Multimodal Imaging of Nonneovascular Age-Related Macular Degeneration

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AMD is the leading cause of irreversible blindness among individuals older than 60 years of age in the western hemisphere.1,2 Although AMD is characterized by a spectrum of macular findings, it has traditionally been divided into two major subtypes. The majority of patients with AMD manifest the nonneovascular (dry or atrophic) form of the disease; while the major cause of blindness (90% of AMD patients with severe vision loss) has historically been due to the neovascular (wet or exudative) subtype.3,4 The hallmark findings of nonneovascular AMD are macular drusen, RPE alterations, and geographic atrophy (GA). Classification schemes for nonneovascular AMD have evolved over the years as major advances in retinal imaging have enabled a greater understanding of disease pathophysiology. The original classifications of nonneovascular AMD were based on color fundus photography (CFP), while more modern schemes rely on a multimodal imaging approach. Effective diagnosis and management of nonneovascular AMD requires a thorough understanding of its multimodal imaging features as detailed in this review. Future imaging modalities and imaging biomarkers that may aid in diagnosis and management are also discussed.

Keywords: multimodal imaging, nonneovascular age-related macular degeneration, dry age-related macular degeneration, geographic atrophy, optical coherence tomography

Nonneovascular (dry) AMD is a retinal disease with potential for significant central visual impairment. The hallmarks of this disease are macular drusen, RPE alterations, and geographic atrophy (GA). Classification schemes for nonneovascular AMD have evolved over the years as major advances in retinal imaging have enabled a greater understanding of disease pathophysiology. The original classifications of nonneovascular AMD were based on color fundus photography (CFP), while more modern schemes rely on a multimodal imaging approach. Effective diagnosis and management of nonneovascular AMD requires a thorough understanding of its multimodal imaging features as detailed in this review. Future imaging modalities and imaging biomarkers that may aid in diagnosis and management are also discussed.

Natural History

Advances in multimodal imaging technology have significantly enriched our understanding of the pathogenesis and natural history of AMD. Despite a long-standing lack of consensus in the classification of AMD, it is generally agreed that the early stages are typically asymptomatic and feature medium- and/or large-sized (soft) drusen and pigmentary abnormalities.6 These eyes are at risk of progression to the late (advanced) stage of AMD, remarkable for either GA (atrophy of the outer retina, RPE, and choriocapillaris), or choroidal or retinal neovascularization (NV) (neovascular AMD) and associated severe vision loss.6,7

It is now clear that the natural history of nonneovascular AMD can demonstrate considerable variability, with more than one pathway leading to an invariable outcome. For example, GA is considered the end-stage form of nonneovascular AMD, but this complication may develop in the course of various pathways, including collapse of large soft drusen or a drusenoid PED8 or progressive outer retinal atrophy (ORA) associated with reticular pseudodrusen and choroidal thinning.9,10 Atrophy of the outer retina, RPE, and choriocapillaris may also be identified in eyes with neovascular AMD that have received long-term antiangiogenic therapy.7,11

As it is currently used, the term AMD describes a group of distinct disorders that have common phenotypic features and final pathways. As our understanding of the pathophysiologic and genetic mechanisms underlying AMD continues to advance, our definition of AMD will become more refined. This review article focuses on the widely recognized pheno-
type of nonneovascular AMD that is remarkable for macular drusen (medium or large in size) and pigmentary abnormalities (hyperpigmentation or hypopigmentation) and ultimately GA.

**Traditional Classification of Nonneovascular AMD**

Classification schemes, severity scales, and grading systems of nonneovascular AMD have been largely based on the imaging technology available to identify characteristics, such as macular drusen, RPE alterations, and atrophy. Over the years, numerous classifications schemes relying on a variety of imaging modalities have been proposed but to date there has been no universal consensus.

**Color Fundus Photography**

CFP provides illustration of a broad range of fundus abnormalities, including different subtypes of macular drusen and pigmentary abnormalities, and closely parallels biomicroscopic examination (Fig. 1). Early funduscopic systems to classify nonneovascular AMD were developed during major clinical trials and were based on stereoscopic flash flood-light illumination. These classifications included descriptions of the following: drusen size (i.e., large versus small), consistency (i.e. soft versus hard), location, number, and area of involvement (Fig. 2). The location and quantitative area of hyperpigmentation or hypopigmentation and GA size, location, and area were also measured in these schemes.8,12-16

While early classification systems all relied on CFP, their specific approaches varied. For example the Beaver Dam Eye Study defined early Age-Related Maculopathy (ARM) by the presence of soft indistinct drusen or reticular drusen or any type of drusen, except hard drusen, with pigmentary changes, while late ARM featured exudative macular degeneration or GA.1 The International ARM Epidemiological Study Group graded the appearance and severity of nonneovascular AMD lesions using a standard grid and sizing circles, with early ARM being defined as drusen and RPE abnormalities and late ARM, including NV or GA.12 The 1995 International ARM Grading Scale included slight modifications and was used as the basis for major AMD trials, including the Age-Related Eye Disease Study (AREDS).8,14,17 The AREDS investigators used the International ARM Grading Scale to develop a severity scale that defined four levels of AMD (from 1-4 with 4 representing advanced AMD). This multistep scale was based on grading the presence and severity of lesions such as drusen (size, type, total area), pigmentary abnormalities, and lesions indicative of NV (i.e., fibrovascular pigment epithelial detachment [PED], serous retinal detachment, or photocoagulation scars), and predicted the risk of progression to advanced AMD.8,14,17

More recently the Beckman Initiative for Macular Research Classification Committee proposed an updated classification system that provided predictive risk of progression to late AMD.7 With this approach normal aging was defined by the presence of small drusen or “druplets” (<63 μm), early AMD was defined by medium drusen (≥63 to <125 μm) without pigmentary abnormalities, intermediate AMD was defined by large drusen (≥125 μm) or pigmentary abnormalities associated with at least medium drusen, and late AMD was defined by GA or NV.

