Clinical Practice Guide for the Diagnosis and Management of Age-related Macular Degeneration

2024

Optometry Australia Age-related Macular Degeneration Clinical Practice Guide - Developed 2019, revised 2024

Optometry AUSTRALIA

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Acknowledgement of Country

Optometry Australia would like to acknowledge the Traditional Custodians across the lands, waters and seas that we work and live on and pay our respects to Elders past and present and thank them for their continuing custodianship.

Optometry Australia acknowledges Māori as tangata whenua and Treaty of Waitangi partners in Aotearoa New Zealand.

We pay our respects to these traditional Custodians and honour their unique cultural and spiritual relationships to the land, waters and seas and their rich and ongoing contribution to society.

Development of this guide

Optometry Australia has updated this Clinical Practice Guide in consultation with an expert working group comprised of 11 experienced practitioners who work extensively in the area of age-related macular degeneration assessment and management.

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We would like to thank all past working group members – Carla Abbott, Sue Kalff, Gary Page, Bill Robertson and Rebecca Tobias (all 2019) - for their enormous contribution to the development of this clinical practice guide.

This Clinical Practice Guide provides evidence-based information about current best practice in the management of age-related macular degeneration. It is a general guide for optometrists and is not a formal treatment or management protocol. See Appendix for further details. Optometry Australia supports the various modes of optometry practice and advises adherence to the Australian Health Practitioner Registration Agency shared Code of Conduct. This guide was originally approved by the Optometry Australia Board of Directors on February 8, 2019 and was revised in February 2024.

Executive summary

Late-stage age-related macular degeneration (AMD) is one of the most common causes of irreversible vision loss in people aged 50 years or older worldwide. In Australia, approximately 1 in 7 people aged 50 years or older have signs of AMD, but not all will progress to significant vision loss.[1]

AMD is a complex, multi-factorial eye disease, with a number of known and suspected risk factors. AMD described in this guideline refers to the retinal phenotype with the hallmark feature of drusen, with or without pigmentary abnormalities, which is associated with progression to geoographic atrophy (GA) and/or macular neovascularisation. AMD has both a significant socioeconomic burden and also a high personal cost for patients with AMD and their caregivers.

This clinical practice guide aims to provide an overview of risk factors, clinical diagnosis (including multimodal imaging and differential diagnoses) and management for optometrists. This includes a discussion on current and emerging AMD therapeutic options, as of early 2024.

A modified Delphi process[2,3] was undertaken to establish recommendations for this age-related macular degeneration (AMD) clinical practice guide (see Appendix for details).

Following this process, the working group has endorsed the following recommendations:
Optometrists should use the Beckman clinical classification system for patients with AMD.
In patients with AMD, optometrists should: • include history-taking, visual acuity measurement, fundus examination and Amsler grid testing in their assessment protocol • screen for new symptoms suggestive of new-onset neovascular AMD and/or other progression during history-taking • document risk factors, including family history of AMD and smoking status and history • document any nutritional supplement use, and advice provided about their use • document driving status
In patients with AMD, the following clinical biomarkers for progression should be considered when determining review timeframes: • presence of large drusen (>125µm) • presence of pigmentary abnormalities • drusen volume – consider the total extent of the drusen in the macular region
Baseline colour fundus photography and/or optical coherence tomography (OCT) should be offered to all patients with AMD, if available.

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Colour fundus photography, OCT and/or fundus autofluorescence imaging is recommended for all patients with late atrophic AMD (geographic atrophy). If not available, patients should be offered a referral to an appropriate practitioner for imaging.
Management for early and intermediate AMD should include counselling for modifiable risk factors, including: • smoking cessation • diet and healthy lifestyle
Patients with AMD should be offered a home Amsler grid for self-monitoring.
Optometrists should counsel patients on the appropriate course of action if they notice a change in their vision.
Optometrists should offer patients a referral to low vision support services as soon as their AMD causes visual impairment.
Patient-centred care is paramount and AMD referral pathways need to be managed to maximise patient access to the practitioner who can provide the most appropriate care.
Patients with early AMD should be reviewed at least annually.
Patients with intermediate AMD should be reviewed 6-12 monthly, depending on risk factors for progression.
Patients with early or intermediate AMD do not require referral to an ophthalmologist, unless they have abnormal structural, functional or historical clinical findings that require a second opinion, including a younger, atypical age of AMD onset (<50 years).
Patients with late AMD (geographic atrophy or non-active neovascular AMD) should be reviewed at least every 6 months.
Patients with symptomatic, new-onset late AMD (neovascular) should be referred to an ophthalmologist urgently (within 1 week).
Patients with asymptomatic AMD (drusen), with macular fluid detected on OCT, should be referred to an ophthalmologist within 2 weeks.
Optometrists should refer patients with geographic atrophy (GA) interested in further advice or considering treatment (when it becomes available in Australia) to an ophthalmologist.
Patients with neovascular AMD (nAMD) should be advised of the typical treatment regime (i.e. anti-VEGF injections) and the importance of adherence to the regime.

Introduction

Late-stage age-related macular degeneration (AMD) is one of the most common causes of irreversible vision loss in people aged 50 years or older worldwide. In Australia, approximately 1 in 7 people aged 50 years or older have signs of AMD, but not all will progress to significant vision loss.[1] This is equivalent to approximately 1.3 million Australians, and is expected to rise to 1.7 million by 2030.[4] Globally, it is expected that the number of people living with AMD will reach 288 million by 2040[5], and it is the cause of over 5% of all cases of legal blindness (over 2 million people).[6]

AMD is a complex, multi-factorial eye disease, with a number of known and suspected risk factors. AMD described in this guideline refers to the retinal phenotype with the hallmark feature of drusen, with or without pigmentary abnormalities, which is associated with progression to GA and/or macular neovascularisation.

AMD has a significant socioeconomic burden. In 2010, the total cost of AMD-related vision loss (including direct and indirect costs) in Australia was estimated at $5.15 billion.[4] Since this time, the utilisation of anti-vascular endothelial growth factor (anti-VEGF) injections has increased dramatically, meaning this value will now likely be higher. Globally, it is estimated that AMD costs over $343 billion, including $255 billion in direct healthcare costs.[7]

In addition, AMD has a high personal cost – including a loss of independence and social interaction[8], decreased quality of life[9], increased risk of falls, and increased levels of depression (up to 1 in 3 people with AMD).[10,11] Caregivers of people with AMD are also at high risk of emotional distress and disruption to their own lives.[12]
It is important that optometrists are competent in assessing patients with or at risk of developing AMD, so that they are able to provide evidence-based management including appropriate communication, diagnosis and referral when indicated. This clinical practice guide aims to provide an overview of risk factors, clinical diagnosis (including multimodal imaging and differential diagnoses) and management. This includes a discussion on current and emerging AMD therapeutic options, as of early 2024.

Risk factors for AMD

The following risk factors make it more likely that a person will either develop AMD and/or progress to late-stage AMD (Table 1). The factors have been divided into those with strong, moderate and weak evidence, as determined by a pivotal systematic review.[13]

Table 1: Risk factors for AMD

Risk factor	Note	Level of evidence
Older age (>60 years)	• The strongest risk factor for AMD.[13,14] • The risk of developing AMD increases more than threefold in patients older than 75 years compared to those aged between 65 and 74 years.[14,15]	Strong
Family history of AMD/genetics	• 34 different loci have been identified.[16,17] • In particular, very strong evidence for risk loci at Complement Factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2) and the HtrA serine peptidase 1 (HTRA1) genes.[18]	Strong
Smoking	• The strongest modifiable risk factor. • Current smoking has been shown to at least double the risk of AMD.[19] • There is a direct correlation between current smoking and the number of cigarettes a person has smoked during their life and their risk of late stage AMD.[20,21] • Smokers, on average, develop age-related macular degeneration 5 to 10 years earlier than non-smokers.[4]	Strong
Hypertension	• Three case control studies have identified a significant association between hypertension and late AMD.[13, 22]	Moderate
Cardiovascular disease	• A history of cardiovascular disease may approximately double the risk of late AMD.[13]	Moderate
BMI of 30kg/m2 or higher	• The Blue Mountains eye study and other major prospective studies have shown that being obese increases the risk of late AMD.[13,23-25]	Moderate

Risk factor	Note	Level of evidence
Poor diet • Low in omega 3 fatty acids, vitamins, carotenoid and minerals[26,27] • High in fat (saturated fats, trans fats)[28]	• There have been a number of studies showing interactions with diet and AMD, particularly from the Age-Related Eye Disease Studies 1 and 2 (AREDS).[29,30] • A diet high in macular carotenoids (zeaxanthin and lutein) and omega-3 long-chain essential fatty acids may be protective.[31] • A 2022 meta-analysis found that higher adherence to the Mediterranean diet (where the major source of fat is monosaturated) is associated with a lower risk of developing AMD and a lower risk of progression to advanced AMD.[32] • A 2014 Melbourne study found that a diet high in fruits, vegetables, chicken, and nuts and a pattern low in red meat seems to be associated with a lower prevalence of advanced AMD.[33]	Weak*
Lack of exercise [34,35]	• A prospective study found that higher doses of vigorous exercise was associated with lower incident risk of AMD.[34]	Weak*

** Although a higher level of evidence is currently lacking, it may be nonetheless prudent for clinicians to advise patients of the potential risk of AMD associated with lifestyle factors, including diet and a lack of exercise.*

Clinical pearls

- The most important three risk factors are age, smoking status, and genetic risk factors.
- A Melbourne-based study found that despite our knowledge of the relationship between diet and smoking with AMD, only one third of a sample of optometry patients had been routinely questioned about smoking status, diet and nutritional supplements.[36]
- Optometrists have a duty of care to raise the issue of smoking as the strongest modifiable risk factor in AMD development and progression.

