CLINICAL AND EXPERIMENTAL
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REVIEW

Developing prognostic biomarkers in intermediate age-related macular degeneration: their clinical use in predicting progression

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Age-related macular degeneration is a common, complex and blinding eye disease. When early and intermediate levels of severity are detected in one or both eyes, there is a wide-ranging 0.4 to 53 per cent risk of progression to advanced disease in five years. In order to maximise visual outcomes for their patients, practising eye-care professionals must be able to stratify patients according to their risk of progression, intervene (for example by recommending smoking cessation or nutritional supplements and Amsler grid self-monitoring in intermediate disease) and monitor accordingly. With the aid of ocular imaging, a range of under-recognised yet meaningful risk factors have been identified. The purpose of this review is to assist the eye-care practitioner in stratifying the risk of progression in intermediate age-related macular degeneration using the range of established and emerging precursory signs that herald loss of vision.

Key words: age-related macular degeneration, disease staging, prognosis, progression

Age-related macular degeneration (AMD) is a leading cause of blindness in Australia and worldwide.[1] Over time, phenotyping of the disease has become more defined: stratification, staging and nomenclature have been clarified and treatment is becoming more targeted. A current clinical classification scale[2] recommends subdividing established disease into three forms: early, intermediate and late. Early and intermediate AMD are phenotypically diverse and when present in one or both eyes pose a 0.4 to 53 per cent risk of progression to advanced AMD in five years.[3] Intermediate AMD is defined by large drusen (≥ 125 μm) or pigmentary abnormalities associated with at least medium drusen, while late stage represents the most advanced form associated with visual impairment due to geographic atrophy (GA) or choroidal neovascularisation (CNV).[2]

With the widespread use of ocular imaging, especially optical coherence tomography (OCT), 'full phenotyping' of AMD is now readily achievable in a clinical setting.[4–7] Concurrently, there has been a shift toward higher standards and greater efficiency in eye care delivery: patients at significant risk of vision loss should be able to see the right professional at the right time. Evidence-based practice guidelines,[8–11] including the most recent iteration developed by the Royal Australian and New Zealand College of Ophthalmologists (RANZCO),[4] clearly emphasise the importance of collaborative care, early detection using imaging and the role of optometrists in AMD screening and management. There is a subsequent onus on all eye-care professionals to accurately separate patients according to their risk of progression and to educate, intervene and monitor accordingly.

Late AMD in the fellow eye, large (especially soft) drusen and AMD-related pigmentary abnormalities represent well-recognised risk factors for progression to advanced AMD.[3] Other risk factors, such as drusen load (height, area and volume), drusen regression (Figure 1), or genetic markers are similarly established in the literature.[12–18] However, such tools and tests may not be widely considered in a clinical setting. Other lesser known signs ('precursor lesions',[19] biomarkers or events; Figure 2) in intermediate AMD that herald a negative prognosis include: hyperreflective foci, reticular pseudodrusen, nascent GA, sub-retinal pigment epithelium hyper-

