MACULAR DEGENERATION

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Macular Degeneration Clinical Guidance- Issued May 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

AMD	Age-related Macular Degeneration
AREDS	Age-Related Eye Disease Study
CHI	Council of Health Insurance
CNV	Choroidal Neovascularization
CVI	Certificate of Vision Impairment
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFA	Fluorescein Angiography
IDF	CHI Drug Formulary
IOP	Intraocular Pressure
LVA	Low Vision Aid
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography – Angiography
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamic Therapy
RPE	Retinal Pigment Epithelium
SFDA	Saudi Food and Drug Authority
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
vPDT	Verteporfin Photodynamic Therapy

Executive Summary

Age-related macular degeneration (AMD) stands as the primary cause of permanent vision loss among older individuals. AMD is a degenerative condition affecting the central portion of the retina, called the macula, leading to a reduction in central vision, which is crucial for most daily tasks. This condition is characterized by a decline in visual acuity due to the degeneration of the choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors, typically commencing with the presence of drusen and pigmentary alterations in Bruch's membrane[1].

This condition impacting a global population of 30 million to 50 million individuals, holds the top position as the primary cause of permanent blindness in developed nations among those who are 50 years of age and older[1]. The prevalence of ARMD increases exponentially every decade after age 50. A retrospective study was conducted in the retina clinic at a tertiary center in Makkah province (Saudi Arabia) to evaluate the prevalence and associated risk factors of age-related macular degeneration. 1,935 patients were enrolled in the study. The prevalence of AMD was shown to be 4%. Looking at non-modifiable risk factors, there was a notable connection between age and having a family history of AMD. As for modifiable risk factors, smoking and hypertension had a significant impact on the development of AMD[2].

The etiology of AMD is multifactorial and the main risk factors include old age, smoking, family history, female gender, obesity, sun exposure, atherosclerosis, hypertension, diabetes, polypharmacy, alcohol, ethnicity, hypothyroidism, and C-reactive protein. AMD is mainly symptomatic in its early stages, yet in some cases, patients may report sudden vision loss, metamorphopsia, blurred vision, scotomas, or persistent visual distortion. An ophthalmologist can employ a range of screening tests to determine a diagnosis. These may encompass assessments of visual acuity, a dilated funduscopic examination, optical coherence tomography, fluorescein angiography, indocyanine green angiography, fundus autofluorescence, and ultrasonography. In more severe instances, a referral to a retinal specialist may be necessary[1].

The strategy employed in AMD management aims to detect and combat the condition during its early phases, thereby decelerating its advancement and mitigating vision impairment. Multiple lifestyle adjustments and dietary components have been recognized as having a positive impact in both preventing the condition and impeding its progression. Thermal laser photocoagulation was the treatment of choice for many years in the management of patients with wet AMD. The outlook for individuals with neovascular AMD has substantially enhanced thanks to the advancement of verteporfin photodynamic therapy (PDT) and antiangiogenic treatment, including intravitreal pegaptanib sodium, intravitreal bevacizumab, and

intravitreal ranibizumab. Considering the role of vascular endothelial growth factor (VEGF) in promoting neovascularization, inhibiting VEGF has emerged as a key focus in the effective treatment of neovascular AMD[1].

CHI issued new guidelines related to the management of Macular Degeneration. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates. Below is a description of sections that need updates.

CHI issued Macular Degeneration clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Macular Degeneration clinical guidance and seeks to offer guidance for the effective management of **Macular Degeneration**. It provides an **update on the** Macular Degeneration **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being **the issuance of updated versions of previously reviewed guidelines** namely **American Academy of Ophthalmology**: Age-Related Macular Degeneration Preferred Practice Pattern **(March 2022 Update).** Moreover, **new guidelines are added to the report** such as **2019 Australian Clinical Practice Guide** for the diagnosis, treatment and management of Age-Related Macular Degeneration and **the royal college of ophthalmologists:** Age Related Macular Degeneration Services **(2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended to include **Brolucizumab** (BEOVU®) and **Faricimab** (Vabysmo®) in the CHI formulary since they are registered on the SFDA. Moreover, there have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits and no medications need to be delisted.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Menopause management.

Below is a table summarizing the major changes based on the different macular degeneration guidelines used to issue this report:

Table 1. General Recommendations for the Management of Macular Degeneration

Management of Macular Degeneration		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are essential diagnostic tools used to identify recent or recurring neovascular disease activity and assist in making treatment decisions.	Not graded	American Academy of Ophthalmology (2022)[3]
It is recommended to follow a healthy diet, which should include an abundance of fresh fruits, vegetables, eggs, and oily fish.	Not graded	Optometrists Association Australia (2019)[4]
Counseling on smoking cessation should be offered for patients with AMD.	Not graded	The royal college of ophthalmologists (2021)[5]
Anti-vascular endothelial growth factor (VEGF) medications like aflibercept, bevacizumab, and ranibizumab, are considered as the first line and most effective treatment for neovascular AMD.	Not graded	American Academy of Ophthalmology (2022)[3]
When it comes to anti-VEGF medications, patients have the option to choose from a variety of initial treatment options, including aflibercept, ranibizumab, or brolucizumab.	Not graded	The royal college of ophthalmologists (2021)[5]
vPDT may serve as an alternative treatment choice for individuals with polypoidal choroidal vasculopathy (PCV) if they do not respond positively to anti-VEGF therapy.	Not graded	The royal college of ophthalmologists (2021)[5]
Thermal laser photocoagulation surgery is no longer the preferred option for	Not graded	American Academy of

treating subfoveal choroidal neovascularization (CNV).		Ophthalmology (2022)[3]
Brolucizumab and Faricimab were recently approved and are now options for the treatment of neovascular wet age-related macular degeneration.	Not graded	American Academy of Ophthalmology (2022)[3]

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI macular degeneration report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 CHI Macular Degeneration Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 **2019 American Academy of Ophthalmology:** Age-Related Macular Degeneration Preferred Practice Pattern	1.1.1 **American Academy of Ophthalmology**: Age-Related Macular Degeneration Preferred Practice Pattern **(March 2022 Update)**
1.2 Age-related macular degeneration **NICE guideline**: Published: **23 January 2018**	N/A*

*****: *No updated versions available*

1.1.1 American Academy of Ophthalmology: Age-Related Macular Degeneration Preferred Practice Pattern (March 2022 Update)

The American Academy of Ophthalmology (AAO): Age-Related Macular Degeneration Preferred Practice Pattern (March 2022 Update)[3] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 3. Definitions and Levels of Evidence

Definitions and levels of evidence	
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)

Table 4. Quality of Evidence Recommendations as Defined by GRADE

Quality of evidence	
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

Table 5. AAO Grading Scheme for Recommendations

Grading Scheme for Recommendations	
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.

- Age-related macular degeneration (AMD) is a condition affecting the macula that exhibits one or more of the following characteristics, as defined in the Glossary:
    1. The existence of drusen of at least an intermediate size, with a diameter greater than 63 µm.
    2. Irregularities in the retinal pigment epithelium (RPE), such as either reduced pigmentation or excessive pigmentation.
    3. The presence of any of the subsequent features: geographic atrophy of the RPE, choroidal neovascularization (CNV) of the exudative, or wet type, polypoidal choroidal vasculopathy (PCV), reticular pseudodrusen, or retinal angiomatous proliferation.
- While approximately 80% of individuals with age-related macular degeneration (AMD) experience the non-neovascular or atrophic form of the condition, it is the neovascular form that predominantly leads to severe central visual acuity (VA) loss in AMD.
- The primary factors that elevate the risk of advanced AMD development encompass advancing age, a northern European heritage, and genetic elements. Notably, cigarette smoking stands out as the most modifiable risk factor consistently identified in numerous research studies. Advising individuals with AMD or those at risk for AMD to quit smoking is strongly encouraged. Currently, routine genetic testing is not recommended.
- Other potential risk factors might encompass low systemic levels of antioxidants.
- Several studies have also identified an association between dietary fat and advanced AMD.
- After conducting a meta-analysis of 10 studies, it was determined that there is no indication of an elevated risk of age-related macular degeneration (AMD) associated with the use of aspirin. As a result, individuals who have been advised by a medical professional to take aspirin should adhere to their prescribed regimen.
- Patients diagnosed with intermediate or advanced age-related macular degeneration (AMD) should contemplate incorporating antioxidant vitamins and mineral supplements in accordance with the Age-Related Eye Disease Study (AREDS2). However, there is no substantiated data endorsing the

utilization of these supplements for individuals with AMD that is less than intermediate in severity. Furthermore, there is no indication of any preventative benefits for family members who do not exhibit signs of AMD.

- Fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are valuable diagnostic tools in clinical settings for identifying fresh or recurring neovascular disease activity and directing treatment decisions.
- In individuals experiencing neovascular age-related macular degeneration (AMD), timely identification and swift treatment lead to enhanced visual results. The primary and most effective approach for managing neovascular AMD is intravitreal injection therapy employing anti-vascular endothelial growth factor (VEGF) medications like aflibercept, bevacizumab, and ranibizumab, serving as the initial treatment choice. Any symptoms hinting at post-injection endophthalmitis or retinal detachment necessitate immediate assessment.
- The Comparison of AMD Treatment Trials (CATT) was a clinical trial conducted at multiple centers to evaluate the safety and efficacy of bevacizumab in comparison to ranibizumab, as well as to assess the effectiveness of an individualized dosing schedule (known as "as needed" or PRN) versus monthly injections. After one year of the CATT study, it was concluded that ranibizumab and bevacizumab exhibited similar improvements in visual acuity (VA) when administered monthly.
- Comparable outcomes were observed in the 2-year Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) trial, which took place in the United Kingdom.
- In a 2018 meta-analysis conducted by Nguyen, which included over 8,000 eyes and compared all three drugs, the findings indicated that bevacizumab and ranibizumab exhibited similar effectiveness in terms of best-corrected visual acuity (BCVA). However, ranibizumab demonstrated a more significant reduction in central macular thickness. Additionally, aflibercept and ranibizumab showed comparable efficacy for both BCVA and central macular thickness. A similar review conducted by Chen in 2015 also yielded parallel results.
- The systemic safety information gathered from the CATT and IVAN studies remains inconclusive, and two Cochrane systematic reviews have likewise determined that if there is any variance in safety among these anti-VEGF drugs, it is negligible. (I+, Good quality, Strong recommendation)
- In the HAWK and HARRIER phase III clinical trials, recently disclosed findings demonstrated that brolucizumab successfully met its primary objective of

achieving noninferiority in terms of best-corrected visual acuity (BCVA) change compared to aflibercept at week 48. Patients receiving brolucizumab experienced more significant reductions in central subfield thickness when compared to those receiving aflibercept. Additionally, fewer patients who received brolucizumab exhibited sub-retinal fluid, inter-retinal fluid, and sub-retinal pigment epithelium (RPE) fluid. As a result of these positive results, brolucizumab obtained FDA approval in October 2019.

- The TENYA and LUCERNE trials demonstrated that patients receiving faricimab-svoa for neovascular AMD, even with dosing intervals of up to 16 weeks, achieved visual acuity improvements that were not inferior to those of patients receiving aflibercept every 8 weeks. Faricimab-svoa received approval from the US Food and Drug Administration (FDA) on January 28, 2022. Vabysmo (faricimab-svoa) is a humanized bispecific monoclonal antibody designed for intravitreal (IVT) use, acting by simultaneously inhibiting both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). It is indicated for the treatment of patients with neovascular (wet) AMD.
- Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment.