Clinical classification

Historically, there has been considerable confusion over even basic terms in AMD, thus terminology consistency is important. For example, although the term “age-related maculopathy” (ARM) is sometimes used to describe exaggerated “normal” age-related changes at the macula, the exact distinction between ARM and early AMD varies. Similarly, the term “dry AMD” has been used in reference to presentations varying from drusen only to geographic atrophy, which is problematic as it encompasses distinct disease severities. To avoid confusion, the working group suggests limiting the use of the terms “age-related maculopathy”, “wet” and “dry” AMD in clinical record keeping and professional communications.

Beckman Classification of Age-related Macular Degeneration

The currently recommended clinical classification scheme for AMD is the Beckman classification (*see Table 2*). This scheme arose from the Beckman Initiative for Macular Research Classification Committee, a panel of expert ophthalmologists, a neuro-ophthalmologist and a methodologist.[37] The classifications are determined based on clinical examination (using common ophthalmoscopy equipment, such as an ophthalmoscope or slit lamp with accessory lenses) or evaluation of a fundus photo. Classification is based on fundus lesions within two-disc diameters of the fovea in patients older than 55 years of age. Note also that this is a person-based, rather than eye-based, classification scheme (e.g., an individual with large drusen in one eye and neovascular AMD in the fellow eye is considered as having late AMD).

Recommendation:

- Optometrists should use the Beckman clinical classification system for patients with AMD.

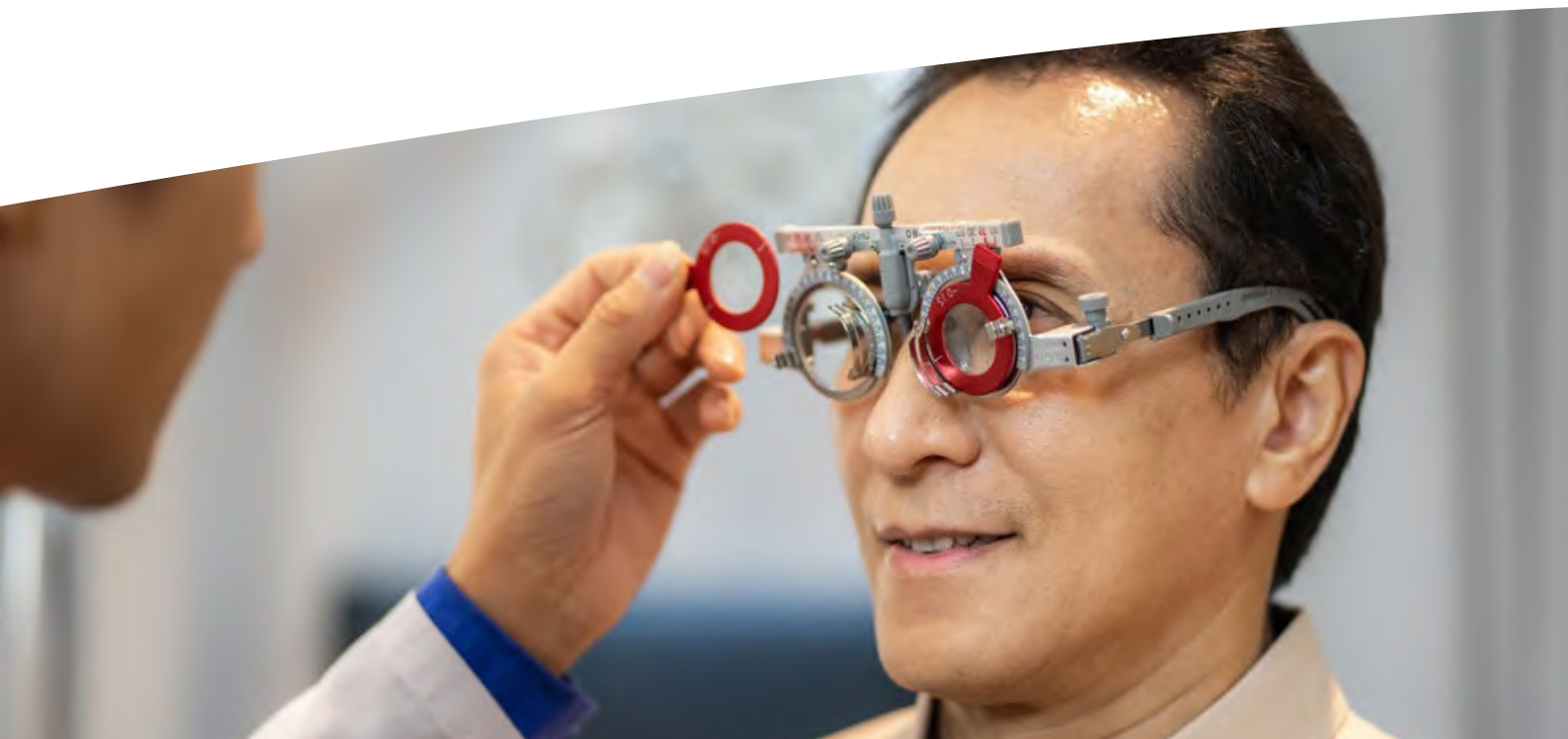


Table 2: Beckmann classification of AMD[37], with corresponding example retinal fundus photos, optical coherence tomography and fundus autofluorescence.