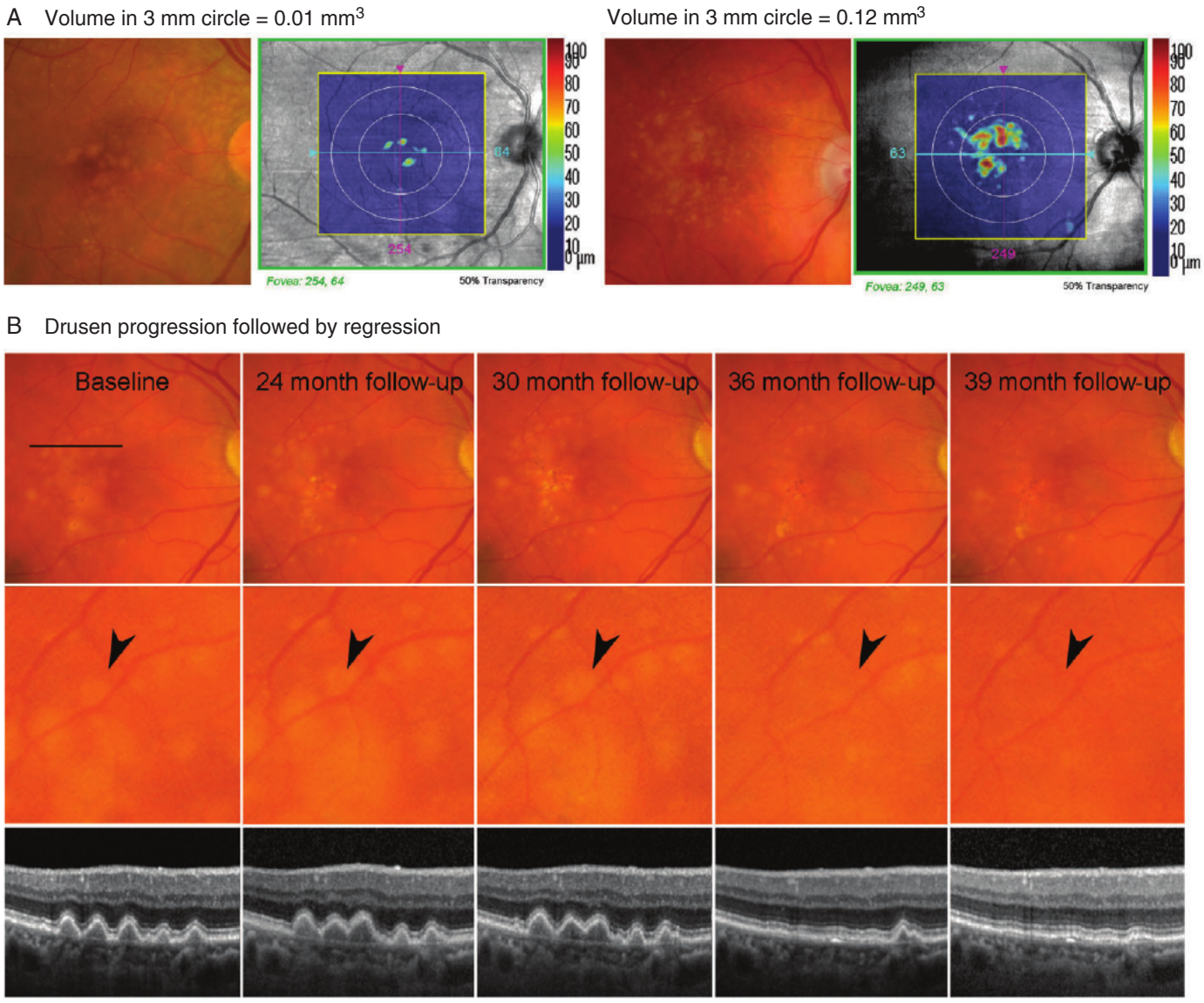

Figure 1. Established prognostic biomarkers in intermediate age-related macular degeneration (AMD): high drusen load and drusen regression or fading. A: Colour fundus photograph from two different eyes with intermediate AMD. The eye on the right has a greater drusen load as determined using the Cirrus optical coherence tomography (OCT) automated advanced retinal pigment epithelium analysis. B: Follow-up findings of a different eye with intermediate AMD showing initial drusen progression followed by later regression (an increase then a decrease in individual drusen size). Spontaneous regression particularly of large drusen represents a negative precursory event that may precede progression to advanced AMD. The black line on the left hand side of the fundus photograph indicates the location of the OCT line scan for all five visits.

reflective columns, small pockets of subretinal fluid in the absence of CNV, abnormal fundus autofluorescence (FAF) patterns and OCT-reflective drusen substructures.

The purpose of this review article is to describe the structural, predictive risk factors for progression that are detectable in intermediate AMD using imaging modalities – OCT, FAF and infrared reflectance imaging. The goal is for the reader to be able to adeptly identify biomarkers for risk stratification in intermediate AMD in a clinical setting.

LITERATURE SEARCH STRATEGY

Articles were identified by searching the National Institutes of Health's PubMed database from the last 10 years using the following combination of keywords and their relevant truncations: age-related macular degeneration, prognosis, progression, prediction or risk, and autofluorescence, optical coherence tomography or infrared. The specific focus of this review was on the clinical signs detectable via imaging in intermediate AMD.

We excluded any biomarkers described in advanced AMD, review articles or studies that

