

# Geographic Atrophy: What's new in 2023?

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GEORGIA RETINA

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## Disclosures

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## Overview

- Impact of Geographic Atrophy (GA)
- Age-related macular degeneration (AMD) classification
- Imaging & Biomarkers
- Research targets
- New treatments
- Practical concerns
- Cases

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## Impact

Population of 10 largest cities in GA  
=  
Population of Americans with GA  
**~1.5 million**

**10 Largest Cities in Georgia**

- Atlanta (490,270)
- Columbus (202,957)
- Augusta (199,894)
- Savannah (145,870)
- Athens (127,793)
- Sandy Springs (105,223)
- Kennesaw (91,819)
- Warner Robins (63,384)
- Johns Creek (61,023)
- Marietta (68,181)

Map: IvericBio.com/mediasite.com/GeographicAtrophyGA  
Wells G, Wessley K, Cuddy KC, et al. Ophthalmology. 2021;128(4):579-585.

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## Impact

Changes in visual function occur before declines in visual acuity

-Gradual loss of central vision leads to difficulty with recognizing faces, depth perception, distinguishing colors, adjusting from bright to dim lighting, driving, near work, etc.

**66%** of patients become blind or significantly visually impaired

**44%** of patients require assistance with daily activities

Early RA, Lerner J, Smith N, et al. Onset of geographic atrophy from first diagnosis to end of the IAMD Collaborative. 2021;38(7):10-20.  
Wells G, Lerner J, Smith N, et al. Onset of geographic atrophy: a study of macular visual quality. Ophthalmology. 2020;147:1412-20.

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## Impact

2 years after enrollment in a GA study:

- 75% of patients lost 5 letters
- 50% of patients lost 10 letters
- 25% of patients lost 15 letters

By **1.6 years** after diagnosis, **67%** of patients lose their ability to drive

Extrafoveal lesions can progress to foveal involvement in **2.5 years**

Chen Y, et al. Impact of GA on visual function in geographic atrophy (GA) lesions from longitudinal trial data. Presented at The Macula Society 40th Annual Meeting February 15-18, 2023, Miami, FL.  
Chen Y, et al. Impact of GA on visual function in geographic atrophy (GA) lesions from longitudinal trial data. Presented at The Macula Society 40th Annual Meeting February 15-18, 2023, Miami, FL.  
Lambert A, et al. Characterizing disease burden and progression of geographic atrophy associated with neovascular age-related macular degeneration. Ophthalmology. 2018;125(10):242-50.  
Lambert A, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study. AREDS Report Number 26. Arch Ophthalmol. 2009;127(10):1408-1414.

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## Dry AMD

Leading cause of vision loss over age 65  
Affects 11 million people in US



**Risk factors**

- **Modifiable:** smoking tobacco, hypertension, diet, physical activity, cardiovascular disease, hypercholesterolemia, obesity, and UV protection;
- **Non-modifiable:** Age, female gender, family history, Caucasian race, hyperopia, light color irides

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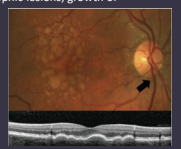
## Dry AMD

**Early AMD:** Multiple small (<63um) drusen or few intermediate (63-124um) drusen

**Intermediate AMD:** Many intermediate (63-124um) drusen or >1 large (>124um) drusen; pigmentary changes and early degeneration of retinal layers.

**Advanced AMD:** Presence of geographic atrophy (GA) or choroidal neovascularization (nAMD)

- Dry AMD progression to GA is characterized by the development of new atrophic lesions, growth of individual areas, or coalescence of multiple lesions
- GA is due to progressive atrophy of RPE, photoreceptors, choriocapillaris

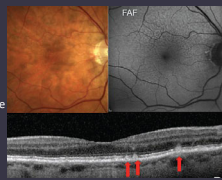


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## Monitoring

**Biomarkers**

- Larger the drusen, the greater the chance of progression to advanced AMD
- Reticular pseudodrusen
- Lesion size, location, and focality may predict the rate of lesion progression in GA.
  - Smaller baseline lesions progress more slowly than larger baseline lesions.
  - Foveal lesions progress more slowly than non-foveal lesions.
  - Unifocal lesions progress more slowly than multifocal lesions.