Many of the earlier classifications systems using CFP are difficult to apply in clinical practice and large clinical studies given their complex nature. Further limitations of CFP include variability of fundus pigmentation and drusen appearance, lack of depth resolution of the retina and choroid, reduced contrast, lack of detailed quantitative information, and the need for an experienced photographer and a compliant patient to acquire high-quality images. Additionally, the high-intensity light used during image acquisition may be uncomfortable for many patients and image quality is reduced in eyes with media opacities or poor mydriasis.18 Despite these limitations and the emergence of newer imaging modalities, CFP remains widely used and the continued application of CFP in future studies is necessary to allow for comparisons with earlier studies and validation of these newer technologies.

**Multimodal Imaging of Nonneovascular AMD**

With the advent of more advanced retinal imaging modalities, there has been a trend away from CFP as the primary method to diagnosis and monitor nonneovascular AMD. Fundus autofluorescence (FAF) and OCT have emerged as essential adjuncts for the monitoring of nonneovascular AMD, while modalities, such as near-infrared reflectance (NIR), near-infrared autofluorescence (NIR-AF), fluorescein angiography (FA), optical coherence tomography angiography (OCTA), and multicolor confocal scanning laser ophthalmoscopy (SLO) may provide complementary and confirmatory information.

Defining several terms may be helpful for the following discussion of imaging modalities.19 SLO is a technique for imaging the eye using horizontal and vertical scanning mirrors to scan a specific region of the retina and create raster images and is used by several of the imaging modalities discussed below. Because the fundus is illuminated with a small spot of monochromatic laser light, only a small portion of the patient’s pupil is used for illumination with the remainder of the pupil being used for reflected light collection (compared with CFP using flood illumination, which uses nearly the whole pupil for illumination), so the intensity of the illuminating beam, and thus patient discomfort may be minimized. SLO may also use a non visible laser wavelength. Another advantage to SLO is the ability to perform confocal imaging. Confocal technology provides higher contrast and depth resolution compared with nonconfocal systems and relies on a confocal aperture moving between two points to capture a number of tomographic slices to extract depth information (i.e., only light reflected by structures very close to the focal plane are detected).

**Fundus Autofluorescence**

FAF is currently considered to be the gold standard modality for evaluation of GA as it provides high-contrast retinal images that are especially useful for detecting areas of atrophy. Atrophic lesions appear as areas of decreased autofluorescence (hypautofluorescence) due to loss of the RPE cells, which contain intrinsic fluorophores, such as lipofuscin (Fig. 1). The absence of signal is associated with loss of retinal sensitivity. Furthermore, contrast between areas of RPE loss and adjacent areas of intact photoreceptors and RPE usually allows for reproducible semiautomated quantification of atrophic areas. As a result, FAF has been accepted as an anatomic outcome parameter for the progression of GA in clinical trials by international regulatory agencies.18,20-22 FAF imaging that employs a confocal SLO with a blue light excitation wavelength filter (488 nm) and an emission filter of 500 to 521 nm is employed. Spaide24 introduced the ‘modified Topcon’ filter set with red-shifted wavelengths, with an excitation spectra of 535 to 585 nm and a 615-715 nm emission barrier filter. Drawbacks to FAF imaging include susceptibility to media opacities, difficulty imaging the fovea due to macular pigment that absorbs blue light, and patient discomfort.25 Alternate wavelengths, such as green light, may...
offer some advantages as it may be more comfortable for patients and limit macular pigment absorption, but still yield excellent visualization of the atrophic areas.

Quantitative Autofluorescence

A new method of FAF has recently been described that enables quantitative FAF by using an internal fluorescent reference to account for variable laser power and detector sensitivity. This approach requires high-quality images to derive reliable quantitative measurements and may be limited by media opacities. Imaging of healthy eyes with this novel methodology has demonstrated that quantitative FAF parameters increase with age and are higher in women and may vary with ethnicity. This modality has increasingly been used to study eyes with retinal dystrophies, such as Stargardt disease and may be useful for studying areas of advanced and nascent atrophy in AMD, although further efforts are needed to validate its utility for this disease.

Color Fundus Autofluorescence

Color FAF is an emerging imaging modality that may provide novel insights into retinal diseases, such as nonneovascular AMD. FAF devices typically employ a 488-nm wavelength excitation filter to isolate the emission autofluorescence of lipofuscin in the RPE. Recently a new confocal blue-light FAF device (EIDON; CenterVue, Padua, Italy) using a 450-nm wavelength and light-emitting diode light source has been described, and is thought to excite minor fluorophores, distinct from lipofuscin, which may provide additional contrast to evaluate macular anatomy. This new system affords a potentially important advantage, as the full-emission spectrum offers...
is detected on a color sensor, producing color FAF images (Fig. 1). Thus, the emission spectrum can be divided into separate short- and long-wavelength (green, 510–560 nm and red, 560–700 nm) emission fluorescence components (EFC), allowing for the isolation of minor fluorophores whose emission spectrum would otherwise be overwhelmed by the strong emission of lipofuscin.

A recent report of eyes with atrophy from AMD using this color FAF system demonstrated that in areas of atrophy the strong red EFC from lipofuscin was absent or reduced, while a residual green EFC signal was detected corresponding to subretinal hyperreflective material and believed to represent drusenoid material partially composed of advanced glycation end products with fluorescent capability.32 Larger longitudinal studies are needed to evaluate the prognostic significance of these findings and to further evaluate color FAF.