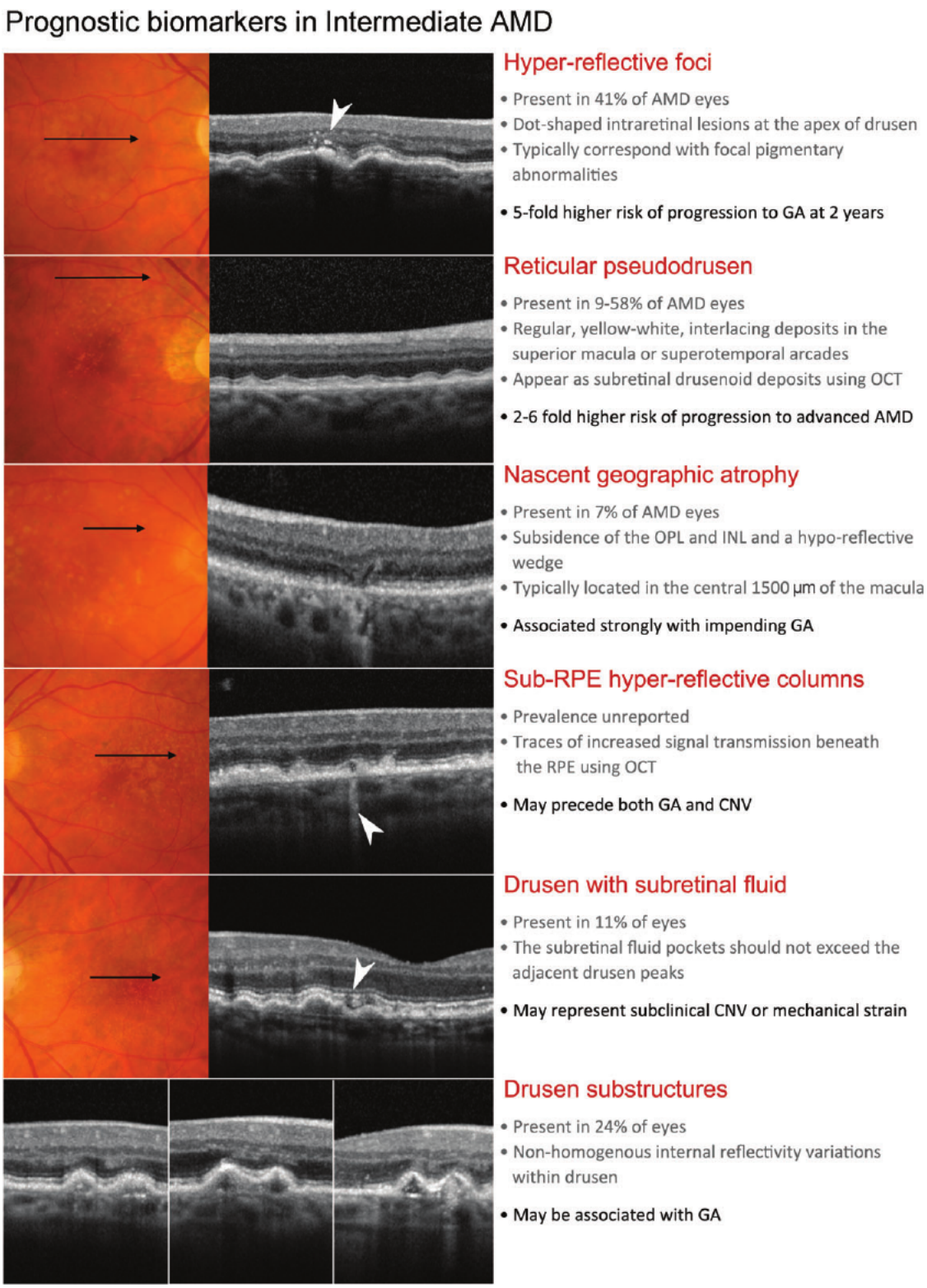

Figure 2. Prognostic biomarkers in intermediate AMD identified in the recent literature using optical coherence tomography. AMD: age-related macular degeneration, CNV: choroidal neovascularisation, GA: geographic atrophy, INL: inner nuclear layer, OCT: optical coherence tomography, OPL: outer plexiform layer, RPE: retinal pigment epithelium.

included subjects receiving treatment, for example anti-vascular endothelial growth factor injections. Historical risk factors for progression, and techniques presently uncommon or impractical in clinical optometric practice (retinal angiographic studies, retinal leakage analysis, flicker perimetry, preferential hyperacuity perimetry, novel automated or semi-automated measures, hyperspectral imaging, quantitative fundus autofluorescence, OCT angiography and laser-induced drusen regression) will not be described but have been reviewed elsewhere.[20–23]

The strength of evidence (Table 1) was evaluated as high or low using the number and type of studies available; prospective, longitudinal studies were favoured over retrospective, case-control studies.

The figures in this review were all generated using the case images of patients seen at the Centre for Eye Health – a referral only, intermediate-tier care clinic that provides imaging and visual function assessment services at no charge to the referrer or patient. The establishment is an initiative of the University of New South Wales and Guide Dogs NSW/ACT. Patient written consent was obtained in accordance with the Declaration of Helsinki and approved by a Biomedical Human Research Ethics Advisory Panel of the University of New South Wales, Sydney, Australia.