1.2. Additional Guidelines

This part includes the added guidelines to the previous CHI Macular Degeneration report, along with their recommendations.

Table 6. List of Additional Guidelines

Additional Guidelines
Australian Clinical Practice Guide for the Diagnosis, Treatment, and Management of Age-Related Macular Degeneration (**2019**)
The **Royal College of Ophthalmologists**: Age Related Macular Degeneration Services (**2021**)

1.2.1 Australian Clinical Practice Guide for the Diagnosis, Treatment and Management of Age-Related Macular Degeneration (2019)

The following recommendations are retrieved from **2019 Australian Clinical Practice Guide** for the diagnosis, treatment, and management of Age-Related Macular Degeneration[6]:

- Older age (> 60 years), family history of AMD/genetics are considered strong risk factors for AMD.

- Smoking is considered the strongest modifiable risk factor for AMD.
- Hypertension, cardiovascular disease, and a BMI of 30kg/m2 or higher are considered moderate risk factors for AMD.
- A diet low in omega 3 fatty acids, vitamins, carotenoid and minerals or high in fat (saturated fats, trans fats and omega-6 fatty acids) and lack of exercise are considered weak risk factors for AMD.
- The most current clinical classification scheme for AMD is the Beckman classification.
- The Beckman classification scheme was designed to reflect the fact that risk profiles are linked to the clinical signs of drusen and pigmentary abnormalities.

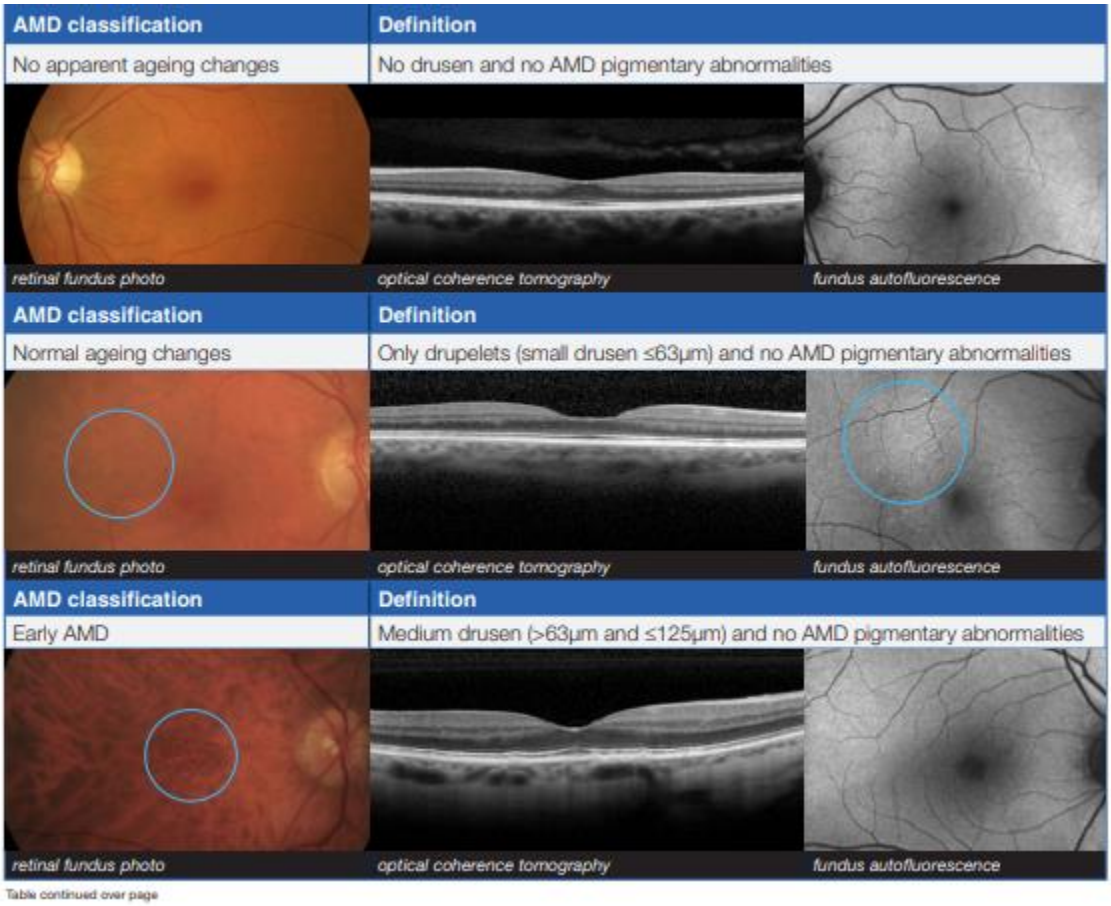


Figure 1. *Beckman Classification of AMD, with Corresponding Example Retinal Fundus Photos, Optical Coherence Tomography and Fundus Autofluorescence (Retrieved from 2019 Australian Clinical Practice Guide)*

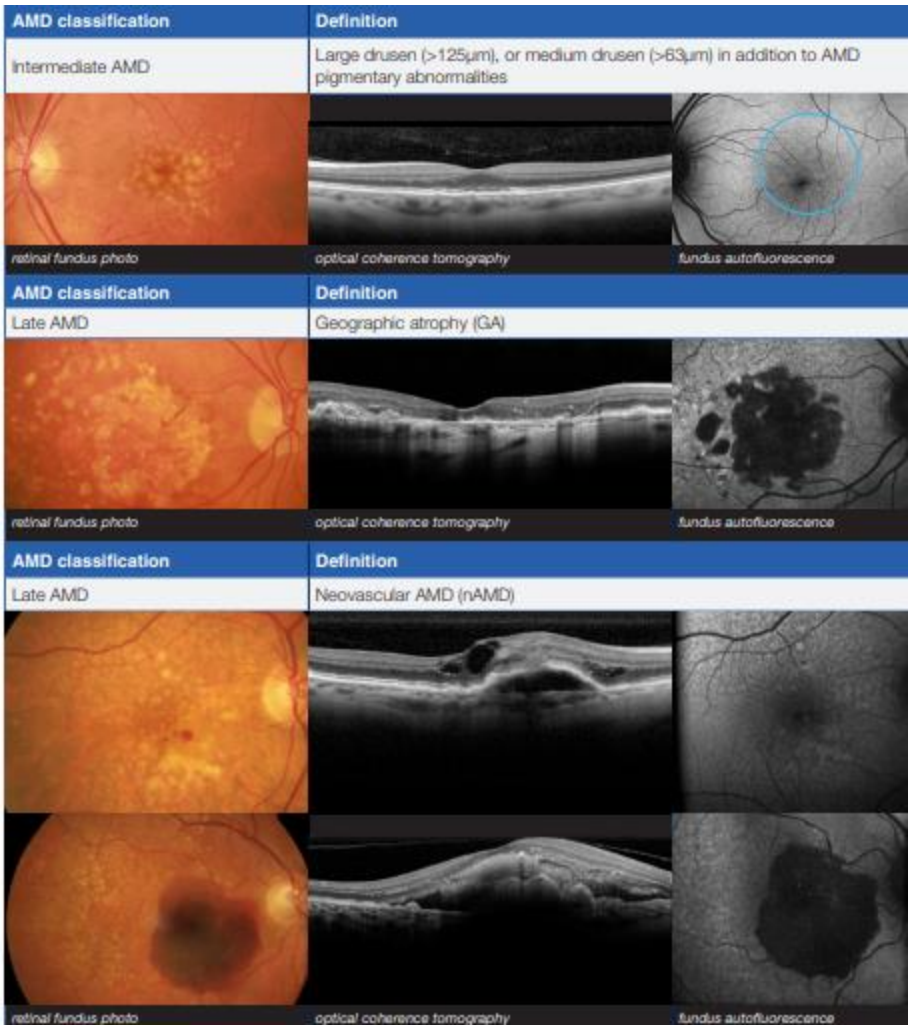


Figure 2. *Beckman Classification of AMD, with Corresponding Example Retinal Fundus Photos, Optical Coherence Tomography and Fundus Autofluorescence (Continued) (Retrieved from 2019 Australian Clinical Practice Guide)*

- The main symptoms of AMD are listed in the table below:

Table 7. Common Signs and Symptoms of AMD (Retrieved from 2019 Australian Clinical Practice Guide)

Stage of disease	Clinical symptoms	Clinical funduscopic signs
Early	– Usually asymptomatic – May have reduced contrast sensitivity and difficulties with dark adaptation[36] e.g. difficulties reading in dim light or adjusting from different lighting conditions.	Medium drusen (≤125µm)
Intermediate		Large drusen (>125µm) and/or pigmentary abnormalities, pigment epithelial detachment due to confluence of large drusen.
Late: geographic atrophy	– Decrease in vision that is not improved with refractive correction – A central field defect or blur that may or may not affect fixation – Visual distortions (scotoma, metamorphopsia, micropsia or macropsia) – Difficulties with visual tasks/ activities of daily living, such as watching television, going down stairs, reading or recognising people – Some people with late AMD and poor vision in both eyes will develop visual hallucinations in Charles Bonnet syndrome[37]. This can be distressing to patients, who will often require counselling.	Area of photoreceptor and RPE atrophy, forming a well-demarcated lesion of at least 250µm in diameter, with choroidal vessels visible in its base.[38]
Late: neovascular		Choroidal neovascularisation (CNV) which may appear as a well-demarcated grey/green area of the retina, macular fluid (sub- or intra-retinal), lipid or haemorrhage, pigment epithelial detachment.
Non-stage specific		Reticular pseudodrusen (subretinal drusenoid deposits) are yellowish, net-like deposits. They are not a unique phenotype to AMD, but they have been shown to be associated with an increased risk of progression to late-stage AMD.[39, 40]

- Patients diagnosed with AMD should undergo a typical thorough optometry assessment, which encompasses a focused medical history, assessment of high-contrast visual acuity, refraction, stereoscopic examination using a slit lamp, and a dilated fundus examination.

Table 8. Optometric Assessment of a Patient with AMD (Retrieved from 2019 Australian Clinical Practice Guide)

Clinical test	Notes
History	Screen for new symptoms suggestive of AMD (see Table 4). Establish risk factors (see Table 1), including family history of AMD, smoking history and status, as well as documentation of nutritional supplement use and driving status.
Visual acuity	Monocular best-corrected visual acuity. Include near monocular visual acuity.
Fundus examination	Dilated fundus exam (DFE), including stereoscopic biomicroscopic evaluation of the macula, is recommended at least annually for those exhibiting signs or symptoms of AMD. Careful consideration of a patient's risk profile (see Table 1 and Table 3) should also help determine if the patient requires a DFE.
Amsler grid	Presentation of the grid at 30cm leads to a retinal projection of 20°, with each square representing a 1° angle.[41] It has been shown that white lines on the black background is more sensitive and reliable than the white background.[41]
Contrast sensitivity	Some patients can have symptoms of poor vision, but good visual acuity; contrast sensitivity provides additional useful information.[41]
Photostress test	The photostress test assesses retinal function, so macular disease will cause a prolonged photostress recovery time, even in early stages of AMD.[41]

- The following ocular imaging tools are recommended for use by optometrists, if available:

Table 9. Recommended Ocular Imaging of a Patient with AMD (Retrieved from 2019 Australian Clinical Practice Guide)

Colour fundus photography (CFP)	CFP is often used for monitoring drusen number, size, presence of pigmentary abnormalities and signs of late disease (CNV and GA); however, may be limited by low contrast.
Optical Coherence Tomography (OCT)	OCT is one the most valuable imaging tools for the detection and management of AMD.[38] It is often used for the detection of signs of active neovascular AMD (such as retinal fluid), and can also be used for monitoring drusen and pigment. Advances in OCT have also enhanced our ability to detect structural retinal and RPE changes that may precede the development of late AMD[43] and vision loss, such as reticular pseudodrusen[39], hyper-reflective foci[43] and nascent geographic atrophy.[44] Refined phenotyping of macular atrophy is also possible.[38] See the 'Prognostic biomarkers' section for more detail.

