate and provide summary background information and rationale for the recommendations that are presented in the Care Process section. A summary of the major recommendations for care is included in Appendix 1.

### ORIENTATION

#### ENTITY

Age-related macular degeneration (ICD-9 #362.51 and 362.52).

#### DISEASE DEFINITION

Age-related macular degeneration (AMD) is a disorder of the macula that occurs most often in patients 50 years old or older and is characterized by one or more of the following:

- Drusen formation
- Retinal pigment epithelial (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Geographic atrophy of the RPE and choriocapillaris
- Neovascular (exudative*) maculopathy such as:
  - Choroidal neovascularization (CNV)
  - Serous and/or hemorrhagic detachment of the sensory retina or RPE
  - Lipid exudates (a secondary phenomenon resulting from chronic leakage from any source)
  - Subretinal and sub-RPE fibrovascular proliferation and a disciform scar
- No other etiology for the above findings

*In this updated document, the term “neovascular” has replaced the term “exudative” that was used in earlier versions as an adjective describing the “wet” form of AMD.

Important terms are defined in the Glossary. Clinical details are available in standard texts and reviews.¹⁻¹²

#### PATIENT POPULATION

Patients are typically 50 years old and older, with or without visual symptoms.

#### ACTIVITY

Evaluation and management of patients with AMD.
PURPOSE

The primary purpose of evaluation and management is to improve vision or to minimize loss in vision and vision-related quality of life related to AMD.

GOALS

- Identify patients at risk of visual loss related to AMD.
- Minimize visual loss and functional impairment in these patients through appropriate detection, treatment, and follow-up examinations.
- Help patients identify sources for visual rehabilitation.
- Educate patients and their families about the disease and engage them in managing it.

BACKGROUND

EPIDEMIOLOGY

Age-related macular degeneration is the leading cause of irreversible severe central visual loss in Caucasians 50 years old and older in the United States and in most of the developed world.

The incidence and progression of all the features of AMD increase significantly with age. Approximately 10% of patients 66 to 74 years of age will have findings of AMD, and the prevalence increases to approximately 30% in patients 75 to 85 years of age.7,8,11

Approximately 2% of patients 65 years old or older have visual acuity of 20/200 or less in one eye due to AMD.11 Using the 1990 U.S. Census, approximately 750,000 people over 65 years of age were estimated to have severe visual impairment in one or both eyes from AMD. The U.S. Census Bureau projects a 107% increase in persons 85 years old or older between the years 1993 and 2020, creating an even greater public health impact from AMD by the year 2020.

Although most people with macular degeneration have the non-neovascular form, the majority (75% to 90%) of patients with severe visual loss (quadrupling or more of the visual angle) from AMD have the neovascular form associated with CNV and/or pigment epithelial detachment.8,12

RISK FACTORS

Some of the risk factors reported in association with AMD include genetic factors13,14 and smoking.15,16 Other potential risk factors possibly associated with increased risk include hyperopia, hypertension, cardiovascular disease, and diet.17-26 A preliminary analysis of data from a large prospective, randomized, controlled trial of vitamin E supplementation versus placebo in 1,193 individuals showed little benefit to AMD prevention or progression from 4 years of vitamin E supplementation [Taylor HR, Tikellis G, Robman LD, et al. Invest Ophthalmol Vis Sci 42(Suppl):S311, 2001]. In 2001, the Age-Related Eye Disease Study (AREDS) results were published, describing benefits for some patients with AMD with high-dose antioxidants and zinc supplementation (see below).26 The incidence of AMD (especially the neovascular form) is higher among Caucasians than among African-Americans.27
NATURAL HISTORY

Age-related macular degeneration can be divided into low, intermediate, and high-risk categories for progression to advanced AMD.

Low-risk Non-neovascular AMD

There is no consensus about the definition of early low-risk non-neovascular AMD. As defined by AREDS, this form of the disease is characterized by small hard drusen and minimal or no pigment epithelial abnormalities in the macula. Patients in this group generally have central visual acuities similar to those of patients who have normal maculae. As many as 10% of these patients will progress to high-risk non-neovascular maculopathy over 5 years. In the prospective AREDS, patients with low-risk AMD had a 1.3% risk of progressing to advanced AMD at 5 years in either eye.

Intermediate-risk Non-neovascular AMD

This level of AMD severity has been defined by the AREDS Group as patients with extensive medium sized drusen or one or more large drusen (≥ 125 microns) in one or both eyes. The progression to advanced AMD at 5 years in this group is approximately 18% in either eye.

High-risk Non-neovascular AMD

High-risk non-neovascular AMD includes patients who have soft drusen, both distinct and indistinct large drusen, confluent drusen, and pigment epithelial abnormalities with or without neovascular changes in the fellow eye. On the basis of previously published studies, these patients have a higher risk of developing CNV and subsequent severe visual loss compared to patients without these features. Population based studies have estimated that approximately 10% of such eyes may develop neovascular changes over 5 years. However, the risk in patients with high-risk drusen referred to retinal centers appears to be higher. In one study, the cumulative risk of choroidal neovascularization over 3 years was 15.6% in all patients and 21.5% in patients over age 65. The AREDS combined this group of patients with soft, large, indistinct drusen with those patients with multiple medium sized drusen and the rate of developing advanced AMD in either eye was 18% in 5 years. Further analyses will determine if these eyes with soft, indistinct large drusen may have a higher rate of progression to advanced AMD.

For patients who presented with advanced AMD in one eye, the rate of development of either neovascular AMD or geographic atrophy in the fellow eye was 43% in the prospective evaluation in the AREDS. The rate of development of advanced AMD, namely neovascular AMD, in the fellow eyes of patients who initially presented with choroidal neovascularization in one eye has been evaluated in a few studies. One study of patients with CNV in one eye documented that risk factors for CNV in the fellow eye include an increased number of drusen (more than five), focal hyperpigmentation, and large drusen (greater than 63 microns or half the width of a major retinal vein at the optic nerve head). Systemic hypertension was an additional risk factor. The 5-year incidence of developing choroidal neovascularization in the second eye varied from 7% with no risk factors present to 87% in the subgroup with all four risk factors present.
**Advanced AMD**

Advanced AMD is defined as geographic atrophy involving the center of the macula (fovea) or features of choroidal neovascularization. Visual acuity is generally affected in this category.

