

AN OVERVIEW OF BIOMARKERS IN RETINAL DISEASE

Advanced imaging modalities and artificial intelligence are opening doors to better diagnostics.
Part 1 of a two-part series.

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Researchers have long understood that the retina can be considered an extension of the brain, and its location allows for detailed anatomical and physiological analyses of neural mechanisms that underpin the brain's primary information processing.¹ Thus, it's no surprise that retinal imaging, and OCT in particular, has grown so rapidly in the field of medicine as a means to diagnose, treat, and study diseases. Its application far exceeds that of ophthalmology, as ocular manifestations exist for a variety of systemic conditions, including hypertension, metastatic carcinoma, autoimmune conditions, acquired immunodeficiency syndrome, and diabetes.²

Unsurprisingly, as imaging of the retina has grown, so has our pattern recognition of retinal biomarkers. This is further aided by the use of artificial intelligence (AI), which has allowed identification of new biomarkers and the recharacterization of previous biomarkers to improve their utility when staging disease.

Several common OCT imaging biomarkers are being used in retinal vascular diseases (Table). Biofluid markers (eg, serum, plasma, aqueous, vitreous, and tears) for systemic conditions and anterior segment markers are not covered in this article, but will be shared in part 2 as they are also crucial in the understanding and treatment of disease.

WATCH THE FLUID & THE PERIPHERY

Separating fluid into its component parts has been an important marker for disease severity since the Comparison of Age-Related Macular Degeneration Treatments Trial, which showed that intraretinal cystoid spaces had a greater negative impact on visual acuity than subretinal fluid at all time points analyzed.³ Logically, fluid can cause disruption

of any of the 10 retinal layers, hindering the processing of visual information.

As with most OCT-based biomarkers, retinal layer disruptions are now easier to discern with the increased resolution of retinal imaging. As newer OCT models increase the scanning speed and depth of penetration and decrease the signal-to-noise ratio, more of the retina will be visible on imaging, such as the choroid, which was inaccessible before the advent of enhanced depth imaging.

With the introduction of OCT angiography (OCTA), further vascular and choroidal neovascular membrane patterns

AT A GLANCE

- ▶ As newer OCT models increase the scanning speed and depth of penetration and decrease the signal-to-noise ratio, more of the retina will be visible on imaging.
- ▶ The relationships between clinical characteristics and imaging markers require advanced analytics such as artificial intelligence to uncover meaningful associations.
- ▶ Retinal fluid distribution, including intraretinal cystoid fluid, subretinal fluid, and subretinal pigmented epithelial fluid, have been investigated as imaging markers for wet AMD.

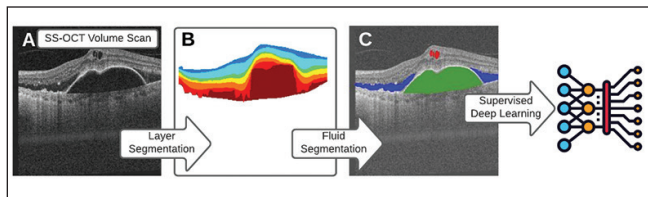


Figure 1. An example of the steps involved when using an AI algorithm to analyze OCT scans. Each swept-source OCT volume scan can first be automatically segmented into retinal layers (A). This results in retinal layers (B) that can be used as an additional information source to encode spatial information regarding the location of fluid within the retina (C).

have been discovered as biomarkers. Further segmentation of OCTA scans into the superficial capillary plexus and deep capillary plexus also adds further information, as clinicians can measure the density of vessels in these layers.

Aside from macular markers, additional biomarkers exist in the peripheral retina that are associated with various retinal vascular conditions, such as peripheral retinal ischemia in diabetic macular edema. Therefore, the field of view provided by an imaging device must be taken into account when assessing biomarkers.⁴

ADVANCED ANALYTICS

As retinal imaging modalities continue to increase in complexity, the relationships between clinical characteristics and imaging markers require advanced analytics such as AI to uncover meaningful associations. AI can now help to analyze OCT images, fundus photography, and other imaging modalities and has demonstrated an accurate diagnostic ability and structure-function mapping of the retina (Figure 1).^{5,6} In addition, using AI to analyze outer retinal thickness, hyperreflective foci, and area of drusen on OCT has demonstrated prognostic capabilities.⁷ For example, in patients with AMD and geographic atrophy (GA), a thinner outer nuclear layer was predictive of functional outcomes on microperimetry using an AI model.⁶ The progression of GA was further evaluated using deep learning analysis of OCT, where increased hyperreflective foci concentrations in the junctional zone were predictive of loss of retinal pigmented epithelium.⁸ Other studies have confirmed hyperreflective foci on OCT, along with drusen, as predictive of AMD progression.^{7,9}

