Outer Retina-Choroid *en face* Image, ORC™: Characterization of A Novel Morphologic Endpoint for Dry Age-Related Macular Degeneration

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PURPOSE

- To characterize Outer Retina Choroid (ORC™) images derived from volumetric Spectral-Domain Optical Coherence Tomography (SD-OCT) scans in a pilot cohort of patients with Age-Related Macular Degeneration (AMD) and Geographic Atrophy (GA).

METHODS

Data set:

- Independent, retrospective morphologic grading was performed using SD-OCT volumetric macular B-scans (97-line, 6mm x 6mm), Fundus Autofluorescence (FAF), and Infrared Reflectance (IR) images from an AMD cohort (N = 29 eyes; Retina Consultants of Texas, Houston, TX).
- All eyes had decreased hypo-autofluorescence consistent with GA on FAF.
- Some of these eyes subsequently appeared to have inactive neovascular AMD manifest by thin fibrosis in parts of the AMD lesions on OCT, indicating Macular Atrophy (MA).
  - In this exploratory analysis, MA was analyzed as GA.

ORC Images:

- ORC *en face* images were formulated by summing voxels from the posterior signal band (including outer retinal and choroidal layers) in a DICOMized OCT scan, with a proprietary advanced noise reduction algorithm applied.
- ORC areas of Retinal Pigment Epithelial (RPE) atrophy were assessed by manually marking boundaries of regions of Compete Retina and Outer Retina Atrophy (cRORA) and Incomplete Retina and Outer Retina Atrophy (iRORA) as verified by the corresponding B scans.
  - The definitions of cRORA and iRORA followed the criteria of the CAM Study Group[1] and were applied in eyes with and without evidence of neovascular AMD.
- The areas of the annotated regions were measured using manual planimetry on the ORC *en face* images (**Figure 1**).

FAF Images:

- 27 eyes had FAF imaging by blue light using the Heidelberg Spectralis instrument and 2 had green light imaging using the Optos California P200DTx wide field instrument.
- GA regions in FAF images were segmented using a deep learning algorithm based on a modified U-Net CNN with batch normalization and a combined loss function, followed by expert reader verification and correction as needed with reference to corresponding IR images.

Analysis:

- Areas of atrophy by ORC and FAF were compared by descriptive statistics.

RESULTS

- ORC image bright areas corresponded to signal hypertransmission from RPE defects per registered OCT B-scans.
- cRORA type RPE defects typically had distinct borders, whereas iRORA atrophy and MA often exhibited a mottled appearance (**Figure 2**).
- The transition between complete and incomplete atrophy was readily clarified using corresponding B-scans.
- Because both iRORA and cRORA feature hypertransmission defects, both types of atrophy together accounted for the bright regions seen on the ORC image.
- FAF regions of decreased autofluorescence corresponded closely with the hypertransmission region on ORC, with some exceptions.
  - Notably, while certain hypofluorescent areas on FAF images retained intact RPE in reference B-scans, these areas exhibited normal intensity on the ORC image (**Figure 2**).
  - It was also common for regions of apparent GA on FAF to correspond to iRORA or to fibrosis on OCT (**Figure 3**).
- Atrophy lesion area per eye by ORC (cRORA + iRORA) was similar to FAF, with a cohort mean mm^2 = 7.00 (range 0.55-19.61) vs 7.08 (range 0.50-18.28) mm^2, respectively.
- The mean difference between modalities by eye was 0.07 (1%), and mean absolute difference was 0.62 mm^2
- The relative percent difference of areas by within-eye modality was 15% (range 0-66).
- Results were similar among the 18 eyes with atrophic AMD compared to the 11 eyes with signs of inactive neovascular AMD (**Table 1**).

Figure 1. A. *En face* ORC image with region of cRORA (blue) and iRORA (orange). **B.** Corresponding FAF image with segmentation. **C.** Representative B-scan shown as green line in A, an area of cRORA (blue lines and asterisk) and iRORA (orange lines and asterisk).

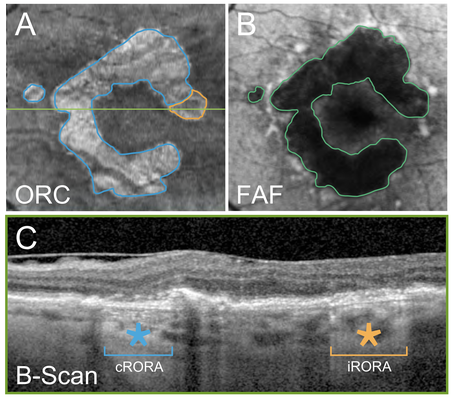
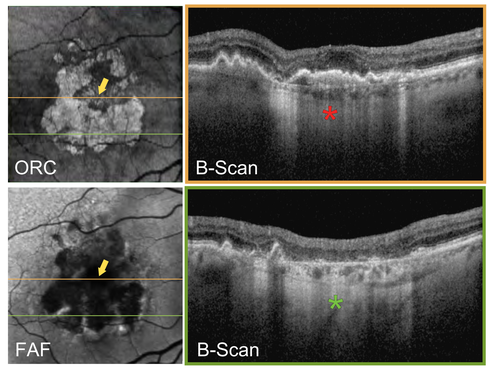


Table. Area assessments derived from ORC versus FAF.