**Geographic Atrophy**

Geographic atrophy is an advanced form of non-neovascular AMD in which there are one or more zones of well-demarcated pigment epithelial and/or choriocapillaris atrophy. Drusen and other pigmentary abnormalities may surround the atrophic areas.

While severe visual loss occurs less commonly in patients with geographic atrophy than in patients with neovascular AMD, geographic atrophy causes approximately 10% to 25% of all AMD-related visual loss of 20/200 or worse. Patients with geographic atrophy may have relatively good distance visual acuity but a significantly decreased capacity for near visual tasks such as reading. Over 2 years, progressive visual loss to doubling of the visual angle may occur in as many as 50% of patients. Choroidal neovascularization also can occur.

**Neovascular AMD**

Although significant functional visual impairment may occur in association with non-neovascular AMD, retrospective studies of patients with non-neovascular macular degeneration and bilateral drusen have shown that, typically, patients develop severe visual loss if they progress to the neovascular form of the disease or develop significant geographic atrophy that involves the foveal center. Neovascular AMD is characterized by occult or classic CNV, serous and/or hemorrhagic detachment of the sensory retina or RPE, and/or various stages of an elevated, fibrovascular disciform scar.

In the Macular Photocoagulation Study (MPS), a series of clinical trials that evaluated laser treatment for selected patients with neovascular AMD, the classification of neovascular AMD with CNV (see Glossary) was based on fluorescein angiography. In the MPS trials of extrafoveal and juxtafoveal lesions, the protocol stipulated that the CNV lesion be well demarcated. During these trials, the angiographic definitions of "classic" and "occult" CNV evolved and were incorporated into the subfoveal photocoagulation portion of the MPS.

The location of well-demarcated CNVs was broken into three categories.

- Extrafoveal: CNV is 200 microns or more from the foveal center
- Juxtafoveal: CNV is between 1 and 199 microns from the foveal center
- Subfoveal: CNV is under the foveal center

In the MPS, the following natural history was documented in eyes that had well-demarcated CNVs:

- Extrafoveal: 60% developed severe visual loss, defined as quadrupling of the visual angle, at both 3 years and 5 years.
- Juxtafoveal: 60% developed severe visual loss by 5 years.
- Subfoveal: 50% developed severe visual loss by 4 years.
In studies of outcomes for cases that did not meet angiographic eligibility criteria (occult CNV without classic CNV, classic and poorly demarcated occult CNV), approximately 40% of patients developed severe visual loss after 2 to 3 years.\textsuperscript{39,40}

**RATIONALE AND MODALITIES FOR TREATMENT**

The cause of AMD remains unknown. Prospective, randomized controlled clinical trials support the use of antioxidant vitamins and minerals in patients with intermediate-risk AMD to reduce the rate of progression to advanced AMD and the use of laser photocoagulation surgery and photodynamic therapy to treat choroidal neovascularization associated with advanced AMD.

### Low-risk Non-neovascular AMD

Oxidative damage to the retina may be involved in the pathogenesis of AMD. Data from epidemiological studies, as well as small, randomized clinical trials, do not show consistent associations between intake of antioxidants or zinc and the risk of AMD. The National Eye Institute of the National Institutes of Health supported a multi-centered randomized clinical trial, the Age-Related Eye Disease Study to assess the value of antioxidant vitamins and minerals in 4,757 participants with varying risks of AMD, ranging from minimal risk (none to little drusen) to high risk (AMD in one eye).\textsuperscript{26} This was a factorial design in which participants were randomized to antioxidant vitamins, zinc, combination of antioxidant vitamins and zinc, or placebo.

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) were evaluated (see Table 1). Only 1.3\% or 15 participants in the low-risk (or early) AMD category progressed to advanced AMD in 5 years. Three hundred sixteen of the low-risk AMD participants progressed to intermediate-risk or advanced AMD. There was no evidence of treatment benefit in delaying the progression of AMD in participants who started the study in this low risk group.

### Intermediate-risk Non-neovascular AMD

In the AREDS, the only participants who benefited from this treatment were those at intermediate AMD risk or higher. For this group of patients with extensive medium drusen in both eyes, one or more large drusen in at least one eye to patients with AMD in one eye, the risk of developing AMD at 5 years was reduced by 25\% by the combination treatment of all the antioxidant vitamins and zinc with copper (see Table 2). The risk of losing vision of 3 or more lines (doubling of the visual angle) was also reduced by this combination treatment by 19\%. Although antioxidant vitamins alone and zinc alone groups were also beneficial in the treatment of AMD, the only statistically significant reduction of both the development of AMD and vision loss was the combination treatment of antioxidant vitamins and minerals.
Table 1
Antioxidant Vitamins and Minerals*

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
</tr>
<tr>
<td>Beta-Carotene</td>
<td>15 mg (25,000 IU)</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>80 mg</td>
</tr>
<tr>
<td>Cupric oxide</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

*As recommended by the AREDS data26

Table 2
Summary of Results of the AREDS for Advanced AMD and Vision Loss

<table>
<thead>
<tr>
<th></th>
<th>Antioxidants Plus Zinc</th>
<th>Zinc Alone</th>
<th>Antioxidants Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of the relative risk of</td>
<td>25%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>developing advanced AMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of the relative risk of</td>
<td>19%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>vision loss (3 or more lines)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neovascular AMD

Thermal laser photocoagulation of the entire CNV lesion is the most widely investigated and accepted technique for treatment of extrafoveal and juxtafoveal lesions of the neovascular form of AMD. This method is the only technique shown to have a statistically significant treatment benefit in appropriately selected cases (i.e., cases meeting the eligibility criteria for the MPS). For subfoveal CNV, in which at least 50% of the lesion exhibits a pattern of classic CNV, photodynamic therapy (PDT) with verteporfin* has been demonstrated to provide a statistically significant visual benefit. More recently, PDT treatment of subfoveal CNV without classic angiographic features has been demonstrated to provide a small but statistically significant benefit at two years.41

*At the time of publication, all clinical studies demonstrating the value of PDT for AMD have described PDT with verteporfin. Therefore, in this publication, the term "PDT" will be used always to indicate "PDT with verteporfin."
Thermal laser photocoagulation has also been shown to provide a benefit in appropriately selected small and well-defined subfoveal lesions. Additional modalities for the treatment of AMD are discussed under Care Process.

