

Beyond Fundus Autofluorescence: Evolving Clinical Endpoints in Geographic Atrophy

A White Paper on Imaging Endpoints in
Dry AMD Clinical Trials

INTRODUCTION

Geographic atrophy (GA) is the advanced non-neovascular or dry form of age-related macular degeneration (AMD) and one of the leading causes of irreversible central vision loss in older adults. As photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris are progressively lost, the resulting scotomas expand into the central field, impairing reading and other visually demanding tasks. Millions are affected globally, and prevalence is rising with an aging population.

Until 2023, no therapies had received regulatory approval for GA. The approvals of pegcetacoplan (Syfovre™) and avacincaptad pegol (Izervay™) established that the pathophysiology of GA is modifiable and that clinical trial infrastructure capable of demonstrating a treatment effect on total lesion growth using fundus autofluorescence (FAF) imaging was achievable, but also surfaced a question now shaping the next generation of trial design: anatomic slowing of lesion growth did not coincide with measurable benefit across prespecified secondary outcomes, including visual function endpoints, in either program. This paper examines the established FAF-based lesion area endpoint paradigm and the considerations driving its evolution, with particular attention to OCT-based approaches including ellipsoid zone (EZ) attenuation, choroidal hypertransmission defects, and the outer retina-choroid (ORC™) imaging approach. It is intended for retinal specialists engaged in clinical trial design and industry stakeholders with an interest in endpoint selection in GA.

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1 Fundus Autofluorescence-Based Lesion Area: The Established Standard and Its Limitations

A reduction in growth rate of total lesion area using FAF images became the primary endpoint for GA clinical trials through a regulatory consensus forged at the 2006 joint NEI/FDA Symposium on Ophthalmic Clinical Trial Design and Endpoints. The central problem was that visual acuity, the conventional primary outcome in retinal disease, is poorly suited to GA. Because RPE loss begins in the parafoveal region, substantial macular tissue can be destroyed before central acuity is affected. Mean visual acuity decline in GA runs approximately 6.2 letters over 12 months with variability of ± 15.6 letters in large clinical trial populations, a signal-to-noise ratio that would require prohibitively large and lengthy trials to detect a treatment effect reliably.¹

The symposium concluded that anatomic progression of GA, quantifiable by FAF, was an acceptable primary endpoint, with the understanding that a demonstrated treatment difference would be clinically relevant even without a concurrent vision benefit.² FAF offered practical advantages: reliable delineation of lesion boundaries through hypoautofluorescent signal, straightforward multi-site image acquisition, and an established body of natural history data linking lesion area to scotoma extent.²

This regulatory framework, along with guidance from a 2017 workshop³, guided the design of every major GA trial that followed, from the intravitreal lampalizumab phase 3 programs through the complement inhibitor trials that ultimately led to the first FDA approvals for GA in 2023. The pivotal OAKS and DERBY trials of intravitreal pegcetacoplan and the GATHER1 and GATHER2 trials of intravitreal avacincaptad pegol all used FAF-measured GA lesion area as the primary endpoint, and both drugs received FDA approval on the basis of statistically significant reductions in lesion growth rate, 17 to 22% for pegcetacoplan at 24 months and 14 to 27% for avacincaptad at 12 months.^{4,5}

Despite demonstrating anatomic efficacy, neither drug showed benefit in any prespecified functional outcome at the time of approval.^{4,5} While the FDA was satisfied with the treatments' impact on GA lesion area, the EMA drew a different conclusion, issuing a negative opinion on pegcetacoplan on the grounds that lesion growth slowing did not lead to clinically meaningful benefits for patients.^{6,7}