Table 10. Advanced Ocular Imaging of a Patient with AMD (Retrieved from 2019 Australian Clinical Practice Guide)

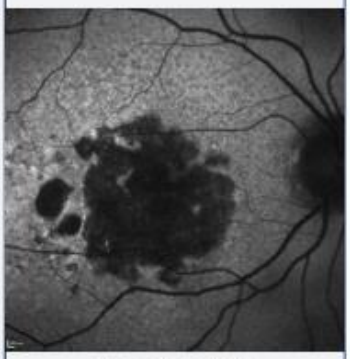
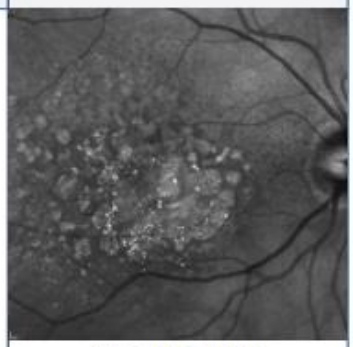
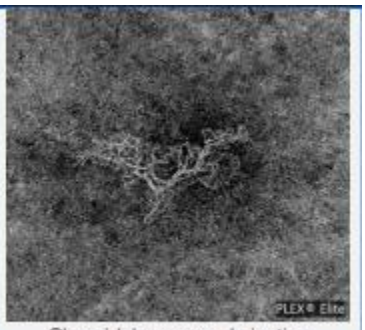
Fundus autofluorescence (FAF)	Fundus autofluorescence (FAF) can show areas of increased lipofuscin accumulation, such as cells in oxidative stress or in drusen (as hyper-fluorescent), and areas where the RPE cells have died (hypo-fluorescent).[46] A simplified interpretation is that atrophic areas of a retina will appear dark on an AF image, whilst the areas surrounding the lesion (junctional zones) will sometimes appear bright, as a sign of an unhealthy RPE.[47] The FAF pattern is also likely to be altered in intermediate and neovascular AMD and its pattern is associated with different rates of growth of GA. Increased background FAF in non-drusenoid location is a strong indicator of inherited retinal disease rather than AMD. **Key indications:** FAF provides better demarcation of areas of GA than a photo,[48, 49] so is commonly used to measure the size and extent of atrophic lesions. Reticular pseudodrusen are more easily seen on FAF than in colour photography.	 Geographic atrophy
Near Infrared Imaging (NIR)	NIR light will be absorbed by molecules such as haemoglobin and water, meaning that any blood or fluid at the retina will be imaged as a dark area (including the normal retinal vasculature). In contrast, geographic atrophy will appear as a bright patch on the IR image due to reflection off the sclera.[50, 51] **Key indications:** NIR imaging is especially useful for imaging of atrophic lesions (particularly those involving the fovea centre) and reticular pseudodrusen.	 Geographic atrophy

Table continued over page

Table 11. Advanced Ocular Imaging of a Patient with AMD (Continued) (Retrieved from 2019 Australian Clinical Practice Guide)

OCT-angiography (OCT-A)	OCT-A allows imaging of the retinal and superficial choroidal vasculature and blood flow without the need for dye injection.[52] However, OCT-A does not detect vessel leakage, meaning that standard fluorescein angiography still has a place in the diagnostic protocol. **Key indications:** OCT-A is useful for diagnosing choroidal neovascularisation and visualising retinal vascular abnormalities.	 Choroidal neovascularisation

Images kindly provided by Prof. Robyn Guymer, Centre for Eye Research Australia. OCT-A image also courtesy of Prof. Guymer as part of the Zeiss ARI network

- The latest guidance from the authoritative Classification of Atrophy Consensus Group suggests that for the purposes of detecting, measuring, and tracking late-stage AMD (geographic atrophy or GA), the assessment strategy should encompass a combination of techniques, including color fundus photography (CFP), confocal autofluorescence (FAF), confocal near-infrared reflectance (NIR), and high-resolution optical coherence tomography (OCT). This approach is referred to as multimodal imaging (MMI).

Management of early and intermediate AMD

- The primary approach to optometric care for individuals with early and intermediate AMD involves advising on risk factors that can be modified furnishing patients with a home Amsler grid for self-monitoring, and offering guidance on the proper steps to take if there is any alteration in their vision. Optometrists should also contemplate collaborating with a patient's general practitioner, who can offer additional assistance in smoking cessation and offer recommendations concerning diet, lifestyle, and dietary supplements.

Table 12. Evidence-Based Management of Early and Intermediate AMD (Retrieved from 2019 Australian Clinical Practice Guide)

Modifiable factor	Evidence-based management
Smoking	Given the known correlation with smoking status and risk of AMD progression,[20-22] all patients who smoke, chew or consume tobacco should be advised to quit.
Diet and lifestyle	A diet rich in green leafy vegetables, fish and antioxidants should be encouraged.[28] Systemic conditions including hypertension and cardiovascular disease, as well as obesity should be discussed with the patient as risk factors for late AMD.[16]
Nutritional supplements	It has been shown that patients with intermediate AMD (large drusen and/or pigmentary changes) may benefit from certain nutritional supplements.[29, 30] The current recommendation for the supplement ingredients is: – 500 milligrams (mg) of vitamin C – 400 international units of vitamin E – 80 mg zinc as zinc oxide* – 2 mg copper as cupric oxide – 10 mg lutein – 2 mg zeaxanthin Supplements are not currently recommended for patients with normal ageing changes, early AMD, late AMD in both eyes, or for those at risk of AMD without any signs of the disease.[61]

- Patients with early or intermediate AMD do not require referral to an ophthalmologist unless:
    - ✓ There is a significant family history, indicating the possibility of a dominantly inherited condition often mistaken for AMD.
    - ✓ In cases where there are unusual clinical findings, structural or functional abnormalities, or historical factors that warrant a second opinion, particularly in instances of AMD occurring at a young age (under 50 years).
    - ✓ Individuals express a desire to participate in a research study or clinical trial.
- If there are no new macular symptoms, the following is recommended:

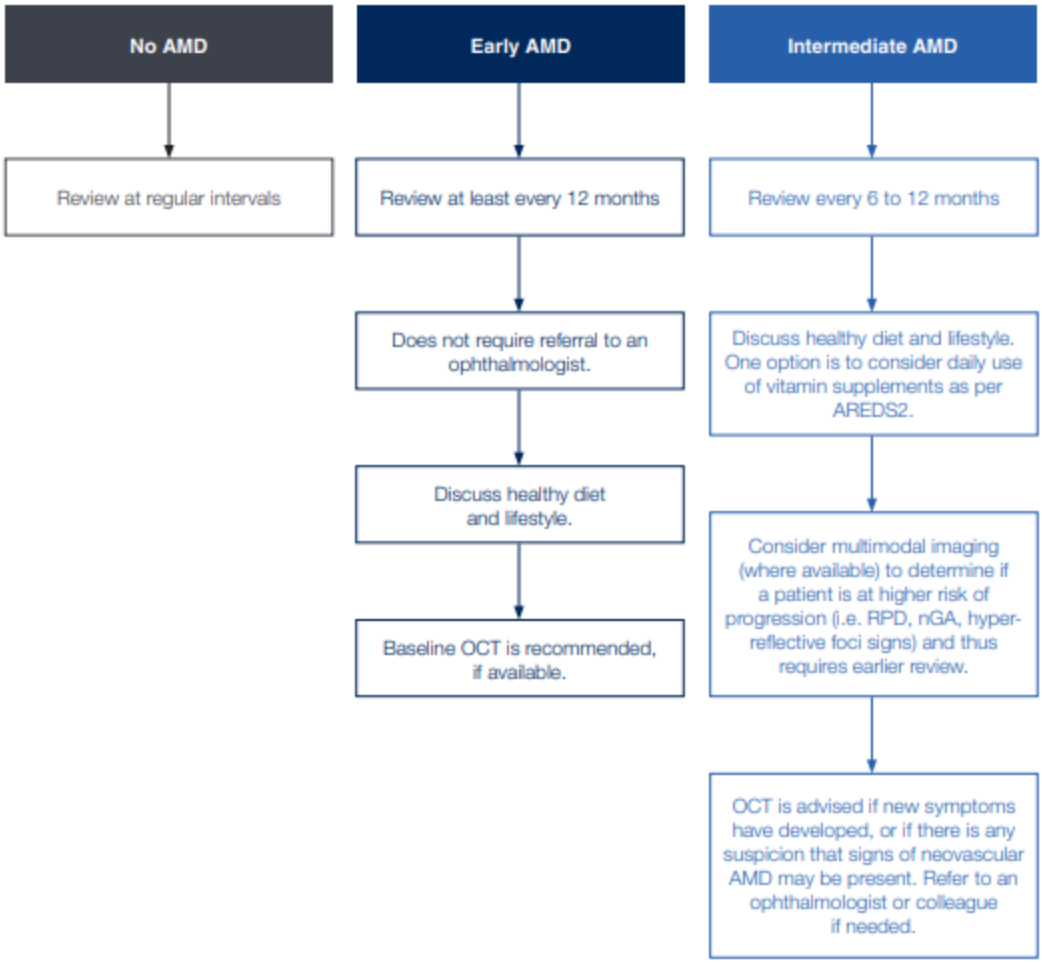


Figure 3. *Referral and Follow-Up for Patients with AMD (Retrieved from 2019 Australian Clinical Practice Guide)*

- For individuals already diagnosed with AMD, it is crucial to stress the significance of consistent self-monitoring using a home Amsler grid during each visit. Patients should be encouraged to seek prompt evaluation if they experience symptoms that could indicate late-stage AMD, such as visual distortion, central blurriness, or a decline in vision.

Geographic atrophy

- At present, there are no treatments approved by regulatory agencies for geographic atrophy. The prevailing approach involves periodic monitoring, typically every six to twelve months, contingent on vision and driving capabilities, as well as the patient's risk of progression. It is highly likely that low vision care will be necessary. Given that geographic atrophy can evolve into neovascular AMD, patients should be educated on the use of the Amsler grid and informed about lifestyle factors that can be modified.