The MPS was the largest randomized and controlled multicenter study to evaluate the efficacy of laser photocoagulation, and it was the first trial demonstrating success in the treatment of selected patients with neovascular AMD. It is important to emphasize that the majority of patients with neovascular macular degeneration were not eligible for photocoagulation and, of those eyes eligible for this treatment, only a minority had an excellent visual outcome (i.e., 20/40 or better). In the MPS, the following categories of CNV lesions showed a treatment benefit.

**Extrafoveal**

Photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a significant reduction in the risk of severe visual loss for the first 2 years. A recurrence rate of approximately 50% reduced this benefit over the last 3 years of follow-up, but laser treatment did result in better vision over a longer period of time, and this is important in elderly patients.

**Juxtafoveal**

Photocoagulation of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit. The rates of "persistence" (CNV leakage within 6 weeks of laser photocoagulation) and "recurrence" (CNV leakage more than 6 weeks after laser photocoagulation) were high (80%) at 5 years. Persistent or recurrent leakage after treatment was associated with a greater incidence of severe visual loss. If it is assumed that most of these juxtafoveal lesions will recur and be eligible for retreatment as recurrent subfoveal CNV lesions with either laser photocoagulation or PDT, the treatment benefit may be greater than reported in the juxtafoveal study. After completion of enrollment, all angiograms of patients in the juxtafoveal study were reviewed, and patients were classified as having classic CNV without occult CNV, mixed classic and occult CNV, and occult CNV without classic CNV. The visual outcome varied significantly among the three groups. In eyes with classic CNV but no occult CNV, the results of treatment were best, paralleling the study of extrafoveal lesions. In eyes with mixed classic and occult CNV, where only the classic CNV was treated in a majority of cases, there was no treatment benefit. There were too few eyes with occult CNV but no classic CNV to conclude whether laser photocoagulation was helpful. Normotensive patients had better visual outcomes than hypertensive patients.

**Subfoveal**

In the MPS, some categories of treated eyes with subfoveal CNV had a reduced risk of visual loss, compared to untreated cases. In the MPS study of new (no prior laser) subfoveal CNV, outcomes varied as a function of the initial size of the CNV and the initial level of visual acuity. When the total group of new (no prior laser) CNV were subdivided, the greatest treatment effect was found in eyes with small CNV lesions (less than or equal to 1 MPS disc area; see Glossary) with poor vision (20/125 or worse) and eyes with medium-sized neovascular lesions (greater than 1 and less than or equal to 2 MPS disc areas) with poor vision (20/200 or worse). Among these
eyes, a treatment benefit was evident throughout follow-up. Treatment of large lesions (2 to 3.5 MPS disc areas) with poor vision (20/200 or worse) also was beneficial throughout the follow-up period, but the benefit was small. Treatment of small lesions with visual acuity of 20/100 or better as well as medium-sized lesions with visual acuity of 20/160 or better had a moderate benefit that was not apparent until one year after treatment. Treatment of recurrent subfoveal lesions was beneficial, regardless of initial visual acuity and lesion size. The MPS study limited the entire area of treatment (old and new) to less than 6 MPS disc areas, and some part of the retina within 1500 microns of the foveal center was spared by the treatment.6,42,43,47

In the PDT study (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study [TAP]),48,49 a treatment benefit was evident at both one and two years following randomization. Lesions up to 5400 microns in the greatest linear diameter were enrolled in these trials, and pre-randomization visual acuity ranged from a letter score of 73 to 34, an approximate Snellen equivalent of 20/40 to 20/200. In the initial publications, a treatment benefit was seen only in lesions in which the classic component was at least 50% of the area of the entire lesion, and these lesions were termed “predominantly classic”. In eyes with predominantly classic CNV, visual loss of less than 15 letters (3 lines) at the 24-month examination occurred in 59% of the verteporfin group and in 31% in the placebo group. Visual acuity better than 20/200 was maintained in 56% of the treated group compared with 32.5% of the controls.

In eyes in which the classic component of a new or recurrent CNV was less than 50% but more than 0% (minimally classic lesions), no significant treatment benefit was observed.48,49

More recent studies indicate that PDT of eyes with subfoveal lesions composed of occult but no classic CNV can reduce the risk of moderate and severe visual acuity loss, particularly if the lesions are relatively small (less than 4 MPS disc areas) and the visual acuity is relatively low (approximate Snellen equivalent worse than 20/50).41 In this report, the outcome was similar for treated and placebo eyes at 12 months following randomization. But at 24 months, 29% of verteporfin-treated eyes compared with 47% of placebo eyes lost at least 30 letters of vision.

Tables 3A and 3B summarize the MPS, TAP and Verteporfin in Photodynamic Therapy (VIP) reports.

Retinal Pigment Epithelial Detachments

No convincing evidence exists to show that laser photocoagulation is effective in patients with serous detachments of the RPE. The MPS excluded most patients with serous RPE detachments associated with choroidal neovascular lesions and consequently could make no statement about laser treatment of such lesions. On two occasions, the Moorfields Macular Study Group evaluated laser treatment for pigment epithelial detachments, which may have been a combination of serous and fibrovascular detachments, by means of a controlled clinical trial, and on both occasions concluded that laser treatment was harmful rather than helpful.50 In selected cases of subfoveal and extrafoveal pigment epithelial detachments associated with extrafoveal well-demarcated CNV, laser photocoagulation of the extrafoveal CNV may be beneficial in selected cases.
Table 3A
Percentage of Eyes with Visual Loss
Defined as Quadrupling of Visual Angle

<table>
<thead>
<tr>
<th>Subgroup of CNV</th>
<th>Study</th>
<th>Treated Eyes (%)</th>
<th>Untreated Eyes (%)</th>
<th>Years After Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrafoveal</td>
<td>MPS</td>
<td>48</td>
<td>62</td>
<td>5</td>
</tr>
<tr>
<td>Juxtafoveal</td>
<td>MPS</td>
<td>52</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>Subfoveal</td>
<td>MPS</td>
<td>22</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>Subfoveal</td>
<td>TAP</td>
<td>18</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Subfoveal *</td>
<td>TAP</td>
<td>15</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Subfoveal †</td>
<td>VIP</td>
<td>29</td>
<td>47</td>
<td>2</td>
</tr>
</tbody>
</table>

* = Predominantly classic  
† = Occult without classic

Table 3B
Percentage of Eyes with Visual Loss
Defined as Doubling of Visual Angle

<table>
<thead>
<tr>
<th>Subgroup of CNV</th>
<th>Study</th>
<th>Treated Eyes (%)</th>
<th>Untreated Eyes (%)</th>
<th>Years After Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subfoveal</td>
<td>TAP</td>
<td>47</td>
<td>62</td>
<td>2</td>
</tr>
<tr>
<td>Subfoveal *</td>
<td>TAP</td>
<td>41</td>
<td>69</td>
<td>2</td>
</tr>
</tbody>
</table>

* = Predominantly classic

EARLY DETECTION

There is no clear indication for public screening for AMD. Patients with early AMD who may develop the intermediate or more severe stages of AMD with characteristics such as large, soft, confluent drusen should be encouraged to have regular dilated eye exams for the early detection of intermediate risk of AMD. Treatment with antioxidants and minerals may be considered for patients who have progressed to intermediate or high risk of AMD.

