In the Trenches:

Managing Geographic Atrophy in Traditional Optometry Practices

COPE ID 90921-TD

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- Horizon
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- Ivantis
- Orasis
- Trukera
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- Oyster Point/Viatris
- Allergan

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- Alcon
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Disclosures – Elise Kramer, OD, FAAO

- Abbvie
- Bio-Tissue
- Dompe
- Euclid Vision Group
- RegenerEyes
- Tarsus

Geographic Atrophy Is an Advanced Form of Age-Related Macular Degeneration

- Globally, AMD is among the **leading causes of blindness** in adults aged ≥50 years[1]
- GA is a **progressive, advanced form** of dry AMD characterized by loss of the RPE, photoreceptors, and choriocapillaris leading to **significant, irreversible loss of visual function**[2]

GA affects more than
5 million
people worldwide[2,3]

~973,000
people in the United States have GA in ≥1 eye[4]

4×

After age 50, **prevalence of GA approximately**
quadruples
every 10 years[5]

GA accounts for
20% of all legal blindness
attributed to AMD[6,7]

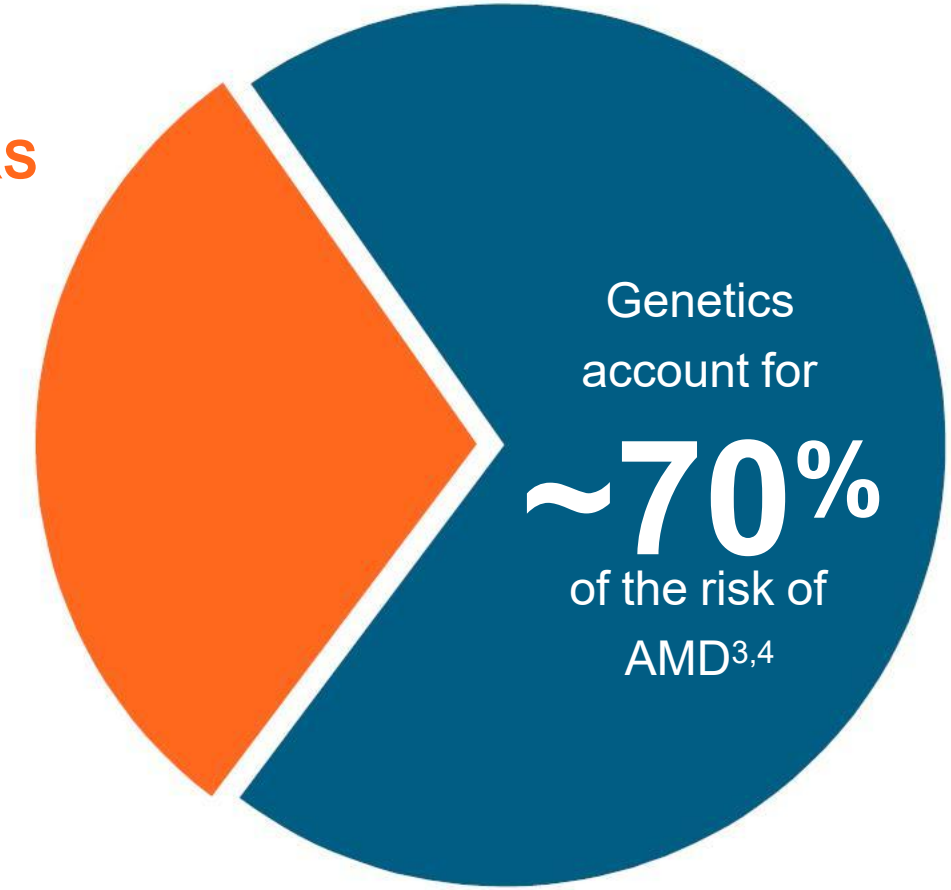
AMD, age-related macular degeneration; GA, geographic atrophy; RPE, retinal pigment epithelium.

1. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144-e160.
2. Fleckenstein et al. *Ophthalmology*. 2018;125(3):369-390. 3. Wong et al *Lancet Glob Health*. 2014;2(2):e106-e116. 4. Friedman et al. *Arch Ophthalmol*. 2004;122(4):564-572.
5. Rudnicka et al. *Ophthalmology*. 2012;119:571-580. 6. Biarnés et al. *Optom Vis Sci*. 2011;88(7):881-889. 7. Ferris et al. *Arch Ophthalmol*. 1984;102:1640-1642.

The Etiology of GA Involves a Complex Interplay Between Age, Environmental Factors, and Genetics

DEMOGRAPHIC AND ENVIRONMENTAL FACTORS

- Age[1,2]
- Smoking[1-4]
- Diet[5]
- High alcohol intake[6]
- High body mass index[2,3]
- Comorbidities[2,3]



GENETIC FACTORS

Variants in genes including **CFH, C3,** and **ARMS2/HTRA1** have been associated with GA and may contribute to[1,7]

