iRORA in Intermediate & Advanced Atrophic AMD: Detection & Assessment by 2 OCT-based Methods

3929-0143

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BACKGROUND/PURPOSE

The hallmark lesion of advanced atrophic age-related macular degeneration (AMD) is geographic atrophy (GA). On spectral-domain OCT (SD-OCT), GA is defined by the Classification of Atrophy Meeting (CAM) group as *complete RPE and outer retinal atrophy* (cRORA; CAM Report No. 4). cRORA is characterized by (1) hypertransmission defect (HTD), (2) a zone of retinal pigment epithelium (RPE) loss or degeneration measuring at least 250 um on a B-scan, and (3) outer retinal atrophy. When HTD, outer retinal atrophy, and RPE atrophy are present but the linear extent of RPE loss is <250 um, the term *incomplete RPE and outer retinal atrophy* (iRORA) is used.

iRORA lesions carry a high risk of progression to cRORA. In the GATHER1 trial of avacincaptad pegol, the 18-month progression rate from iRORA to cRORA was 27-42% in sham-treated eyes and 8-27% in treated eyes (Corradetti et al., 2021). Over 24 months, most iRORA lesions convert to cRORA (Corradetti et al., 2025). Although GA expansion rate remains the primary outcome in clinical trials of atrophic AMD therapies, iRORA may identify eyes at higher overall risk of GA progression. Tracking the incidence and progression of iRORA may be particularly useful in studies of intermediate AMD before the onset of GA.

Identification of iRORA has typically relied on manual grading of OCT B-scans, often with assistance from registered *en face* images (CAM Report No.4). We compared two approaches for iRORA identification: (1) manual grading using registered *en face* ORC™ images (which visually highlight HTD) with corresponding B-scans, and (2) automated co-localization of ellipsoid zone (EZ) loss and RPE loss on en face thickness maps generated by machine-learning-assisted OCT segmentation, followed by automated size classification (Layer Loss Analysis, LLA).

Figure 1. Image of an eye with GA showing FAF image (top left) and ORC (bottom left) with corresponding B-scan images. Blue and yellow arrows mark two regions with HTD, identified by ORC features but not well seen on FAF, that were further assessed using B-scans. In both cases, the lesions of HTD did not meet the criteria of iRORA.

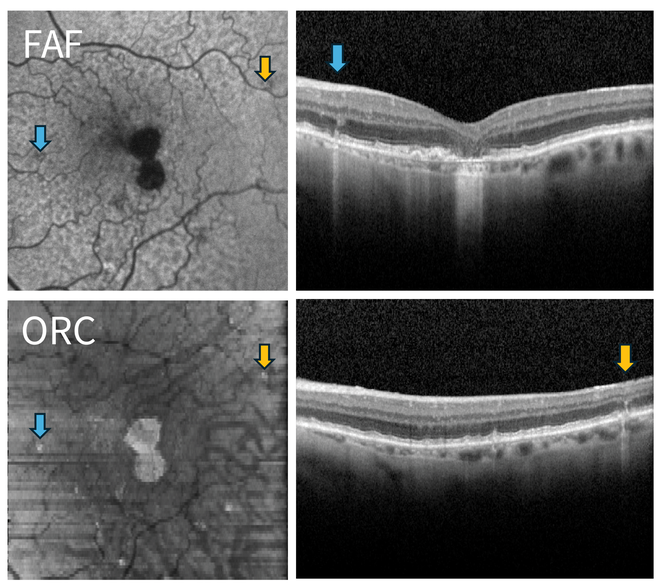
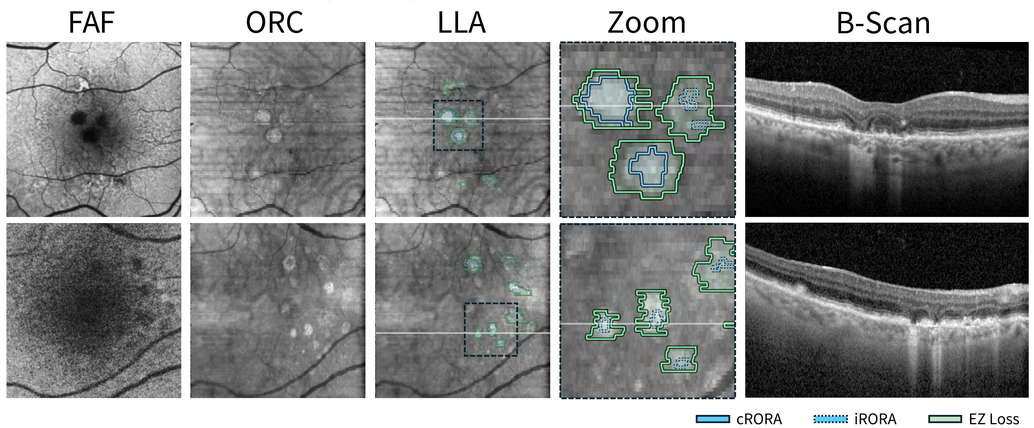