Education of patients with early AMD who are at an increased risk of visual loss or of progression to advanced AMD should include methods of detecting new symptoms of
Follow-up examinations for patients at increased risk of visual loss or of progression to advanced AMD may permit early detection of treatable neovascular lesions, which might improve the visual outcome. A comprehensive medical eye evaluation performed every 2 to 4 years for patients between ages 40 and 64 and every 1 to 2 years for patients 65 years old and older seems to offer a reasonable approach to detect patients with risk factors for visual loss. If all patients were to check the vision in each eye on a daily basis using the technique of alternate occlusion, it seems likely that more patients would become aware of subtle visual symptoms due to CNV. Early recognition of symptoms will increase the likelihood of detecting neovascularization at a treatable stage.

CARE PROCESS

The care process includes a history, ophthalmic examination, treatment when indicated, follow-up examinations, diagnostic and ancillary testing when indicated, and patient education. Many patients with poor vision benefit from visual rehabilitative services.

Because a treatment benefit has been demonstrated only for patients with features similar to defined subsets of cases enrolled in the MPS, TAP, VIP and AREDS studies, this document will focus on patients with these forms of neovascular AMD. It must be recognized, however, that the majority of patients with neovascular maculopathy and CNV may not have features similar to cases enrolled in the MPS, TAP, VIP and AREDS trials.

PATIENT OUTCOME CRITERIA

Patient outcome criteria include the following:

- Minimization of visual loss
- Minimization of functional impairment

DIAGNOSIS

The initial evaluation of a patient with signs and symptoms suggestive of AMD should include relevant and baseline components of the comprehensive adult medical eye evaluation.

History

The following elements of history are recommended for the initial visit:

- Symptoms
  - Metamorphopsia
  - Decreased vision (e.g., altered ability to read mail, newsprint, and road signs; to recognize faces; or to identify details on a television screen)
- Medications
- Medical and ocular history
- Family history, especially family history of AMD
- Social history, especially smoking
**Examination**

Patients should receive a comprehensive eye evaluation. Components of the evaluation that are particularly relevant for management of AMD include the following elements:

- Assessment of best corrected visual acuity [A:I]
- Vision testing with an Amsler grid [B:III]
- Biomicroscopic examination of the macula [A:I]
- Peripheral retinal examination [B:III]

In eyes with visual acuity 20/40 or better, the use of an Amsler grid is an accepted but imperfect method for detecting abnormalities in the central visual field, delineating areas of involvement, and establishing a baseline against which to judge progression, especially new areas related to leakage from CNV. Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical clues of CNV. These include small areas of hemorrhage, hard exudate, subretinal fluid, or pigment epithelial elevation.

**Diagnostic Tests**

**Fluorescein Angiography**

Intravenous fundus fluorescein angiography in the clinical setting of AMD is indicated in the following situations:

- To detect the presence of and determine the extent and location of CNV and calculate the percentage of the lesion composed of or consisting of classic CNV. If laser photocoagulation or PDT is being considered, the angiogram is also used as a guide to direct treatment.
- To detect persistent or recurrent CNV following treatment.
- To assist in determining the cause of visual loss not explained by the clinical examination.

In the MPS, TAP, and VIP protocols, a 30-degree photographic field centered on the macula was used. Stereo angiography offers an advantage over nonstereoscopic studies in detecting the presence, extent, type, and location of the neovascularization.

If CNV 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. Promptness is essential, because extrafoveal or juxtafoveal lesions can extend rapidly, creating more irreversible damage. Also, subfoveal lesions may grow too large and thus preclude any treatment benefit. It is important to work with highly skilled retinal photographers and to have prompt photographic processing and interpretation.

If fluorescein angiography is performed, the physician must be aware of potential risks and serious complications associated with this procedure. Although serious complications are rare, each angiographic facility must have an emergency plan and establish a protocol to manage these complications. The ophthalmic photographer should be trained and experienced in stereoscopic fluorescein angiography. Intravenous injection of fluorescein dye can be done by anyone legally designated, provided that a physician is responsible for ordering the test and for ensuring that reasonable safety precautions are observed.
Fundus Photography

Stereo color fundus photographs are usually obtained when angiography is performed, since they are useful in finding landmarks, evaluating serous detachments of the sensory retina and RPE, and in determining the etiology of blocked fluorescence or late leakage of an undetermined source. They also may be used as a baseline for selected patients with high-risk non-neovascular macular degeneration and for follow-up of treated patients.

Table 4
Indications for Fundus Photography and Angiography

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Photography</th>
<th>Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk non-neovascular AMD</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>High-risk non-neovascular AMD</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>Unexplained visual loss, symptoms, suspect CNV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neovascular AMD</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Post-treatment of neovascular AMD</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Disciform scar</td>
<td>Rarely</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

* See text for follow-up recommendations.

Ancillary Tests

Computer-enhanced indocyanine green video angiography (ICG) is a technique that allows viewing of the choroidal circulation. It may prove useful in evaluating certain types of macular degeneration such as pigment epithelial detachments and poorly defined CNVs. The value of this test in evaluating and treating AMD remains unknown.\textsuperscript{61}

TREATMENT

The majority of eyes with suspected CNV do not meet MPS, TAP, VIP or AREDS criteria for treatment. Even patients who have eligible neovascular AMD and who are appropriately treated generally experience visual outcomes that are limited, with visual acuity averaging approximately 20/160.

Indications for Treatment

Based on the data from the AREDS, it is recommended that patients with intermediate or higher risk of AMD consider taking the combination of antioxidants and minerals.\textsuperscript{26[A1]} Patients with low risk for AMD should wait for the development of intermediate or high risk of AMD before taking the combination treatment.\textsuperscript{26[A3]}
Such patients should also have dilated eye exams on a regular basis, as recommended in the Comprehensive Adult Medical Eye Evaluation PPP\textsuperscript{31} for the detection of progression to the intermediate-risk AMD stage\textsuperscript{26} \[A:III\].