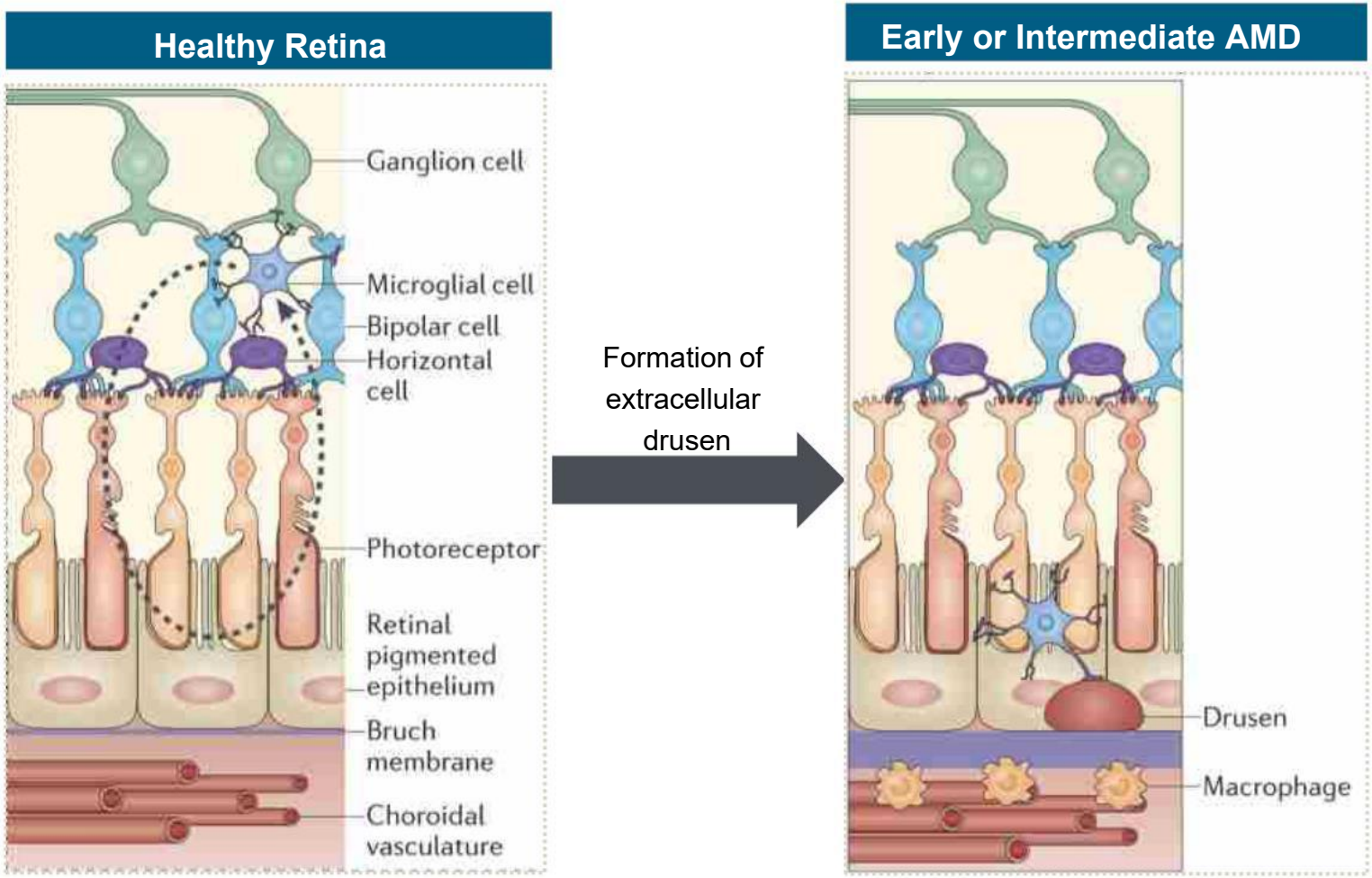
- Drusen formation
- Oxidation of phospholipids
- Immune response
- Inflammation

AMD, age-related macular degeneration; GA, geographic atrophy.

1. Heesterbeek et al. Ophthalmic Physiol Opt. 2020;40(2):140-170. 2. Chakravarthy et al. BMC Ophthalmol. 2010;10:31. 3. Ersoy et al. Invest Ophthalmol Vis Sci. 2014;55(3):1842-1847. 4. Seddon et al. Arch Ophthalmol. 2005;123(3):321-327. 5. Sobrin and Seddon. Prog Retin Eye Res. 2014;40:1-15. 6. Adams MKM et al. Am J Epidemiol. 2012;176:289-298. 7. Boyer et al. Retina. 2017;37(5):819-835.

Damage Caused By Intrinsic and Extrinsic Stressors Results in Drusen Formation

- With aging, the **RPE is exposed to oxidative stress** caused by retinal metabolic demands, photo-oxidation, and environmental stressors
- Damage caused by these stressors can accumulate, resulting in formation of **extracellular drusen**

