PREDICTING PROGRESSION TO GA USING IMAGING BIOMARKERS

Several OCT findings can help clinicians better understand a patient's risk of progression to sight-threatening disease.

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The modern parameters for dry AMD disease staging were first outlined by the Beckman classification in 2013.[1] In 2017, the Classification of Atrophy Meeting provided an updated consensus on OCT-based classification of geographic atrophy (GA).[2] Dry AMD disease staging relies on a combination of dilated fundus examination, color fundus photography (CFP), fundus autofluorescence (FAF), and OCT. Disease progression is gauged by these same modalities, with OCT being the most reliable for assessing interval anatomic changes. FAF is particularly well-suited for tracking GA lesion topography over time, with active expansion of GA lesion(s) on FAF representing the key indication for considering anticomplement therapy.

Other structural and functional testing modalities are also under investigation as adjuncts for assessing the progression of dry AMD. For example, there is burgeoning interest in using OCT angiography to evaluate regional flow features of the choriocapillaris in different stages of dry AMD.[3] In addition, functional measurements can be used to quantify *sub-anatomic* AMD progression in patients, with studies validating functional metrics such as microperimetry, dark adaptation, contrast sensitivity, and low-luminance visual acuity.[4,5]

In clinic, the most granular assessment of retinal anatomy is derived from OCT, which has generated most modern imaging biomarker candidates. A variety of tomographic disease features have been reported, providing us with broad insight into the diversity of anatomic changes that can occur during the natural history of dry AMD. The ability to leverage these imaging biomarkers into risk stratification algorithms will improve our ability to counsel patients and direct clinical trial design.

While the dry AMD pipeline is overwhelmingly focused on curbing progression of established GA, it would be ideal to intervene prior to irreversible loss of retinal tissue. The confident prediction of areas of retina at high risk for progression to GA would facilitate testing therapeutic candidates for potential effect on the incidence of GA.

KEY TAKEAWAYS

- In the clinic, the most granular assessment of retinal anatomy is derived from OCT, which has generated most modern imaging biomarker candidates.
- Promising dry AMD imaging biomarkers include drusenoid lesions, intraretinal hyperreflective foci, loss of outer retinal integrity, choriocapillaris perfusion and thickness, and pigmentary changes.
- Eventually, the integration of multivariable risk calculators may provide composite progression estimates for patients, clinicians, and researchers.

TABLE. AMD BIOMARKER RISK ASSOCIATIONS

Biomarker	Hazard Ratio [95% CI]	Odds Ratio [95% CI]	Other	Prognostic Accuracy (AUC)[22]	Median Time to Conversion (years)[22]
Large drusen (> 125 µm)	6.26 [1.46-26.73]	5.53 [3.21-9.53]		59.7 [55.2-64.5]^	
Hyporeflective drusen core	2.85 [1.94-4.2]	3.84 [1.23-15.45][22#^]		50.9 [32.3-65]^	3.35^
	2.83 [1.89-4.26][21]	2.52 [1.59-3.98]			
Reticular pseudodrusen	1.8 [0.97-3.32] (not significant)	2.1 [1.16-3.81]		45.9 [27.6-60.8]^	
	1.95 [1.34-2.82][21]				
Drusenoid pigment epithelial detachment	2.36 [1.98-2.8][30]	4.19 [1.49-11.81]	62% of 37 eyes[13]	57.5 [38.1-73.3]^	4.81^
		6.66 [1.32-42.71][22#^]			
Serous pigment epithelial detachment			21% of 71 eyes[31]		
			50% of 20 eyes[12]		
Calcified drusen		6.36 [2.99–13.53][14]			
Drusen volume (≥ 0.03 mm^3)	2.08 [1.58-2.73]				
	1.74 [1.14-2.66][21]	4.3 [1.87-9.86]	RR 3.86 [2.40-6.21][32*]		
Intraretinal hyperreflective foci	9.97 [4.85, 20.49]	14.9 [2.7- 279.3][22]		61.6 [48.7-71]^	3.61^
	10.66 [4.96-22.89][21]	5.53 [3.21-9.53]			
External limiting membrane abnormality	17.34 [5.88-51.19]			54.4 [40.5-64.4]^	
Ellipsoid zone abnormality	6.1 [3.03-12.25]			58 [47-65.8]^	
Choroidal thickness		0.47 [0.28-0.8]			
Hypertransmission defect	80 [10.7-614][33]				
iRORA		29.60 [6.86-127.84]^			
Nascent geographic atrophy	78.1 [13.6-448.0][34]	28.27 [2.44-545.3][22#^]		65.1 [36.3-84]^	2.74^
Pigmentary changes on color fundus photography		20.5 [3.69-385.1][22#^]		63.6 [49.7-73.5]^	3.35^

Abbreviations: AUC, area under the curve; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; RR, relative risk. Note: All associated *P*-values are ≤ 0.05 unless otherwise noted. Risk associations are derived from Trinh et al unless otherwise cited.[6] Only studies not already included in meta-analysis are shown individually.