Optical Coherence Tomography

Spectral-domain (SD)-OCT provides high-quality, cross-sectional, and en face analysis of the retina, RPE, and choroid with depth-resolved segmentation with resolution approaching histology performed with light microscopy.34 This widely available modality has been validated to assess and quantify atrophy and has been used as a critical adjunct in several large AMD clinical trials (Fig. 1). Recent studies have demonstrated that specific SD-OCT features, such as splitting of the RPE/Bruch’s membrane complex band may indicate a high risk for progression to GA.35 Anatomic tracking functions are especially important and employ precise alignment of baseline and follow-up images enabling meticulous and accurate analysis of the evolution of morphologic findings. The introduction of enhanced-depth imaging (EDI) SD-OCT provides better penetration and visualization of the choroid with depth resolution, and some reports have suggested that choroidal thickness may be reduced in the late stages of AMD36 and may be associated with certain nonexudative AMD phenotypes, including reticular pseudodrusen.37

There are currently three types of OCT devices commercially available.38–40 The earliest OCT devices used time-domain (TD) technology. TD-OCT systems use a light source centered at a wavelength of 840 nm, acquire 400 A-scans per second using six radial slices oriented 30° apart, and achieve axial resolutions of 10 to 15 μm. This early technology was soon surpassed by SD-OCT devices, which offer faster scanning speeds and improved resolution. SD-OCT devices use a wavelength of 840 nm, acquire 25,000 to 85,000 A-scans per second of a 6-mm area, and achieve axial resolutions of approximately 4 to 7 μm. Swept source (SS)-OCT is a recently developed technology that uses a longer wavelength (~1050 nm) light source that penetrates more deeply into the choroid than wavelengths used by SD-OCT imaging. Current SS-OCT devices can scan at rates up to 100,000 A-scans per second, achieve axial resolutions of 6 to 8 μm, and have the capability for widefield imaging.

A new approach for the analysis of the macula employs en face OCT images, producing a coronal view of the retina and choroid that varies depending on the segmentation depth of the image. This approach may complement the traditional OCT B-scans by providing additional anatomic insights and has been shown to be a reliable method to detect and quantify GA.41,42

Drawbacks of OCT include a limited scan field, dependence on image quality for interpretation, imperfect automated image segmentation, and fewer large studies using SD-OCT, as compared with CFP and FAF, to study the features of nonneovascular AMD. The growing availability of SS-OCT will provide images with greater penetration of the choroid with more detailed images, higher scanning rates, and wider scan areas.18

Near-Infrared Reflectance

NIR imaging employs wavelengths of light at the higher end of the visible spectrum (787–820 nm), which are minimally absorbed by media opacities, neurosensory retinal layers, and macular luteal pigments. In contrast to blue-light FAF imaging, atrophic areas appear brighter than nonatrophic regions and patient discomfort is minimized (Fig. 1).18,36 Reticular pseudodrusen are especially well visualized with NIR (Fig. 3).43–45 However, the importance of NIR imaging has not been validated in large studies, and this imaging modality currently remains a potentially valuable adjunct to blue-light FAF, especially for confirming or excluding involvement of the foveal center by the atrophic lesion.

Near-Infrared Autofluorescence

NIR-AF relies on the presence or absence of melanin to visualize areas of atrophy.36,43,46 As melanin is autofluorescent under infrared light and typically present in functioning RPE cells, atrophic areas appear hypofluorescent. Like NIR imaging, NIR-AF provides the capability to identify RPE atrophy. Eyes with dark irides, however, may have strong autofluorescence from choroidal melanocytes, which can “wash out” the signal from areas of RPE loss. Commercial
devices are available to obtain NIR-AF images or these images can be acquired (but not as easily) with SLO devices using the indocyanine green angiography (ICGA) filters.\textsuperscript{45,47}

**Fluorescein Angiography**

FA has long been the gold standard method to detect and assess the neovascular form of AMD, but this modality may also readily identify drusen and GA, the hallmarks of the non-neovascular form. Drusen typically stain while atrophic areas may show early transmission hyperfluorescence or a “window defect,” due to atrophy of the RPE and an intact choriocapillaris.\textsuperscript{6,50} Disadvantages of this system include the need for invasive dye injection, risk of allergic reaction to the dye, long image acquisition times, and lack of depth-resolved segmentation and lateral resolution.

**Indocyanine Green Angiography**

While ICGA is most useful in demonstrating the neovascular and exudative complications of AMD, this modality may hold some utility for the nonneovascular form.\textsuperscript{18} Indocyanine green (ICG) has greater binding affinity to plasma proteins than fluorescein, leaks minimally from the choriocapillaris, and provides improved visualization of the choroidal vasculature. ICGA may be useful in the diagnostic evaluation of atrophy. For example, with AMD there is typically late ICG staining of the area of GA, while Stargardt disease illustrates “dark atrophy” without dye staining.\textsuperscript{48} ICGA may also detect nonexudative type 1 (sub-RPE or occult) NV as a plaque of late hyperfluorescent staining in eyes that appear to have the non-neovascular form of AMD on funduscopic examination or FA.\textsuperscript{49} Given the availability of noninvasive and superior imaging modalities, ICGA is not routinely performed in the management of nonneovascular AMD.

**Widefield Imaging**

Widefield systems provide a larger field of view than traditional imaging modalities and images may extend to greater than 100° (depending on the point of reference and the individual eye).\textsuperscript{18} Commercially available widefield systems include the capability to support FA, reflectance, and dye-based angiographic (i.e., FA, ICGA) imaging. Prior reports have demonstrated that the grading of macular features with widefield imaging, using magnification, is similar to the results obtained with traditional CFP.\textsuperscript{70} This technology is optimal for the detection and monitoring of peripheral lesions (i.e., drusen, pigment alterations such as reticular degeneration, paving stone degeneration, and atrophy) associated with AMD, which may be an important biomarker of disease.\textsuperscript{51-53}