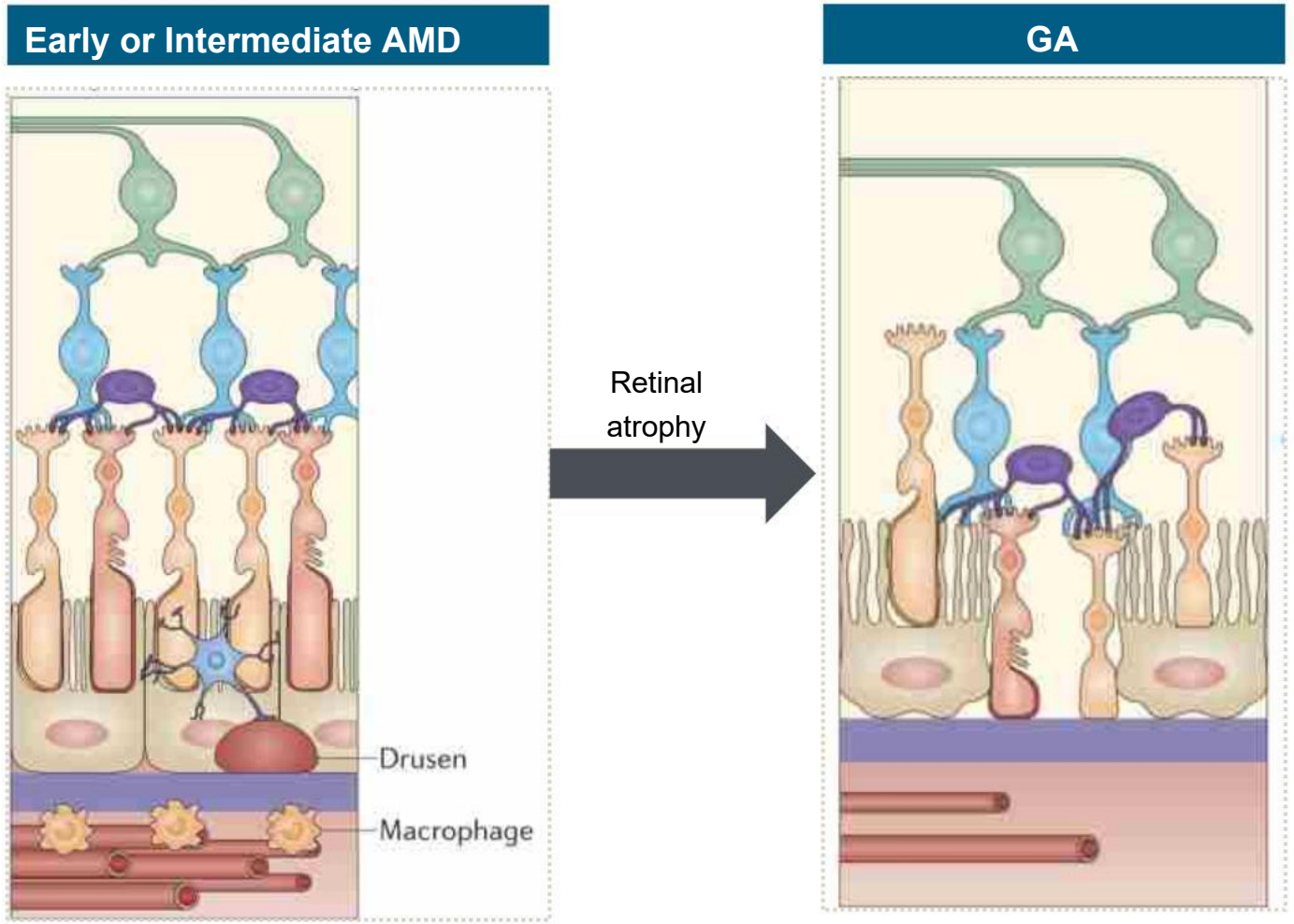


RPE, retinal pigment epithelium.

Boyer et al. Retina. 2017;37(5):819-835.

Cumulative Retinal Damage Can Trigger Inflammation and Lead to Widespread Retinal Atrophy

- Excessive drusen accumulation may trigger inflammation via multiple pathways (eg, the complement cascade), leading to **photoreceptor, RPE, and choriocapillaris cell death**[1,2]
- Loss of photoreceptors, RPE, and choriocapillaris results in **sharply defined atrophic lesions**, characteristic of GA[1]

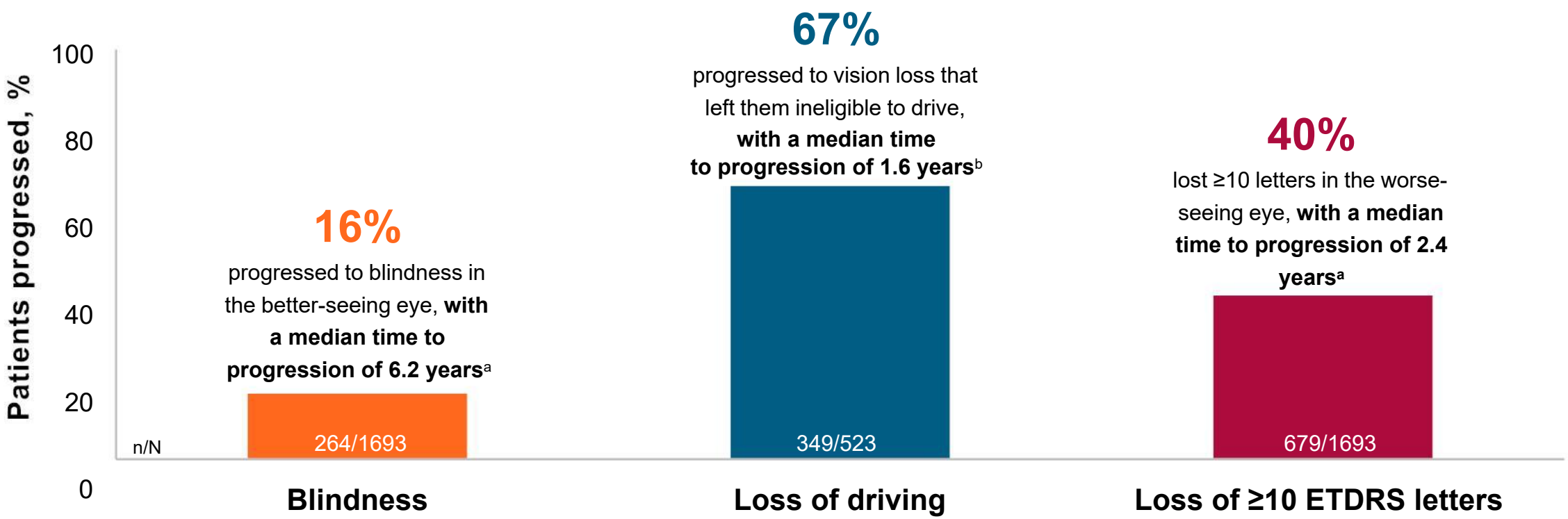


GA, geographic atrophy; RPE, retinal pigment epithelium.

1. Boyer et al. Retina. 2017;37(5):819-835. 2. van Lookeren Campagne et al. Immunobiology. 2016;221(6):733-739. 3. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390.

Vision Loss in GA Can Progress Quickly and Can Have Profound Impacts

Retrospective cohort analysis of a 10-center EMR database across the UK in patients aged ≥50 years with bilateral GA



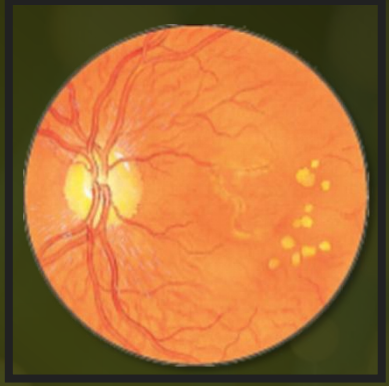
[a]Of patients with bilateral GA who had VA follow-up and who did not meet the UK definition of blindness at baseline. [b]Of patients who had VA follow-up and a level of VA in their better-seeing eye that would have placed them in a category of eligible to drive at baseline.

EMR, electronic medical record; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; VA, visual acuity.

Chakravarthy et al. Ophthalmology. 2018;125(6):842-849.