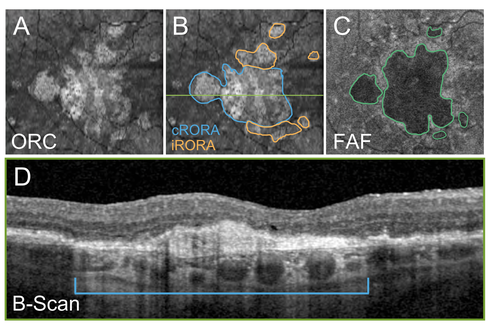
	Area ORC mm^2 (iRORA+cRORA)	Area FAF mm^2	Difference FAF-ORC	Absolute Difference	Percent Difference
All Eyes n=29	7.00	7.08	0.07	0.62	15%
Dry AMD n=18	6.37	6.28	-0.10	0.61	10%
Wet AMD n=11	8.04	8.39	0.35	0.64	19%

Figure 2. ORC and FAF images demonstrate similar lesion patterns, with presumed macular pigment artifact in FAF (yellow arrows).



OCT scan (orange) indicates incomplete RPE atrophy in the macular area (red asterisk) corresponding to mottled appearance in ORC and dark region in FAF (yellow arrows). OCT scan (green) indicates area of hyper choroidal transmission due to the missing RPE layer (green asterisk), corresponding to white regions in ORC and dark regions in FAF.

Figure 3. A. ORC image **B.**, with annotation showing cRORA (total absence of RPE) in blue region and iRORA in orange. **C.** corresponding FAF image **D.** B-scan line from A and B with area of fibrosis.



CONCLUSIONS

- ORC enables comparable anatomical characterization of RPE atrophy lesions to FAF with the advantage of a single modality that uses anatomical confirmations using registered B-scans.
- *En face* ORC images display hypertransmission defects on OCT that correspond closely to areas of decreased autofluorescence on FAF, but without the macular pigment artifacts that may be present in FAF.
- Potentially clinically relevant findings such as iRORA versus cRORA and fibrosis are revealed on ORC/OCT which cannot be distinguished on FAF.
- This study utilized a deep learning-based algorithm for the assessment of FAF regions. Similar deep learning-based tools for analysis of RPE atrophy in ORC images and outer retinal segmentation of B-scans, including ellipsoid zone (EZ) thickness, are now being piloted across patient data sets.
  - Preliminary results indicate improved efficiency and reproducibility.
- The ORC *en face* image was designed to be OCT manufacturer-independent by explicitly accounting for image variations across different vendors.
  - Preliminary data support its vendor-agnostic performance (see presentation #PB0011 from ARVO Imaging In The Eye 2025).
- Further development of the methodology should employ longitudinal assessment of GA in a clinical trial data set.

DISCLOSURES

HA: Abbvie, Alimera, Annexon, Apellis, Eyepoint, Genentech, Ocular Therapeutix, Regeneron; RPD: MERIT CRO, Inc.; CW: Commercial Relationship(s);4DMT, Adverum, AffaMed, Alexion, Alimera, Alkahest, Allgenesis, Amgen, Annexin, Annexon, Apellis, Ascidian, Asclepix, Aviceda, Bayer, Boehringer Ingelheim, Chengdu Kanghong, Chengdu Origen, Clearside, Curacle, Eluminex, EyeBiotech, EyePoint, Gemini, Genentech, GlaxoSmithKline, Gyroscope, IONIS, IVERIC bio, Janssen, Kodiak, Kyoto DDD, Kyowa Kirin, Nanoscope, Neurotech, NGM, Novartis, Ocugen, Ocular Therapeutix, Ocuphire, OcuTerra, OliX, Opthea, Outlook Therapeutics, Oxular, Oxurion, Oyster Point, Perceive Bio, Pykus, RecensMedical, Regeneron, RegenXBio, Rezolute, Roche, SamChunDang Pharm, Sandoz, Shanghai Henlius, Skyline, Stealth, UNITY, Valo, Verily, Xbrane:Code F (Financial Support):none;4DMT, AbbVie, Adverum, Aerie, AGTC, Alcon, Alimera, Alkeus, Allgenesis, Alnylam, AMC Sciences, Annexon, Apellis, Arrowhead, Ascidian, Aviceda, Bausch + Lomb, Bayer, Biocryst, Bionic Vision, Boehringer Ingelheim, Cholgene, Clearside, Curacle, Emmecell, EyeBiotech, EyePoint, Foresite, Frontera, Genentech, Gyroscope, IACTA, InGel, IVERIC Bio, Janssen, Kato, Kiora, Kodiak, Kriya, Merck, Merit, Nanoscope, Neurotech, NGM, Notal Vision, Novartis, OccuRx, Ocular Therapeutix, Ocuphire, Ocuterra, OliX, ONL, Opthea, Osanni, Oxular, Palatin, Perceive Bio, Perfuse, Ray, RecensMedical, Regeneron, RegenXBio, Resonance, RetinAI, Roche, Sandoz, Sanofi, Santen, SciNeuro, Stealth, Surrozen, Suzhou Raymon, Sylentis, THEA, Therini, TissueGen, Valo, Verana, Visgenx, Zeiss:Code C (Consultant/Contractor):none;InGel, ONL, Osanni, Panther, PolyPhotonix, RecensMedical, TissueGen, Visgenx, Vitranu:Code I (Personal Financial Interest):none; JL, JA, YH, MERIT CRO, Inc.; DB: MERIT CRO, Inc., PanOptica, Inc, Visgenx, Inc.

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