**Optical Coherence Tomography Angiography**

OCTA employs motion contrast to detect blood flow and acquires three-dimensional volumetric information of the retina and choroid to provide high-resolution, depth-resolved segmentation of these microscopic vascular layers. While the use of OCTA in AMD has focused mostly on detecting retinal and choroidal NV, OCTA has also been applied to the study of nonneovascular AMD. Changes in the choriocapillaris appear to be present during all stages of this disease.\textsuperscript{18,52,54,57} Recently, there has been great interest in the subject of “signal flow voids” readily identified and quantified in the choriocapillaris using OCTA and possibly representing progressive areas of nonperfusion or loss in the distinctive capillary meshwork of the choroid associated with both the nonneovascular and neovascular forms of AMD. In the OCTA choriocapillaris scans the areas of “signal flow voids” appear as dark regions along the granular bright areas representing choriocapillaris flow. It has been proposed that an ischemic choroidopathy demonstrated by these “signal flow voids” may predispose to the development of late AMD. Such imaging methods may more precisely document progressive morphologic changes in the choriocapillaris and choroid may prove to have an important role in better understanding the pathogenesis of nonneovascular AMD and detecting and monitoring the progression of abnormalities in this common disorder. Like ICGA, OCTA may detect nonexudative or quiescent type 1 NV in eyes that might otherwise be considered to have nonneovascular AMD.\textsuperscript{54}

**Confocal White Light Imaging**

Recently a white light (i.e., using a white light-emitting diode with a wavelength of 440- to 650-nm) scanning confocal instrument has become available (EIDON; CenterVue; Fig. 1), which produces high-quality true color fundus images similar to that directly observed on funduscopic examination. This new technology has several advantages over traditional flash flood-illuminated systems, including improved contrast and therefore better visualization of atrophic borders due to its confocality. In addition, the system provides high-resolution imaging that is less susceptible to media opacities and poor mydriasis, and automation that reduces the need for a skilled operator. Large studies of this device are needed to validate its utility.\textsuperscript{18}

**Multicolor Confocal Scanning Laser Ophthalmoscopy**

Multicolor confocal SLO is a novel imaging modality that uses three simultaneous laser wavelengths to penetrate different depths of the retinal layers, resulting in a composite image that provides details at multiple layers. Blue reflectance (486 nm) highlights the inner retina and vitreoretinal interface; green reflectance (518 nm) the deeper retinal layers, and NIR (815 nm) best illustrates structures of the outer retina and choroid (Fig. 1).\textsuperscript{58,59} While only a few studies using this novel technique have been published, multicolor imaging has been used to visualize atrophic areas in AMD, and it may allow for improved visualization of GA boundaries with less interference from media opacities compared with traditional CFP.\textsuperscript{58-60}

**Fluorescence Lifetime Imaging Ophthalmoscopy**

Fluorescence lifetime imaging ophthalmoscopy (FLIO) is a novel noninvasive imaging modality providing in vivo measurement of the lifetimes of endogenous retinal fluorophores and is closely related to FAF.\textsuperscript{61-65} When photons from an external light source are applied to excite endogenous fluorophores of the retina, the fluorophores achieve a higher level of energy before returning to their ground state, and the average time between these two events can be quantified as the fluorescence lifetime. While conventional FA, fluorescence lifetime imaging ophthalmoscopy (FLIO) is a novel noninvasive imaging modality providing in vivo measurement of the lifetimes of endogenous retinal fluorophores and is closely related to FAF. When photons from an external light source are applied to excite endogenous fluorophores of the retina, the fluorophores achieve a higher level of energy before returning to their ground state, and the average time between these two events can be quantified as the fluorescence lifetime. While conventional FA provides spatial-resolved information on fluorescence intensities, FLIO additionally measures fluorescence lifetimes; thus, providing both space and time resolution. FA is also limited in its ability to measure nonlipofuscin fluorophores, such as melamin given the predominance of lipofuscin in the retina, while FLIO is able to capture lipofuscin as well as other fluorophore emissions. As a result, FLIO is able to provide information about the integrity of retinal tissues, such as photoreceptors.

This new imaging modality has been studied in a broad range of retinal disease, including retinal artery occlusion, diabetic retinopathy, hereditary retinal dystrophy, macular hole formation, central serous chorioretinopathy, and AMD.\textsuperscript{61-65}
Studies have indicated that eyes with AMD have longer mean AF lifetimes compared with age-matched controls. Specifically, areas of complete outer retinal and RPE atrophy associated with GA have demonstrated long lifetimes likely due to fluorophore emission from the underlying choroid and connective tissue components, while eyes with RPE atrophy but remaining photoreceptor segments have displayed shorter fluorescence lifetimes.

Further research into the dynamics of macular fluorophores especially as pertains to metabolic changes is needed. Currently, FLIO can provide insights into the structural alterations associated with nonneovascular AMD that may be complementary to the more common retinal imaging modalities, but it may one day serve as a primary tool for visualizing retinal changes and monitoring therapeutic effects for a broad spectrum of macular disorders.

**Multimodal Imaging Features of Nonneovascular AMD**

**Drusen**

Drusen are the clinicopathologic hallmark of nonneovascular AMD and have been classified according to size, margin, and consistency. Various types of drusen have been described and include small (hard) drusen, medium drusen, large (soft) drusen, cuticular (basal laminar) drusen, mineralized (calcified) drusen, and reticular pseudodrusen (referred to as subretinal drusenoid deposits by SD-OCT; Figs. 2–4). The number and size of drusen confer a greater risk for the development of GA and NV.

Small (hard) drusen are by definition less than 63 μm in size and appear as discrete small yellow–white sub-RPE deposits with distinct borders at the level of Bruch’s membrane. They are a common finding in patients greater than 40 years of age and, in isolation, do not confer an increased risk of vision loss. Medium drusen are 63 to 125 μm in size, while large (soft) drusen are greater than 125 μm and have indistinct borders and can coalesce to form a drusenoid PED. On histology, large drusen are mounds of lipid-rich basal linear deposits between the RPE basal lamina and the inner collagenous layer of Bruch’s membrane. Large drusen are a high-risk biomarker for the development of GA and NV.