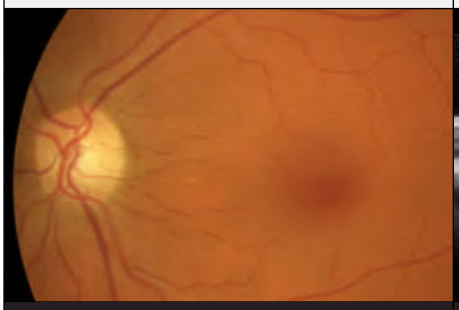
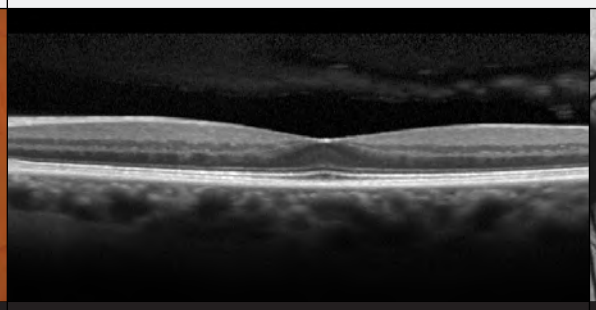
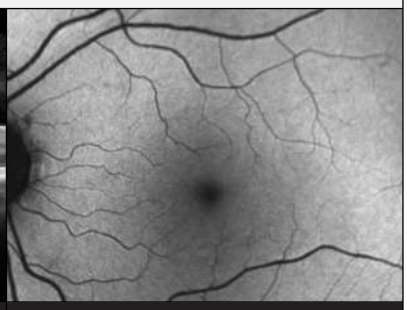
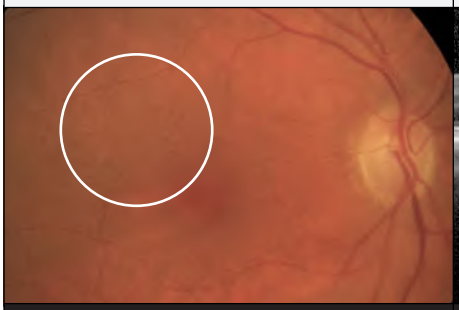
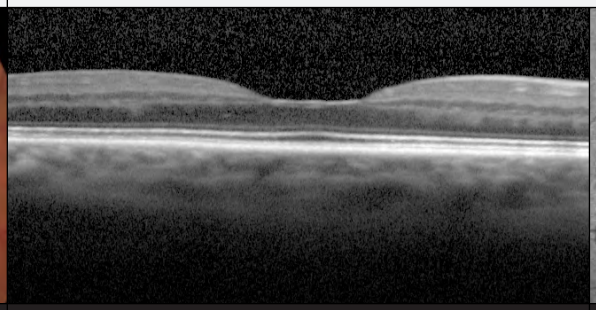
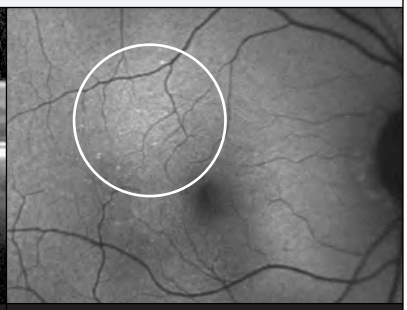
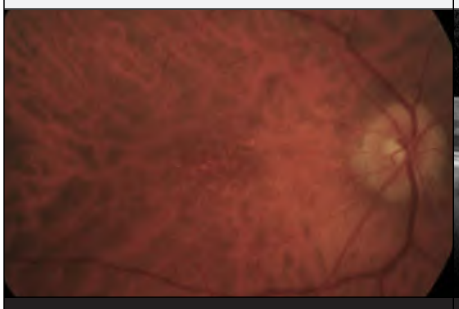
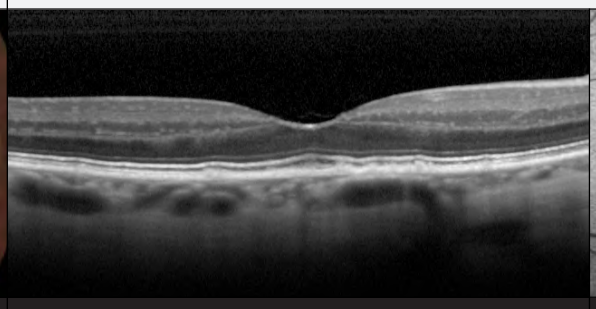
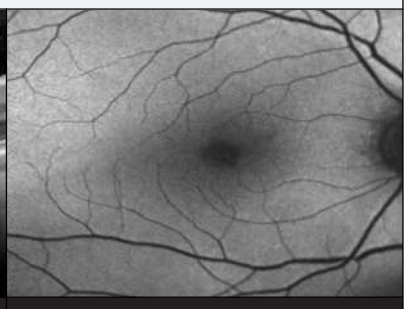
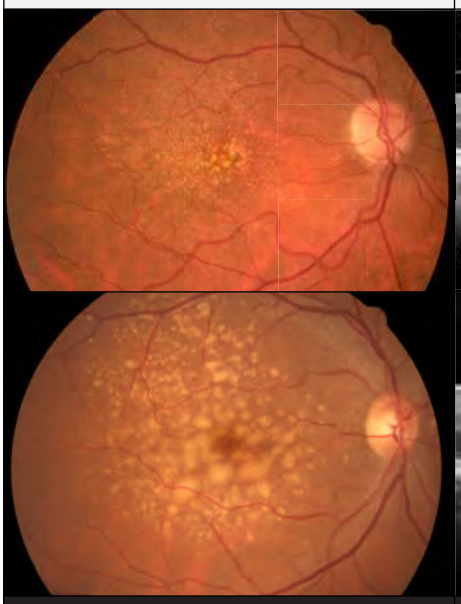
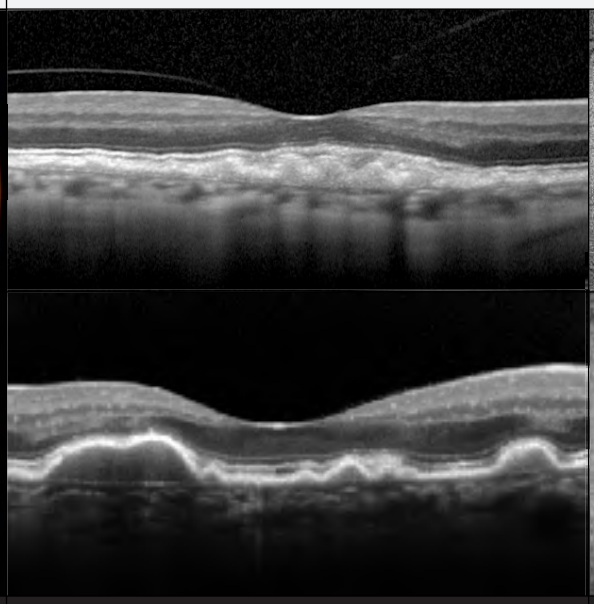
AMD classification	Definition	
No apparent ageing changes	No drusen and no AMD pigmentary abnormalities	
		
Retinal fundus photo	*Optical coherence tomography*	*Fundus autofluorescence*
AMD classification	**Definition**	
Normal ageing changes	Only drupelets (small drusen ≤63µm) and no AMD pigmentary abnormalities	
		
Retinal fundus photo	*Optical coherence tomography*	*Fundus autofluorescence*
AMD classification	**Definition**	
Early AMD	Medium drusen (>63µm and ≤125µm) and no AMD pigmentary abnormalities	
		
Retinal fundus photo	*Optical coherence tomography*	*Fundus autofluorescence*

Table 2: Beckmann classification of AMD[37], with corresponding example retinal fundus photos, optical coherence tomography and fundus autofluorescence.

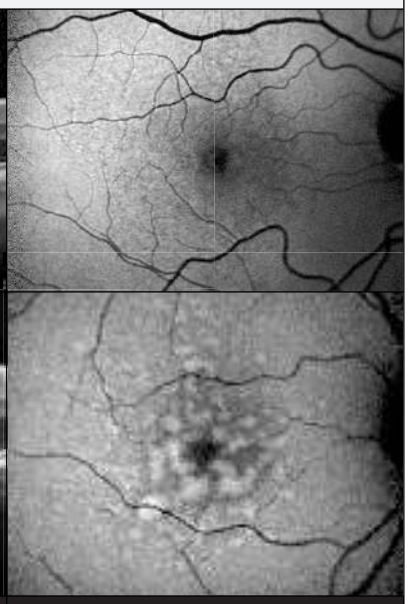
AMD classification	Definition
Intermediate AMD	Large drusen (>125µm), or any AMD pigmentary abnormalities (associated with medium or large drusen >63µm)



Retinal fundus photo

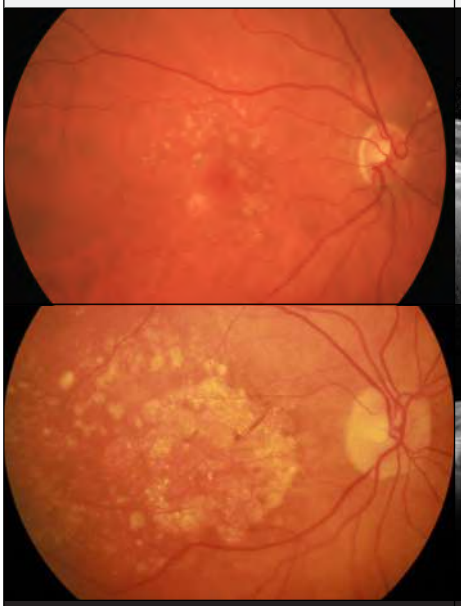


Optical coherence tomography

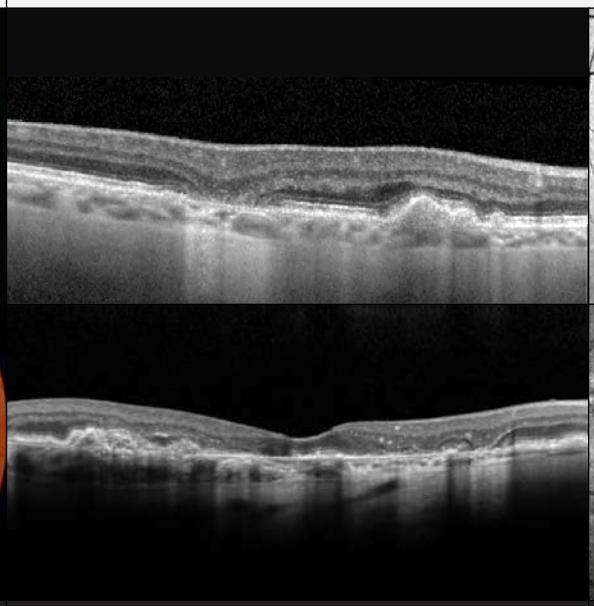


Fundus autofluorescence

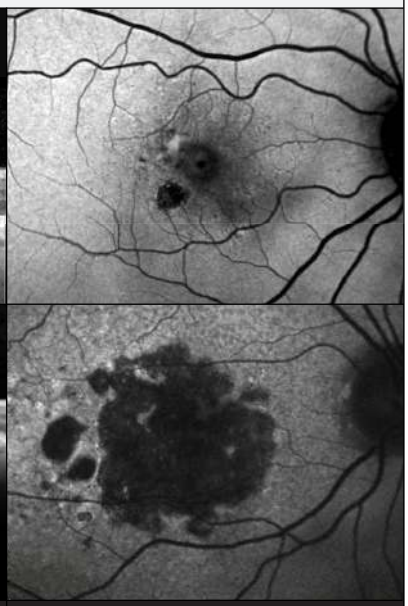
AMD classification	Definition
Late AMD	Geographic atrophy (GA): sharply demarcated area of RPE hypopigmentation with increased visibility of the underlying choroidal vessels in an area at least 175µm in diameter[38]