	Strength of evidence	
Strength of risk	**High**	**Low**
High	• Drusen load (volume, area)[12–14,16] • Drusen regression[26–28,35] • Hyper-reflective foci[24,25,28,34,38] • Reticular pseudodrusen[40–43]	• Nascent geographic atrophy[28,52] • Sub-RPE hyper-reflective columns[55] • Small pockets of subretinal fluid between drusen, not exceeding their peaks[56]
Low	–	• OCT reflective drusen substructures[31,61,62]
Inconclusive	• Drusen height[24,25,29–31] • Patchy, linear or reticular FAF patterns[57–59]	–

Late AMD in the fellow eye, large drusen and AMD related pigmentary abnormalities are not included as they represent already well-recognised risk factors for progression.
AMD: age-related macular degeneration, FAF: fundus autofluorescence, OCT: optical coherence tomography, RPE: retinal pigment epithelium.

Table 1. Prognostic biomarkers for progression in intermediate AMD, organised by strength of associated risk and the strength of the supporting evidence

PROGNOSTIC BIOMARKERS IN INTERMEDIATE AMD

Drusen load (height, area and volume)

Drusen, the hallmark sign of AMD, are focal deposits of extracellular debris that may spontaneously appear, disappear or change over time.[26] Remarkably, drusen have been shown to follow a similar growth pattern across individuals.[27] Additionally, routine quantification of total drusen area and volume in a clinical setting is now possible using commercially available, automated spectral domain OCT (SD-OCT) algorithms. Such measures of drusen load are able to accurately predict the development of advanced AMD whereby eyes with larger drusen volumes are at a greater risk of progression to advanced AMD.[12–14,16] For example, a drusen volume greater than 0.03 mm^3 in the central 3 mm-diameter circle of the macula occurring in up to 25 per cent (22/89) of intermediate AMD eyes has been connected to a four-fold higher risk of progression to advanced AMD.[14]

Increased drusen height, that is 'taller" drusen disrupting or compressing the ellipsoid zone, external limiting membrane and outer nuclear layer on OCT are also likely to carry a negative prognosis.[24,25,28–31] Such changes correlate minimally with drusen width and can be best visualised using OCT whereby elevated drusen appear to protrude into the overlying layers without disturbing the inner retina.[24] These findings have been characterised both qualitatively and quantitatively, although the sensitivity of the sign and best clinical method of evaluation require further study. It has been related to displacement, degeneration and/or focal loss of the overlying photoreceptor layer.[24,31]

Using mesopic, fundus-tracked microperimetry, a strong point-to-point inverse correlation between focal integrity of the external limiting membrane and ellipsoid zone (graded by experts as either continuous or discontinuous or using a four-point scale), with retinal sensitivity and fixation instability has been described.[32–34]

Drusen regression

Drusen regression or fading occurs in approximately 50 per cent of intermediate AMD eyes over a two-year period.[35] It is more likely in eyes with greater baseline measurements of drusen area and volume[26] and may be more easily identified by a relative focal reduction in FAF, compared to fundus photography.[35] Using the same cut-off described in the preceding section, 17/82 eyes (21 per cent) with a drusen volume ≥ 0.03 mm^3 (in the central 3 mm-diameter circle of the macula) developed a > 50 per cent reduction in drusen volume at 24 months. Fourteen of those 17 (82 per cent) developed advanced AMD (GA or CNV) in the same 24-month follow-up period.[26]

The age-related eye disease study (AREDS) research group[19] reported that of 95 eyes that went on to develop GA, the following features were present: large drusen (≥ 125 μm in 96 per cent, very large or ≥ 250 μm in 83 per cent), confluent drusen (94 per cent) and focal hyperpigmentation (96 per cent), followed by drusen regression/fading and hypopigmentary changes (82 per cent) occasionally accompanied by the deposition of refractile deposits (23 per cent).[36] Subject to wide individual variation, the average lead time between when these signs were first observed and the emergence of GA was several years: confluent drusen, 6.1 years; large drusen, 5.9 years; focal hyperpigmentation, 5.0 years; hypopigmentary changes, 2.5 years; and refractile deposits, 2.5 years.[19] Refractile deposits

presumably represent calcified drusen or the calcification of residual material resistant to macrophage clearance.[19]

Similarly, in a study involving 50 eyes with early to intermediate AMD, drusen regression was identified in 44 per cent (22/50) of the study eyes. The onset of GA or CNV was never observed without previous drusen regression; seven of the 22 eyes with drusen regression converted to advanced AMD over a mean study follow-up period of 37.7 months.[27] Thus, the spontaneous regression, particularly of large drusen, should be interpreted by clinicians as a negative precursory event that may precede progression to advanced AMD. The underlying reasons are a current topic of investigation.