Well-demarcated extrafoveal choroidal neovascular lesions should be strongly considered for laser photoocoagulation\textsuperscript{36}. Well-demarcated juxtafoveal CNV lesions should be considered for treatment as long as the patient and physician understand the high recurrence rate and the need for subsequent treatment\textsuperscript{37}.

Recurrent and new subfoveal CNVs also should be considered for treatment in selected, well-informed patients\textsuperscript{38,42,43,47-49}. The practical outcomes of the MPS, TAP, and VIP trials, and the apparent advantages and disadvantages of both PDT and thermal laser should be discussed. Eyes with a predominantly classic subfoveal CNV lesion and relatively good vision would be more likely to retain better than 20/200 visual acuity with PDT than with thermal laser therapy.

**Treatment Technique**

The criteria for treatment of CNV and the techniques of laser therapy are described in the MPS, TAP, and VIP literature. Assessment and treatment plans for different categories of AMD are listed in Table 5.

---

**Table 5**

**Assessment and Treatment Plans for Age-Related Macular Degeneration**

<table>
<thead>
<tr>
<th>Type of AMD</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk non-neovascular AMD\textsuperscript{8,11}</td>
<td>No treatment. Follow-up as recommended in Comprehensive Adult Medical Eye Evaluation\textsuperscript{31}</td>
</tr>
<tr>
<td>Intermediate-risk non-neovascular AMD\textsuperscript{26,14}</td>
<td>Consider high-dose antioxidant vitamins and minerals (as used in AREDS).</td>
</tr>
<tr>
<td>High-risk non-neovascular AMD\textsuperscript{6,26,31-35} and geographic atrophy</td>
<td>No treatment. Color photos sometimes. No fundus fluorescein angiography unless symptoms. Monitoring of monocular vision (patient monitoring/Amsler grid). Follow-up exam 6-24 months if no symptoms. Consider high-dose antioxidant vitamins and minerals (as used in AREDS).</td>
</tr>
</tbody>
</table>

*(Table continued on next page)*
### Table 5 (continued)

**Assessment and Treatment Plans for Age-Related Macular Degeneration**

<table>
<thead>
<tr>
<th>Type of AMD</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular AMD</td>
<td>If in one eye only, consider high-dose antioxidant vitamins and minerals (as used in AREDS).&lt;sup&gt;26&lt;/sup&gt; [A:I] &lt;br&gt; Fundus fluorescein angiography and color photos for possible treatment.&lt;sup&gt;36-38&lt;/sup&gt; [A:I]</td>
</tr>
<tr>
<td>No CNV seen on fundus fluorescein angiography&lt;sup&gt;8,53&lt;/sup&gt; [A:III]</td>
<td>No treatment. &lt;br&gt; Monitoring of monocular vision. &lt;br&gt; Follow-up 4 weeks to 6 months, or sooner if new symptoms.</td>
</tr>
<tr>
<td>CNV possibly present but no classic component; and ill-defined occult component&lt;sup&gt;39,40,46&lt;/sup&gt; [A:I]</td>
<td>No treatment. &lt;br&gt; Monitoring of monocular vision. &lt;br&gt; Follow-up 4 weeks to 6 months, or sooner if new symptoms.</td>
</tr>
<tr>
<td>CNV present and well demarcated</td>
<td>Strongly consider thermal laser treatment.</td>
</tr>
<tr>
<td>New subfoveal with evidence of classic CNV&lt;sup&gt;6,38,42,43,47-49&lt;/sup&gt; [A:I]</td>
<td>Consider PDT for lesions that are predominantly classic CNV. &lt;br&gt; Consider thermal laser, particularly if small CNV (≤ 1 MPS disc area) and poor vision (20/125 or worse) or if medium CNV (&gt; 1 to ≤ 2 MPS disc areas) and poor vision (20/200 or worse).</td>
</tr>
<tr>
<td>Recurrent subfoveal with evidence of classic and well-demarcated CNV&lt;sup&gt;6,42,43,47-49&lt;/sup&gt; [A:III]</td>
<td>Consider PDT for recurrent lesions that are predominantly classic CNV. &lt;br&gt; Consider thermal laser if recurrence and area of prior treatment ≤ 6 MPS disc areas and an area within 1500 microns of foveal center will be spared by treatment.</td>
</tr>
<tr>
<td>New or recurrent subfoveal with evidence of classic and occult CNV&lt;sup&gt;48,49&lt;/sup&gt; [A:III]</td>
<td>Consider PDT for lesions that are predominantly classic CNV and are less than or equal to 5400 microns in greatest diameter.</td>
</tr>
<tr>
<td>Subfoveal CNV with occult but no classic CNV&lt;sup&gt;41&lt;/sup&gt; [A:III]</td>
<td>Consider PDT; particularly if the lesion size is relatively small (&lt; 4 MPS disc areas) or lower levels of visual acuity (approximate Snellen equivalent worse than 20/50).</td>
</tr>
</tbody>
</table>

The following is recommended for treatment of CNV that meets MPS criteria:

- Discuss risks, benefits, and complications with the patient and obtain informed consent (see Counseling).<sup>[A:III]</sup>
- Treat as promptly as possible after fluorescein angiography.<sup>[A:I]</sup> (The MPS used a protocol requiring treatment within 72 hours for extra- and juxtafoveal CNV<sup>34,38</sup> and 96 hours for subfoveal CNV<sup>6,38,42,43,47</sup>).
The following is recommended for treatment of subfoveal CNV that meets TAP or VIP criteria for a predominantly classic lesion or an occult lesion with no classic CNV:

- Discuss risks, benefits and complications with the patient and obtain informed consent (See Counseling).
- Treat promptly after fluorescein angiography. (The TAP and VIP used a protocol in which treatment was performed within 1 week of angiography.)

The following therapies represent some that are being evaluated in either randomized or nonrandomized clinical trials, but none can be recommended as a preferred practice at present.