Retinal fundus photo



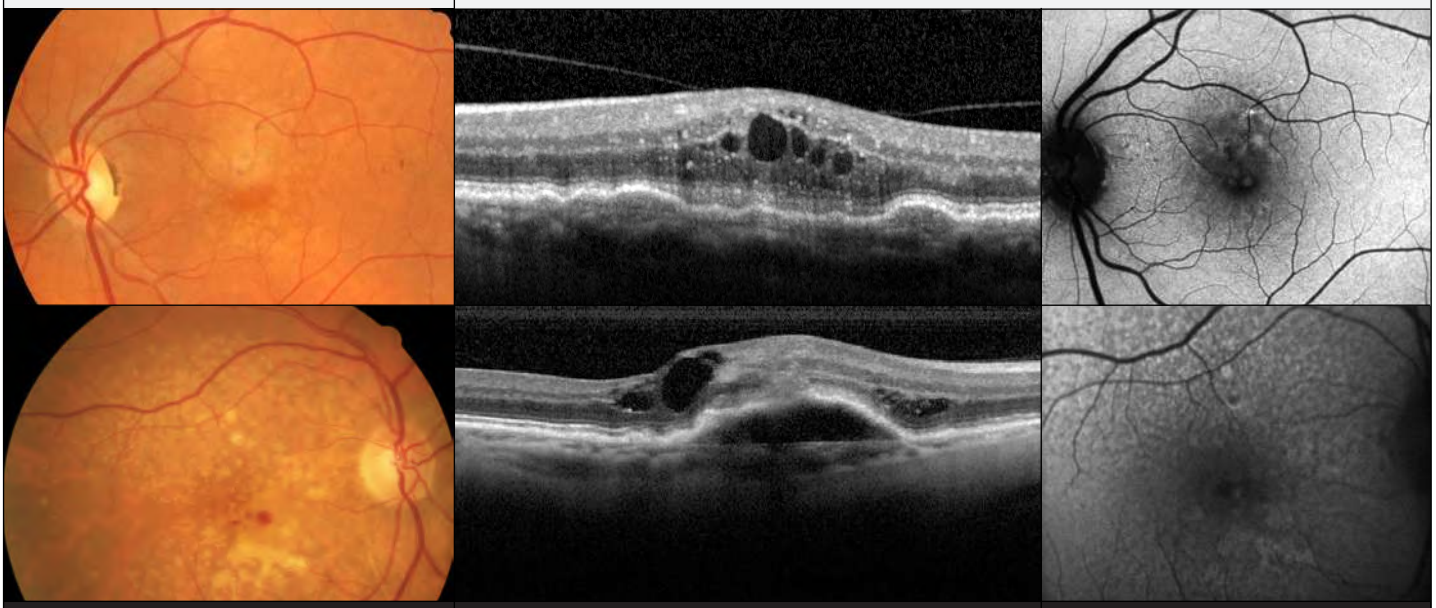
Optical coherence tomography



Fundus autofluorescence

Table 2: Beckmann classification of AMD [37], with corresponding example retinal fundus photos, optical coherence tomography and fundus autofluorescence.

AMD classification	Definition
Late AMD	Neovascular AMD (nAMD): presence of neovascularisation – blood (macular haemorrhage), subretinal fluid, intraretinal fluid, serous pigment epithelium detachments, lipid (hard exudates), subretinal hyper-reflective material (SHRM).[38]



Retinal fundus photo	*Optical coherence tomography*	*Fundus autofluorescence*

NB. These are examples of what each stage could look like; AMD may manifest and present differently. Please refer to Chair-side reference: Age-related Macular Degeneration, Centre for Eye Health for more detail on what to look for on various imaging modalities.

Images kindly provided by Prof. Robyn Guymer, Centre for Eye Research Australia

The Beckman classification scheme was designed to reflect the fact that risk profiles can be linked to the clinical signs of drusen and pigmentary abnormalities (*see Table 3*). AMD pigmentary abnormalities are defined as any hyper-pigmentary or hypo-pigmentary abnormalities associated with medium or large drusen, but not associated with other known disease entities (e.g., inherited retinal degenerations).

In early AMD (medium drusen only), people have a 0.9% chance of progressing to late AMD within 5 years.[37,39] However, once a person has intermediate AMD, this risk increases to 20.5%,[37] although the variation in this severity can range widely. For instance, a person with only large drusen in one eye has a 3.9% risk of developing late AMD, whilst a person with large drusen and pigmentary abnormalities in both eyes has a risk of 47.3%.[37]

A simplified risk stratification system can be used, based on the number of risk factors present across both eyes, as described in Table 3.[37]

Table 3: Five-year risk of progression to late AMD[39]

Risk factors	Risk of progression for patients without late AMD in either eye at baseline*^
0	0.5%
1	3%
2	12%
3	25%
4	50%

* Assign one risk factor:

- for each eye with large drusen
- for each eye with pigmentary abnormalities associated with medium drusen
- if neither eye has large drusen and both eyes have medium drusen (early AMD)

^ These values also provide a reasonable estimate of the risk of progression to late AMD in the fellow eyes of patients with late AMD in one eye by assigning two risk factors for the eye that has late AMD. Assign an additional risk factor if the eye at risk (i.e., without late AMD) has large drusen and/or an additional risk factor if the eye at risk has pigmentary abnormalities associated with medium drusen.

Whilst this simplified risk stratification is useful, it is helpful to note that the total amount of drusen present (e.g., drusen area or volume) is also strongly associated with progression to late AMD.[40,41] This means for example that an individual with extensive, very large drusen in both eyes (two risk factors) may have a much higher risk of progression than an individual with a single large druse in both eyes (two risk factors as well), and should be monitored more regularly.

Until a simple-to-implement method for risk stratification based on drusen extent is well-established (e.g., based on automated segmentation of drusen area on colour fundus photographs or drusen volume on OCT imaging as an input into a risk calculator), clinical judgment is required when considering this important prognostic factor.

Clinical Pearls

- The average width of the central retinal vein at the optic disc margin is 125µm, so drusen larger than this are considered large drusen. Medium drusen are between half and one-full width of the vein (63µm - 125µm), and small drusen are less than half the vein width (<63µm).[37,39]
- The presence of large drusen is a risk factor for developing late stage AMD.[14]
- The presence of pigmentary abnormalities means a higher risk of developing late stage disease.[37,39,42]
- Increasing drusen extent in eyes with large drusen is independently associated with an increased risk of late AMD development.[43]

Recommendations:

In patients with AMD, the following clinical biomarkers for progression should be considered when determining review timeframes:

- presence of large drusen (>125µm)
- presence of pigmentary abnormalities
- drusen volume – consider the total extent of the drusen in the macular region

Classification of Neovascular AMD

It is important to note that the terminology around neovascular AMD has recently changed. Given our better understanding of the disease process, it has now been proposed that the term “macular neovascularisation” be used instead of “choroidal neovascularisation” for this late form of AMD. This is to recognise that neovascularisation does not necessarily originate from the choroid. [44]

There are now three sub-types of macular neovascularisation (MNV) recognised by the global “Classification of Macular Neovascularization Group”[44]:

1. Type 1 MNV: ingrowth of blood vessels from the choriocapillaris into and within the sub-RPE space. This type of MNV leads to the development of pigment epithelial detachments (PEDs). Polypoidal choroidal vasculopathy (PCV) is an important subclassification of Type 1 MNV, which is characterised by aneurysmal dilations called polyps. PCV is more common in people of Asian descent (20 – 60% with nAMD), compared to Caucasian descent (8 – 13% of nAMD).[45]

2. Type 2 MNV: ingrowth of blood vessels begins in the choroid, traverses the RPE, and then proliferates in the subretinal space.