Hyper-reflective foci

These dot-shaped intra-retinal lesions are present in approximately 41 per cent of AMD eyes.[24] They appear at the apex of drusen using OCT, cause posterior shadowing and correspond with focal hyperpigmentary abnormalities[37] as well as locally reduced retinal sensitivity, measured using mesopic microperimetry.[32,34] During follow up, the lesions are likely to proliferate, becoming more numerous and migrate from the outer to the inner retina.

The foci have been ascribed most commonly to pigment migration, displacement, deposition or clumping and may represent degenerated retinal pigment epithelium (RPE) cells.[24,31] Other aetiologies, including infiltration of inflammatory cells, extracellular pigment, calcification, intraretinal haemorrhage or degenerated cell debris, have been also suggested.[24,39]

The AREDS2 ancillary SD-OCT study revealed that eyes with hyper-reflective foci at baseline have a five-fold higher risk of progression to GA at two years, compared to eyes without such foci.[38] This effect was also significantly greater with a greater number of lesions and inner retinal migration.[38] No statistically significant effect was described for CNV.

Reticular pseudodrusen

First described in 1990, reticular pseudodrusen[40–43] typically appear in the superior macula or among the superotemporal arcades and three subtypes have been described: dot, reticular or confluent.[43] The reticular variant presents most often and adopts a relatively regular, yellow-white, interlacing, ribbon-like appearance.[40] Unlike the former two, the confluent subtype rarely presents in isolation and may represent an advanced variant.[43] The distinction between reticular pseudodrusen and other drusen subtypes has been described comprehensively elsewhere.[40,44]

Pseudodrusen are best identified using near infrared reflectance,[7,40] FAF scanning laser ophthalmoloscopy, or SD-OCT. Using OCT, they appear as collections of granular, hyper-reflective material in the subretinal space, explaining the synonym 'subretinal drusenoid deposits'.[45] Colour fundus photography is the least sensitive method of detection[40,46] and typically necessitates post-acquisition filtering (green or blue filters) and adjustments in contrast or brightness.

Former studies have described a correlation between mean photopic retinal sensitivity of the macula with the distribution and number of subretinal drusenoid deposits.[47,48] However, the area is still an active topic of investigation. The deficit is likely to be more pronounced under scotopic conditions.[48] Most recently, Neely et al.[49] explored the association between AMD and a range of photopic visual function measures and found no statistically significant deficit in visual function due to subretinal drusenoid deposits in normal or AMD eyes (outside of an age-related effect).

The prevalence of reticular pseudodrusen in early-intermediate AMD has been estimated at nine to 58 per cent (varying with the definition, population characteristics and the type of imaging).[41–43,46] Using histology, they have been associated with diffuse choroidal thinning, loss of large vessels and hyalinisation of the stroma and are consequently hypothesised to signify disruptions in cholesterol homeostasis and lipid transfer.[50] They represent an additional two- to six-fold higher risk of progression to advanced AMD[41,51] and carry a stronger association with the development of GA than CNV.[42] Counter-intuitively, the risk for progression appears to be higher with reticular pseudodrusen located outside rather than within the macular area.[51]

Nascent geographic atrophy

First proposed by Wu et al. in 2014,[28] nascent GA[28,52] has been defined as the sum of unique morphological characteristics preceding the development of GA. The features are detectable using SD-OCT and include 'subsidence' of the outer plexiform layer and inner nuclear layer and a 'hyporeflective wedge', without definite RPE and photoreceptor loss.[52] Nascent GA is typically (> 90 per cent of instances) located in the central 1,500 μm of the macula, which corresponds with the location predisposition of GA. Its prevalence has been estimated at 31/442 (seven per cent) of intermediate AMD eyes.[28]

In contrast to nascent GA, established GA characteristics of advanced AMD should span at least 175 μm with sharply demarcated 'punched out' borders, thinning or absence of the RPE and visibility of underlying choroidal vessels.[19,53] Using OCT, the inner segment ellipsoid zone, external limiting membrane and outer nuclear layer are typically absent. Accordingly, areas of nascent GA may present with predominantly mixed-, hyper- or hypo-FAF patterns, evolving into more frank hypo-autofluorescence as GA ensues.[52]

In a study of 28 areas afflicted with nascent geographic atrophy versus 84 reference areas in 24 eyes with bilateral intermediate AMD, mean retinal sensitivity measured by microperimetry was reduced by at least 3.4 dB.[54] Signs of nascent GA (one or both) were present in all areas on average 11 months prior to the development of GA (range 5–21 months).[28] An association with neovascular AMD has not been reported.