Neovascular AMD (nAMD)

- Optometrists are advised to make an urgent referral to an ophthalmologist within a week if there are suspicions or clear indications of a new-onset choroidal neovascular membrane (CNVM).
- The proposed criteria for an "urgent referral" in cases of neovascular age-related macular degeneration (nAMD) include:
- A recent history (within the past 3 months) of vision decline, self-reported distortion, or the sudden appearance of a missing or blurred area in central vision.
- Any of the following clinical signs: suspected or confirmed new-onset choroidal neovascular membrane (CNVM), presence of macular fluid (either subretinal or intraretinal), or macular hemorrhage when there is no other apparent cause.
- Over the last ten years, the primary approach to treating neovascular age-related macular degeneration (nAMD) has revolved around anti-vascular endothelial growth factor (anti-VEGF) agents. In Australia, the primary medications currently employed for this purpose include ranibizumab (sold as Lucentis) and aflibercept (marketed as Eylea). Bevacizumab (known as Avastin) is also used off-label. These drugs exhibit comparable effectiveness, which makes factors such as drug availability, treatment frequency, and cost significant considerations when selecting the appropriate treatment medication.
- Typically, the initial anti-VEGF treatment begins with a set monthly schedule until there is no evidence of ongoing activity, like the presence of fluid visible on the OCT scan. More recently, tailoring the treatment according to the patient's response has become more common, such as implementing treat-and-extend protocols.
- Under the treat-and-extend approach, the duration between treatments is extended by two weeks on each occasion when there are no indications of active choroidal neovascularization (CNV), such as the presence of fluid on the OCT scan or a decline of 5 letters in visual acuity or the occurrence of new hemorrhaging.
- Visual acuity outcomes in treat and extend are similar to monthly injections.
- Ophthalmologists may also choose to treat on a pro re nata (PRN) basis, monthly or bi-monthly basis, or an “observe and plan” regime, but in general results are not as good as treat and extend or monthly.
- Under the treat-and-extend approach, the duration between treatments is extended by two weeks on each occasion when there are no indications of

active choroidal neovascularization (CNV), such as the presence of fluid on the OCT scan or a decline of 5 letters in visual acuity or the occurrence of new hemorrhaging.

- A strong indicator of long-term visual acuity in neovascular age-related macular degeneration (nAMD) is the initial visual acuity when treatment begins. Individuals who commence treatment earlier have a greater likelihood of preserving or enhancing their vision. This underscores the crucial role that optometrists play in promptly addressing the needs of patients with nAMD.

1.2.2 The Royal College of Ophthalmologists: Age Related Macular Degeneration Services (2021)

"The guidance follows the RCOphth guidance development process and is based on best available evidence obtained from systematic review of the literature (see appendix A) and is compliant with the National Institute for Health and Care Excellence (NICE) Clinical Guideline on AMD NG82 dated 23-01-2018."

The following recommendations are retrieved from the royal college of ophthalmologists: Age Related Macular Degeneration Services (2021)[5]

- There are several classification systems that describe the disease progression in AMD. The staging of severity of AMD is important because visual impairment increases with severity of AMD.

Table 13. AMD Classification in NICE Guidance (Retrieved from the RCO 2021 Guidelines)

AMD Classification in NICE Guidance	Definition in NICE Guidance	Frequently Used Terminology
Normal Eyes	No signs of age-related macular degeneration (AMD) Small ('hard') drusen (less than 63 micrometres) only	No AMD
Early AMD	Low risk of progression: • medium drusen (63 micrometres or more and less than 125micrometres) or pigmentary abnormalities Medium risk of progression: • large drusen (125micrometres or more) or • reticular drusen or • medium drusen with pigmentary abnormalities High risk of progression: • large drusen (125 micrometres or more) with pigmentary abnormalities or • reticular drusen with pigmentary abnormalities or • vitelliform lesion without significant visual loss (best-corrected acuity better than 6/18) or • atrophy smaller than 175 micrometres and not involving the fovea	Early AMD or Age-related maculopathy Intermediate AMD
Late AMD (indeterminate)	Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of detectable neovascularisation) Serous pigment epithelial detachment (PED) without neovascularisation	

Table 14. AMD Classification in NICE Guidance (Continued) (Retrieved from the RCO 2021 Guidelines)

AMD Classification in NICE Guidance	Definition in NICE Guidance	Frequently Used Terminology
Late AMD (wet active)	Classic choroidal neovascularisation (CNV) – Type 2 Occult (fibrovascular PED & serous PED with neovascularisation – Type 1 Mixed (predominantly or minimally classic CNV with occult CNV) Retinal angiomatous proliferation (RAP) – Type 3 Polypoidal choroidal vasculopathy (PCV)	Neovascular AMD (nAMD) or wet AMD
Late AMD (dry)	Geographic atrophy (in the absence of neovascular AMD) Significant visual loss (6/18 or worse) associated with: • dense or confluent drusen or • advanced pigmentary changes and/or atrophy or • vitelliform lesion	Advanced dry AMD / Geographic atrophy
Late AMD (wet inactive)	Fibrous scar Sub foveal atrophy or fibrosis secondary to an RPE tear Atrophy (absence or thinning of RPE and/or retina) Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment) NB Eyes may still develop or have a recurrence of late AMD (wet active)	Advanced wet AMD/ Disciform scar
Do not refer to late AMD (wet inactive) as 'dry AMD'.		

The risk factors for AMD are listed in the tables below:

Table 15. Non-Modifiable Risk Factors for the Development and Progression of AMD (Retrieved from the RCO 2021 Guidelines)

Increasing drusen area and volume	Patients with a drusen volume over 0.03 mm3 in the 3mm circle of the macula centred at the fovea has a greater than 4-fold increased risk for developing late AMD compared with those with lower drusen volumes [16,17].
Subretinal Drusenoid Deposits (SDD)	Subretinal Drusenoid Deposits (also known as reticular pseudodrusen) are an independent risk factor for AMD development progression [18,19].
Genetics	Although 52 genetic variants have been identified for AMD, almost 15% of patients with AMD have no risk variants [20,21]. Additionally, no genetic score has been defined to assess risk for AMD [22].
Fellow eye of wet AMD eyes	There is a 10% per year risk of developing wet AMD in the fellow eyes in people with unilateral wet AMD [23,24].

Table 16. Modifiable Risk Factors for the Development and Progression of AMD (Retrieved from the RCO 2021 Guidelines)

Smoking history	Smoking is an established strong modifiable risk factor for AMD [25]. Being a current smoker quadruples the risk of progression to late AMD [26,27]. A synergistic effect has been documented between smoking and genetic factors [28]. Current smokers develop late wet AMD at an average of 5.5 years younger than those who never smoked and 4.4. years younger than past smokers [29]. The risk of AMD goes back to that of a non-smoker wth 10 years of quitting, therefore smoking cessation should be recommended to these patients [30].
Body Mass Index	A higher body mass index (BMI) (>30) increases the risk for progression to advanced AMD (RR 2.35). A wider waist circumference is associated with a two-fold increased risk for progression[31]. There is a direct association with higher BMI leading to higher risk of AMD[32].
Nutrition	A diet low in omega-3 and -6 fatty acids, antioxidant vitamins, carotenoids and minerals are a risk factors for AMD. Adherence to a Mediterranean diet is associated with a 41% reduced risk of incident late AMD. The effect is due to the increased consumption of fruits and diet rich in antioxidants that aid in prevention of AMD[33]. A diet of 200 grams per day of vegetables, fruit two times per day, and fish two times per week is associated with a significantly reduced risk of AMD[34]. The original Age-Related Eye Disease Study (AREDS) showed that supplements containing vitamin C, vitamin E, beta carotene, and zinc reduced the 5-year likelihood of developing late AMD by an estimated 25% in at risk individuals[35]. These individuals were those with bilateral large drusen or fellow eyes with large drusen with late AMD in the first eye. The primary analysis of Age-Related Eye Disease Study 2 (AREDS 2) showed no additional value of adding lutein and Zeaxanthin, omega-3 long-chain polyunsaturated acid or the combination on the progression to advanced AMD or changes in visual acuity compared with placebo. However, secondary exploratory analyses suggest that due to the risk in smokers lutein/zeaxanthin is more appropriate than beta carotene in the AREDS supplementation[36]. These supplements may be obtained over the counter; and is an item not routinely prescribed in primary care (NHS England, *Items which should not be routinely prescribed in primary care: Guidance for CCGs* (2019).
Sunlight exposure	Meta-analysis on the association between sunlight exposure and AMD indicated no relationship between exposure to sunlight and increased risk of AMD[37].

- Most diagnosis can be made by clinical examination, Optical Coherence Tomography (OCT) and Optical coherence tomography –angiography (OCTA).

- In exceptional circumstances, optical coherence tomography (OCT) can serve as the only diagnostic tool for identifying neovascular age-related macular degeneration (nAMD). This might occur under the following conditions:
    - ✓ When access to confirmatory tests like OCT-A or FFA is unavailable, to prevent delays in initiating initial treatment within two weeks of diagnosis.
    - ✓ Due to patient-related factors, such as challenges in obtaining informed consent, allergies to fluorescein dye which contraindicate FFA, or inconclusive results from both OCTA and/or FFA.
- The use of fluorescein angiography (FFA) along with indocyanine green (ICG) is specifically recommended in situations involving inconclusive findings on OCT-A scans, individuals showing only partial or inadequate responses to anti-VEGF therapy, and cases where there may be additional retinal signs that could lead to confusion or misinterpretation.
- Information and guidance regarding smoking cessation services should be accessible to patients through local services.
- It is advisable to maintain a healthy diet, which should include an abundance of fresh fruits, vegetables, eggs, and oily fish. Licensed multivitamin supplements containing the AREDS2 formulation are not available through NHS prescriptions. Patients may choose to purchase these over-the-counter supplements independently. The original AREDS formulation, comprising vitamins C, E, beta-carotene, and zinc, reduced the 5-year risk of late AMD development by approximately 25% in individuals at risk. This includes those with either large drusen in both eyes or large drusen in one eye and late AMD in the other. Nonetheless, additional research is needed to assess its role in early AMD.
- Genetic screening is not advised.
- It is important to evaluate the necessity for low vision aids for individuals who meet the criteria of having low vision at any stage during their medical journey. Low vision is defined as a condition where a person's visual impairment significantly impacts their daily activities and cannot be corrected with glasses or contact lenses.
- Regular OCT monitoring of the unaffected eye should be carried out when the affected eye is undergoing treatment or under observation (as per NICE Quality Standard QS180). There is limited evidence regarding the monitoring of fellow eyes once patients are discharged from the service, and this remains an area that requires further research.

- While patients are in the process of receiving treatment or undergoing monitoring, it is advisable to promote their ongoing visits to their regular optometrist. This practice enables the early detection of any coexisting health issues and the correction of refractive errors.

Early AMD

- Refrain from referring patients to secondary care once the diagnosis of early AMD is confirmed.
- In cases where the diagnosis of early AMD is confirmed within secondary care, patients can be discharged with the recommendation to undergo regular vision assessments with their primary care optometrist. Please note that general ophthalmic services (GOS) provide funding for vision assessments every two years. It is crucial to keep the primary care optometrist informed about the diagnosis and treatment plan to facilitate better referrals and reduce the likelihood of unnecessary re-referrals.
- Self-monitoring using the Amsler chart is a commonly recommended practice but exhibits low sensitivity. Patients should report any signs of distortion, abrupt vision loss, or scotoma within their central visual field. However, it's important to recognize that the diagnostic accuracy of the Amsler chart or self-reported changes in visual function is inferior to OCT screening. The implementation of routine OCT monitoring would necessitate additional infrastructure and resources but offers the most precise monitoring method.
- Subthreshold nanosecond laser or any other forms of laser is not recommended for early AMD.

Late dry AMD (Geographic Atrophy)

- If patients with late dry AMD develop nAMD (wet active), they should be treated as late nAMD (wet active) unless there is no potential for visual improvement.
- Depending on the visual acuity of both eyes, it is advisable to explore options like refraction, low vision aids, or considering the potential impact on driving eligibility according to DVLA standards.
- Ophthalmic nursing support, well-trained healthcare professionals (HCPs), and services provided by Eye Clinic Liaison Officers (ECLO) are strongly recommended due to their vital role in offering support, educational resources, and facilitating appropriate referrals to multidisciplinary teams (MDT) or third-sector organizations for these patients.