Technical Limitations of the Modality

FAF also carries intrinsic technical constraints. Blue-light FAF signal is attenuated by macular pigment in the foveal region, complicating assessment of foveal involvement.⁸ Cataract reduces blue-light transmission into the eye and can further degrade signal quality, introducing a confound that is difficult to control across multi-site trial populations. FAF imaging for GA grading has historically been performed on the Heidelberg Spectralis, a high-cost device that is not uniformly available across potential clinical sites, which may limit feasibility in broader trial networks. En face images provide no depth information, so FAF cannot distinguish which retinal layers are involved at a given locus or whether photoreceptor degeneration is extending beyond the lesion boundary. Clinicopathologic work has shown that FAF signal in GA is locally multifactorial, with both RPE morphology and photoreceptor integrity contributing, meaning phenotypically distinct RPE states can produce overlapping FAF signatures that standard hypo/hyperautofluorescence classification does not resolve.⁹

2 OCT-Based Structural Endpoints: Capturing What FAF Imaging Cannot

OCT has been available as a clinical imaging modality since the 1990s, and the emergence of OCT-based structural measures as primary endpoints in GA trials is now gaining momentum, supported by an accumulating body of biological rationale, validated measurement methodology, and explicit regulatory endorsement. The field is reassessing its endpoint framework in light of the results observed with the first approved therapies, and OCT-based structural measures have moved from a supporting role to primary contention as that reassessment proceeds.

OCT in GA: Clear Advantage in Revealing Structure

The fundamental advantage of OCT over FAF in GA is depth resolution. FAF produces a single en face signal reflecting RPE lipofuscin fluorescence, collapsing the outer retinal and choroidal stack into a two-dimensional image. OCT resolves individual tissue layers with micrometer precision. GA involves the progressive loss of photoreceptors, RPE, and choriocapillaris, and these losses do not proceed simultaneously. Their relative timing has direct implications for how disease activity and treatment response are measured.⁵

Photoreceptor degeneration, visualized as loss of the EZ band on OCT, consistently precedes and spatially exceeds RPE loss. A post hoc analysis of OAKS and DERBY trial data using deep learning segmentation found that EZ loss reduction with pegcetacoplan was substantially greater than RPE loss reduction: 53% and 46% EZ reduction versus 22% and 20% RPE reduction in OAKS; 47% and 46% versus 27% and 21% in DERBY, for monthly and every-other-month dosing.¹⁰ This suggests OCT captures a biologically earlier and more sensitive signal of disease activity, and that treatment effects measured at the photoreceptor level may be larger than those captured by FAF alone.

OCT-Defined Precursor Lesions: iRORA, cRORA, and Choroidal Hypertransmission Defects

FAF is largely insensitive to the OCT-defined precursor changes, including incomplete RPE and outer retinal atrophy (iRORA), nascent GA, and choroidal hypertransmission defects, that represent the transition from intermediate AMD to established GA. These features, defined by the Classification of Atrophy Meeting group as requiring vertically co-localized photoreceptor degeneration, RPE disruption, and choroidal hypertransmission on OCT, are not reliably visible on FAF imaging.¹¹ This limits FAF's utility for trials targeting earlier disease stages, where the opportunity for meaningful intervention may be greatest.

Lesion Type	Key OCT Criteria and Definition
iRORA (Incomplete RPE and Outer Retinal Atrophy)	Co-localized photoreceptor degeneration, abnormal RPE band (attenuation or disruption), and outer nuclear layer subsidence on OCT, without a confluent choroidal hypertransmission defect meeting the 250 micron threshold.
cRORA (Complete RPE and Outer Retinal Atrophy)	All iRORA criteria plus a confluent choroidal hypertransmission defect of 250 microns or greater; the OCT correlate of geographic atrophy, closely concordant with the FAF-measured lesion.
Nascent GA	Early photoreceptor atrophy on OCT that precedes FAF-detectable lesion formation.
Choroidal Hypertransmission Defects (hyperTDs)	Focal increased choroidal reflectance on OCT caused by RPE loss; detectable before iRORA criteria are met and predictive of progression to iRORA or cRORA.