Reger DL, Schmidt-Grohe U, van Leeuwen-Christen M, Herzig LC, Witzke C. The pathogenesis of geographic atrophy secondary to age-related macular degeneration and the experimental animal as biomarker target. *Retina*. 2017;37(18):3235-3245. doi:10.1097/RET.0000000000001482

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## Detection

**OCT**

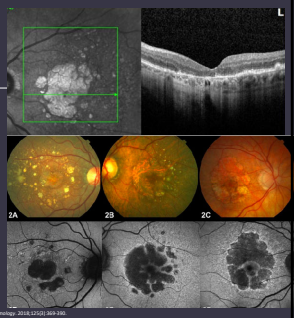
- Look at both the B-scan and near infrared images

**Fundus photography**

- Atrophic GA lesions are sharply demarcated with increased visibility of choroidal vessels

**Fundus autofluorescence**

- Atrophic lesions are hypoautofluorescent with sharply demarcated border
- Hyperautofluorescent borders surrounding atrophic lesions can indicate excessive lipofuscin / cellular dysfunction. Prognostic of GA progression



Phatakaram M, Mitchell P, Freund EA, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(2):268-280. doi:10.1016/j.ophtha.2017.09.042

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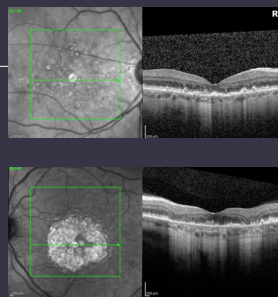
## Biomarkers

**IRORA** – Incomplete RPE and outer retinal atrophy:

- "Nascent" GA, earlier phase of disease progression
- Photoreceptor degeneration, discontinuous choroidal hypertransmission, attenuated and disrupted RPE with basal laminar deposits

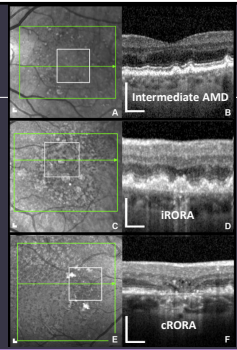
**cRORA** – Complete RPE and outer retinal atrophy

- Area of choroidal hypertransmission >250um
- Attenuated and disrupted RPE >250um
- Overlying photoreceptor degeneration (ellipsoid zone loss, ELM loss, ONL thinning)



Saisho H, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125(6):1573-1581. doi:10.1016/j.ophtha.2018.02.042

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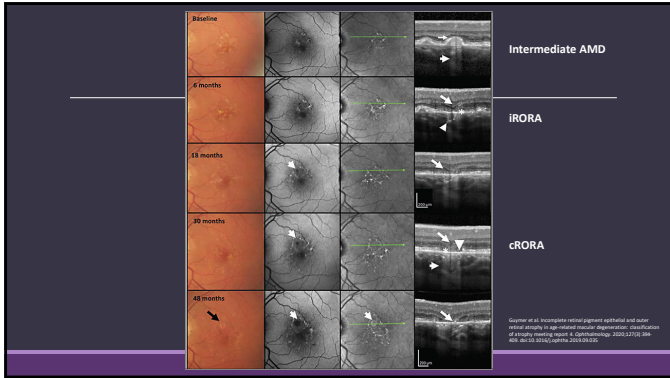
**Intermediate AMD**

**IRORA**

**cRORA**

Wu W. OCT Signs of Early Atrophy in Age-Related Macular Degeneration: Consensus Agreement Classification of Atrophy Meeting Report 6. *Ophthalmology*. 2018;125(6):1582-1591. doi:10.1016/j.ophtha.2018.02.042

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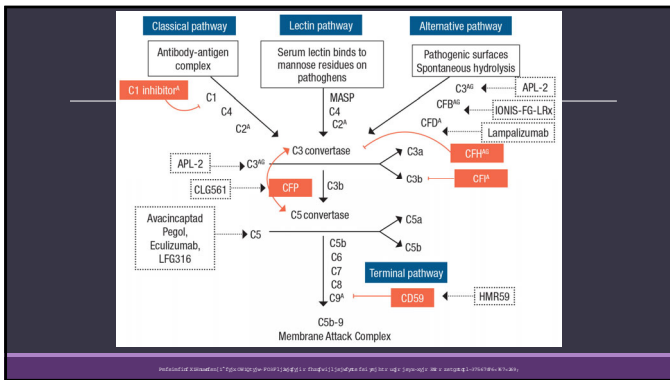
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## Research

2022  
Vabysmo (faricimab, Genentech/Roche);  
Biosimilars: Cimerli, (Coherus Biosciences) and Biooviz, (Biogen) ranibizumab biosimilars

2023 is the year for Geographic Atrophy  
Complement cascade is a major target for GA therapeutics