- Pharmacological therapy, especially angiogenesis inhibitors
- Prophylactic laser treatment in high-risk non-neovascular AMD
- Submacular surgery
- Photodynamic therapy with drugs other than verteporfin
- External beam radiation therapy
- Macular translocation
- Transpupillary thermal therapy (TTT)
- Feeder vessel treatment with high-speed ICG angiography

**COMPLICATIONS**

When using high-dose antioxidant vitamins and minerals to reduce the rate of progression to advanced AMD, the adverse effects observed in AREDS consisted mainly of urinary tract disorders (7.5% in those treated with zinc vs. 4.9% in those not treated with zinc, \( P = \) 0.001). Participants in the antioxidant vitamin treatment group reported more frequently the yellowing of the skin (8.3% vs. 6.0%, \( P = 0.008 \)). The previously reported risk of potential copper deficiency anemia associated with zinc supplementation was reduced by the concomitant administration of copper. The adverse effect of primary concern is the increased risk of lung cancer associated with beta-carotene in participants who are smokers. This was found in two previous studies of chemoprevention clinical trials of lung cancer supported by the National Cancer Institute. When considering long-term supplementation, some people may have reason to avoid one or more of the ingredients evaluated in the AREDS. Persons who smoke cigarettes should probably avoid taking beta-carotene. Because of the potential adverse effects, such as increased genitourinary conditions that may require hospitalizations, the high doses of antioxidant vitamins and minerals recommended by AREDS results should be administered under the guidance of the patient’s physician.

When treating CNV with thermal laser photocoagulation, the most severe complications are rupture of Bruch's membrane with subretinal and/or vitreous hemorrhage, RPE rips, and unintended treatment of the fovea. Retrobulbar or peribulbar anesthetic injections are sometimes used with thermal photocoagulation and may cause additional complications. If these injections are used to limit ocular motility and/or pain, plans should be made to manage anticipated complications. Serious complications are rare.

Introduction or enlargement of a pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal photocoagulation, but it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of the CNV, or the development of a new
CNV and further visual deterioration following adequate thermal laser treatment is usually a result of the disease process and is not a complication. These realities must be emphasized to the patient and family prior to treatment.31,48,49

Treatment of CNV with PDT can be associated with transient visual disturbances and, in unusual cases (1% to 4%), with more severe loss of ≥ four lines shortly after treatment.41,48,49 The effect is transient in most patients and requires no additional therapy, but it can be permanent in some of these cases. Infusion site extravasation is an unusual complication that requires covering the infiltrated area for at least five days or until it is normal in appearance. Back pain occurs during the infusion in about 2% of patients. This usually will pass as the infusion continues. Having the patient stand may help relieve the symptoms. Although photosensitivity reactions have been reported, they are unusual (< 3%), especially if the patient takes proper precautions for avoiding direct sunlight exposure.

The use of verteporfin is contraindicated in patients with porphyria or a known allergy or sensitivity to the drug, and careful consideration should be given to patients with liver dysfunction, pregnancy, breast-feeding, or of pediatric age because these patients were not studied in published reports.

FOLLOW-UP

A history and examination are the recommended elements of the follow-up visits.

**History**

The follow-up history should take into account the following symptoms and changes.

- Symptoms,29,53 [A:II] including decreased vision (e.g., altered ability to read mail, newsprint, and road signs; to recognize faces; or to identify details on a television screen) and metamorphopsia
- Changes in medications51 [B:III]
- Changes in medical and ocular history19,34,54 [B:III]
- Changes in family history13,14 [B:II]
- Changes in social history (smoking)15,16 [B:II]

**Examination**

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

- Assessment of best corrected visual acuity36-38 [A:I]
- Vision testing with an Amsler grid53 [B:III]
- Slit-lamp biomicroscopy (to detect media opacity as a cause for visual loss)[A:III]
- Biomicroscopic examination of the fundus36-38 [A:I]

Diagnostic tests used in the follow-up examination are identical to those listed under Diagnosis, and the treatment plan is identical to the one described under Treatment.

Recommended follow-up intervals when no laser treatment is indicated are listed in Table 5.
Follow-up of Postoperative Patients

Patients who have been treated with either thermal laser or PDT should be examined at regular intervals by means of biomicroscopy of the fundus. Fundus photography and fluorescein angiography should be employed when indicated. The recommended frequency of postoperative examinations and angiography is based upon previous trials and is as follows:6,36-38,42,43,47-49 [A41]

- 1st visit (2 to 4 weeks after thermal laser; this examination occurred in the TAP and VIP 3 months after PDT) for examination, fluorescein angiography, and possible repeat thermal laser or PDT.
- 2nd visit (4 to 6 weeks after thermal laser; 3 months after last visit following PDT) for examination, fluorescein angiography, and possible repeat thermal laser or PDT.
- 3rd visit (6 to 12 weeks after thermal laser; 3 months after last visit for PDT) for examination, fluorescein angiography, and possible thermal laser or PDT.
- 4th visit (3 to 6 months after thermal laser; 3 months after last visit for PDT) for examination, fluorescein angiography and possible thermal laser or PDT.
- Thereafter, every 3 to 6 months for examination. Fluorescein angiography may be needed every 3 months through 2 years for patients receiving PDT.

Following thermal laser photocoagulation, frequent postoperative examinations and fluorescein angiograms are justified because of the high rates of persistence and recurrence and because of the documented benefit of treating marginal subfoveal recurrences in the MPS. A follow-up examination should be performed 2 to 4 weeks following initial treatment to confirm that the CNV has been obliterated. Subsequent examinations and angiography should be performed at 4 to 6 weeks and thereafter depending on clinical findings and the judgment of the treating physician. Subsequent angiograms can be used to complement the clinical examination because persistent or recurrent neovascularization is common and may be clinically subtle or nondetectable.65 Treated patients who report new symptoms may need to be re-examined promptly and before their next scheduled follow-up visit.

Following PDT for subfoveal CNV, follow-up examinations and angiograms may be recommended every three months up to 2 years, since this was the TAP/VIP protocol and since patients required an average of 3.4 treatments over one year and 5.5 treatments over 2 years.48,49 In the TAP protocol, any detectable leakage of fluorescein from CNV was considered an indication for re-treatment as often as every 3 months. Since the TAP/VIP protocols did not allow treatment any sooner than every three months, it is not known if more frequent follow-up and treatment would be of benefit to those patients who have early signs of persistent detectable leakage.

If patients treated with thermal laser or PDT notice visual loss or change prior to the next scheduled visit, return evaluation that may include angiography is recommended.