Ellipsoid Zone Attenuation: From Exploratory to Approvable

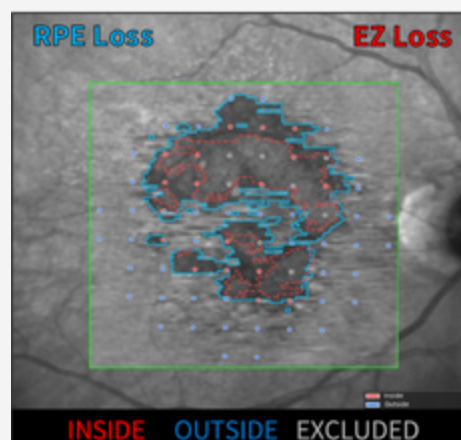
The EZ band on OCT reflects photoreceptor integrity directly, providing a readout of viability that FAF, which reflects RPE lipofuscin rather than photoreceptor status, cannot provide. EZ assessment encompasses two measures: total EZ attenuation, representing complete loss of the EZ band corresponding to irreversible photoreceptor death; and partial EZ attenuation, defined as EZ-to-RPE thickness of 20 microns or less, representing a zone of photoreceptor outer segment damage that precedes complete loss and may represent a therapeutic target for rescue.¹²

The regulatory pathway for EZ attenuation as a primary endpoint was established through the ReCLAIM-2 phase 2 trial of elamipretide, which prespecified EZ integrity preservation as a secondary endpoint and demonstrated a 43% reduction in total EZ attenuation and 47% reduction in partial EZ attenuation at 48 weeks compared with placebo.¹² Although the trial did not meet its primary endpoints of GA lesion progression and LL-BCVA change, the EZ attenuation findings prompted direct FDA engagement, and in 2023 the agency confirmed total EZ attenuation as an approvable primary endpoint for elamipretide's mitochondrial-protection mechanism in dry AMD.^{12,13} This regulatory confirmation has directly enabled the design of the phase 3 ReNEW and ReGAIN trials of elamipretide, both of which use the rate of change in macular area of photoreceptor loss assessed by OCT EZ mapping as their primary endpoint.¹⁴

Several properties of EZ-based measurement are directly relevant to trial design. EZ loss extends beyond and precedes FAF-defined lesion boundaries, capturing photoreceptor degeneration in the perilesional zone before it is incorporated into the FAF-defined atrophic area.^{10,13} OCT is not subject to the macular pigment attenuation that limits blue-light FAF in the foveal region, enabling reliable assessment of foveal involvement.¹⁵ The baseline EZ-RPE difference, the spatial discordance between photoreceptor degeneration and RPE loss at treatment start, predicts both progression rate and treatment response magnitude. Eyes in the highest EZ-RPE difference quartile showed the greatest benefit from pegcetacoplan in the OAKS and DERBY post hoc analysis, suggesting a potential stratification tool for trial enrichment.¹⁰ OCT-based GA area measurements also show strong concordance with FAF ($r=0.93$ sustained through 18 months in GATHER1 post hoc data), confirming OCT as a reliable method for lesion area measurement in trials.¹⁵

Structure/Function Correlation with Microperimetry and Layer Loss Analysis

Correlate Foci + Multiple Layers. Al-kherson, Wykoff, et al. Microperimetric Sensitivity and RPE and Photoreceptor Outer Segment Loss by En Face OCT Analysis Using Outer Retina Choroid (ORC) in Eyes with GA. *ARVO 2027 Abstract submission in press.*



Choroidal Hypertransmission Defects: From Precursor Biomarker to Validated Endpoint

A parallel line of OCT endpoint development has focused on choroidal hypertransmission defects (hyperTDs) as a measurable en face OCT biomarker with particular relevance to earlier-stage disease. Where RPE is attenuated or absent, light passes through into the choroid rather than being absorbed, producing increased reflectivity on B-scan and appearing as focal bright areas on a sub-RPE en face slab. This is the same hypertransmission signal that defines both iRORA and cRORA in the CAM classification, and en face imaging makes it measurable as a continuous area variable in a manner directly analogous to FAF-based lesion area measurement.^{11,16}