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Product name (manufacturer)	Description	Status
ALK-001 (Alkermes Pharmaceuticals)	Oral formulation of modified vitamin A	Completion of Phase II/III trial (n=300) due later in the year.
ANX007 (Anexon Biosciences)	Intravitreal antigen-binding fragment (Fab) to complement factor q1	Phase II trial (n=270) topline data expected by summer.
NEW: Danicopan (Alexion Pharmaceuticals)	Oral factor D inhibitor	Phase II trial (n=332) under way. Completion due in 2025.
Elamipretide (Stealth Biotherapeutics)	Mitochondria-targeting, cell-permeable peptide for subcutaneous injection	Phase II trial (n=176) failed to meet primary endpoints.
IONIS-FB-LRx (Ionis Pharmaceuticals)	Anti-sense oligonucleotide inhibiting complement factor B	Phase II trial (n=330) recruiting patients. Completion expected 2024.
NGM521 (NGM Biopharmaceuticals)	Humanized IgG1 monoclonal antibody inhibiting complement component 3	Phase II trial (n=320) failed to meet endpoints. Update expected in February 2023.
OpRegen (Lineage Cell Therapeutics)	Subretinally administered allogeneic retinal pigment epithelium cells	Phase I/IIa (n=24) results demonstrated safety. Phase IIa trial (n=60) recruiting.
Pegcetacoplan (APL-I, Apellis)	CC3 inhibitor	Phase III results (n=1268) reported. Regulatory action date February 28, 2023.
NEW: RPESC-RP-4Q (Luna Biotechnology)	Allogeneic retinal pigment epithelium stem cell (RPESC)-derived RPE cells isolated from the RPE	Phase I/IIa trial (n=18) initiated. Completion due in 2025.
Tinirebant/LBS-008 (Beigle Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist	Phase III trial pending.
Xilifam (Inflamx)	Oral small-molecule connexin43 hemichannel blocker	Reportedly in Phase IIb trials for intermediate dry AMD and GA. No trials listed at ClinicalTrials.gov
Zimura (IVERIC bio)	Avacincaptad pegol CFCS inhibitor	Phase III trial (n=448) showed efficacy signal. New Drug Application filed with FDA.

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## Pegcetacoplan

SYFOVRE™, Apellis Pharmaceuticals

FDA approved on Feb 17<sup>th</sup>, 2023

- 1<sup>st</sup> treatment for GA
- Targets C3
- Broad approval (extrafoveal and foveal lesions, concurrent wet AMD)
- Flexible dosing regimen (every 25-60 days)

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## Pegcetacoplan

**DERBY / OAKS**

- 2 years, 1200 patients, ~12,000 injections

**Inclusion criteria**

- Lesion size 2.5 mm<sup>2</sup> to 17.5 mm<sup>2</sup>
- With and without subfoveal involvement
- Unifocal and multifocal lesions
- Presence of perilesional hyperautofluorescence
- Age ≥60 years; BCVA ≥24 letters using ETDRS charts in the study eye

**Exclusion criteria**

- History of or active CNV in the study eye or GA due to another condition (Stargardt disease)
- Prior participation in any other GA study

• Either GA, CNV, or both were permitted in the fellow eye

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## Pegcetacoplan

### DERBY / OAKS

Both monthly and every-other-month (EOM) SYFOVRE reduced the rate of GA lesion growth on autofluorescence through 24 months compared to sham:

OAKS: 22% monthly; 18% EOM  
DERBY: 18% monthly; 17% EOM

### Adverse events:

- Conversion to neovascular AMD by 24 months: 12% monthly; 7% EOM; 3% control
- Ischemic optic neuropathy (NAION): 1.7% monthly, 0.2% EOM, 0% control
- Intraocular inflammation: 4% monthly, 2% EOM, <1% control
- Temporary IOP rise
- No retinitis or vasculitis

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## Avacincaptad Pegol

Zimura, Iveric Bio  
Complement C5 inhibitor

Feb 2023 – FDA accepted the company's New Drug Application

Aug 19<sup>th</sup>, 2023 – Prescription Drug User Fee Act (PDUFA) goal date

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## Avacincaptad Pegol

### GATHER1 / GATHER2

- GATHER1 (n=286) Zimura 1mg vs. 2mg vs. 4mg vs. sham monthly x 18 months
- GATHER2 (n=447) Zimura 2mg vs. sham monthly x 12 months

Monthly Zimura slowed the rate of GA lesion growth on autofluorescence at 12-18 months compared to sham

GATHER1: 27.38% (2mg) and 27.81% (4mg) difference between Zimura and sham  
GATHER2: 14.3 – 17.7% difference between Zimura 2mg and sham

- Post-hoc analysis: Reduction for patients receiving Zimura in the U.S. was 25.5 – 32.05%
- Hypothesis that Zimura may be more impactful in earlier stages of GA, and US patients had 13% smaller baseline lesions

- For BCVA, a favorable trend for Zimura 2 mg was observed in GATHER1 and GATHER2.
- For Low luminance BCVA, a favorable trend was not observed.