For patients with unilateral disease, the second eye (without neovascularization) remains at high risk for the development of CNV.32,33 The patients should be instructed to monitor their vision in multiple ways, including using the Amsler grid and other subjective assessments of visual function.53 However, the Amsler grid may not be valuable for many patients, since the ability to interpret change is variable, particularly for those whose vision is already impaired.53 They should return to the
ophthalmologist periodically even in the absence of symptoms, but promptly following the onset of any new visual symptoms. Patients at exceptionally high risk may be examined more frequently in an effort to detect asymptomatic CNV at a treatable stage.

There are high persistence and recurrence rates following treatment of well-demarcated CNV in patients with AMD. The majority of recurrences occur within the first year, after which there is a slow increase over the next 3 to 4 years. The MPS reported a 5-year persistence/recurrence rate of 54% for the extrafoveal study and a 4-to-5-year rate of 78% for the juxtafoveal study; the 3-year persistence/recurrence rate was 56% for the subfoveal study. More than 90% of recurrences are on the foveal side following laser treatment of extra- and juxtafoveal CNVs.36,37,43

PROVIDER

Treatment of CNV is difficult,6,66 and referral to an ophthalmologist with special training or experience in managing this condition is appropriate.35-38 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. While it is assumed that the ophthalmologist will perform most of the examination and all treatment, certain aspects of data collection may be conducted by other trained individuals under the ophthalmologist’s supervision (see Comprehensive Adult Medical Eye Evaluation).51

COUNSELING/REFERRAL

All patients with AMD should be educated about the prognosis and potential value of treatment as appropriate for their ocular and functional status. Patients can be told that although central visual loss is common, peripheral visual loss is exceedingly rare. Patients with macular degeneration can be reassured that there is no harm using their eyes, and that the effect of light, and other factors on vision remains uncertain and is under study. Patients with CNV for whom surgical treatment may be indicated, based on MPS, TAP, and VIP guidelines, should be counseled about the effects of laser treatment, some of which are as follows.

- Treatment will reduce but not eliminate the risk of severe visual loss.
- Thermal laser treatment will produce permanent scotomas. The location, size, and anticipated effect of the scotoma on central visual function (e.g., reading vision) should be explained.
- PDT will reduce the risk of moderate and severe visual loss, but most patients will still lose some vision over 2 years, and improvement in visual acuity is unusual.
- There is a high risk of CNV persistence or recurrence that could require additional laser treatment. This risk is greatest during the first year after initial treatment.
- Multiple fluorescein angiograms are necessary for appropriate post-laser follow-up.

Treatment is not indicated for most patients with neovascular AMD.1 When treatment is not indicated, the reason why and the prognosis should be explained. Patients also appreciate being informed that there is a considerable amount of basic science and clinical research being conducted and that at some point in the future some of the research findings may lead to more effective treatment, including prevention strategies. By referring
patients with low vision or with anticipated low vision to the community resources available for the visually impaired, the ophthalmologist can play an important role in rehabilitation, giving patients hope as they face the challenge of coping with vision loss. Patients eligible to participate in randomized clinical trials should be encouraged to do so. Patients groping for miracles should be cautioned about subjecting themselves to potentially harmful, expensive treatments that have not been proven effective and that are not being evaluated by means of controlled clinical trials.

Patients with reduced visual function may benefit from vision rehabilitation services. Patients with severe visual loss related to macular degeneration who are referred for vision rehabilitation services often have unrealistic expectations. Special optical or electronic magnifying lenses, bright lights, and other reading aids may help patients to read more effectively, but not as well as they did prior to the onset of AMD. Depression and visual hallucinations are frequent accompaniments of central vision loss. The ophthalmologist should inquire about symptoms of clinical depression and, when appropriate, suggest that the patient seek professional advice.

When patients' expectations are appropriate, the benefits from vision rehabilitation consultants may be substantial. Those consultations and comprehensive vision rehabilitation services should be considered in order to help patients deal constructively with their disability.

REFERENCES


APPENDIX 1. SUMMARY OF MAJOR RECOMMENDATIONS FOR CARE

The following is a summary of major recommendations for care of patients with age-related macular degeneration.

History

The following elements of history are recommended for the initial visit:

- Symptoms[A:I]
- Medications[B:III]
- Medical and ocular history[B:III]
- Family history[B:II]
- Social history, especially smoking[B:II]

Examination

Patients should receive a comprehensive eye evaluation. Components of the evaluation that are particularly relevant for management of AMD include the following elements:

- Assessment of best corrected visual acuity[A:I]
- Vision testing with an Amsler grid[B:III]
- Biomicroscopic examination of the macula[A:I]
- Peripheral retinal examination[B:III]

Diagnostic Tests

Indications for diagnostic tests are listed in Table 4 in the main body of the text.
Treatment

Assessment and treatment plans for the different categories of age-related macular degeneration are listed in Table 5 in the main body of the text.

Patients with intermediate or higher risk of AMD (including neovascular AMD in one eye only) should consider taking the combination of antioxidants and minerals. Patients with lower risk for AMD should wait for the development of intermediate or higher risk of AMD before taking the combination treatment.

The following plan is recommended for treatment of CNV that meets MPS criteria:

- Discuss risks, benefits, and complications with the patient and obtain informed consent.
- Treat as promptly as possible after fluorescein angiography.

The following is recommended for treatment of subfoveal CNV that meets TAP or VIP criteria for a predominantly classic lesion or an occult lesion with no classic CNV:

- Discuss risks, benefits and complications with the patient and obtain informed consent.
- Treat promptly after fluorescein angiography.

Follow-up

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

- Symptoms
- Changes in medications
- Changes in medical and ocular history
- Changes in family history
- Changes in social history

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

- Assessment of best corrected visual acuity
- Vision testing with an Amsler grid
- Slit-lamp biomicroscopy
- Biomicroscopic examination of macula

Follow-up intervals when no laser treatment is indicated are listed in Table 5 in the main body of the text.

Patients who have been treated with laser surgery should be examined at regular intervals by means of macular biomicroscopy, stereoscopic photos, and fluorescein angiography. The recommended frequency of postoperative examinations is based upon previous trials and is as follows:

- 1st visit (2 to 4 weeks after thermal laser; this examination occurred in the TAP and VIP 3 months after PDT) for examination, fluorescein angiography, and possible repeat thermal laser or PDT
- 2nd visit (4 to 6 weeks after thermal laser; 3 months after last visit following PDT) for examination, fluorescein angiography, and possible repeat thermal laser or PDT
3rd visit (6 to 12 weeks after thermal laser; 3 months after last visit for PDT) for examination, fluorescein angiography, and possible thermal laser or PDT

4th visit (3 to 6 months after thermal laser; 3 months after last visit for PDT) for examination, fluorescein angiography, and possible thermal laser or PDT

Thereafter, every 3-6 months for exam. Fluorescein angiography may be needed every 3 months through 2 years in patients receiving PDT.