Cuticular (basal laminar) drusen are an uncommon subtype of drusen first described by Gass in 1977 and most frequently identified in patients 40 to 60 years of age (Fig. 4). They appear as numerous small yellow–white semitranslucent accumulations under the RPE in a densely packed manner and are typically 50 to 75 μm in size. These drusen represent nodular excrescences of a thickened inner aspect of Bruch’s membrane. They demonstrate a classic “starry-sky” or “milky-way” pattern with FA most evident during the arteriovenous phase, and additional lesions may be detected with FAE. With OCT they may demonstrate a characteristic “sawtooth” pattern. Cuticular drusen are commonly associated with vitelliform maculopathy and may confer a higher risk for the development of GA and NV.

Mineralized drusen are associated with refractile deposits, which presumably represent calcification or lipid mineralization of residual lipopholic material within chronic drusen that have not been removed by macrophages. The appearance of refractile deposits within drusen may indicate a higher rate of GA development.

Reticular pseudodrusen (subretinal drusenoid deposits on SD-OCT) appear as an interlacing network or focal dots of yellow–white material on CFP, but are best illustrated with NIR, blue light photography, or red-free imaging (Fig. 3). They represent subretinal deposits above the RPE, and are believed to indicate a high risk of progression to GA and NV, specifically type 3 NV. With FAE reticular pseudodrusen typically show hypoautofluorescence. With NIR, reticular pseudodrusen are usually hyporeflective.

Subretinal drusenoid deposits were initially classified into the following three stages: in stage 1 the ellipsoid zone (EZ) appears undulated or ribbon-like, stage 2 features an inwardly deflected EZ, and stage 3 shows an interrupted EZ and an inwardly deviated external limiting membrane (ELM). A more recent report using multimodal imaging described three subtypes of pseudodrusen, with all three appearing as subretinal drusenoid deposits on SD-OCT, although only one formed a reticular pattern with CFP. The first type, termed dot pseudodrusen (stage 3 by the original classification) appear as an orderly array of whitish discrete accumulations primarily in the superior perifovea. Dot pseudodrusen are best detected with NIR showing hyporeflective spots. The second type is a reticular pattern, or ribbon pseudodrusen (stage 1 by the original classification), and the third type is called peripheral pseudodrusen. This latter form is an uncommon subtype visualized as yellow–white globules primarily located peripheral to the perifoveal region and appear hyperreflective with NIR. It has been suggested that each type of pseudodrusen may be composed of different constituent elements and may confer varying risks of progression to late AMD.

Until the advent of multimodal imaging, drusen were most frequently described using CFP. While CFP may allow for qualitative evaluation of drusen adequate for routine clinical practice, quantitative analysis is generally limited. Manual quantification of drusen is time consuming and requires extensive grader training to obtain reproducible results. Automated segmentation of drusen based on CFP has improved reproducibility. OCT imaging can best identify the broad spectrum of drusen morphologies and can provide reproduc-
sani et al. [17] also demonstrated the effectiveness of OCT imaging in the diagnosis of AMD, as it can distinguish between different types of drusen and PEDs, which are critical for treatment planning.

In summary, OCT imaging provides a non-invasive and accurate method for the diagnosis and monitoring of AMD. Its high resolution and contrast make it an indispensable tool in modern ophthalmology, enabling early detection and timely intervention for this progressive retinal disease.

References:
Best disease or adult-onset foveomacular dystrophy which typically have a lower age of presentation with bilateral and symmetric retinal findings.

**Outer Retinal Atrophy**

While retinal atrophy often accompanies RPE atrophy in GA, ORA has recently been proposed to describe a form of late AMD, distinct from GA, and characterized by ORA with photoreceptor loss in the absence of RPE atrophy.\(^\text{101}\) This entity has been reported to develop in eyes after regression of reticular pseudodrusen and is demonstrated with SD-OCT as thinning of the outer retina with loss of the outer retinal hyperreflective anatomic bands associated with photoreceptor viability, including the ELM and the inner segment EZ band. Eyes with ORA may also display decreased choroidal thickness and may be at a greater risk of developing NV and/or GA.\(^\text{101}\) The high-risk nature of reticular pseudodrusen was demonstrated in a recent study of 21 eyes with these deposits.\(^\text{101}\) Nine eyes showed regression of the pseudodrusen with the development of ORA and choroidal thinning, while four eyes developed noncentral GA, and nine eyes developed CNV.

**Outer Retinal Tubulations**

Outer retinal tubulations (ORTs) are a nonspecific OCT finding that may be identified in any disorder complicated by irreversible outer retinal damage, including GA and subretinal fibrosis.\(^\text{79,102--106}\) ORTs appear on OCT B-scans as circular or ovoid structures in the outer nuclear layer, which may show a branching morphology with en face OCT reconstruction. The hyperreflective lumen of ORTs is delimited by a hyperreflective band representing the ELM. ORTs are found frequently overlying areas of subretinal fibrosis and can occur at the border of atrophy (Fig. 5) where they display a characteristic scalloped pattern with en face OCT.\(^\text{102}\) ORTs develop as activated Müller cells scroll and barricade nonviable photoreceptors. Only approximately 20% of GA lesions, however, demonstrate evidence of tubulation.\(^\text{107}\)

**Outer Retinal Corrugations**

Another recently described OCT signature of advanced AMD is outer retinal corrugations,\(^\text{108}\) identified as undulating hyperreflective lesions above Bruch's membrane occurring in areas of complete RPE and outer retinal atrophy (cRORA) (Fig. 5). This OCT signature has been correlated with persistent basal laminar deposits in nonneovascular AMD, but is more commonly found as a late-stage finding in eyes with neovascular AMD.

**Plateau**

The plateau is a recently reported OCT finding in eyes with GA.\(^\text{109}\) Originally described by Querques et al.\(^\text{110}\) as an uncommon “wedge-shaped subretinal hyporeflectivity,” the distinctive plateau signature typically develops during the collapse of large drusenoid PEDs.\(^\text{109}\) With OCT the plateau is identified as a wide-based mound-like signature with flattened apices characterized by a hyporeflective and heterogeneous interior and an overlying hyperreflective exterior. Tan et al.\(^\text{109}\) have hypothesized that during progressive RPE atrophy, Müller cell processes extending through defects in residual basal laminar deposit may contribute to the heterogeneous internal reflectivity of this OCT signature.