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## Avacincaptad Pegol

### GATHER1 / GATHER2

### Adverse events:

- Conversion to neovascular AMD by 12 months: 6.7% monthly (n=15) vs. 4.1% (n=9) control
- Ischemic optic neuropathy (NAION): no incidents
- Intraocular inflammation: no incidents

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## Practical concerns

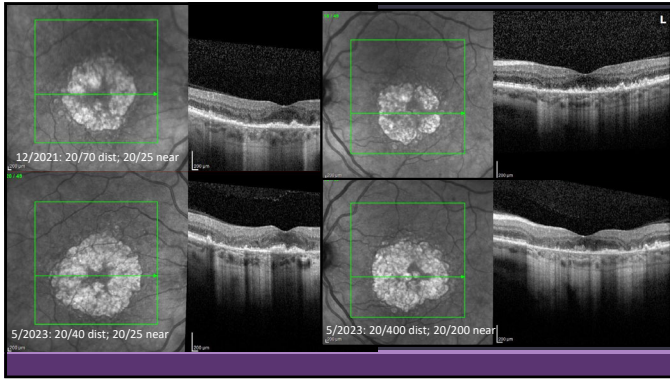
- Selection criteria
- Setting expectations
- Treatment burden
- Risk/benefit discussion
- When to refer?



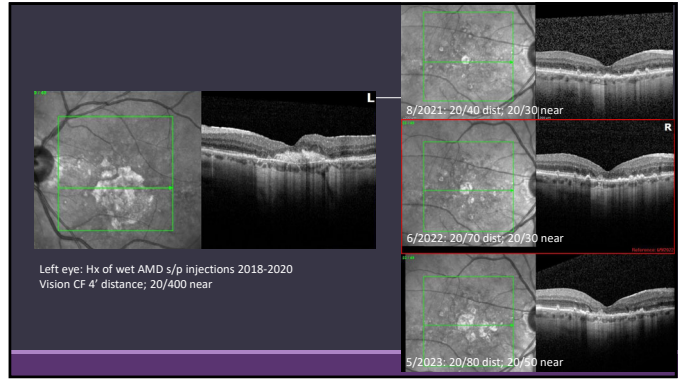
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## Cases

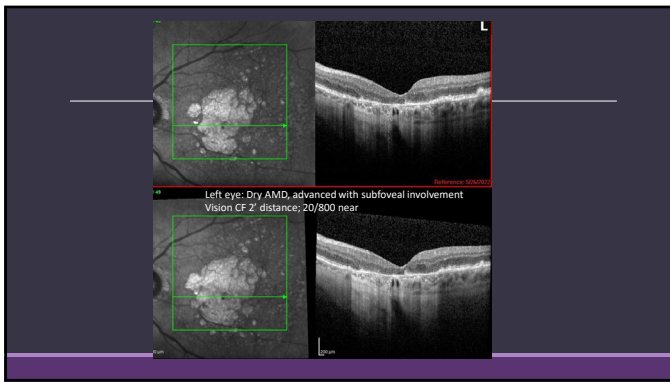
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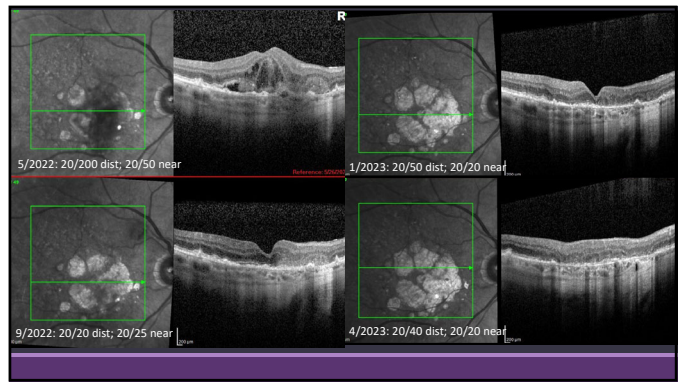
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Questions?

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25 Years of Service Excellence

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