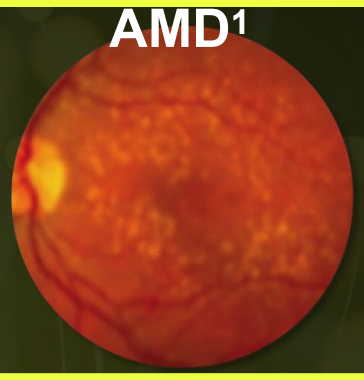
AMD Staging and Referral

Early AMD[1]



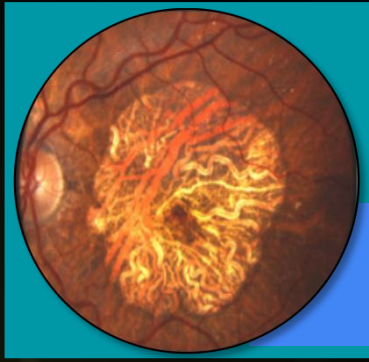
- Medium drusen (>63 µm, ≤125 µm)
- No AMD pigmentary abnormalities

Intermediate AMD[1]



- 1 large drusen (>125 µm) and/or
- Numerous medium-sized drusen and/or
- AMD pigmentary abnormalities

Geographic Atrophy[1]



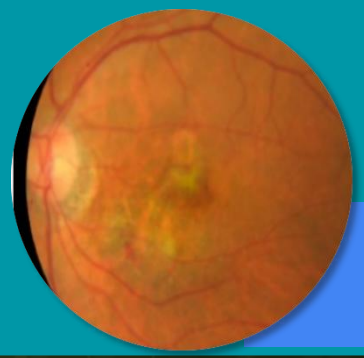
10-y risk of progression for highest risk category

53.9%

Advanced AMD

REFERRAL REQUIRED

nAMD[1]



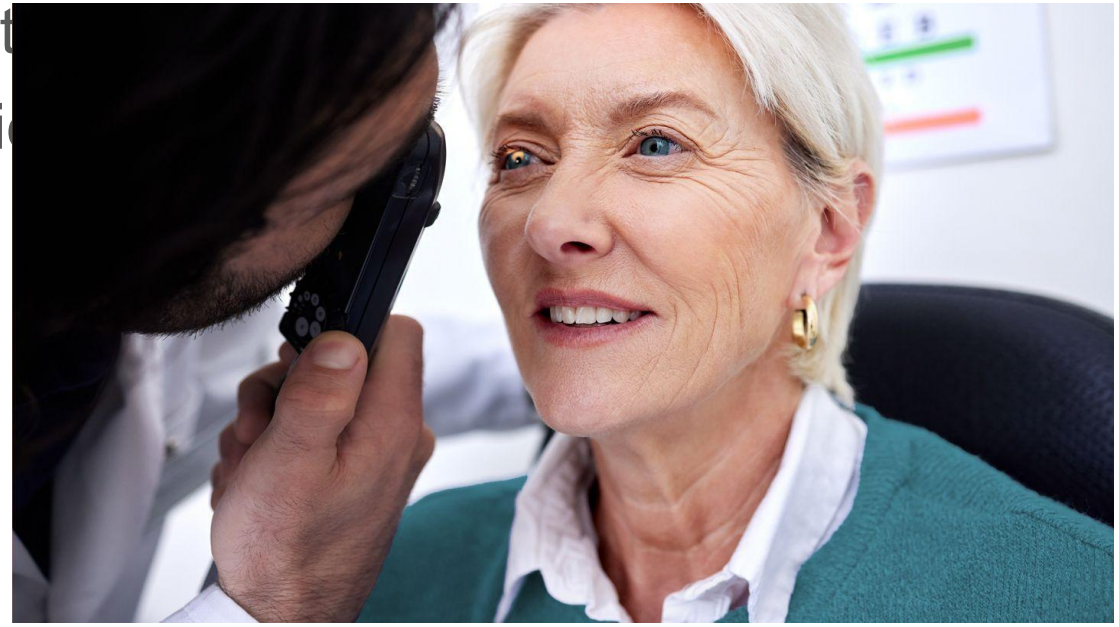
10-y risk of progression for highest risk category

47.6%

AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study

1. Flaxel CJ et al. *Ophthalmology*. 2020;127(1):1-65. 2. Chew EY et al. *JAMA Ophthalmol*. 2014;132(3):272-277.

- Important to identify patients at risk of developing and progressing GA
- Helps in effective patient management
- Facilitates provision of appropriate educat
- Enables offering treatment recommendati
- Aimed at slowing GA advancement
- Preserving vision for an extended period



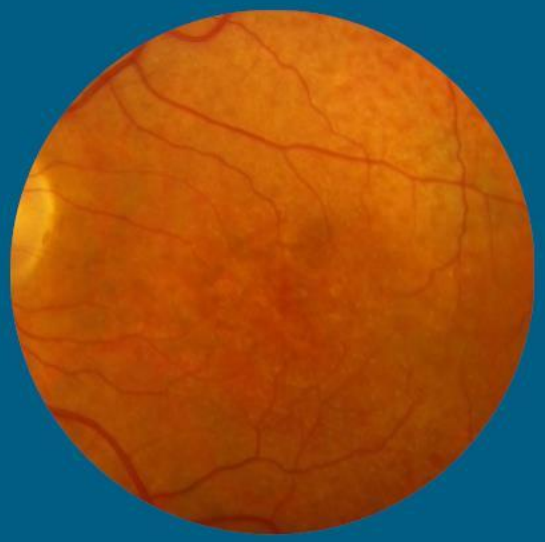
- Essential for eyecare practitioners specializing in anterior segment to assess the entire eye comprehensively
- Overlooking other eye segments may lead to missed opportunities for early detection and intervention of ocular pathologies
- Dilating the eyes allows thorough examination of the posterior segment
- Comprehensive eye evaluation ensures all aspects of ocular health are addressed
- Dilation is crucial for proactive identification and management of potential issues