Treated patients who report new symptoms may need to be re-examined before their next scheduled follow-up visit.

For patients with unilateral disease, the second eye (without neovascularization) remains at high risk. The patients should be instructed to monitor their vision in multiple ways, including use of the Amsler grid and other subjective assessments of visual function.

**Provider**

Treatment of CNV is difficult, and referral to an ophthalmologist with special training or experience in managing this condition is appropriate.

Ancillary clinical personnel should be aware that patients with the onset of new symptoms suggestive of AMD (e.g., new visual loss, distortion, or metamorphopsia) should be examined promptly.

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**GLOSSARY**

*Advanced age-related macular degeneration (Advanced AMD):* This is the most severe form of AMD defined as geographic atrophy involving the center of the macula (fovea) or features of choroidal neovascularization.

*Age-related macular degeneration (AMD):* There is no universally accepted definition of this term. The condition is characterized by the presence of drusen and alterations of the retinal pigment epithelium as well as the fundus abnormalities associated with choroidal neovascularization (CNV) and generally occurs in persons over 50 years old. The visual acuity may vary from normal to severe impairment.

*Choroidal neovascularization (CNV):* 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.

*Classic choroidal neovascularization:* The angiographic findings in which the choroidal neovascularization is recognized as an area of bright, well-demarcated hyperfluorescence identified in the early phase of the angiogram with progressive pooling of dye in the overlying subsensory retinal space during the late phases of the angiogram.

*Contrast sensitivity testing:* An additional method of testing visual function. Routine visual acuity testing utilizes objects of high contrast to determine the limit of spatial resolution of the central retina. Contrast sensitivity testing involves determining the minimal contrast required to detect different spatial frequencies.
**Disciform scar:** Subretinal fibrovascular tissue that usually becomes more fibrous within a few years and is often the end result of choroidal neovascularization.

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

**Drusen:** Yellow excrescences at the level of the basement membrane of the retinal pigment epithelium. They are the ophthalmoscopic and histologic hallmark of age-related macular degeneration. (See Hard drusen and Soft drusen).

**Extrafoveal choroidal neovascularization:** Choroidal neovascular membrane that comes no closer than 200 microns to the center of the foveal avascular zone, as defined by the Macular Photocoagulation Study.

**Neovascular macular degeneration:** Manifestations of choroidal neovascularization and/or retinal pigment epithelial detachment associated with subretinal serous fluid, exudates, and/or blood.

**Fibrovascular retinal pigment epithelial detachment (FVPED):** A form of occult choroidal neovascularization that is diagnosed by contact lens biomicroscopy and/or stereo fluorescein angiography. It includes areas of irregular elevation of the retinal pigment epithelium associated with stippled hyperfluorescence that appears 1 to 2 minutes after IV fluorescein injection.

**Foveal avascular zone (FAZ):** An area usually 300 to 500 millimeters in diameter centered on the foveola and lacking retinal blood vessels, also known as the capillary-free zone.

**Geographic atrophy:** One or several well-demarcated zones of retinal pigment epithelial atrophy (and sometimes choriocapillaris atrophy). Drusen are usually present surrounding these zones. This is an advanced form of neovascular age-related macular degeneration.

**Hard drusen:** Small, discrete drusen. Histologically, these represent localized deposits between the basement membrane of the retinal pigment epithelium and Bruch's membrane.

**Ill-defined choroidal neovascularization:** Choroidal neovascularization that has indistinct or poorly demarcated boundaries on fluorescein angiography.

**Juxtafoveal choroidal neovascularization:** Well-demarcated choroidal neovascularization that is between 1 and 199 microns from the center of the foveal avascular zone but does not reach its center, as defined by the Macular Photocoagulation Study.

**Late leakage of undetermined source (LLUS):** A form of occult choroidal neovascularization in which leakage is noted at the level of the retinal pigment epithelium during the late phase of the fluorescein angiogram, without areas of well-demarcated hyperfluorescence in the early phase to account for the leakage.

**Legal blindness:** Best-corrected visual acuity of 20/200 or less in both eyes or visual fields equal to or less than 20°. Legally blind patients qualify for certain disability benefits, including an additional income tax deduction.
**Macular Photocoagulation Study (MPS):** A series of prospective, randomized multicenter clinical trials funded by the National Eye Institute to determine the efficacy of laser photocoagulation in choroidal neovascularization caused by age-related macular degeneration, ocular histoplasmosis, and idiopathic causes.

**Non-neovascular macular degeneration:** Macular changes characterized by drusen, retinal pigment epithelial abnormalities, and atrophy, but not by choroidal neovascularization or pigment epithelial detachment.

**Occult choroidal neovascularization:** Angiographic findings characterized by a fibrovascular retinal pigment epithelial detachment and/or late leakage of an undetermined source.

**PDT:** See photodynamic therapy.

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

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

**Predominantly classic lesion:** Area of CNV occupying ≥ 50% of the entire lesion area.

**Pigment epithelial detachment (PED):** Accumulation of fluid (serous retinal pigment epithelial detachment) or blood (hemorrhagic retinal pigment epithelial detachment) beneath the retinal pigment epithelium. Associated choroidal neovascularization 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 choroidal neovascularization.

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

**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 geographic atrophy.

**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).

**Soft drusen:** Soft drusen are larger than hard drusen (i.e., usually 64 microns or more in diameter or half the width of a major retinal vein of the optic nervehead), and they usually have ill-defined, nondiscrete margins. Histologically, these represent diffuse deposits of amorphous material between the basement membrane of the retinal pigment epithelium and Bruch's membrane.

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

**TAP:** An abbreviation for “Treatment of Age-related Macular Degeneration with Photodynamic Therapy”. Usually refers to reports by the TAP study group reporting on a prospective, randomized multicenter clinical trial sponsored by QLT Inc, Vancouver, British Columbia, and Novartis Ophthalmics, Bülach, Switzerland.
Verteporfin (Visudyne): A drug used as a photosensitizer in conjunction with a non-thermal laser (PDT).

VIP: Verteporfin in Photodynamic Therapy Study.

Well-defined choroidal neovascularization: Choroidal neovascularization, with classic or occult features, that has well-demarcated boundaries on fluorescein angiography.

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