3. Type 3 MNV: neovascularisation begins within the retinal circulation, especially the deep capillary plexus, and then grows towards the outer retina. This is also known as a retinal angiomatous proliferation (RAP) lesion.[46]

Classification of Atrophic AMD

Traditionally, the term “geographic atrophy (GA)” is used to define the late-stage atrophic form of AMD. GA is characterised by the loss of RPE cells and accompanied by degeneration of the overlying photoreceptors. GA can be seen clinically or on colour fundus photographs as a sharply demarcated area of RPE hypopigmentation with increased visibility of the underlying choroidal vessels of at least 175µm in diameter.

GA can be particularly well visualised by short-wavelength fundus autofluorescence (FAF) imaging, since the RPE loss associated with GA appear more clearly as regions of hypoautofluorescence (i.e., dark patches on this imaging modality). This is because the signal from short-wavelength FAF imaging arises primarily from fluorophores accumulated in the RPE.[47]

On OCT imaging, GA lesions correspond with regions of choroidal signal hypertransmission and RPE disruption and loss (the former occurring as a result of the latter), with accompanying evidence of overlying photoreceptor degeneration.[48]

Subsidence of the outer plexiform layer (OPL) and inner nuclear layer (INL), and/or presence of a hyporeflective wedge-shaped band, are features seen in regions of well-established GA and also appear to be distinctive OCT features that portend GA development.[49,50] These features have been termed “nascent geographic atrophy” (nGA; Figure 1), and they have been reported to be a high-risk factor for GA development[51,52], including being associated with a >180-fold increased rate of developing GA in a recent five-year longitudinal study.[53]

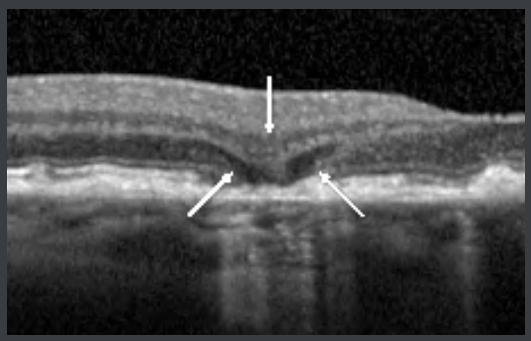


Figure 1:
Nascent Geographic Atrophy (nGA)
Vertical arrow indicates the region of outer plexiform layer (OPL) and inner nuclear layer (INL) subsidence, and diagonal arrows indicate the hyporeflective wedge-shaped bands. Note that the presence of either of these two features is sufficient to define the presence of nGA.

There is an ongoing international effort to derive a refined classification of end-stage atrophy and its precursor on OCT imaging. Previous work led to the development of a classification system that was intended to provide common nomenclature to unify the field moving forward.[54-56] Terms including incomplete RPE and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA) were proposed. However, the reports for such work stressed the need for future longitudinal studies to validate the implied risk of the proposed classification,[54,55] and such current work is ongoing to enable further refinements to this classification system.

Common signs and symptoms

Table 4: Common signs and symptoms of AMD

Stage of disease	Clinical symptoms	Clinical funduscopic signs
Early	• Often asymptomatic, but can be increasingly symptomatic with increasing drusen volume under the fovea • May have reduced contrast sensitivity and difficulties with dark adaptation[57] e.g. difficulties reading in dim light or adjusting from different lighting conditions • May in some cases be associated with impairment of driving performance[58]	Medium drusen (>63µm and ≤125µm) without AMD pigmentary abnormalities
Intermediate		Large drusen (>125µm) and/or AMD pigmentary abnormalities associated with medium 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 reading, watching television, going downstairs, or recognising people • Some people with late AMD and poor vision in both eyes will develop visual hallucinations in Charles Bonnet syndrome.[59] This can be distressing to patients, who will often require counselling. Support is available through the Charles Bonnet Syndrome Association - **www.charlesbonnetsyndrome.org** • Note that the development of late atrophic or neovascular AMD can both be asymptomatic, especially if such changes develop outside of the fovea. Both forms of late AMD can also be sudden in onset and associated with new symptoms, especially when pathological changes develop at the fovea.	Area of RPE loss, forming a well-demarcated lesion of at least 175µm in diameter, with increased visibility of the underlying choroidal vessels[60]
Late: neovascular		Macular neovascularisation (MNV) 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, or subretinal hyper-reflective material (SHRM)

Optometric assessment

Standard examination

A standard comprehensive optometry examination (including targeted history, high-contrast visual acuity, refraction, stereoscopic slit lamp examination and dilated fundus examination) should be performed. Table 5 provides more detail on some of these tests:

Table 5: Optometric assessment of a patient with AMD

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.
Fundus examination	Dilated fundus exam (DFE), including stereoscopic biomicroscopic evaluation of the macula, is recommended at least annually for those exhibiting signs of AMD.
Amsler grid	Presentation of the grid at 30cm leads to a retinal projection of 20°, with each square representing a 1° angle.[61] It has been shown that white lines on the black background is more sensitive and reliable than the black lines on the white background.[61] The sensitivity and specificity of the Amsler grid to diagnose neovascular AMD is only moderate in at-risk patients, so patients should be encouraged to attend regular eye examinations, regardless of the results of their Amsler grid self-assessment.[62]

Recommendations:

In patients with AMD, optometrists should:

- include history-taking, visual acuity measurement, fundus examination and Amsler grid testing in their assessment protocol
- screen for new symptoms suggestive of new-onset neovascular AMD and/or other progression during history-taking
- document risk factors, including family history of AMD and smoking status and history
- document any nutritional supplement use, and advice provided about their use
- document driving status

It is not expected that all the above recommendations will need to be addressed at every visit. Optometrists should tailor their examination to the individual patient.

Recommended ocular imaging

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

Table 6: Recommended ocular imaging of a patient with AMD

Colour Fundus Photography (CFP)	**Key indications:** CFP is often used for monitoring drusen number, size, presence of pigmentary abnormalities and signs of late disease (MNV and GA); however, may be limited by low contrast, especially in the presence of imaging artifacts with small pupils, and/or ocular media opacities.
Optical Coherence Tomography (OCT)	**Key indications:** same as with CFP, but invaluable for identifying signs of late neovascular AMD (such as retinal fluid) or early signs of atrophic AMD (such as nascent geographic atrophy [nGA]) not seen on CFP. Can also be used for improved three-dimensional visualisation of drusen extent.
Fundus Autofluorescence (FAF)	**Key indications:** FAF provides better demarcation of areas of GA than CFPs[63,64], so it is especially useful for measuring the size and extent of atrophic lesions.

If you do not have access to these above imaging tools, consider referral to a colleague or ophthalmologist with access to such tools, to enable a more comprehensive assessment and reliable monitoring of AMD over time.

If possible, it is important to establish if a patient has already had imaging performed and determine whether it is also needed at your practice. For example, if a patient is under the continuing care of an ophthalmologist for their GA, they are unlikely to need repeat imaging with their optometrist.

Recommendations:

- Baseline colour fundus photography and/or OCT should be offered to all patients with AMD, if available.
- Colour fundus photography, OCT and/or fundus autofluorescence imaging is recommended for all patients with late atrophic AMD (GA). If not available, patients should be offered a referral to an appropriate practitioner for imaging.

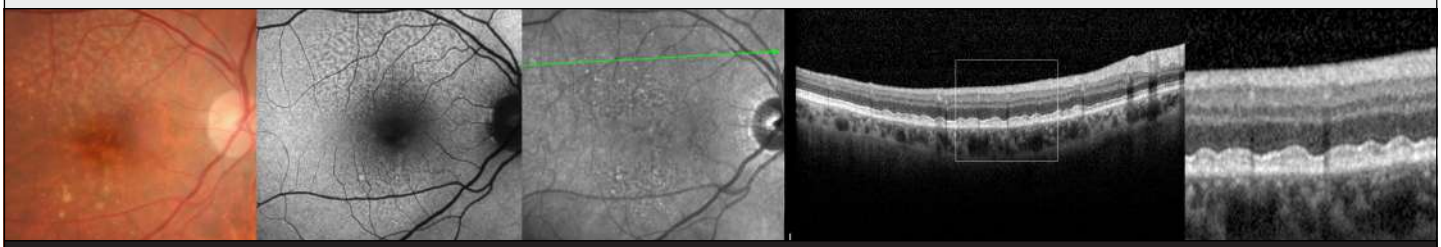
Imaging biomarkers

In addition to drusen and pigmentary abnormalities, there are several imaging biomarkers seen in the early stages of AMD. Further research will need to be conducted before we can clearly establish some aspects of their clinical significance, but the following biomarkers are noteworthy (*Table 7*).