Diagnostic Testing KOETTING

Diagnosing And Monitoring

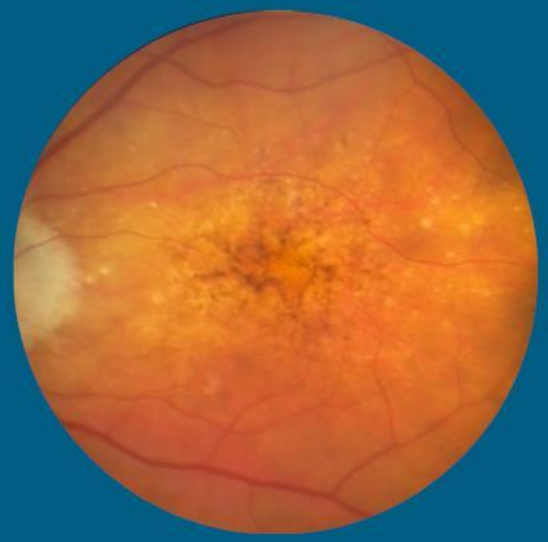
GA Is Characterized by Atrophic Lesions Resulting From the Loss of RPE, Photoreceptors, and Underlying Choriocapillaris

The clinical course of AMD includes 3 stages



Early AMD

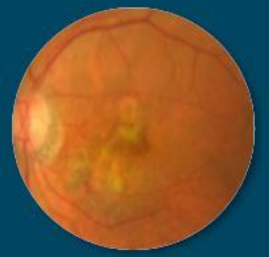
Combination of **multiple small drusen**, few intermediate drusen (63-124 µm), or **RPE abnormalities**[1,2]



Intermediate AMD

Extensive **intermediate** (63-124 µm) or at least 1 **large drusen** (≥125 µm)

GA: 53.9%[3,a]



Neovascular disease: 47.6%[3,a]

Advanced AMD

May present as GA or neovascular disease. GA is characterized by **atrophic lesions resulting from the loss of RPE, photoreceptors, and underlying choriocapillaris**[1,2]

[a]Represents 10-year risk of progression for the highest risk category (AREDS simple scale)[3]

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; RPE, retinal pigment epithelium.

1. Ambati et al. Nat Rev Immunol. 2013;13(6):438-451. 2. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 3. Chew et al. JAMA Ophthalmol. 2014;132(3):272-277.

Atrophic Lesion Growth Is Associated With Progressive, Irreversible Vision Loss

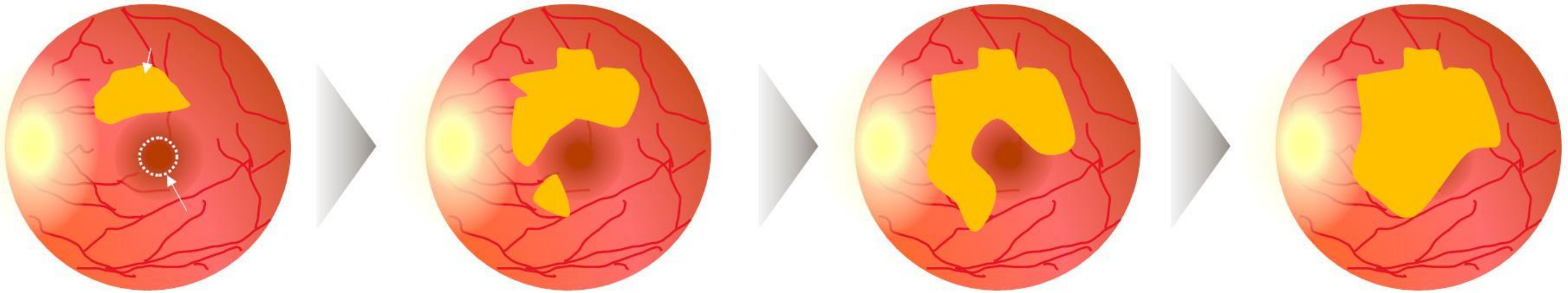
Even though **central visual acuity is largely preserved** until atrophy encroaches on the fovea, **functional vision continues to decline as lesions grow**[1]

Some loss of peripheral, low light vision

Loss of peripheral, low light vision

Loss of peripheral, low light vision; patches of central vision loss

Loss of central vision



Median* of **2.5 years** from first appearance to foveal GA, with **extrafoveal lesions progressing faster than foveal lesions**[1-3]

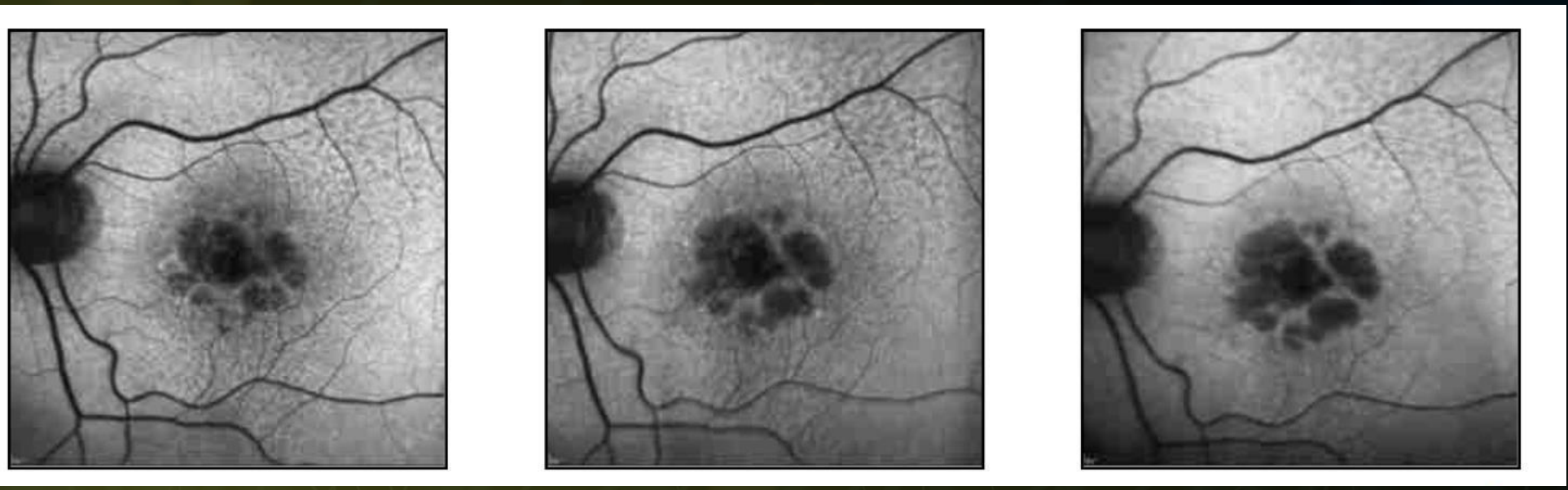
*n=181 of 4757 AREDS participants

1. Boyer et al. Retina. 2017;37(5):819-835. 2. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174. **3.** Fleckenstein et al. Ophthalmology. 2018;125(3):369-390.