* When the fellow eye has advanced AMD

Adjusted odds ratio shown when available

^ Conversion to advanced AMD (geographic atrophy or macular neovascularization)

Here, we highlight a list of promising dry AMD imaging biomarkers and the associated risk of developing GA or advanced AMD (GA and/or macular neovascularization; Table). The predictive value of many of these markers has been evaluated by various groups over the years, including in a recent Cochrane-style meta-analysis by Trinh et al.[6]

DRUSENOID LESIONS

While the array of drusen and drusenoid lesion subtypes continues to grow,[7-9] only a subset has been shown to confer significant risk for progression to advanced dry AMD (Figure). They range widely in size (small < 63 µm, medium ≥ 63-125 µm, and large > 125 µm), location, morphology, and reflectance pattern. Drusen with hyporeflective or hollow cores have been associated with reduced choriocapillaris flow on OCT angiography.[10] Reticular pseudodrusen (RPD), or subretinal drusenoid deposits, are distinguishable by their subretinal location and typically have a distinctive reticular or "leopard spot" pattern on FAF.[8] Drusenoid and serous pigment epithelium detachments

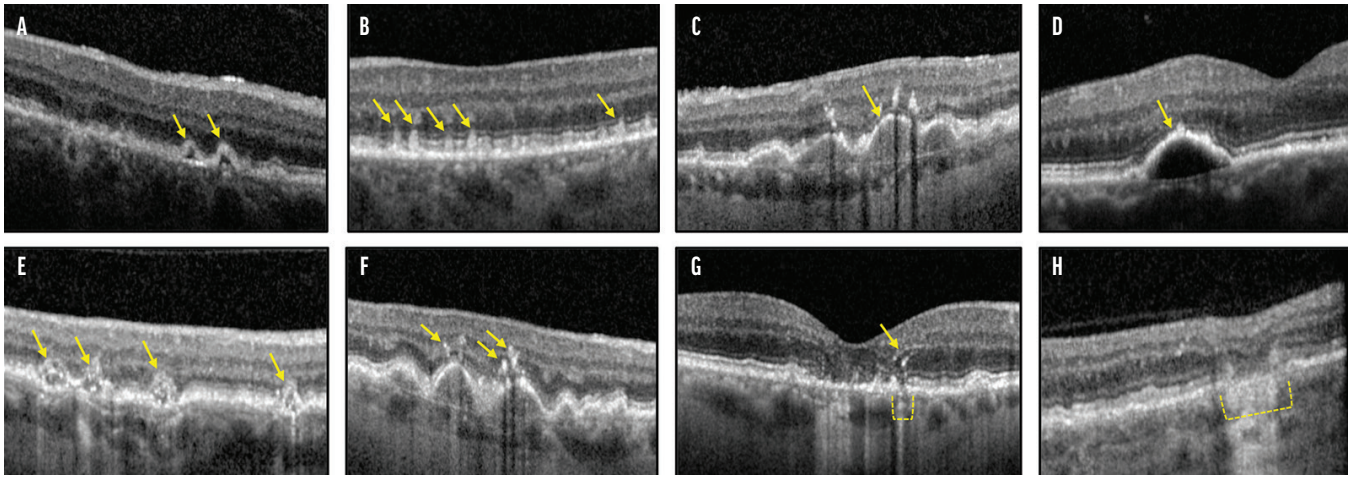

Figure. OCT biomarkers associated with the risk of progression to GA include drusen with hyporeflective cores (A), RPD (B), drusenoid PED (C), serous PED (D), calcified drusen (E), IRHF (F), nascent GA (G), and iRORA (H). The lesion of interest is indicated by a yellow arrow or dashed bracket. Of note, iRORA is also present in panel A, IRHFare present in panel C, and drusenoid PEDs are present in panel F.