- Optometrists and Dispensing Opticians practicing in primary care settings can also offer these support services if they are commissioned to do so.
- Substantial support is available from third-sector organizations, addressing both visual and psychological challenges faced by individuals coping with this condition, including those experiencing Charles Bonnet Syndrome.
- In some cases, patients may transition from secondary care to local optometrists for routine vision tests and self-management.
- Patients with late dry AMD may have the option to participate in clinical research involving new treatments, conducted within the hospital eye service (HES). There is a critical need for clinical research to explore novel therapies for late dry AMD. Clinical trials must adhere to established procedures and local policies.

Pharmacological management of nAMD (late wet active AMD)

- The currently available anti-VEGF agents are ranibizumab, aflibercept, brolucizumab and bevacizumab. Ranibizumab, aflibercept and brolucizumab are licensed for this indication and recommended by NICE. Bevacizumab is not licensed for this indication and its off-label use requires pre-requisites to be met.
- Ranibizumab became the inaugural licensed anti-VEGF medication for the treatment of neovascular age-related macular degeneration (nAMD), gaining approval from NICE in 2008. Initially, the recommended treatment regimen followed a pro-re-nata (PRN) approach, where treatment commenced with a loading dose comprising three injections. Subsequent treatment decisions were guided by monthly assessments of visual acuity and anatomical characteristics through OCT scans. Although clinical trials demonstrated the effectiveness of this approach, it posed a considerable capacity challenge, which most ophthalmic units were unable to meet. Real-world data indicated that clinical outcomes fell significantly below expectations.
- Subsequently, the recommended treatment regimens for each drug have evolved, with the preferred approach now focusing on achieving optimal visual improvements while managing capacity demands effectively. This approach is commonly known as "treat and extend."
- In the case of ranibizumab, the treat and extend approach suggests extending treatment intervals by two weeks when the macula remains stable. For aflibercept, the most recent treatment regimen recommends a minimum treatment interval in the first year, set at 8 weeks following three initial loading doses. Subsequently, extensions can be made at two- or four-week intervals, with a maximum extension period of sixteen weeks if stability is

maintained. There has been discussion about the potential additional efficacy of aflibercept due to its enhanced binding affinity for VEGF and the possibility of added benefits from targeting placental growth factor. These distinctions in potential treatment regimens may reflect biochemical variations between the two agents, although direct head-to-head data comparing them is limited, and recent findings suggest less disparity between the two agents.

- Bevacizumab is commonly used internationally, though not within the UK, as an off-label choice for treating late active wet AMD. It's important to note that bevacizumab does not hold any ophthalmic-specific licensing. Cost savings are realized by dividing a full vial of this drug, originally intended for intravenous administration in the treatment of colorectal cancer. Clinical trials have provided comparative data against ranibizumab but not aflibercept. These trials have indicated that equivalent effectiveness can be achieved either through monthly dosing or by following a treat-and-extend regimen, provided that monthly monitoring is maintained. Some studies have shown that a greater number of injections are needed with bevacizumab compared to ranibizumab when using an individualized regimen. This increased injection frequency places a greater treatment burden and, consequently, greater treatment risk on individual patients and adds to the capacity challenges faced by intravitreal services as a whole.
- As of the development of this guidance, brolucizumab has recently become available in the UK market. The outcomes of significant clinical trials have indicated that brolucizumab exhibits superior anatomical effectiveness when compared to aflibercept. Furthermore, brolucizumab has shown comparable visual acuity improvements compared to aflibercept, with data spanning 96 weeks revealing that 39-45% of patients can maintain a treatment interval of 12 weeks (as per NICE TA672). However, it is essential to note that additional evidence from clinical trials and real-world usage is necessary to confirm any potential advantages fully.
- vPDT serves as a treatment alternative for patients with polypoidal choroidal vasculopathy (PCV) who do not exhibit a positive response to anti-VEGF therapy.
- There is no substantiated evidence supporting the efficacy of any form of photo biomodulation utilizing various wavelengths for any stages of AMD. Additionally, there is no proof of the advantages of employing lasers to make drusen disappear or to address subfoveal choroidal neovascularization. The role of radiotherapy in treating nAMD has limited supporting evidence at this point. We are currently awaiting the results of the STAR study, which aims to assess the impact of stereotactic radiotherapy on reducing the necessity for pro re nata ranibizumab injections during the initial 24 months.

- Ensure that treatment is provided within a maximum of 2 weeks from the date of referral, adhering to the AMD service's audit standard. In cases where the better-seeing eye is affected, immediate treatment on the same day of diagnosis is a viable option.
- Compliance with minimum standards is essential, including the recording of visual acuity using ETDRS letters and the use of OCT for diagnosing and treating patients. Treatment is recommended for patients with a visual acuity of 6/96 (logMAR 1.20, 25 ETDRS letters) or worse. For patients with advanced disease, a specialist assessment is necessary to determine the extent of structural damage and potential treatment benefits, particularly if the patient maintains excellent vision in the unaffected eye and is unlikely to experience functional improvements. In cases where visual acuity is worse than 6/96, treatment may be considered only if it is the patient's sole functional or better-seeing eye.
- Commence anti-VEGF therapy with a mandatory loading dose administered monthly for a total of 3 injections.
- Patients have the option to choose among anti-VEGF medications, including aflibercept, ranibizumab, or brolucizumab, as their first-line therapy.
- It is advisable to reassess the diagnosis because very few patients with active wet AMD exhibit no response to anti-VEGF therapy. This reevaluation may necessitate additional imaging through FFA and/or ICG angiography where applicable.
- Inadequate therapy due to protocol deviations is the most common reason for non-response, making it crucial to strictly adhere to a re-loading followed by a treat-and-extend protocol to prevent further vision loss. Implementing fail-safe administrative processes is essential to monitor patients with poor compliance due to co-existing health conditions.
- When patients experience allergies or presumed tachyphylaxis, switching to another anti-VEGF agent is recommended. In a minority of cases, a patient may need to revert to the previous agent or transition to a different one if their condition worsens following the initial switch. There are practical considerations for such regimen changes; for instance, it may be more convenient to switch to a fixed treatment schedule rather than adhering to a treat-and-extend protocol for some individuals to enhance treatment compliance.
- As new treatments become available, it is worthwhile to assess their effectiveness based on improved visual or anatomical outcomes or a reduction in treatment burden. Agents with a lower treatment burden are

particularly beneficial for patients with co-existing conditions that may affect compliance and are also valuable in ensuring timely delivery of care services.

- In certain cases, eyes may present with submacular hemorrhage and exhibit poor visual acuity. According to current evidence, it is advisable to initiate anti-VEGF therapy on a monthly basis until the hemorrhage improves or it is determined that treatment is futile. In such instances, an FFA/ICG examination is recommended because PCV is more prone to bleeding when compared to active CNV.
- Referring the patient to a vitreo-retinal team is advised, as they can explore the possibility of pneumatic displacement and/or the use of recombinant tissue plasminogen activator (tPA). Some patients may also find benefit in undergoing a vitrectomy procedure involving subretinal tPA and air tamponade.
- Polypoidal choroidal vasculopathy (PCV) can manifest in various locations within the fundus. When PCV occurs near the optic disc (peripapillary PCV), it has the potential to lead to fluid accumulation in the macular region, resulting in visual impairment. Additionally, PCV may also manifest directly in the macular area, often accompanied by visual impairment. In cases where PCV affects the macula and leads to fluid accumulation, initiating anti-VEGF monotherapy is recommended as the first-line treatment. If there is an inadequate response to anti-VEGF therapy, photodynamic therapy (PDT) may be considered as an alternative treatment option.
- Retinal Pigment Epithelium (RPE) rips can develop in patients with significant pigment epithelial detachments either at the initial diagnosis or at any stage during their treatment course. They may also occur in untreated eyes as a result of the natural progression of the condition. In such cases, the administration of intravitreal injections should be maintained unless there is an RPE rip involving the fovea with no potential for visual acuity improvement, as determined by the treating clinician's judgment.

Complications

- The likelihood of endophthalmitis following anti-VEGF therapy is estimated to be around 0.02-0.09% based on data from randomized controlled trials, while real-world evidence from extensive patient groups indicates a risk of 0.028%. This risk per individual grows as the number of injections increases.
- The precautions to avoid endophthalmitis include use of topical Povidone Iodine 5% pre-injection as the most effective step, supported by the use of surgical hand disinfection with sterile gloves (changed for each injection) and a “no lid touch” technique. The use of a lid speculum and face mask are

mandatory. A sterile drape over the patient's face may also be helpful or a "no-talking" technique whilst the injection is performed. Additionally, there are also injector devices available which may combine the functions of drape, caliper and speculum. Bilateral cases can be treated but separate equipment must be used for each eye and preferably different drug batches. Peri-operative or take-home topical antibiotics are not recommended. Intravitreal injections should be performed in a designated clean room compliant with RCOphth standards.

- There is a risk of ocular hypertension with increasing number of injections. Eyes with ocular hypertension or glaucoma should have controlled (Intraocular pressure) IOP prior to injections. Post injection all patients get an initial spike in IOP, however only a small percentage may get sustained rise in IOP requiring treatment. The initial pressure spike may be reduced to a small degree in higher risk patients with the use of apraclonidine before injection.
- Patients with persistent ocular hypertension should be referred to the glaucoma team for further management.
- Routine IOP testing post injection is not recommended but annual IOP monitoring is required to identify sustained IOP rise from repeated injections.
- In cases of Central Retinal Artery Occlusion (CRAO), immediate care such as anterior chamber paracentesis, acetazolamide and digital massage is indicated if there is a potential for vision improvement as determined by the clinician.
- For people being monitored for late AMD (wet active), both eyes should be assessed at their monitoring appointments.
- Patients diagnosed with AMD should receive guidance from a trained healthcare provider concerning the available strategies. None of the methods for monitoring visual function at home are presently sensitive enough to detect disease recurrences, with Optical Coherence Tomography (OCT) being the most sensitive detection tool.
- Patients diagnosed with wet active nAMD should undergo continuous OCT monitoring for both eyes while receiving care at the Hospital Eye Services.
- If OCT scans indicate stability, but there is a decrease in visual acuity or the patient experiences a decline in visual function, consider offering a fundus examination or color photography.
- If OCT findings remain stable, but there is a deterioration in visual acuity or the patient reports a decline in visual function, contemplate performing a Fluorescein Angiography (FFA) to detect any neovascularization that may have gone unnoticed.

- In cases where OCT results indicate macular abnormalities that are unresponsive to treatment, it is advisable to explore alternative diagnoses.
- Patients might find it advantageous to use low vision aids, particularly for reading, and they should be given the opportunity to schedule appointments for low vision aid consultations. Additionally, patients should be informed about the possibility of using electronic devices as low vision aids.

Section 2.0 Drug Therapy in Macular Degeneration

This section comprises four subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been FDA and/or EMA approved, but are not yet SFDA registered.

2.1 Additions

2.1.1 Faricimab

This section includes pertinent information regarding the use of Faricimab (Vabysmo®) for the treatment of **wet age-related macular degeneration (AMD)**[7].