BCVA Doesn't Capture GA Progression

BCVA is poorly correlated to lesion size. Functional vision declines as lesions grow[1,2]

Visit 1	Visit 9 (1 year)	Visit 11 (18 months)
2.71 mm^2	4.82 mm^2	6.18 mm^2
BCVA = 73	**BCVA = 60**	**BCVA = 60**

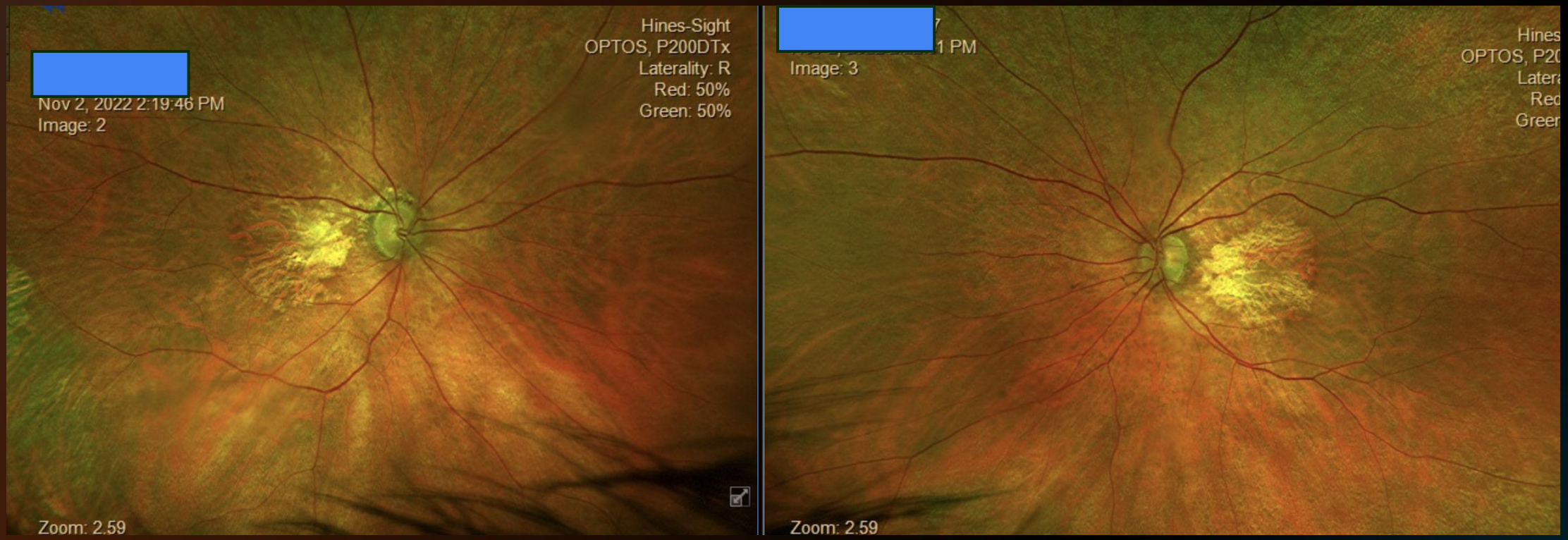


GA progression

BCVA, best-corrected visual acuity; GA, geographic atrophy.

1. Sunness et al. Ophthalmology. 1997;104(10):1677-1691. Sunness et al. Ophthalmology. 2007;114(2):271-277.

Fundus Photos



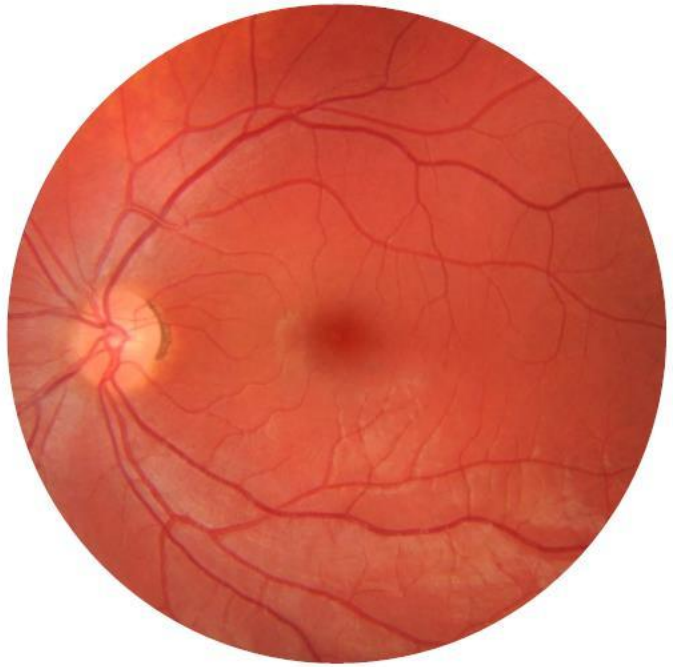
Color Fundus Photography Shows GA Lesions as Clearly Demarcated Areas of Hypopigmentation