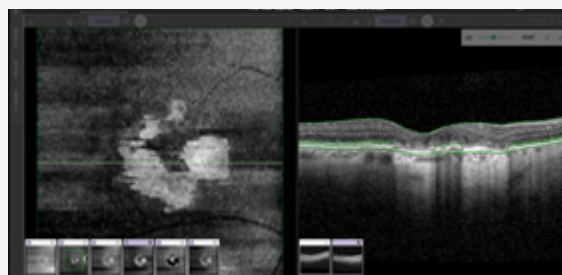
Natural history studies have shown that persistent hyperTDs with a greatest linear dimension of 250 μm or more predict progression to iRORA or cRORA in a substantial majority of intermediate AMD eyes over two years, and that the hyperTD signal can precede nascent GA on B-scan.^{14,17} Intergrader reliability studies have reported high agreement for hyperTD detection on en face images, and automated detection algorithms have been developed and tested across spectral-domain and swept-source OCT platforms.¹⁸ A consensus trial design paper from the CAM group noted that hyperTD onset and enlargement, alongside progressive EZ loss, are the OCT features that have to date been characterised as continuous variable endpoints suitable for intermediate AMD trials.^{18,16} More recently, a prospective natural history cohort study modelled two iAMD trial designs using hyperTD growth rate as the primary endpoint and demonstrated that a 50% reduction in progression could be detected with 80% power using fewer than 100 eyes per arm over two years, supporting the practical feasibility of this endpoint in early-phase interventional trials.¹⁹

This work is relevant to the ORC imaging approach described in Section 3. Both measure choroidal hypertransmission through areas of RPE loss from a sub-RPE en face slab. The hyperTD approach identifies discrete lesions above a size threshold. ORC sums the full posterior voxel signal across the slab using a vendor-agnostic noise reduction algorithm. The approaches are methodologically distinct but address the same biological signal, with the hyperTD literature providing the more developed longitudinal and endpoint validation evidence to date.

OCT-based structural endpoints offer greater biological specificity than FAF imaging, capturing earlier disease events and resolving layer-specific pathology that a single en face signal cannot. Whether these advantages translate into more sensitive primary endpoints in prospective trials remains an active area of investigation, and the sections that follow examine how the regulatory landscape and emerging imaging approaches are advancing that question.

Hypertransmission Defect on ORC *en face* Imaging

The decomposed *en face* ORC image optimizes visualization of HTDs.



3 Advancing OCT-Based GA Assessment: The Outer Retina-Choroid Imaging Approach

The ORC imaging approach is a further OCT-based method for measuring GA lesion area, currently at proof-of-concept stage and not yet formally qualified as a clinical trial endpoint. It generates en face images by summing voxels across the posterior signal band, encompassing outer retinal and choroidal layers, from a DICOMized OCT scan processed with a noise reduction algorithm, without relying on layer-by-layer segmentation. The resulting image captures choroidal hypertransmission through areas of RPE loss in a manner that is designed to be independent of OCT manufacturer, with preliminary data across two major platforms.^{20,21}

Validation Evidence

Three proof-of-concept studies provide the current evidence base for ORC, drawn from independent cohorts at two clinical sites.

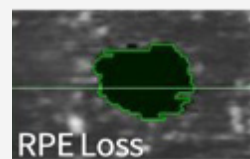
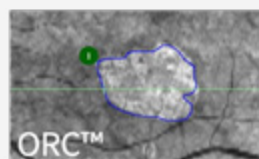
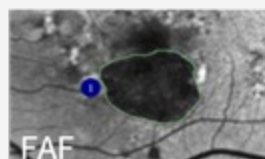
In a study of 44 GA eyes imaged with both Heidelberg Spectralis and Zeiss Cirrus OCT devices at the Wisconsin Reading Center, ORC-derived GA area measurements showed close concordance with FAF-based measurements (mean difference -0.02 mm^2 , ICC 0.99) and with cRORA-based OCT measurements (mean difference -0.65 mm^2 , ICC 0.98).²⁰ No significant difference in GA area estimates was found between the two OCT platforms ($P > 0.79$). In eyes with calcified drusen, ORC provided cleaner lesion boundary definition than cRORA annotation, where segmentation errors are more likely.²⁰