**Choroidal Abnormalities**

The choroid has been proposed to play an important role in the pathogenesis of both nonneovascular and neovascular AMD. Reduction in choroidal perfusion and resulting outer retinal ischemia has been suggested as an important patho-
genic mechanism in the development of both forms of AMD.111–114 Choriocapillaris alternations have been demonstrated during all stages of nonneovascular AMD.75 and these abnormalities increase with age and in association with drusen based on histopathologic studies.115,116. In early AMD, there may be patchy thinning of the choriocapillaris while areas of GA may have underlying choriocapillaris loss and asymmetric alterations of the choriocapillaris at the junctional zone.18,54–57,117,118 Some reports have shown a significant association between choroidal thickness and AMD status, with a thinner choroid observed at later stages of disease, especially in the nonneovascular form of AMD.119,120 although other studies have not confirmed this finding.121,122 Reticular pseudodrusen, however, are associated with a thin choroid.123 More recent OCTA studies have displayed choriocapillaris “signal flow voids” associated with macular drusen and nonneovascular AMD.117

**Age-Related Choroidal Atrophy**

EDI SD-OCT and SS-OCT have provided improved choroidal imaging and enabled precise measures of choroidal thickness. These advances have led to the recent identification of a new entity referred to as age-related choroidal atrophy (ARCA), which presents in older patients with posterior pole abnormalities that appear distinct from the more typical AMD findings.9,79,124 Eyes with ARCA may show a central absence of visible large choroidal vessels or a tesselated fundus appearance with peripapillary atrophy and focal hyperpigmentation (Fig. 5). While ARCA is believed to represent an entity distinct from AMD, eyes with ARCA may have increased rates of reticular pseudodrusen and may be at a greater risk of progression to late AMD. ARCA may therefore represent an earlier form of AMD.

**Classification in the Era of Multimodal Imaging**

Advanced retinal imaging has provided new insights into our understanding of nonneovascular AMD and opportunities to develop new classification systems. For many decades, the grading of nonneovascular AMD relied primarily on CFP identification of macular drusen and associated pigmentary abnormalities, and GA. Soft macular drusen (many medium or at least 1 large drusen) in association with pigmentation represented the most important biomarker for the development of late AMD (i.e., GA or NV).77 While this concept and the associated classification schemes that developed were widely adopted, evidence has accumulated through multimodal imaging and genetic studies suggesting that many features of AMD may not subscribe to this traditional paradigm, including reticular pseudodrusen, type 3 NV, and polypoidal choroidal vasculopathy (PCV); thus, raising the question regarding the proper definition of AMD.

In recent years, new classification systems and constructs for AMD have been proposed in an attempt to harmonize prior disease models with this new information in hopes of ultimately providing improved prognostic information and better management of AMD. While these new systems are promising, further longitudinal studies are needed to validate them and it remains to be seen whether these proposals will be widely adopted.

**A New Classification System for AMD**

Spaide37 recently proposed a more complete classification system for AMD that includes the diverse spectrum of presentations of this disease and that may better predict future outcomes. This approach considers choroidal thickness by OCT as an important factor determining the phenotype of disease. AMD patients with a thin choroid are more likely to present with reticular pseudodrusen (subretinal drusenoid deposits with SD-OCT) and these eyes are at a greater risk for the development of ORA (with SD-OCT) and type 3 NV, both indicators of late AMD. AMD eyes with a thick choroid (i.e., pachychoroid phenotype) may harbor pachychydrusen (larger amorphous drusen) and are at a greater risk of developing type 1 NV (late AMD), including aneurysmal type 1 NV (also known as PCV). Patients with normal choroidal thickness may display medium and large drusen that may be complicated by any of the three forms of NV or GA.

**Classification of Atrophy Meetings Definition for Atrophy**

Early classification systems of AMD established specific CFP definitions for GA that continue to be used in studies today,3 but CFP has significant drawbacks, including difficulty in differentiating atrophic lesion boundaries and poor quantification capability. FAF has emerged as an essential modality in phenotyping and quantifying areas of atrophy in AMD (see section ‘Traditional Imaging Biomarkers’ for FAF phenotypes and associated prognostic implications for GA progression).

OCT provides depth-resolved segmentation of the retina and choroid and quantitative assessment of tissue loss of specific layers, and identification of atrophic borders that may vary by layer and precursor lesions that may predate and predict frank atrophy. Because of these considerations the Classification of Atrophy Meeting (CAM) group, an international meeting of retinal experts, recently proposed a consensus definition and nomenclature for SD-OCT-defined atrophy in the setting of AMD which applies various imaging modalities such as CFP, FAF, and NIR for complementary and confirmatory analysis (Fig. 6). This system is based on the observation that photoreceptor (or outer retinal) atrophy may occur without RPE atrophy (e.g., as with reticular pseudodrusen) while RPE atrophy is always associated with overlying thinning or loss of the outer retina, and the understanding that atrophy can undergo an evolution of different stages and paths. The CAM group proposed the following four terms to describe atrophy in AMD: cRORA, incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy (cORA), and incomplete outer retinal atrophy (iORA). GA represents a CFP subset of cRORA without NV, while cRORA refers to macular atrophy that may occur with or without NV. Nascent Ga1,25 represents a subset of iRORA without NV. Additionally, the CAM group proposed the following set of three specific OCT criteria that are required for the definition of cRORA: (1) a region of choroidal hypertransmission of at least 250 μm in diameter, (2) a zone of attenuation or loss of the RPE of at least 250 μm in diameter, and (3) evidence of overlying photoreceptor degeneration (loss of the interdigitation zone, EZ, and ELM and thinning of the outer nuclear layer in the absence of a scrolled RPE or other signs of an RPE tear). In patients with borderline features, it was recommended that other imaging modalities be used to assist the OCT interpretation.