Table 7: Imaging biomarkers seen in the early stages of AMD

Reticular pseudodrusen

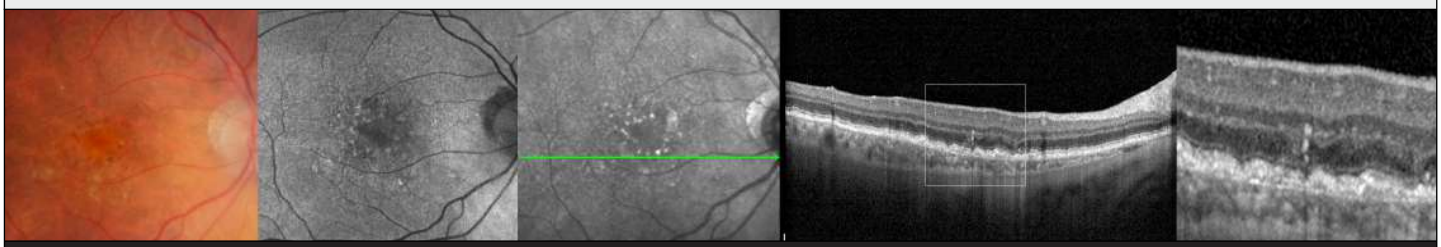
Reticular pseudodrusen (RPD): distinctive subretinal drusenoid deposits, localised above the RPE (unlike drusen, which are localised below the RPE) and can be distinguished using OCT imaging. Missed in approximately half to three quarters of eyes on colour fundus photographs,[41] and are associated with impairments in dark adaptation.[65,66] Also associated with an increased risk of progression to late AMD when present in the fellow eyes of those with unilateral neovascular AMD,[67] but evidence is equivocal for those with non-late AMD (e.g., intermediate AMD).[41]



Case figures (CFP, FAF, NIR, OCT) illustrating the appearance of RPD. *Images kindly provided by Angelica Ly, Centre for Eye Health*

Hyper-reflective foci

Hyper-reflective foci (HRF): focal, discrete, and well-circumscribed material on, or above, the RPE. Often spatially corresponds to regions with hyperpigmentary abnormalities on colour fundus photographs, but not always (and may thus be of non-RPE origin).[68,69] Regions with hyperpigmentary abnormalities also do not always show evidence of HRF.[68] Current evidence indicates that considering HRF that do not correspond with hyperpigmentary abnormalities does not improve the prediction of late AMD development than considering hyperpigmentary abnormalities alone.[69]



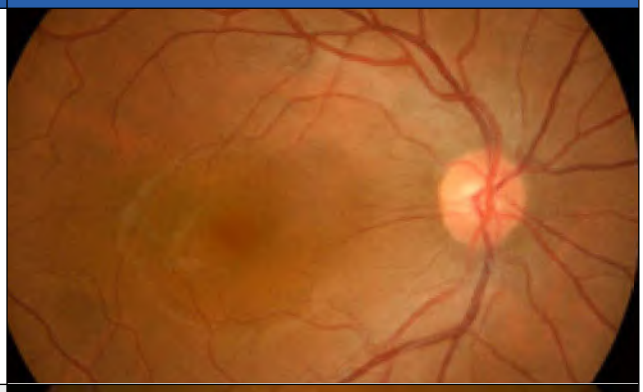
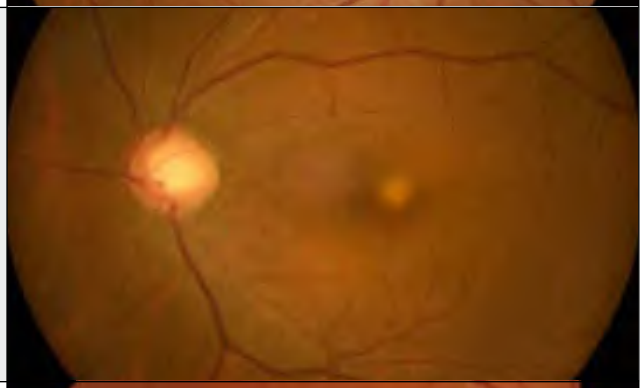
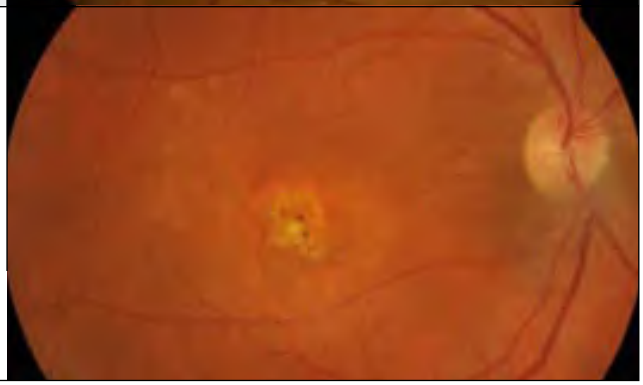
Case figures (CFP, FAF, NIR, OCT) illustrating the appearance of HRF. *Images kindly provided by Angelica Ly, Centre for Eye Health*

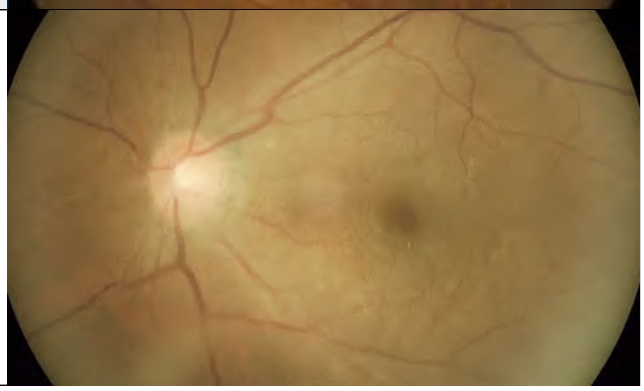
Differential diagnoses

As the cardinal sign of AMD is drusen, it is possible for rarer drusen-associated retinal conditions to be misdiagnosed as AMD. Differences in drusen appearance (size and distribution), strong family history and patient age remain the key distinguishing factors in these other drusen-associated diseases.

In addition, conditions which present with central serous retinal detachments (such as central serous chorioretinopathy, adult-onset vitelliform dystrophy and Best disease) can be mistaken for AMD (*Table 8*).

Table 8: Differential diagnosis of age-related macular degeneration

Disease	Image
Chronic central serous chorioretinopathy (CSCR)[70] A serous detachment of the neurosensory retina occurs over an area of leakage from the choriocapillaris. It most often occurs in young and middle-aged adults, and in men more often than women. Vision loss is usually temporary and acute, but in chronic CSCR the impact and signs can be longer lasting. CSCR has been linked to the use of corticosteroids, pregnancy, hypertension, Cushing's syndrome, sleep apnoea and to patients with emotional distress and/or "Type A" personalities.	
Adult-onset vitelliform dystrophy[70] Similar features to Best disease, but a later onset age (usually mid-adulthood). It is characterised by a solitary, oval, slightly elevated yellowish subretinal lesion of the fovea typically spanning one third of a disc diameter in size that is similar in appearance to the vitelliform or egg-yolk stage of Best disease. Prognosis is more optimistic than for Best disease, with most patients retaining useful central vision throughout life.	
Best disease[71] Also known as Best vitelliform dystrophy, Best disease is a hereditary condition. Patients will often present in childhood or early adulthood with central vision loss and a characteristic bilateral yellow "egg-yolk" appearance of the macula. The stage of the disease dictates the clinical appearance, which may progress through: vitelliform, pseudohypopyon, vitelliruptive (see image) and atrophic stages.	

Disease	Image
Stargardt's disease / Fundus flavimaculatus[72] Stargardt's disease is the most common inherited macular dystrophy which typically presents with foveal atrophy surrounded by discrete, pale-yellow, fleck-like or round retinal deposits in childhood.	
Familial dominant drusen[73] The drusen have a radial and symmetrical appearance, and present very early in life (usually by the third decade via autosomal dominant inheritance although expressivity varies).	
Epiretinal membrane (ERM)[74] ERM is an acquired formation of a semitransparent fibrocellular membrane at the macular and often occurs after a posterior vitreous detachment, or secondary to retinal detachment surgery or a retinal break.	