An independent cohort study of 29 eyes at Retina Consultants of Texas, including both atrophic AMD and macular atrophy secondary to inactive neovascular AMD, found comparable ORC and FAF area measurements (mean difference 0.07 mm^2 , 1%) across both subtypes.²¹ Two observations from this study are relevant to ORC's relationship with FAF. Certain hypofluorescent areas on FAF that retained intact RPE on B-scan showed normal signal on ORC, suggesting ORC may avoid some measurement error attributable to macular pigment or non-atrophic hypoautofluorescence. Additionally, regions classified as GA on FAF sometimes corresponded to iRORA or fibrosis on OCT rather than cRORA, distinctions that ORC with registered B-scans can help clarify.²¹

A third study comparing ORC and Layer Loss Analysis for iRORA detection in 37 eyes with intermediate AMD and GA showed high agreement between approaches (94.6% by eye, 88.6% by locus).²² ORC images identified hypertransmission defects at the GA border and in the perilesional zone that were not well seen on FAF.

GA Area Correlation

Lesion areas by all 3 modalities are highly correlated. Presented at Clinical Trials at the Summit, R. Danis, June 2025.



Context and Outlook

The available data establish consistent measurement concordance with FAF and cRORA-based OCT methods across independent cohorts and two OCT platforms, and sensitivity to hypertransmission features at the GA border and in eyes with calcified drusen where segmentation-based methods can be less reliable.

The current evidence base is cross-sectional and longitudinal data demonstrating sensitivity to GA progression over time have not yet been published. Formal biomarker qualification with FDA, and EMA Scientific Advice for programs targeting global registration, would be required before ORC could serve as a primary or co-primary endpoint in a pivotal trial. Deep learning-based automated analysis tools are in development.²¹ ORC is appropriately positioned today as a secondary structural imaging approach and a candidate for the prospective validation and qualification work that would determine its role as an endpoint in pivotal trial design.^{21,22}

FAF-based GA assessment has always been a multimodality approach: near-infrared reflectance (NIR) imaging is routinely used alongside FAF to aid lesion boundary delineation, and color fundus photography is incorporated at some sites. MERIT now advocates that FAF grading employ ORC as the primary complementary imaging modality, alongside NIR and fundus photography where available, to provide a more complete structural characterization of lesion extent and boundary definition than FAF alone affords.

CONCLUSION

The first approved therapies for geographic atrophy demonstrated that slowing lesion growth as measured by FAF is an achievable and regulatory-recognized therapeutic objective. They also exposed the limitations of relying on a single en face imaging modality: anatomic area reduction did not differentiate treatment effects at the layer level, could not detect perilesional disease activity, and was insufficient for regulatory approval outside the United States. Understanding what drives those limitations, and how imaging endpoints can be designed to address them, now shapes the endpoint strategies of every program that follows.

OCT-based structural endpoints have moved from exploratory tools to regulatory-endorsed primary outcomes. The regulatory landscape has shifted, with EMA and MHRA requiring demonstrated clinical meaningfulness and the FDA endorsing OCT-based photoreceptor measures as approvable primary endpoints. Choroidal hypertransmission defects have been validated as a continuous, measurable endpoint particularly well suited to earlier-stage disease.

OCT-based approaches that measure choroidal hypertransmission directly, including both hyperTD analysis and integrated posterior signal methods, extend the endpoint toolkit to earlier disease stages. Longitudinal validation will determine what role they ultimately play. Multimodality imaging employing FAF and OCT as complementary structural imaging modalities represents an enhanced approach that offers improved precision and accuracy in lesion characterization and is currently being employed in MERIT GA studies. Critically, improved morphologic endpoints that capture layer-specific pathology are expected to reveal tighter structure-function relationships than FAF alone can provide, with the expectation that layer-specific structural measures will correlate more directly with clinically meaningful functional outcomes than lesion area alone. Establishing these relationships is an active area of investigation and will be essential for achieving multi-national regulatory approval of new therapies for dry AMD.

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