Sub-RPE hyper-reflective columns

Rarely, observed traces of increased transmission beneath the RPE may portend the development of advanced AMD.[28,55] These appear as narrow columns of hyperreflectivity beneath the RPE and may occur in 27 per cent (4/15) of eyes that develop neovascular AMD.[55] The overlying RPE appears intact and the sign may be present at least three months (average of 15 months[28]) before the onset of CNV-related exudative changes or GA.[55] This biomarker has been hypothesised to occur secondary to fine RPE cracks, representing loss of RPE integrity that may allow the easier movement of new vessels into the subretinal space.[55] Larger, masked studies confirming the association are required.

Drusen with accompanying fluid underneath the sensory retina without CNV

As reported by one study, large confluent drusen may be accompanied by subretinal fluid in the adjoining depression in 11 per cent of eyes with intermediate AMD.[56] This fluid accumulation should not exceed the drusen peaks and was reported in a total of eight eyes with no evidence of CNV detectable using fluorescein angiography or indocyanine green angiography. It has been hypothesised to represent subclinical CNV mandating referral or close surveillance and may occur due to mechanical strain.[56]

Fundus autofluorescence

In addition to enhancing the visualisation of drusen regression, different phenotypes of FAF have been reliably described in eyes with intermediate AMD.[57–59] An exact mesopic microperimetry functional correlate with increased FAF (particularly in association with underlying large drusen and/or pigmentary abnormalities) in intermediate AMD is likely, although requires further study.[33,60] Three patterns have been associated with a higher risk of conversion to CNV, including: (i) patchy – featuring ill-defined, large (> 200 μm) areas of hyper-autofluorescence; (ii) linear – at least one, well-defined area of hyper-autofluorescence often corresponding to pigmentary changes on fundus photography; and (iii) reticular – clustered, round, networked areas of decreased autofluorescence.[57] Another study[58] found no particular pattern to be associated with conversion. However, FAF abnormalities were able to predict the likelihood of progression with 93 per cent sensitivity.[58]

Drusen ultrastructure

Using OCT, soft indistinct drusen in AMD typically appear convex (dome-shaped), with homogenous medium internal reflectivity separating the RPE from the underlying Bruch's membrane without overlying foci.[39,61] However, clinicians using OCT routinely will also be aware of morphology and reflectivity variations of drusen that appear otherwise similar using fundus photography.[31,39,61,62] Consequently and in addition to volumetric characteristics, deviations from this norm described above may hold the potential to predict risk of progression,[61,62] including differences in shape (pointed, dome-shaped or saw-toothed), reflectivity (low, medium or high) and internal homogeneity (homogeneous, non-homogeneous with or without a central 'core'). It has been posited that these dynamic variations may reflect drusen diversity and compositional differences (such as in the distribution of amyloid β) also apparent using histology.[61] More generally, these atypical drusen may also represent a biomarker or manifestation of AMD that just precedes or coincides with drusen regression.[62] Authors of the AREDS2 ancillary SD-OCT study termed these appearances 'optical coherence tomography-reflective drusen substructures' (ODS).[62]

At least one ODS was identified in the macula of 74/307 eyes (24 per cent) and four subtypes have been described (in order of prevalence): H-type (high-reflective core), L-type (low-reflective core), C-type (conical debris) and S-type (split drusen). Drusen with low or high (rather than commonly medium) internal reflectivity are more likely to feature an internal core and carry an association with GA.[39,62] Follow-up data over a two-year period has further revealed a specific association between C-type ODS with new onset GA (3/8, 37.5 per cent versus 8/163 or 4.91 per cent of eyes with no ODS at baseline; p = 0.0094). However, no such association was found with CNV or other ODS subtypes. Notably, the study was limited by a small number of eyes with ODS. The corresponding appearance of ODS on other modalities (such as FAF) and their relevance as a prognostic biomarker in AMD require further study.

IN SEARCH OF THE OPTIMUM BIOMARKER

Early detection of progression to neovascular AMD is critical to maximising visual and functional outcomes.[63] The AREDS simplified severity scale[2,3] proposed convenient and clinically useful risk categories for the development of advanced AMD. However, that scale is now a decade old and preceded many of the structural, predictive risk factors described in this review. Accurate risk stratification will likely take on increased importance as new treatments for non-neovascular AMD become available. However, key questions surrounding the positive predictive value and true utility of these clinical biomarkers remain unanswered.