Figure 2. Top row, an eye with multiple loci of abnormality on both FAF and ORC. Three regions of interest are shown from the LLA analysis with a representative B-scan that passes through an area of cRORA and iRORA (top right). The LLA and Zoom images show 1) areas of EZ defect outlined in green, and 2) areas of RPE defect outlined in blue. Lesions meeting the size criteria for iRORA are shown with dashed lines while those larger have solid lines. Bottom row, a second eye with multiple loci of iRORA on FAF and more notably on ORC™ and LLA. The representative B-scan passes through two regions of iRORA.



METHODS

This post hoc analysis used a convenience sample of 37 eyes from 23 participants at a single center. Eyes had intermediate AMD or GA without neovascular features and were imaged with Spectralis SD-OCT (Heidelberg Engineering). De-identified images were converted to DICOM format and uploaded to the EXCELSIOR™ platform (MERIT CRO), where a machine-learning algorithm segmented the EZ, RPE, and Bruch's membrane (BM) layers. A single grader (RPD) performed manual correction on each B-scan.

ORC™ method:

En face ORC™ images were generated by summing voxels from the posterior signal band (outer retina and choroid) within each DICOM-formatted OCT scan, followed by a proprietary noise-reduction algorithm. A single grader (MDV) manually reviewed registered B-scans to confirm iRORA features and marked iRORA loci on the corresponding *en face* ORC™ image, often using the HTD signal to aid localization (**Figure 1**).

Layer Loss Analysis (LLA):

Regions of EZ loss and RPE loss were automatically derived from *en face* thickness maps generated from layer segmentation (**Figure 2**). Loss regions were then segmented, overlaid, and RPE-loss areas were categorized by greatest linear dimension (GLD) in any direction as >250 um versus <250 um. iRORA regions were defined as loci with overlapping EZ loss and RPE loss and GLD <250 um. All candidate iRORA loci were manually verified to demonstrate HTD.

Additional grading rules included:

- Regions were not counted if they were within 125 um of a cRORA boundary.
- If two iRORA lesions were within 125 um of each other, they were counted as a single iRORA region.

The two graders then reviewed the ORC™ and LLA outputs together at each candidate iRORA locus to determine agreement. Agreement by eye and by locus was analyzed.

Figure 3. Agreement tables.

EYES

ORC \ LLA	Positive	Negative	Total
Positive	17	1	18
Negative	1	18	19
Total	18	19	37

Overall agreement
94.6%

FOCI

ORC \ LLA	Positive	Negative	Total
Positive	39	2	41
Negative	3	0	3
Total	42	2	44

Overall agreement
88.6%

RESULTS

Approximately half of eyes had at least one iRORA lesion. Agreement between methods was very high both by eye and by locus (**Figure 3**) with overall 88.6% agreement on classification by lesion. Disagreements were uncommon and related to:

1. RPE-defect measurements near the 250 um threshold or
2. whether the RPE layer was sufficiently attenuated to be classified as loss.

CONCLUSIONS

ORC™- and LLA-based approaches showed very high agreement for iRORA detection.

LLA appears to be an efficient, semi-automated approach for identifying iRORA. LLA and ORC™ should be evaluated in a larger longitudinal data set.

ACKNOWLEDGEMENTS

Special thanks to Dr. Malena Daich Valera for grading assistance.

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