What to look for

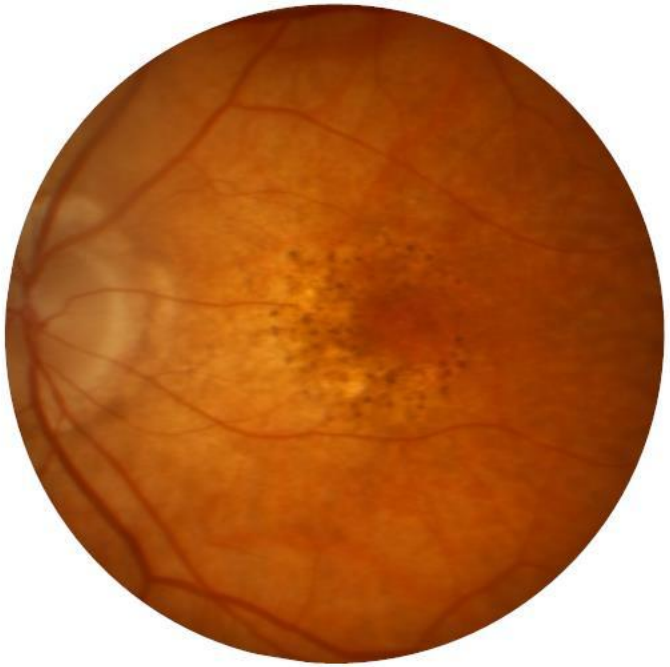
- Visible choroidal vasculature[1]
- Areas of hypopigmentation with sharply demarcated borders[1]

Color fundus photography can define GA lesions; however, it cannot visualize many lesion characteristics associated with progression[1]

Healthy



GA



While atrophy encroaches on the foveal center, visual deficits may become more pronounced[2]

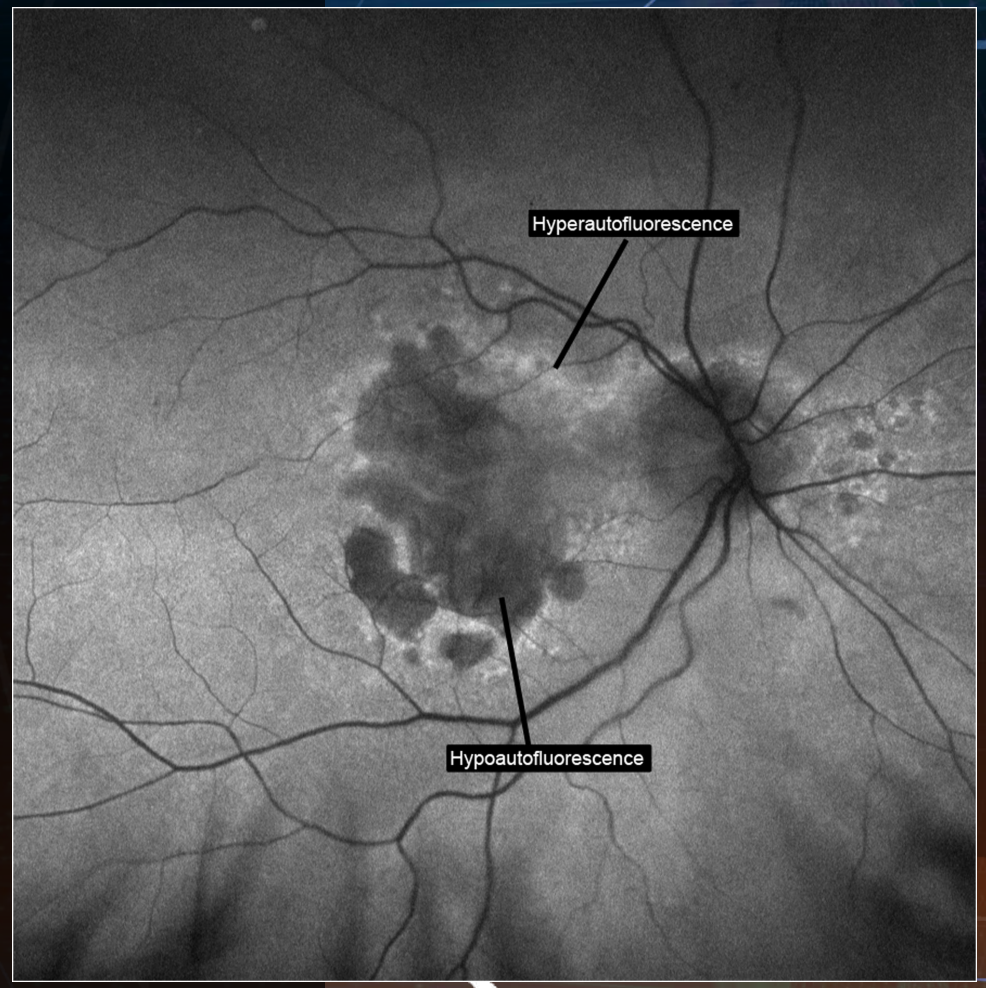
GA, geographic atrophy.

1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Boyer et al. Retina. 2017;37(5):819-835.

Healthy fundus image from Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine.

Fundus Autofluorescence

- Ultra-widefield fundus autofluorescence (FAF)
  - subjective assessment of the overall health of the retinal pigment epithelium as reflected by the amount of lipofuscin component
  - Areas of increased lipofuscin concentration→ hyperfluorescent,
  - Areas where RPE cells have atrophied or are absent →hypofluorescent



FAF Shows Characteristic Hypoautofluorescence Corresponding To GA Lesions

What to look for

- Depigmented, hypoautofluorescent regions corresponding to RPE atrophy[1,2]
- Abnormal hyperautofluorescence surrounding the atrophic regions representing areas of ongoing RPE cell dysfunction[2]

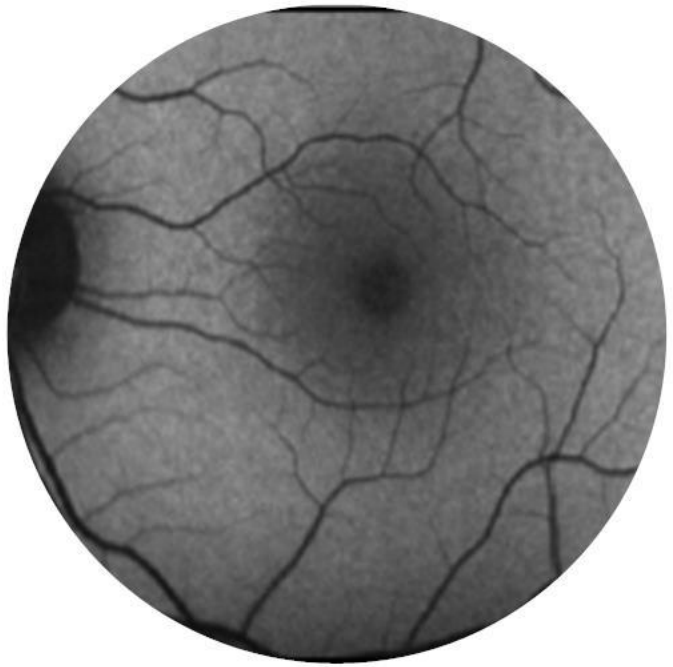
FAF, fundus autofluorescence; GA, geographic atrophy; RPE, retinal pigment epithelium.