Although routine ocular imaging in the clinical assessment of AMD is useful, there is as yet no accurate, single or combination of biomarkers that is able to reliably identify the eye that will progress from that which will not. It is likely that in the near future, we can expect a greater understanding of lesion prevalence, lead times and odds/risk ratios for progression associated with these markers.

Reproducible risk calculators for the stratification of AMD patients are already available and becoming more refined with time.[12,64] The ideal risk calculator should integrate a combination of demographic, historical, genetic, functional and structural risk factors accumulated over time. It should be able to provide a clinically meaningful and accurate absolute risk score. However, analogous to the experience with risk prediction in cardiovascular disease, these tools require greater scrutiny of predictive performance, internal and external validation and head-to-head comparison.[65] Until such a tool is available, clinicians should be wary of misapplying the evidence and the potential for risk misclassification.

We propose that, until more precision is available, the recommended review time and management strategies (including advice regarding nutritional supplements or Amsler grid self-monitoring) in eyes with intermediate AMD should be weighted based on any nascent structural findings identified using imaging, the level of associated risk and the strength of the evidence (Table 1).

For instance, a current clinical guideline in intermediate AMD recommends re-examination every six to 18 months.[10] However, patients with high-risk signs supported by high-level evidence (high drusen load, drusen regression, hyper-reflective foci and/or reticular pseudodrusen) may be reviewed sooner (in six months) than those without any additional findings or inconclusive signs (in 18 months). Clinical confidence, measurement variability, sign prevalence and sensitivity are also relevant. Additionally, similarities between the sign and other more sinister changes should be considered: small pockets of subretinal fluid in the depression between drusen visualised using OCT may still require investigation by angiography with fluorescein or indocyanine green dye, followed by closer surveillance. Risk identification using cumulative data from multiple visits rather than a single visit may also yield greater

accuracy.[66,67] Consequently, there is an additional unmet need for improved clinical software algorithms for the better co-registration of images across visits.

In AMD, in addition to visual acuity, assessing contrast sensitivity, colour vision, visual field, dark adaptation, photostress test (dynamic measures of visual function) and multifocal electroretinography have proven useful in understanding the deficits in visual function, prior to funduscopically visible changes.[68–73] We know that there is greater rod than cone loss in AMD both anatomically and psychophysically.[72,74,75] 'Conventional', high-contrast visual acuity measured alone does not detect the transition from normal to early AMD and is prone to measurement variability.[76] Thus, an eye with visual acuity of 6/6 may yet experience a range of impairments, which are not routinely captured or available in a clinical setting because they require specific and/or extensive equipment, expertise or time. Other tests may suffer from a lack of validation or standardisation.[77]

Testing under low luminance rather than photopic conditions is more effective and provides a stronger predictor of future visual impairment.[78–80] Contrast sensitivity may also be useful, particularly as an early predictor of visual discrimination activities such as reading.[68,77,81] Reading rate and near word visual acuity are also affected in the early stages of disease and correlate poorly with distance visual acuity.[77,82]

Specialty testing including dark adaptometry, microperimetry and electrophysiology may also be more sensitive to measuring change over time, with or without therapeutic intervention.[83] Dark adaptation of both rods and cones measured psychophysically is significantly delayed in intermediate AMD, although seldom captured in routine clinical practice.[72,74,84] A surrogate indirect measure such as the photostress test may be more feasible.[77,85,86] Similarly, many studies[32–34,48,60,70,83,87–89] have reported on a corresponding microperimetry-measured reduction in retinal sensitivity overlying drusen and other RPE changes, especially under mesopic or scotopic conditions. Multifocal electroretinography in intermediate AMD shows a decrease in responses localised to the central five degrees.[89] Visual function tests for self-monitoring may also be useful.[90] While studies regarding acquired colour vision loss in AMD have reported varying results,[90] a tritan defect measurable clinically using the standard or desaturated D-15 panel tests is common.[69,77]

In short, data clarifying the exact correlation between structural and functional changes in AMD are still emerging and measuring high-contrast, distance visual acuity alone may be insufficient (Figure 3). Nonetheless, clinical need for ocular imaging may be prompted by questioning regarding difficulties with night vision or adapting to changing light levels in the case history, validated questionnaires or visual function assessment.[91] Ongoing efforts persist to identify clinically meaningful, reliable and appropriately sensitive, functional measures in early to