The CAM group proposals have only recently been published and it remains uncertain whether these recommendations will gain widespread approval. This SD-OCT classification system of atrophy in AMD was proposed in hopes that the international community will adopt this consistent nomenclature that offers increased granularity and an objective OCT grading method for use by reading centers and large clinical trials. This detailed classification scheme will better define risk factors for progression and provide the platform to develop improved therapeutic strategies.3
**DIFFERENTIAL DIAGNOSIS OF AMD**

The clinical presentation and natural history of AMD may be variable and unpredictable. In addition, numerous degenerative and dystrophic diseases of the retina and RPE, with pigmentary abnormalities or lipofuscin accumulation, may have similar imaging features as that identified with non-neovascular AMD. As a result many conditions may mimic non-neovascular AMD, including various forms of pattern dystrophy, Best disease, Stargardt disease, central serous chorioretinopathy, the pachychoroid spectrum diseases, cone–rod dystrophy, hydroxychloroquine toxicity, cancer associated retinopathy, and myotonic dystrophy.

**IMAGING BIOMARKERS**

With the advent of multimodal imaging and computerized processing, there are current efforts to define which imaging features are most predictive of the prognosis of non-neovascular AMD. As there is tremendous heterogeneity in this disease, elucidating prognostic imaging biomarkers should improve management of the disease both at the individual patient and at the population levels.

**Traditional Imaging Biomarkers**

Early efforts have employed CFP to correlate drusen and pigmentary abnormalities with the risk of AMD progression. The number, area, and consistency of drusen have been positively correlated with AMD progression in many studies over the years as has the size, area, and location of pigmentary abnormalities observed with CFP.

Based on data from the AREDS trials, the 5-year risk of progression to advanced AMD (i.e., GA or NV) may be estimated based on the maximum drusen size and the presence or absence of pigmentary abnormalities in one or both eyes. For example, the progression risk for a patient with multiple medium drusen in one eye is 0.5% in the absence of pigmentary abnormalities, 5.0% with unilateral pigmentary abnormalities, and 12.9% with bilateral pigmentary abnormalities. Bilateral medium drusen confer a 2- to 4-fold increase in these rates. For unilateral large drusen the risk for progression is 3.9% in the absence of pigmentary abnormalities, 10.1% with unilateral pigmentary abnormalities, and 25.6% with bilateral pigmentary abnormalities, while bilateral large drusen have a 13.0% risk of progression in the absence of pigmentary abnormalities, 27.3% with unilateral pigmentary abnormalities, and 47.3% with bilateral pigmentary changes.

**Qualitative FAF patterns of the hyperautofluorescence surrounding the GA lesions have been shown to correlate with growth rates of GA.**

**SUMMARY**

- **Distinct OCT Imaging Classification**
  - **cRORA** defined by continuous absence of the EZ and interdigitation zone and severe thinning of the outer retina with an intact RPE band.
  - **iRORA** does not fulfill all three criteria for cRORA and typically demonstrates discontinuous hypertransmission.
  - **GA** represents a subset of cRORA without neovascularization identified with color fundus photography.

- **New OCT-based Classification System**
  - **B1, B2** iRORA does not fulfill all three criteria for cRORA and typically demonstrates discontinuous hypertransmission.
  - **C1, C2** cRORA is defined by continuous absence of the EZ and interdigitation zone and severe thinning of the outer retina with an intact RPE band.
  - **D1, D2** iRORA demonstrates thinning of the outer retina, an intact RPE band, and no hypertransmission.

- **AMD Risk Factors**
  - **Bilateral medium drusen** confer a 2- to 4-fold increase in progression rates as compared with unifocal lesions.
  - **GA** demonstrated the diffuse FAF pattern at baseline examination.
  - **Progression rates** of GA were significantly higher in eyes with baseline unifocal lesions progressing to multifocal, horseshoe, ring, or solid configurations had greater GA progression rates than eyes with a stable configuration.

- **Categorization System of GA**
  - **5-year risks** of GA progression range from 0.5% in healthy age-related changes to 12.9% with bilateral pigmentary abnormalities.

- **OCT Imaging and Prognosis**
  - **GA** enlargement in eyes with multifocal lesions compared with eyes with unifocal lesions.
  - **FAF patterns** are associated with progression rates.

**Multinucleate Cells and Optical Coherence Tomography**

- **Multinucleate cells** have been correlated with progression rates.

**Conclusion**

- **The Beckman Initiative** proposes a new methodology for assigning risk of progression to late AMD.

**FIGURE 6.** Description of new SD-OCT–based classification system recently proposed by the CAM group. The first and second rows illustrate OCT B-scans of each atrophy phenotype, without and with annotations respectively. The first and second rows illustrate OCT B-scans of each atrophy phenotype, without and with annotations respectively. The first and second rows illustrate OCT B-scans of each atrophy phenotype, without and with annotations respectively. The first and second rows illustrate OCT B-scans of each atrophy phenotype, without and with annotations respectively.
have been replicated to some extent in subsequent reports. Additionally, the extent of hyperautofluorescence surrounding atrophic lesions, defined as the rim-area focal hyperfluorescence or the convex hull (the convex polygon outlining the hyperautofluorescent area surrounding the lesion), have been positively correlated with lesion growth rates.

**OCT Biomarkers**

OCT analysis in particular provides various anatomic biomarkers, with qualitative and quantitative capability that could offer robust predictive information on visual outcomes, although results to date have been variable. This imaging modality provides data regarding drusen diameter, height, area, volume, shape, internal reflectivity, and homogeneity and direct evaluation of the RPE.