Table 17. Faricimab Drug Information

SCIENTIFIC NAME **Faricimab**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	H35.3
Drug Class	Angiopoietin-2 Inhibitor; Ophthalmic Agent
Drug Sub-class	Vascular endothelial growth factor inhibitor (Anti-VEGF)
ATC Code	S01LA
Pharmacological Class (ASHP)	52:56 - Vascular Endothelial Growth Factor Antagonists

DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravitreal use

Dose (Adult) [DDD]*	**Age-related macular degeneration, neovascular (wet):**
	- Intravitreal: Initial: 6 mg once every 4 weeks (approximately every 28 days) for 4 doses. Subsequent doses are individualized based on visual assessments, and are administered as one of the following regimens:
	  o Every-8-week regimen: 6 mg on weeks 20, 28, 36, and 44
	  o Every-12-week regimen: 6 mg on weeks 24, 36, and 48
	  o Every-16-week regimen: 6 mg on weeks 28 and 44

Maximum Daily Dose Adults*	6 mg once every 4 weeks
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: - CrCl ≥15 mL/minute/1.73 m2: No dosage adjustment necessary. - CrCl <15 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	MD, ST, PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	

MD (Physician Specialty Edit): It can only be obtained with a prescription and must be given by a qualified doctor who is experienced in giving intravitreal injections.	
PA (Prior Authorization): This medication is expensive, needs to be prescribed by a specialized physician and is usually used as second-line therapy if other agents have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used as second like after other agents have failed.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Cataract Most serious: - Ophthalmic events: Cataract, conjunctival hemorrhage, increased intraocular pressure (IOP), intraocular inflammation (including iridocyclitis, iritis, uveitis, vitritis), retinal pigment epithelium tear, and vitreous opacity, Conjunctival hyperemia, corneal abrasion, decreased visual acuity (may be transient), endophthalmitis, ocular hyperemia, rhegmatogenous retinal detachment, retinal hole without detachment, and vitreous hemorrhage. - Thromboembolic events: Arterial thromboembolism, including acute myocardial infarction and cerebrovascular accident.
Drug Interactions*	No interactions of Risk Level A or greater identified.
Special Population	N/A
Pregnancy	Based on the mechanism of action, in utero exposure to faricimab may cause fetal harm. Faricimab is a vascular endothelial growth factor (VEGF)

	inhibitor; VEGF is required to achieve and maintain normal pregnancies. Reproductive considerations: Based on the mechanism of action, faricimab may affect fertility. Patients who may become pregnant should use effective contraception during treatment and for at least 3 months after the last dose of faricimab.
Lactation	It is not known if faricimab is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, rash, pruritus, urticaria, erythema, severe intraocular inflammation) to faricimab or any component of the formulation; ocular or periocular infections; active intraocular inflammation.
Monitoring Requirements	Monitor intraocular pressure (via tonometry) and optic nerve head perfusion immediately following administration; symptoms of endophthalmitis and retinal detachment (eg, eye redness/pain, photophobia, blurred vision, other vision changes).
Precautions	Retinal vasculitis/retinal vascular occlusion: Cases of retinal vasculitis and/or retinal vascular occlusion have been reported with other vascular endothelial growth factor inhibitors (eg, brolucizumab) but not faricimab.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of macular degeneration treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Faricimab.**

Table 18. Faricimab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Faricimab	NICE	06/2022: Faricimab is recommended as an option for treating wet age-related macular degeneration in adults, only if: - the eye has a best-corrected visual acuity between 6/12 and 6/96 - there is no permanent structural damage to the central fovea the lesion size is 12-disc areas or less in greatest linear dimension - there are signs of recent disease progression (for example, blood vessel growth as shown by fluorescein angiography, or recent visual acuity changes) - the company provides faricimab according to the commercial arrangement[8]
	CADTH	08/2022: Vabysmo should only be reimbursed if prescribed by an ophthalmologist with experience managing nAMD and if the cost per administration is not more than the least costly drug covered by the public drug plans for the treatment of nAMD[9]
	HAS	01/2023: Favourable opinion for reimbursement "the treatment of neovascular (wet) retrofoveal age-related macular degeneration (AMD) in adults"[10]
	IQWIG	Not available
	PBAC[11]	**Subfoveal choroidal neovascularisation (CNV)** Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather arrangements. Treatment criteria:

		Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist. Clinical criteria: The condition must be due to age-related macular degeneration (AMD), AND The condition must be diagnosed by optical coherence tomography, OR The condition must be diagnosed by fluorescein angiography, AND Patient must have received non-PBS-subsidised treatment with this drug for this PBS indication prior to 1 January 2023, AND The treatment must be the sole PBS-subsidised therapy for this condition.

Conclusion Statement – Faricimab

Faricimab is recommended as an option for the treatment of age-related macular edema and neovascular (wet) age-related macular degeneration. NICE, CADTH, PBAC and HAS recommend the use of Faricimab under specific conditions. However, no relevant information could be retrieved from IQWIG.

2.1.2 Brolucizumab

This section includes pertinent information regarding the use of Brolucizumab (BEOVU®) in **Age-related macular degeneration, wet (neovascular)**.

Table 19. Brolucizumab Drug Information

SCIENTIFIC NAME **Brolucizumab**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No

PMDA	No
Indication (ICD-10)	H35.3
Drug Class	Antiangiogenic ophthalmic agent, Monoclonal Antibody
Drug Sub-class	Vascular endothelial growth factor inhibitor (Anti-VEGF)
ATC Code	S01LA
Pharmacological Class (ASHP)	52:56 - Vascular Endothelial Growth Factor Antagonists
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravitreal use
Dose (Adult) [DDD]*	**Age-related macular degeneration, neovascular (wet): Intravitreal:** 6 mg once per month (approximately every 25 to 31 days) for 3 months, followed by 6 mg once every 8 to 12 weeks.
Maximum Daily Dose Adults*	6 mg once per month
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: No dosage adjustment necessary Hepatic Impairment: No dosage adjustment necessary
Prescribing edits*	MD, PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): It can only be obtained with a prescription and must be given by a qualified doctor who is experienced in giving intravitreal injections.	
PA (Prior Authorization): This medication is a monoclonal antibody which is expensive, therefore a prior approval should be granted.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	Most common: Immunologic: Antibody development Most serious: Arterial thromboembolism, blindness
Drug Interactions*	There are no known significant interactions
Special Population	N/A
Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, brolucizumab may cause fetal harm if administered to a pregnant female. Reproductive considerations: Evaluate pregnancy status prior to use in females of reproductive potential. Females of reproductive potential should use highly effective contraception (methods with pregnancy rates <1%) during therapy and for ≥1 month following the last brolucizumab dose.
Lactation	It is not known if brolucizumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for ≥1 month following the last brolucizumab dose.
Contraindications	Hypersensitivity (e.g., rash, pruritus, urticaria, erythema, severe intraocular inflammation) to brolucizumab or any component of the formulation; ocular or periocular infections; active intraocular inflammation
Monitoring Requirements	Intraocular pressure (via tonometry) and optic nerve head perfusion immediately following administration; symptoms of endophthalmitis and retinal detachment; symptoms of retinal vasculitis and retinal vascular occlusion

	(especially in patients with intraocular inflammation), vision changes.
Precautions	- Endophthalmitis and retinal detachment - Increased intraocular pressure. - Retinal vasculitis/retinal vascular occlusion Thromboembolic events
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of age-related macular degeneration treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for brolucizumab.**

Table 20. Brolucizumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Brolucizumab	NICE[12]	02/2021: Brolucizumab is recommended as an option for treating wet age-related macular degeneration in adults, only if, in the eye to be treated: - the best-corrected visual acuity is between 6/12 and 6/96 - there is no permanent structural damage to the central fovea - the lesion size is less than or equal to 12 disc areas in greatest linear dimension and - there is recent presumed disease progression (for example, blood vessel growth, as shown by fluorescein angiography, or recent visual acuity changes).
	CADTH[13]	05/2020: The CADTH Canadian Drug Expert Committee (CDEC) recommends that brolucizumab should be reimbursed for the

		treatment of nAMD only if the following conditions are met. - Initiation criteria: Patient is diagnosed with mild-to-moderate nAMD and are treatment naive. - Discontinuation criteria: Brolucizumab should be discontinued if any of the following occurs: 1. reduction in best-corrected visual acuity (BCVA) in the treated eye to less than 15 letters (absolute) on two consecutive visits attributed to AMD in the absence of other pathology. 2. reduction of BCVA of 30 letters or more compared to baseline and/or best recorded level since baseline as this may indicate either poor treatment effect or adverse event or both. 3. evidence of deterioration of the lesion morphology despite treatment over three consecutive visits. - **Prescribing conditions:** 1. Patients should be under the care of an ophthalmologist. 2. The interval between doses should be no less than eight weeks. - **Pricing conditions:** The drug plan cost of treatment with brolucizumab should not exceed the drug plan cost of the least costly treatment reimbursed for nAMD.
	HAS[14]	07/2023: Favorable opinion for reimbursement, in adults, in the treatment of exudative (neovascular, wet) subfoveal age-related macular degeneration (AMD).
	IQWIG[15]	07/2020: No data are available for the assessment of added benefit of brolucizumab in adult patients with neovascular (wet) age-related

		macular degeneration in comparison with the appropriate comparator therapy. An added benefit of brolucizumab is therefore not proven.
	PBAC[16]	**Subfoveal choroidal neovascularisation (CNV)** Treatment Phase: Initial treatment Treatment criteria: Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist. Clinical criteria: The condition must be due to age-related macular degeneration (AMD), AND Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of PBS-subsidised treatment with: 1. Aflibercept and/or 2. Ranibizumab and/or 3. Faricimab, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.

<u>Conclusion Statement – Brolucizumab</u>

Brolucizumab is recommended as an option for the treatment of neovascular wet age-related macular degeneration. NICE, CADTH recommend the use of Brolucizumab (Beovu) under specific conditions. HAS had a favorable opinion for the use of Brolucizumab in the treatment of exudative (neovascular, wet) subfoveal age-related macular degeneration (AMD). However, IQWIG states that Brolucizumab presents no added benefit for the treatment of neovascular (wet) age-related macular degeneration in adults when compared with the appropriate comparator therapy.

2.2 Modifications

No modifications have been made since May 2020.

2.3. Delisting

No drugs were delisted from the SFDA list.

2.4 Other Drugs

Pegcetacoplan intravitreous injection (SYFOVRE)

Approved by FDA on Feb 17, 2023, for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). (Available on SFDA under the Brand name of Empaveli for subcutaneous use for the treatment of Paroxysmal Nocturnal Hemoglobinuria)[17].

Avacincaptad pegol (Izervay)

Approved by the FDA on August 4, 2023, for the treatment of Geographic atrophy (GA) secondary to age-related macular degeneration (AMD)[18].

Section 3.0 Key Recommendations Synthesis

- The main risk factors for the development and progression of AMD include increasing age, northern European ancestry, and genetic factors. Cigarette smoking is considered the most important modifiable risk factor that has been consistently identified in many studies. Therefore, it is highly advisable to encourage AMD patients or those at risk to quit smoking. Currently, routine genetic testing is not advised[3].
- Patients who are taking aspirin as prescribed by their physician should continue with this treatment since there was no association found between the use of aspirin and an increased risk of AMD according to a meta-analysis of 10 studies[3].
- It is recommended to follow a healthy diet, which should include an abundance of fresh fruits, vegetables, eggs, and oily fish[4].
- In clinical settings, Fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) serve as essential diagnostic instruments for detecting recent or recurrent neovascular disease activity and guiding treatment choices[3].
- Counselling on smoking cessation should be offered for patients with AMD[5].