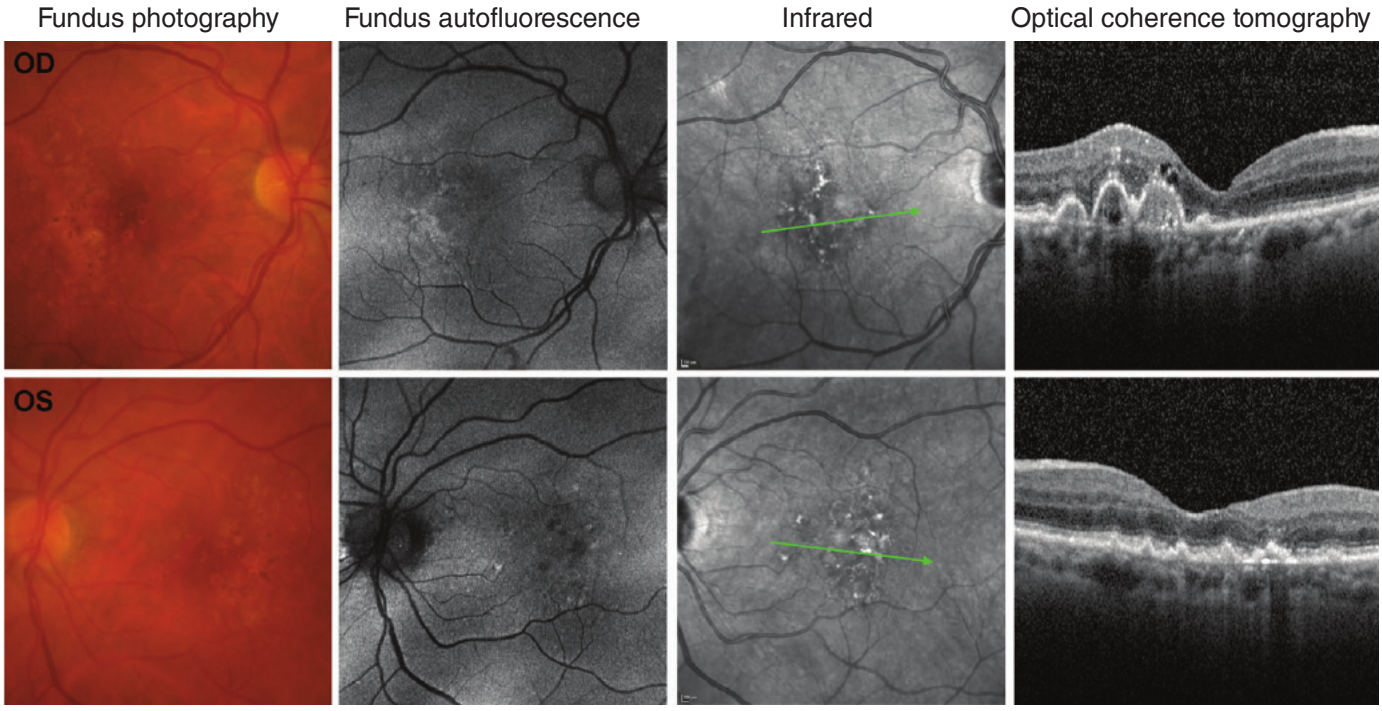

Figure 3. Illustrative example showing how high-contrast, distance visual acuity and contrast sensitivity may be minimally affected despite signs of advanced disease. These case images are from a 75-year-old Caucasian woman who was referred to Centre for Eye Health (CFEH) for a macular assessment with entering aided visual acuities of 6/9.5 OD (right eye) and 6/12 OS (left eye). The clinical findings from CFEH pictured were consistent with late age-related macular degeneration (AMD) in both eyes: neovascular AMD OD and geographic atrophy OS. Contrast sensitivity measured using the Mars test was also better in the more affected eye at 1.56 units OD and 1.48 units OS (normal range 1.52 to 1.76 log units for patients older than 60 years of age).

intermediate AMD. More detailed reviews of visual function deficits in AMD are available elsewhere.[71,77,92–94]

In conclusion, optometrists have a key role in the screening and management of AMD, especially in patient populations over the age of 50 years. Colour fundus photography remains the current gold standard for staging in AMD. Although there exists no current consensus strategy for identifying patients at greatest risk of progression,[95] clinicians can use the currently available evidence to better stratify and manage patients with intermediate AMD generally. The ability to predict progression from intermediate to late AMD has high clinical usefulness and requires full phenotyping via the deliberate interpretation and application of ocular imaging. If ocular imaging is not available, referral to a colleague should be considered.[4]

Finally, management plans should be tailored to the level of risk: patients with a higher probability of progression should be recommended more regular surveillance and intervention strategies, such as nutritional supplements or Amsler grid self-monitoring.

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