Images kindly provided by Meri Galoyan, Centre for Eye Health

Several conditions should be considered as a differential diagnosis to neovascular AMD. In these, macular neovascularisation can form, but they will not typically present with related drusen. Examples include polypoidal choroidal vasculopathy, ocular histoplasmosis syndrome[75], pathologic myopia[76], choroidal rupture[76], angioid streaks[76] and idiopathic choroidal neovascularisation. Diabetic macular oedema may be another differential diagnosis to consider when macular haemorrhage, lipid, exudate, sub- or intra-retinal fluid are detected at the macula.

Please refer to the Chair-side references - **Macular Dystrophies** and **Pachychoroid disease spectrum** - from the Centre for Eye Health for some differential diagnoses and what to look for on various imaging modalities.

Management of early and intermediate AMD

Modifiable risk factors

The mainstay of optometric management for early and intermediate AMD is counselling on modifiable risk factors (*see Table 9 below*), especially smoking cessation, providing a home Amsler grid for self-monitoring and counselling on the appropriate course of action if the patient notices a change in their vision.

It is essential that optometrists make it clear to patients that modifiable risk factors, such as smoking, should be addressed to reduce the risk of disease progression. Optometrists should also liaise with a patient's general practitioner who can provide additional support to quit smoking and advice regarding diet, lifestyle and nutritional supplements.

Counselling from an optometrist usually includes providing information about the risk factor and its impact on the potential progression of AMD. If needed, a referral to an appropriate health practitioner may also be offered, for example, if the patient wishes to pursue smoking cessation with pharmacotherapy. The Optometry Australia **lifestyle medicine for optometry** clinical note can be accessed for further information and guidance.

Optometrists also have an essential role in ensuring that patients are aware of the importance of regular eye examinations, whether that be in primary eyecare (optometry) or with their specialist (ophthalmology).

Table 9: Recommended management of early and intermediate AMD

Modifiable factor	Evidence-based management
Smoking	Given the known correlation with smoking status and risk of AMD progression[19-21], all patients who smoke, chew or consume tobacco should be strongly advised by optometrists to quit.
Diet and lifestyle	A diet rich in green leafy vegetables, fish and antioxidants should be encouraged.[27] Systemic conditions including hypertension and cardiovascular disease, as well as obesity should be discussed with the patient as risk factors for late AMD.[13]

Recommendations:

Management for early and intermediate AMD should include counselling for modifiable risk factors, including:

- smoking cessation
- diet and healthy lifestyle

Recent high-level evidence from a Cochrane review suggests that there is moderate-certainty evidence that antioxidant vitamin and mineral supplementation may slow down progression to late AMD[77]. However, the National Institute for Health and Care Excellence (NICE) guidelines[78] specifically state that it is not possible to conclude whether the benefits of nutritional supplements outweigh the risks, as the guideline development committee was sceptical about the treatment effects reported in relevant studies assessed. Instead, the NICE guideline made a research recommendation that a large randomised-controlled trial was needed to provide further evidence.

For this reason, it is suggested that optometrists consider best-evidence and assess each patient individually before deciding whether to recommend nutritional supplements. In particular, supplements are not currently recommended for patients with no macular changes, normal ageing changes, early AMD, late AMD in both eyes, or for those at risk of AMD without any signs of the disease[79].

Patients with intermediate AMD have a higher chance of benefitting from antioxidant supplements.[29,30,77]
The current Age Related Eye Disease Study 2 (AREDS2) formula 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

** This dosage of zinc exceeds the upper level of intake guidelines for Australia and New Zealand.[80]*

Because of the potential adverse effects of various components of antioxidant supplements, it is recommended that their use be discussed in conjunction with the patient's general practitioner.[81]

Referrals

Patients with any stage of AMD can be encouraged to access patient support services, such as those offered by the Macular Disease Foundation Australia (MDFA). MDFA provides patient-tailored resources on their website, as well as free patient support services, including a referral service, peer support programs and a **national helpline** (**1800 111 709**).

Referral to low vision services should be suggested as soon as AMD causes visual impairment. Vision 2020 Australia has produced an **Adult Referral Pathway for Blindness and Vision Services**, including a service provider resource.

Additionally, there are natural history studies and clinical research trials into the early and intermediate stages of AMD. Interested patients can be referred to their local research organisation, who is working in this space.

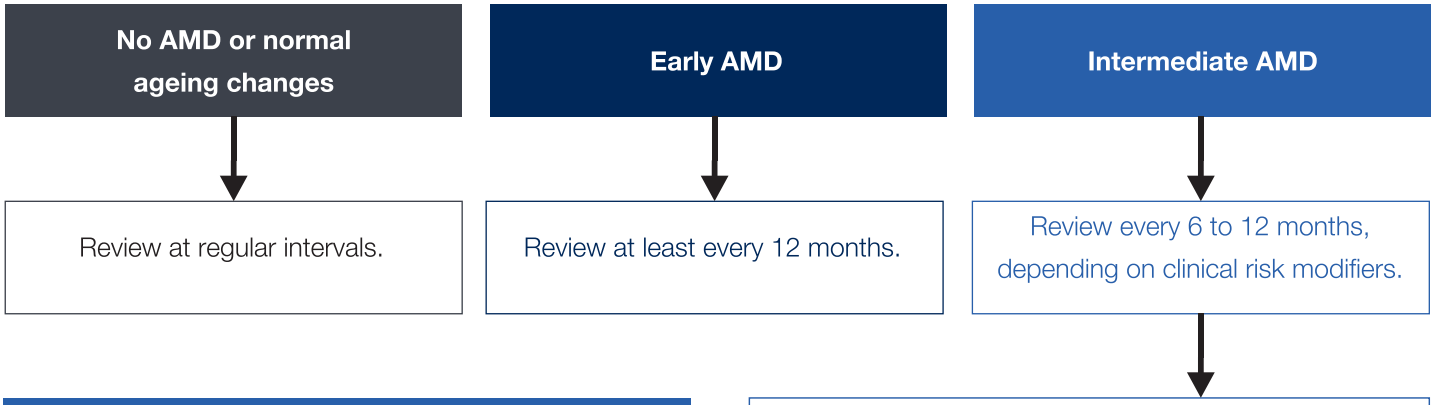
Patients with early or intermediate AMD do not generally require referral to an ophthalmologist[82] UNLESS they have several signs that could indicate an inherited retinal disease (IRD), rather than AMD. These include:

- a family history of IRD
- a young age for AMD (<50years)
- atypically symmetrical presentation between the two eyes
- overall background hyper-autofluorescence in a FAF image

If an IRD is suspected, referral to an ophthalmologist is required for diagnosis, including genetic testing. Family planning and counselling on the likelihood of affected family members is particularly important in IRDs. Additionally, there are emerging treatments available for some forms of IRD.

Management pathways

The following management pathways are recommended for patients with stable early or intermediate AMD:



General advice:

- Discuss healthy diet and lifestyle.
- Baseline CFP and/or OCT should be offered, if available.
- Does not generally require a referral to an ophthalmologist.
- Note that macular nutritional supplements are **NOT** recommended for patients with no macular changes, normal ageing changes, early AMD, late AMD in both eyes, or for those at risk of AMD without any signs of the disease.

- Clinical risk modifiers such as the presence of large drusen, AMD pigmentary abnormalities, and larger drusen extent (area or volume) all increase the risk of progression to late AMD, and should be considered in management (i.e. more regular review).
- Ensure continues to meet driving standards.
- Instruct on home monitoring (Amsler grid).
- Reinforce symptoms of nAMD, and need for immediate review if they emerge.
- If patient <50 years, consider referral to ophthalmologist to rule out DDx.

For those with established AMD, it is important to emphasise the importance of vigilant self-monitoring with a home Amsler grid at each visit. The patient should be advised to present for immediate review if symptoms suggestive of late AMD develop e.g. visual distortion, central blur or loss of vision.

Recommendations:

- Patient-centred care is paramount and AMD referral pathways need to be managed to maximise patient access to the practitioner who can provide the care that is required.
- Patients with AMD should be offered a home Amsler grid for self-monitoring.
- Optometrists should counsel patients on the appropriate course of action if they notice a change in their vision.
- Optometrists should offer patients a referral to low vision support services as soon as their AMD causes visual impairment.
- Patients with early AMD should be reviewed at least annually.
- Patients with intermediate AMD should be reviewed 6-12 monthly, depending on risk factors for progression.
- Patients with early or intermediate AMD do not require referral to an ophthalmologist, unless they have abnormal structural, functional or historical clinical findings that require a second opinion, including a younger, atypical age of AMD onset (<50 years).

As primary eyecare practitioners, optometrists play a key role in managing patient referrals and reviews. Some practitioners, including those working in remote or rural locations, or those offering aged and home-care services, will need to adapt the recommended pathways to suit local circumstances.