(PEDs) can be quite large (hundreds of microns). Collapse of either lesion type is frequently followed by loss of outer retinal and retinal pigment epithelium (RPE) architecture, and for drusenoid PEDs, thinning of the underlying choroid.[11-13] Calcified drusen demonstrate either hyporeflective or heterogeneous internal reflectivity on OCT and appear refractile on examination.[14] Total drusen volume can be computed by automatic segmentation software. A greater than 0.03 mm^3 drusen volume constitutes a high drusen burden but only has a weak risk association with GA. Drusen undergo dynamic formation and regression with undulating total drusen volumes.[15] Progression to GA may be preceded by drusen regression, especially larger drusen.[16,17] While the total drusen volume trend may be more informative than any single absolute value, consideration of individual drusen attributes remains vastly more predictive.

INTRARETINAL HYPERREFLECTIVE FOCI (IRHF)

These foci are observed by OCT in the retina, often overlying drusen and drusenoid PEDs. They can be clustered or singular, and 87% are located below the junction between the outer plexiform layer and inner nuclear layer.[18] IRHF have a 66% correlation with pigment clumping on CFP.[18] These foci are hypothesized to be migrated RPE cells or infiltrating macrophages.[19,20] IRHF carry a significant risk for progression to advanced AMD with a risk association ranging between 5 and 15 and an estimated time to late AMD of 3.35 to 3.61 years.[6,21,22]

LOSS OF OUTER RETINAL INTEGRITY

The Classification of Atrophy Meeting group outlined the criteria and terminology for staging structural retinal deterioration preceding GA as well as defining GA. These stages are termed *incomplete RPE and outer retinal atrophy* (*iRORA*) and *complete RPE and outer retinal atrophy* (*cRORA*).[2] cRORA is defined by outer retinal and RPE loss with choroidal hypertransmission ≥ 250 µm in diameter. iRORA lesions include all three of these features but do not quite fulfill cRORA criteria.

A separate, somewhat intermediate imaging entity is nascent GA, which is defined by either subsidence of the outer plexiform layer and inner nuclear layer, or a hyporeflective wedge in Henle nerve fiber layer.[16] It may be accompanied by RPE attenuation and choroidal hypertransmission and often overlaps with iRORA lesions.[16] Objectively, iRORA and nascent GA lesions represent later stages of disease in which irreversible tissue loss has already occurred. Predictably, they are both highly associated with progression to GA. While this is useful for preparing patients for impending vision loss, these biomarkers are impractical for potential trials aiming to modify GA incidence. Imaging biomarkers that precede these substantive anatomic lesions would be more useful for any therapeutic attempts to forecast and modify GA incidence.

CHORIOCAPILLARIS PERFUSION AND THICKNESS

Focal thinning of the choriocapillaris has been associated with drusen, particularly drusen with hyporeflective cores. RPE loss correlates linearly with choriocapillaris loss, and focal flow impairments have been found in relation to drusen, as well as in areas of nascent GA.[23-25] In a meta-analysis, total choroidal thickness was inversely correlated with risk for GA (odds ratio = 0.476).

PIGMENTARY CHANGES

In a follow-up study to their meta-analysis, Trinh et al evaluated the accuracy of biomarker risk associations to predict advanced AMD.[22] The highest risk biomarkers from their prior analysis were compared with their prognostic accuracy against CFP in a real-world, longitudinal

study. Surprisingly, pigmentary abnormalities on CFP had the most impressive profile in terms of prevalence and prognostic performance (area under the curve = 77.7% [68.1, 87.3]) and sensitivity (92%). Pigmentary changes were previously independently identified as a risk factor for the presence of nascent GA (odds ratio = 16.84 [2.42-117.24]),[16] which is itself not distinguishable on examination or CFP. This study re-establishes that macular pigmentary changes should remain a reliable and highly predictive biomarker for progression to advanced dry AMD and may be especially useful in under-resourced clinics, remote screening programs, and AI algorithms.

IMPLEMENTING BIOMARKERS IN THE CLINIC

OCT is the cornerstone for dry AMD staging and risk stratification. Retina specialists should be aware of the range of possible structural changes in this heterogenous disease and their relative prognostic implication for progression to vision-threatening disease. Eventually, the integration of multivariable risk calculators may provide composite progression estimates for patients, clinicians, and researchers.

Progress toward this goal is underway, as our group and others have already developed deep-learning algorithms to predict progression to GA.[26,27] Automated prediction systems are already in use, as AI-based software (eg, RetInSight, Topcon) was approved in Europe, Australia, and New Zealand, and under investigational use in the United States.[28,29] Time will tell whether these systems will be integrated into the retina clinic, employed for patient screening, monitoring, and outcome quantitation in clinical research, or both. ■

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