- Anti-vascular endothelial growth factor (VEGF) medications like aflibercept, bevacizumab, and ranibizumab, are considered as the first line and most effective treatment for neovascular AMD[3].
- vPDT can be considered as an alternative treatment option for patients suffering from polypoidal choroidal vasculopathy (PCV) when they do not show a favorable reaction to anti-VEGF therapy[5].
- Subthreshold nanosecond laser or any other forms of laser is not recommended for early AMD[5].
- Patients can select from a range of initial treatment choices, such as aflibercept, ranibizumab, or brolucizumab, when it comes to anti-VEGF medications[5].
- Usually, the initial anti-VEGF treatment starts with a fixed monthly regimen until there are no signs of ongoing activity, like fluid detected on the OCT scan. However, in recent times, customizing the treatment based on the patient's response has gained popularity, including the adoption of treat-and-extend protocols[4].
- Brolucizumab and Faricimab have received recent approval and are now available as choices for treating neovascular wet age-related macular degeneration[3].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Macular Degeneration report** and aims to provide recommendations to aid in the management of Macular Degeneration. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Macular Degeneration. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Macular Degeneration Scope

2020	Changes	2023	Rationale
Section 1.0 Macular Degeneration Clinical Guidelines			
2019 American Academy of Ophthalmology: Age-Related Macular Degeneration Preferred Practice Pattern	Updated	American Academy of Ophthalmology: Age-Related Macular Degeneration Preferred Practice Pattern (March 2022 Update)[3]	• After conducting a meta-analysis of 10 studies, it was determined that there is no indication of an elevated risk of age-related macular degeneration (AMD) associated with the use of aspirin. As a result, individuals who have been advised by a medical professional to take aspirin should adhere to their prescribed regimen. • Patients diagnosed with intermediate or advanced age-related macular degeneration (AMD) should contemplate incorporating antioxidant vitamins and mineral supplements in accordance with the Age-Related Eye Disease Study (AREDS2). However, there is no substantiated data endorsing the utilization of these supplements for individuals with AMD that is less than intermediate in severity. Furthermore, there is no indication of any preventative benefits for family members who do not exhibit signs of AMD. • Fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are valuable diagnostic tools in clinical settings for identifying fresh or recurring

			neovascular disease activity and directing treatment decisions. • In individuals experiencing neovascular age-related macular degeneration (AMD), timely identification and swift treatment lead to enhanced visual results. The primary and most effective approach for managing neovascular AMD is intravitreal injection therapy employing anti-vascular endothelial growth factor (VEGF) medications like aflibercept, bevacizumab, and ranibizumab, serving as the initial treatment choice. Any symptoms hinting at post-injection endophthalmitis or retinal detachment necessitate immediate assessment. • The Comparison of AMD Treatment Trials (CATT) was a clinical trial conducted at multiple centers to evaluate the safety and efficacy of bevacizumab in comparison to ranibizumab, as well as to assess the effectiveness of an individualized dosing schedule (known as "as needed" or PRN) versus monthly injections. After one year of the CATT study, it was concluded that ranibizumab and bevacizumab exhibited similar improvements in visual acuity (VA) when administered on a monthly basis. • Comparable outcomes were observed in the 2-year Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) trial,

			which took place in the United Kingdom. • In a 2018 meta-analysis conducted by Nguyen, which included over 8,000 eyes and compared all three drugs, the findings indicated that bevacizumab and ranibizumab exhibited similar effectiveness in terms of best-corrected visual acuity (BCVA). However, ranibizumab demonstrated a more significant reduction in central macular thickness. Additionally, aflibercept and ranibizumab showed comparable efficacy for both BCVA and central macular thickness. A similar review conducted by Chen in 2015 also yielded parallel results. • The systemic safety information gathered from the CATT and IVAN studies remains inconclusive, and two Cochrane systematic reviews have likewise determined that if there is any variance in safety among these anti-VEGF drugs, it is negligible. (I+, Good quality, Strong recommendation) • In the HAWK and HARRIER phase III clinical trials, recently disclosed findings demonstrated that brolucizumab successfully met its primary objective of achieving noninferiority in terms of best-corrected visual acuity (BCVA) change compared to aflibercept at week 48. Patients receiving brolucizumab experienced more significant reductions in central subfield thickness when compared to those

			receiving aflibercept. Additionally, fewer patients who received brolucizumab exhibited sub-retinal fluid, inter-retinal fluid, and sub-retinal pigment epithelium (RPE) fluid. As a result of these positive results, brolucizumab obtained FDA approval in October 2019. • The TENYA and LUCERNE trials demonstrated that patients receiving faricimab-svoa for neovascular AMD, even with dosing intervals of up to 16 weeks, achieved visual acuity improvements that were not inferior to those of patients receiving aflibercept every 8 weeks. Faricimab-svoa received approval from the US Food and Drug Administration (FDA) on January 28, 2022. Vabysmo (faricimab-svoa) is a humanized bispecific monoclonal antibody designed for intravitreal (IVT) use, acting by simultaneously inhibiting both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). It is indicated for the treatment of patients with neovascular (wet) AMD.
Age-related macular degeneration NICE guideline: Published: 23 January 2018	N/A		
	Missing	2019 Clinical Practice Guide for the diagnosis, treatment and management of	• A diet low in omega 3 fatty acids, vitamins, carotenoid and minerals or high in fat (saturated fats, trans fats and omega-6 fatty acids and lack

		Age-Related Macular Degeneration[4]	of exercise are considered weak risk factors for AMD. • The most current clinical classification scheme for AMD is the Beckman classification. • Patients diagnosed with AMD should undergo a typical thorough optometry assessment, which encompasses a focused medical history, assessment of high-contrast visual acuity, refraction, stereoscopic examination using a slit lamp, and a dilated fundus examination. **Management of early and intermediate AMD** • The primary approach to optometric care for individuals with early and intermediate AMD involves advising on risk factors that can be modified furnishing patients with a home Amsler grid for self-monitoring, and offering guidance on the proper steps to take if there is any alteration in their vision. Optometrists should also contemplate collaborating with a patient's general practitioner, who can offer additional assistance in smoking cessation and offer recommendations concerning diet, lifestyle, and dietary supplements. **Geographic atrophy** • At present, there are no treatments approved by regulatory agencies for geographic atrophy. The prevailing approach involves periodic monitoring, typically every six to twelve months, contingent on vision and

			driving capabilities, as well as the patient's risk of progression. It is highly likely that low vision care will be necessary. Given that geographic atrophy can evolve into neovascular AMD, patients should be educated on the use of the Amsler grid and informed about lifestyle factors that can be modified. **Neovascular AMD (nAMD)** • Over the last ten years, the primary approach to treating neovascular age-related macular degeneration (nAMD) has revolved around anti-vascular endothelial growth factor (anti-VEGF) agents. In Australia, the primary medications currently employed for this purpose include ranibizumab (sold as Lucentis) and aflibercept (marketed as Eylea). Bevacizumab (known as Avastin) is also used off-label. These drugs exhibit comparable effectiveness, which makes factors such as drug availability, treatment frequency, and cost significant considerations when selecting the appropriate treatment medication. • Typically, the initial anti-VEGF treatment begins with a set monthly schedule until there is no evidence of ongoing activity, like the presence of fluid visible on the OCT scan. More recently, tailoring the treatment according to the patient's response has become more common, such

			as implementing treat-and-extend protocols. • Under the treat-and-extend approach, the duration between treatments is extended by two weeks on each occasion when there are no indications of active choroidal neovascularization (CNV), such as the presence of fluid on the OCT scan or a decline of 5 letters in visual acuity or the occurrence of new hemorrhaging. • Visual acuity outcomes in treat and extend are similar to monthly injections. • Ophthalmologists may also choose to treat on a pro re nata (PRN) basis, monthly or bi-monthly basis, or an "observe and plan" regime, but in general results are not as good as treat and extend or monthly. • Under the treat-and-extend approach, the duration between treatments is extended by two weeks on each occasion when there are no indications of active choroidal neovascularization (CNV), such as the presence of fluid on the OCT scan or a decline of 5 letters in visual acuity or the occurrence of new hemorrhaging.
	Missing	The royal college of ophthalmologists: Age Related Macular Degeneration Services (2021)[5]	• There are several classification systems that describe the disease progression in AMD. The staging of severity of AMD is important because visual impairment increases with severity of AMD. • Most diagnosis can be made by clinical examination,

			Optical Coherence Tomography (OCT) and Optical coherence tomography –angiography (OCTA). • In exceptional circumstances, optical coherence tomography (OCT) can serve as the only diagnostic tool for identifying neovascular age-related macular degeneration (nAMD). This might occur under the following conditions: • When access to confirmatory tests like OCT-A or FFA is unavailable, to prevent delays in initiating initial treatment within two weeks of diagnosis. • . • The use of fluorescein angiography (FFA) along with indocyanine green (ICG) is specifically recommended in situations involving inconclusive findings on OCT-A scans, individuals showing only partial or inadequate responses to anti-VEGF therapy, and cases where there may be additional retinal signs that could lead to confusion or misinterpretation. • Information and guidance regarding smoking cessation services should be accessible to patients through local services. • Nutrition and Supplements: It is advisable to maintain a healthy diet, which should include an abundance of fresh fruits, vegetables, eggs, and oily fish. Licensed multivitamin supplements containing the AREDS2 formulation are not available

			through NHS prescriptions. Patients may choose to purchase these over-the-counter supplements independently. The original AREDS formulation, comprising vitamins C, E, beta-carotene, and zinc, reduced the 5-year risk of late AMD development by approximately 25% in individuals at risk. This includes those with either large drusen in both eyes or large drusen in one eye and late AMD in the other. Nonetheless, additional research is needed to assess its role in early AMD. **Early AMD** • Refrain from referring patients to secondary care once the diagnosis of early AMD is confirmed. • Subthreshold nanosecond laser or any other forms of laser is not recommended for early AMD. **Late dry AMD (Geographic Atrophy)** • If patients with late dry AMD develop nAMD (wet active), they should be treated as late nAMD (wet active) unless there is no potential for visual improvement. • Depending on the visual acuity of both eyes, it is advisable to explore options like refraction, low vision aids,

			or considering the potential impact on driving eligibility according to DVLA standards. • In some cases, patients may transition from secondary care to local optometrists for routine vision tests and self-management. **Pharmacological management of nAMD (late wet active AMD)** • The currently available anti-VEGF agents are ranibizumab, aflibercept, brolucizumab and bevacizumab. Ranibizumab, aflibercept and brolucizumab are licensed for this indication and recommended by NICE. Bevacizumab is not licensed for this indication and its off-label use requires pre-requisites to be met. • Ranibizumab became the inaugural licensed anti-VEGF medication for the treatment of neovascular age-related macular degeneration (nAMD), gaining approval from NICE in 2008 • Subsequently, the recommended treatment regimens for each drug have evolved, with the preferred approach now focusing on achieving optimal visual improvements while managing capacity demands effectively. This approach is commonly known as "treat and extend." • In the case of ranibizumab, the treat and extend approach suggests extending treatment intervals by two weeks when the macula remains stable. For aflibercept, the most

			recent treatment regimen recommends a minimum treatment interval in the first year, set at 8 weeks following three initial loading doses. Subsequently, extensions can be made at two- or four-week intervals, with a maximum extension period of sixteen weeks if stability is maintained. There has been discussion about the potential additional efficacy of aflibercept due to its enhanced binding affinity for VEGF and the possibility of added benefits from targeting placental growth factor. These distinctions in potential treatment regimens may reflect biochemical variations between the two agents, although direct head-to-head data comparing them is limited, and recent findings suggest less disparity between the two agents. • Bevacizumab is commonly used internationally, though not within the UK, as an off-label choice for treating late active wet AMD. • As of the development of this guidance, brolucizumab has recently become available in the UK market. The outcomes of significant clinical trials have indicated that brolucizumab exhibits superior anatomical effectiveness when compared to aflibercept. • vPDT serves as a treatment alternative for patients with polypoidal choroidal vasculopathy (PCV) who do not exhibit a positive response to anti-VEGF therapy.