Management of late AMD

Optometrists are not expected to make treatment decisions for late AMD. Timely referral to an ophthalmologist, as per the below guidelines, is essential for patients who may need or want to access treatments.

Geographic atrophy

Currently, there are no regulatory-approved treatments for geographic atrophy, and the standard of care is monitoring **every six months** depending on vision/driving status and the individual's risk of progression. Low vision care is most likely indicated. Geographic atrophy can progress to neovascular AMD, so patients should be instructed on Amsler grid use, modifiable lifestyle factors and advised to return for immediate review if new symptoms suggestive of neovascular AMD develop.

However, this conservative management protocol is likely to change in the near future. Several emerging therapeutics are showing real promise in this space[83], and it is possible that there will be regulatory-approved treatments to consider in the next few years.

Most trials for GA therapeutics target the complement pathway, which is known to be involved in AMD pathogenesis. Two complement modifying drugs, pegcetacoplan (Syfovre; Apellis) and avacincaptad pegol (Izervay; Iveric Bio) have been approved by the United States regulatory body. As of February 2024, neither of these drugs have been approved by the Therapeutics Goods of Australia, and several treatments continue to be trialled.

For a more thorough recent update on GA treatments, refer to the 2021 Current Opinions in Ophthalmology review by Mahmoudzadeh et al.[84]

Even when an effective treatment for slowing GA progression is approved, the indications for whom treatments are warranted will need to be established. However, crucial factors to this consideration will include the extent of GA present, its proximity to or involvement of the fovea, and rate and topography of its progression. In anticipation of treatments becoming available in the horizon, it is therefore recommended that optometrists undertake imaging, CFP, FAF and/or OCT over time (and ideally using the same imaging modalities over time) on patients with GA[85], or to refer to someone that can, so that the above factors can be assessed.

When a treatment for GA becomes approved in Australia, patients who are interested in receiving advice about the potential of receiving such treatments should be offered an opportunity to be non-urgently referred to an ophthalmologist.

Communication tip:

Optometrists are encouraged to communicate with their patients to support improved understanding of geographic atrophy and its management options. Some important considerations are highlighted below:

- Explain that until recently GA has had no treatment options. However, there are new treatments that may become available in the future.
- Explain that baseline and follow up images of the macula are useful to help determine if GA is progressing.
- Discuss any potential costs involved with imaging.
- When a treatment becomes available in Australia, offer a referral to an ophthalmologist as they are the practitioner that would provide the new treatment. However, eligibility for treatment cannot be guaranteed.
- The outcome of any discussions should be documented.

Optometrists can consider referral to patient support organisations for further information on living with geographic atrophy, including treatment and research updates and practical and emotional support in between visits to their clinician.

Recommendations:

- Optometrists should refer patients with GA interested in further advice or considering treatment (when it becomes available in Australia) to an ophthalmologist
- Patients with late AMD (GA or non-active nAMD) should be reviewed at least every 6 months.

Neovascular AMD (nAMD)

It is recommended that optometrists refer to an ophthalmologist urgently, within **one week**, if there is suspected or definite new-onset neovascular AMD. A telemedicine opinion may be sought via e-referral, within one week, if practising in a location with limited access to ophthalmology services.

The 'urgent referral' criteria for nAMD is:

- a recent (within 3 months) history of vision loss, spontaneously reported distortion or onset of missing patch/blurring in central vision
- suspected or definite new-onset macular haemorrhage
- macular fluid (sub- or intra-retinal)

It is possible to detect apparent fluid on OCT imaging in a patient who is completely asymptomatic and without other clinical signs of neovascular AMD (e.g., macular haemorrhage). In a recent study of >160 individuals with intermediate AMD, 14 individuals developed retinal fluid on a prescheduled 6-monthly follow-up over 36 months. None of these individuals reported any symptoms on direct questioning, and none were able to identify a defect on the Amsler grid, at the clinical visit.[86] Therefore, if there are no symptoms, nor other clinical signs of nAMD, then it is acceptable to refer to an ophthalmologist within **two weeks**.[87]

In the past decade, the mainstay of nAMD treatment has been anti-vascular endothelial growth factor (anti-VEGF) agents.[88-90] The main drugs in use in Australia today are ranibizumab (Lucentis®) and aflibercept (Eylea®). Bevacizumab (Avastin®) is used off-label. All drugs have similar efficacy, so drug availability, treatment frequency and cost are often key factors when choosing the treatment drug. Thermal laser photocoagulation and photodynamic therapy (PDT) are now only considered in rare cases or in a subset of AMD - polypoidal choroidal vasculopathy, where laser or PDT is sometimes used when the neovascular lesion is well defined and extrafoveal.

Generally, initial anti-VEGF treatment is commenced with a fixed monthly interval until there are no signs of ongoing activity (e.g. fluid visible on the OCT).[91] From there, the treatment protocol is personalised using treat and extend protocols. In treat and extend, the period between treatments is increased by 2-weeks each time there are no signs of active CNV, such as fluid on the OCT or a loss of 5 letters or fresh haemorrhage. Visual acuity outcomes in treat and extend are similar to monthly injections.[92] 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.[93]

One of the best predictors of long term visual acuity in nAMD is the presenting visual acuity; the earlier a person receives treatment, the better their chances of maintaining or improving their vision.[94] This highlights the important role optometrists play in the comprehensive monitoring of those with the early stages of AMD to detect nAMD development (with monitoring frequency depending on the individual's risk of progression), and prompt referral of patients who develop nAMD.

Optometrists can also consider referral to patient support organisations for information on living with neovascular AMD, including treatment support (treatment adherence, cost of treatment, travel to appointments) and psychosocial support.

Recommendations:

- Patients with symptomatic, new-onset late AMD (neovascular) should be referred to an ophthalmologist urgently (within 1 week).
- Patients with asymptomatic AMD (drusen), with macular fluid detected on OCT, should be referred to an ophthalmologist urgently (within 2 weeks).
- Patients with neovascular AMD should be advised of the typical treatment regime - anti-VEGF injections - and the importance of adherence to the regime.

Conclusion

Recent advances in nAMD research have shown that early detection and treatment is vital for best patient outcomes. As such, optometrists have a major role to play in the management of those with the early stages of AMD to ensure that appropriate ongoing monitoring based on clinical risk factors and comprehensive assessments at each visit is performed to facilitate the earliest detection of nAMD possible.

There are likely to be new AMD treatments in the near future. In particular, there are currently clinical trials underway for new early AMD interventions and possible pharmaceuticals for GA, which will significantly change the management pathways.

Due to the rapid growth in the research of AMD, there are opportunities for patients to be involved in research studies (both natural history and interventional treatment trials). A list of relevant trials can be found on the following websites: **https://clinicaltrials.gov/ct2/home** or **https://www.anzctr.org.au/**

Appendix

Scope and purpose

The purpose of this clinical practice guide is to aid clinicians in their diagnosis and management of age-related macular degeneration with the intent that all patients with AMD will receive a high standard of care from their optometrist.

The literature review undertaken by LA in 2019 aimed to:

- Assist optometrists in making the correct diagnosis of AMD based on current classification guidelines;
- Understand the present best-practice optometry management as supported by evidence and consensus guidelines;
- Determine the most appropriate presentations for referral.

This was framed in the Australian clinical and practice context.

An update of the literature was undertaken in 2023 (LA) and again in 2024 (LA and ZW) to ensure the revised clinical practice guide was contemporary.

Stakeholder involvement

An expert working group was established via a combination of direct invitation and a call for expressions of interest from Optometry Australia members. A rubric was created to ensure a breadth of expertise was included in the AMD CPG working group – from those who worked in academia, private practice, corporate practice, low vision, patient support services, and aged/domiciliary care. Representation from across the country was also sought.

The Macular Disease Foundation Australia (MDFA) and the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) were also invited to provide feedback on the final draft of the clinical practice guide.

Development

The process for development of recommendations was undertaken via a modified Delphi process.[2,3] Following a literature review update (LA and ZW) in 2024 and a first working group meeting, a list of recommendations was established (KH and LA). These recommendations went through 2 iterative rounds of voting by 9 working group members, excluding KH and LA. Feedback was provided to Delphi participants after each round of voting, and a final working group meeting was held to discuss any contentious recommendations. This meeting included a third round of voting to improve the clarity of some recommendations. The final recommendations are included in the executive summary and at the end of each sub-section of this CPG.

The working group considered the potential health benefits and risks for AMD patients when voting on all recommendations. They also considered the potential resource implications of applying the recommendations (e.g., equipment required) on optometrists and the health system more broadly.

The clinical practice guide will be reviewed as new evidence becomes available, or in a maximum of 7 years' time.

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