Drusen, reticular pseudodrusen, and hyperreflective foci are the pathognomonic features of early AMD. Studies have shown that drusen are dynamic structures that demonstrate repeated cycles of volume increase and decrease. Because of the known increased risk of AMD progression for patients with medium or large drusen on CFP, efforts have focused on determining which drusen-related features may indicate an increased risk of progression to late AMD. Particular drusen characteristics, such as moderate internal reflectivity may indicate progression to late AMD. Heterogeneous drusen reflectivity or hyporeflective spaces within drusen have been associated with the onset of focal RPE atrophy (Fig. 8). Greater height of drusenoid lesions as with a drusenoid PED indicates a greater risk of focal atrophy. As demonstrated by the AREDS results, 19% of eyes with drusenoid PEDs will progress to GA in 5 years. Greater height of drusenoid lesions as with a drusenoid PED indicates a greater risk of focal atrophy. Eyes with higher baseline drusen volume have an increased risk of progression to GA or NV. In a report by Folgar et al., abnormal thinning of the RPE-drusen complex at baseline was associated with progression to central GA in eyes with baseline noncentral GA. Drusen regression has been associated with rapid progression to late AMD, and refractile drusen may represent a form of regressing drusen the presence of which indicates an increased risk of progression to atrophy. The development and migration of outer retinal hyperreflective foci with SD-OCT, identified as pigmentary abnormalities with CFP, are directly associated with RPE atrophy and correlate with an increased risk of progression to focal atrophy (Fig. 8).

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**Figure 7.** Various FAF features and patterns associated with variable rates of progression of GA. Larger baseline lesion size, multifocal lesions, extrafoveal location, and increased convex hull have been associated with more rapid GA growth rates. Convex hull refers to the convex polygon outlining the hyperautofluorescent area surrounding the lesion. Adjacent FAF patterns have also been studied. The banded, diffuse, and especially diffuse-trickling patterns have also been associated with higher growth rates of GA. The diffuse trickling pattern is defined by gray atrophy (rather than the more typical black atrophy) with increased hyperautofluorescence at the lesion margins seeping toward the periphery. Dotted line: extent of convex hull. Reprinted from Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369–390. © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license.
greater risk for late AMD and ORA, but it remains unclear whether their presence predicts lesion growth rates, although they may predict future locations of GA and the development of multifocal lesions. Additional OCT anatomic biomarkers with prognostic value have been identified. Abnormalities of the junctional zone of atrophy, such as irregular RPE elevations, splitting of the RPE/Bruch’s membrane complex, and increased inner nuclear layer thickness, are associated with increased growth rates of GA lesions versus lesions with smooth margins (Fig. 9). Areas of EZ disruption may predict the location but not the growth rate of future GA lesions. A decrease in retinal thickness often occurs at the junctional zone prior to atrophic progression, resulting primarily from thinning of the outer retinal layers. The significance of ORTs remains unclear, as both the presence and absence of these lesions have been found to be associated with enlargement of atrophic areas. Eyes with GA have reduced subfoveal choroidal thickness compared with age-matched controls, although the prognostic significance of this finding is uncertain. While OCTA is still developing as an adjunct imaging modality, this modality has demonstrated absence of choriocapillaris flow in areas of GA and may eventually be used to detect choriocapillaris alterations (i.e., “signal flow voids”) that precede GA.

Multimodal imaging provides a wealth of data regarding retinal anatomy, but manual grading of increasingly large data sets, particularly in the context of large prospective epidemiologic studies, is not feasible. As a result, numerous automated and semiautomated algorithms for analysis of one or multiple AMD biomarkers have been proposed with promising results that can rival or outperform manual grading. Advances in computational analysis and machine learning should further improve these results, but these algorithms need
validation using large groups of patients before they are widely adopted in the routine management of AMD.

Recently, Lei et al. proposed a simple OCT-based grading system for scoring the risk of developing advanced AMD, which could potentially be adapted for clinical application. This system required the user to identify the presence of reticular pseudodrusen, outer retinal hyperreflective foci, hyporeflective drusen, and large central drusen volume (>0.03 mm³) in each eye, with one point assigned for each feature (yielding a maximum total risk score of 8). While there were no cases that progressed to advanced AMD over 18 months with a score of 2 or less, 70% of cases with a score of 7 or more progressed during this time period.

**Additional Risk Factors**

Many studies have identified demographic and environmental characteristics associated with the development and progression of AMD. Risk factors include advancing age, Caucasian ethnicity, female sex, and associated social and past medical factors, including smoking, obesity, cardiovascular disease, hypertension, and hypercholesterolemia. In recent years, significant efforts have attempted to identify genetic risk factors, and it is now believed that genetic variants associated with AMD account for approximately 70% of the overall risk of the condition. Two major loci have been identified at chromosomes 1q32 and 10q26, with these two loci accounting for half of the heritable risk of AMD. These loci include the Complement Factor H (CFH) gene involved in the alternative complement pathway, the age-related maculopathy susceptibility 2 (ARMS2) gene, and the adjacent high-temperature requirement factor A1 (HTRA1) gene. Many other mutations have been implicated in the development of AMD, including genes involved in the complement cascade, lipid metabolism, and extracellular matrix remodeling nearly all of which confer similar risks of GA and NV. These studies have yet to identify unique genetic factors specifically associated with the various phenotypes of AMD (i.e., no consistent single nucleotide polymorphism has been singularly linked to GA progression rates). Future endeavors should allow for greater understanding of the complex molecular genetics and harmonization of the various manifestations of this disease.

**CONCLUSIONS**

Nonneovascular AMD is a disease that has remarkable propensity to cause significant and progressive anatomic retinal disruption and represents a major burden of vision loss in the elderly population worldwide. Effective diagnosis and management relies heavily on a complete understanding of the broad multimodal imaging features of this disorder that are discussed in this review. Careful interpretation of the detailed features of nonneovascular AMD available with advanced multimodal retinal imaging will provide significant prognostic indicators, or biomarkers, of visual and anatomical outcome and will facilitate the guidance and optimal treatment and follow-up of patients with this disease.

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53. Domalpally A, Clemons TE, Danis RP, et al.; Writing Committee for the OPTOS Peripheral Retina (OPERA) study (Ancillary Study of Age-Related Eye Disease Study 2). Peripheral retinal changes associated with age-related