			• There is no substantiated evidence supporting the efficacy of any form of photo biomodulation utilizing various wavelengths for any stages of AMD. Additionally, there is no proof of the advantages of employing lasers to make drusen disappear or to address subfoveal choroidal neovascularization. The role of radiotherapy in treating nAMD has limited supporting evidence at this point. We are currently awaiting the results of the STAR study, which aims to assess the impact of stereotactic radiotherapy on reducing the necessity for pro re nata ranibizumab injections during the initial 24 months. • Ensure that treatment is provided within a maximum of 2 weeks from the date of referral, adhering to the AMD service's audit standard • Commence anti-VEGF therapy with a mandatory loading dose administered monthly for a total of 3 injections. • Patients have the option to choose among anti-VEGF medications, including aflibercept, ranibizumab, or brolucizumab, as their first-line therapy. • It is advisable to reassess the diagnosis because very few patients with active wet AMD exhibit no response to anti-VEGF therapy. This reevaluation may necessitate additional imaging through FFA and/or ICG angiography where applicable. • Inadequate therapy due to protocol deviations is the most

			common reason for non-response, making it crucial to strictly adhere to a re-loading followed by a treat-and-extend protocol to prevent further vision loss. Implementing fail-safe administrative processes is essential to monitor patients with poor compliance due to co-existing health conditions. • When patients experience allergies or presumed tachyphylaxis, switching to another anti-VEGF agent is recommended. In a minority of cases, a patient may need to revert to the previous agent or transition to a different one if their condition worsens following the initial switch. • As new treatments become available, it is worthwhile to assess their effectiveness based on improved visual or anatomical outcomes or a reduction in treatment burden. Agents with a lower treatment burden are particularly beneficial for patients with co-existing conditions that may affect compliance and are also valuable in ensuring timely delivery of care services. • In certain cases, eyes may present with submacular hemorrhage and exhibit poor visual acuity. According to current evidence, it is advisable to initiate anti-VEGF therapy on a monthly basis until the hemorrhage improves or it is determined that treatment is futile. In such instances, an FFA/ICG examination is recommended

			because PCV is more prone to bleeding when compared to active CNV. • Referring the patient to a vitreo-retinal team is advised, as they can explore the possibility of pneumatic displacement and/or the use of recombinant tissue plasminogen activator (tPA). Some patients may also find benefit in undergoing a vitrectomy procedure involving subretinal tPA and air tamponade. • Polypoidal choroidal vasculopathy (PCV) can manifest in various locations within the fundus. When PCV occurs near the optic disc (peripapillary PCV), it has the potential to lead to fluid accumulation in the macular region, resulting in visual impairment. Additionally, PCV may also manifest directly in the macular area, often accompanied by visual impairment. In cases where PCV affects the macula and leads to fluid accumulation, initiating anti-VEGF monotherapy is recommended as the first-line treatment. If there is an inadequate response to anti-VEGF therapy, photodynamic therapy (PDT) may be considered as an alternative treatment option. **Complications** • The precautions to avoid endophthalmitis include use of topical Povidone Iodine 5% pre-injection as the most

			effective step, supported by the use of surgical hand disinfection with sterile gloves (changed for each injection) and a “no lid touch” technique. The use of a lid speculum and face mask are mandatory. A sterile drape over the patient’s face may also be helpful or a “no-talking” technique whilst the injection is performed. Additionally, there are also injector devices available which may combine the functions of drape, caliper and speculum. Bilateral cases can be treated but separate equipment must be used for each eye and preferably different drug batches. Peri-operative or take-home topical antibiotics are not recommended. Intravitreal injections should be performed in a designated clean room compliant with RCOphth standards. • There is a risk of ocular hypertension with increasing number of injections. Eyes with ocular hypertension or glaucoma should have controlled (Intraocular pressure) IOP prior to injections. Post injection all patients get an initial spike in IOP, however only a small percentage may get sustained rise in IOP requiring treatment. The initial pressure spike may be reduced to a small degree in higher risk patients with the use of apraclonidine before injection • Patients with persistent ocular hypertension should be referred to the glaucoma

			team for further management. • . • In cases of Central Retinal Artery Occlusion (CRAO), immediate care such as anterior chamber paracentesis, acetazolamide and digital massage is indicated if there is a potential for vision improvement as determined by the clinician. • Patients diagnosed with AMD should receive guidance from a trained healthcare provider concerning the available strategies. Patients should also be emphasized that none of the methods for monitoring visual function at home are presently sensitive enough to detect disease recurrences, with Optical Coherence Tomography (OCT) being the most sensitive detection tool. • . • If OCT scans indicate stability, but there is a decrease in visual acuity or the patient experiences a decline in visual function, consider offering a fundus examination or color photography. • If OCT findings remain stable, but there is a deterioration in visual acuity or the patient reports a decline in visual function, contemplate performing a Fluorescein Angiography (FFA) to detect any neovascularization that may have gone unnoticed. • Patients might find it advantageous to use low vision aids, particularly for reading, and they should be given the opportunity to schedule appointments for

			low vision aid consultations. Additionally, patients should be informed about the possibility of using electronic devices as low vision aids.

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Macular Degeneration

The following is the result of the PubMed search conducted for macular degeneration guideline search:

Query	Filters	Search Details	Results
((((((((((((((((((Macular Degeneration[MeSH Terms]) OR (Degeneration, Macular[Title/Abstract])) OR (Macular Degenerations[Title/Abstract])) OR (Maculopathy[Title/Abstract])) OR (Maculopathies[Title/Abstract])) OR (Macular Dystrophy[Title/Abstract])) OR (Dystrophy, Macular[Title/Abstract])) OR (Macular Dystrophies[Title/Abstract])) OR (Age-Related Macular Degeneration[Title/Abstract])) OR (Age Related Macular Degeneration[Title/Abstract])) OR (Age-Related Macular Degenerations[Title/Abstract])) OR (Macular Degeneration, Age-Related[Title/Abstract])) OR (Macular Degeneration, Age Related[Title/Abstract])) OR (Maculopathies, Age-Related[Title/Abstract])) OR (Maculopathy, Age-Related[Title/Abstract])) OR (Maculopathy, Age Related[Title/Abstract])	Guideline, in the last 5 years	("macular degeneration"[MeSH Terms] OR "degeneration macular"[Title/Abstract] OR "macular degenerations"[Title/Abstract] OR "Maculopathy"[Title/Abstract] OR "Maculopathies"[Title/Abstract] OR "macular dystrophy"[Title/Abstract] OR "dystrophy macular"[Title/Abstract] OR "macular dystrophies"[Title/Abstract] OR "age related macular degeneration"[Title/Abstract] OR "age related macular degeneration"[Title/Abstract] OR "age related macular degenerations"[Title/Abstract] OR "macular degeneration age related"[Title/Abstract] OR "macular degeneration age related"[Title/Abstract] OR "maculopathies age related"[Title/Abstract] OR "maculopathy age related"[Title/Abstract] OR "maculopathy age related"[Title/Abstract] OR "age related maculopathies"[Title/Abstract] OR "age related maculopathies"[Title/Abst	7

) OR (Age-Related Maculopathies[Title/Abstract])) OR (Age Related Maculopathies[Title/Abstract])) OR (Age-Related Maculopathy[Title/Abstract])) OR (Age Related Maculopathy[Title/Abstract])		ract] OR "age related maculopathy"[Title/Abstract] OR "age related maculopathy"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])	

Appendix D. Treatment Algorithm

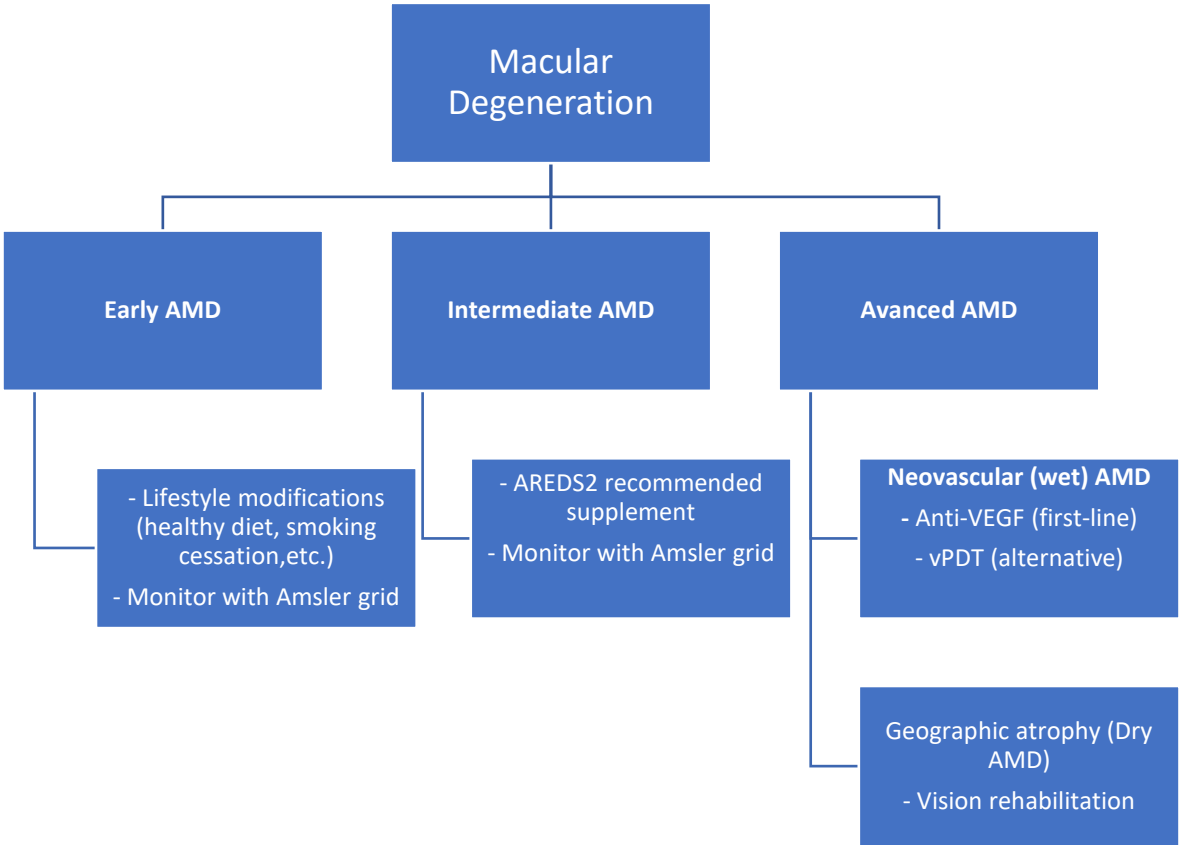

Figure 4. *Treatment Algorithm for the Management of Macular Degeneration*