Although similar biomarkers are analyzed on fundus photographs using AI with the intention of diagnosing patients with AMD, many of these studies do not report imaging findings but rather the algorithm's diagnosis accuracy.¹⁰

AI AND THE FUTURE

Imaging markers for wet AMD are distinct from those for GA, with OCT being the most commonly investigated imaging modality.¹¹ Retinal fluid distribution, including intraretinal cystoid fluid, subretinal fluid, and subretinal pigmented epithelial fluid have been investigated as imaging markers for wet AMD.¹²⁻¹⁴ Image-segmenting AI could help

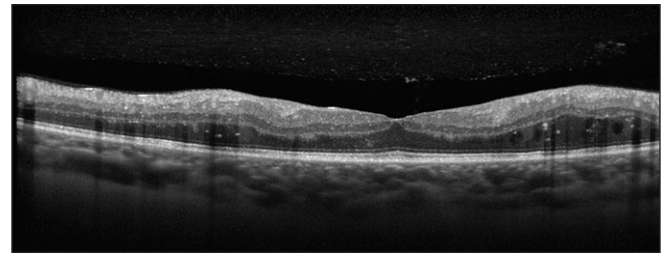


Figure 2. A swept-source OCT volume scan showing hyperreflective foci.

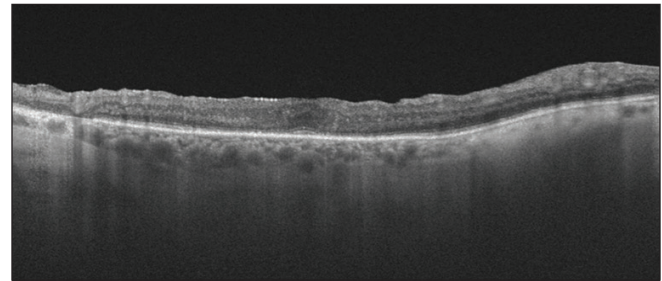


Figure 3. A swept-source OCT volume scan showing the disorganization of retinal inner layers in a patient with diabetic macular edema.

TABLE. RETINAL IMAGING BIOMARKERS IN WET AMD, DIABETIC MACULAR EDEMA, AND RETINAL VEIN OCCLUSION

Imaging Focus	Biomarker
Fluid	Subretinal fluid, intraretinal fluid, serous pigment epithelial detachment (PED)
Retinal layers	Detection of apoptosing retinal cells, subretinal hyperreflective material, photoreceptor layer integrity (including external limiting membrane and ellipsoid zone), hyperreflective retinal dots/foci (Figure 2), outer retinal tubulations, retinal pigment epithelium (RPE) tears, vitreomacular traction and adhesion, disorganization of retinal inner layers (Figure 3), intraretinal cystoid spaces, bridging retinal processes, photoreceptor outer segment, taut posterior hyaloid membrane, drusen (cuticular, reticular, calcified soft, pseudo), drusenoid PED, acquired vitelliform lesion
Choroid	Sub-RPE hyperreflective columns, prechoidal clefts, choroidal caverns, sub-foveal choroid thickness and volume, choroidal vascular index, hyperreflective choroidal foci
Vasculature	Ischemic index, foveal avascular zone, vessel density, deep-superficial flow ratio
Choroidal neovascular membrane	Type (1, 2, 3), medusa form, sea-fan form, pruned vascular tree pattern, tangled network pattern, vascular loop, shallow irregular RPE elevation

quantify these fluids, providing a more accurate evaluation of their clinical effect and relationship to visual morbidity.

Some of the structural markers common in GA also have been associated with wet AMD development, including compromised photoreceptor layer integrity; hyperreflective bands and foci on OCT; retinal pigment epithelium tears; and choroidal features.¹¹ OCT is particularly conducive to AI analysis given it's structured and segmented presentation, and the biomarkers identified above could plausibly be investigated using AI. Thus, AI algorithms could be implemented in clinical contexts to improve diagnostics and support clinical decision making for retina specialists treating patients with wet AMD and other conditions.¹⁵ ■

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