1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Yung et al. Int J Retina Vitreous. 2016;2:12.

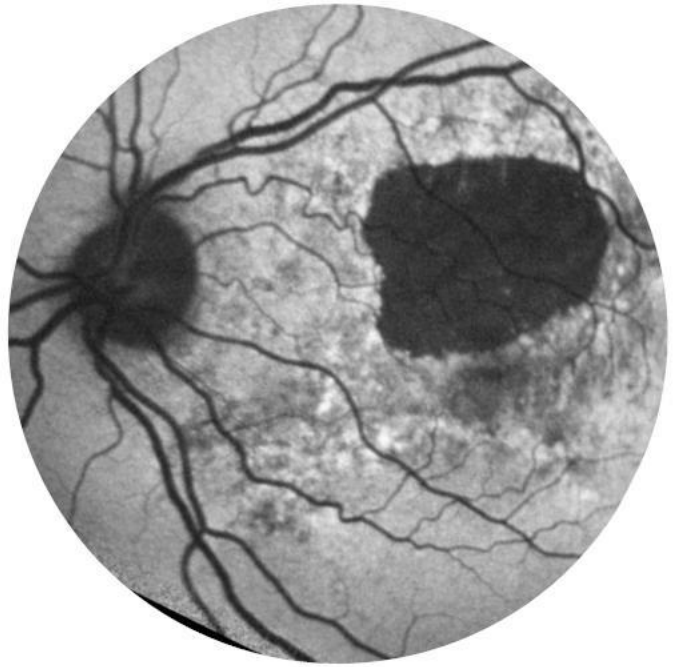
Healthy FAF image from Yung et al. Int J Retina Vitreous. 2016 Apr 8;2:12. Geographic atrophy FAF image courtesy of Nancy Holekamp, MD, Pepose Vision Institute.

FAF is the primary imaging modality used to assess lesion size and progression in GA[1]

Healthy



Geographic atrophy



FAF Risk Factors Greater GA Progression Rate

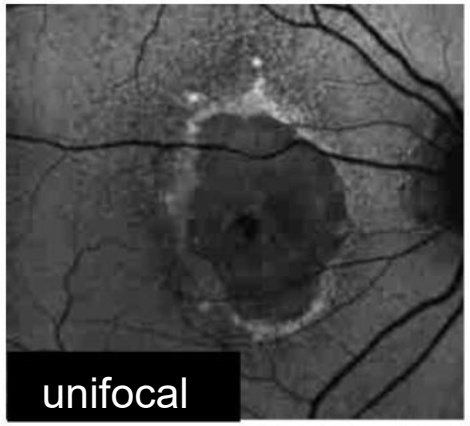
Factors associated with increased GA progression rate

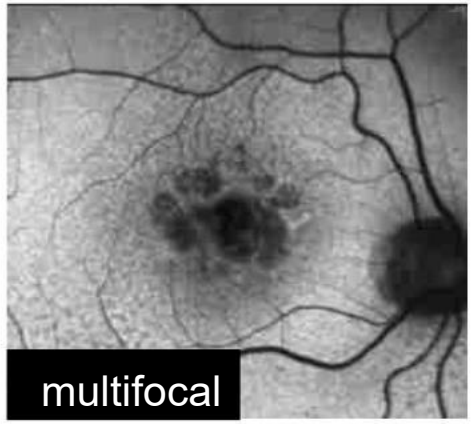
Affected eye

- Larger baseline lesion size[1,2]
- Multifocality[3,4]
- Abnormal FAF pattern: banded, diffuse FAF phenotypes[2]
- Nonfoveal location and progression toward periphery; extrafoveal GA lesions progress faster than foveal lesions[4,5]

Fellow eye

- Bilateral GA[3,5,6]
- Higher progression rate in fellow eye[5]





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1. Sunness et al. Ophthalmology. 2007;114:271-277. 2. Holz et al. Am J Ophthalmol. 2007;143(3):463-472. 3. Wang and Ying. Ophthalmic Res. 2021;64(2):205-215. 4. Steinle et al. Am J Ophthalmol. 2021;227:116-124. 5. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 6. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174.

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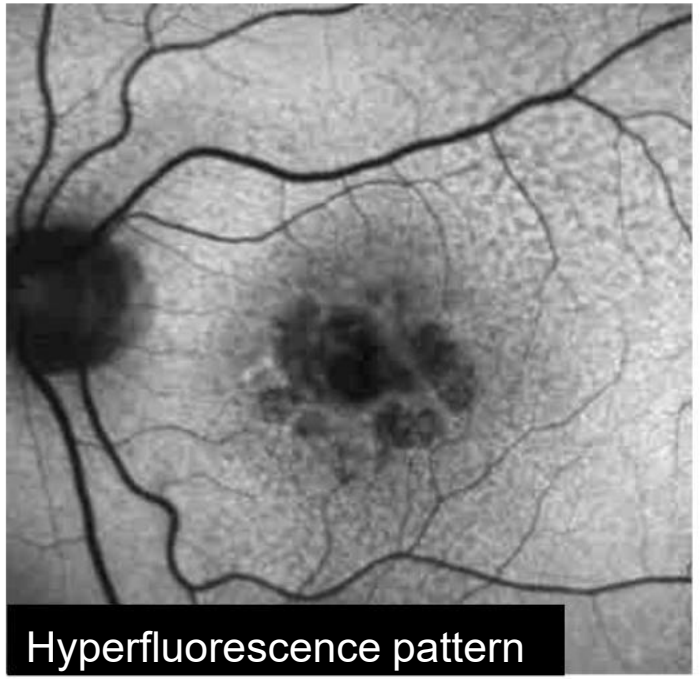

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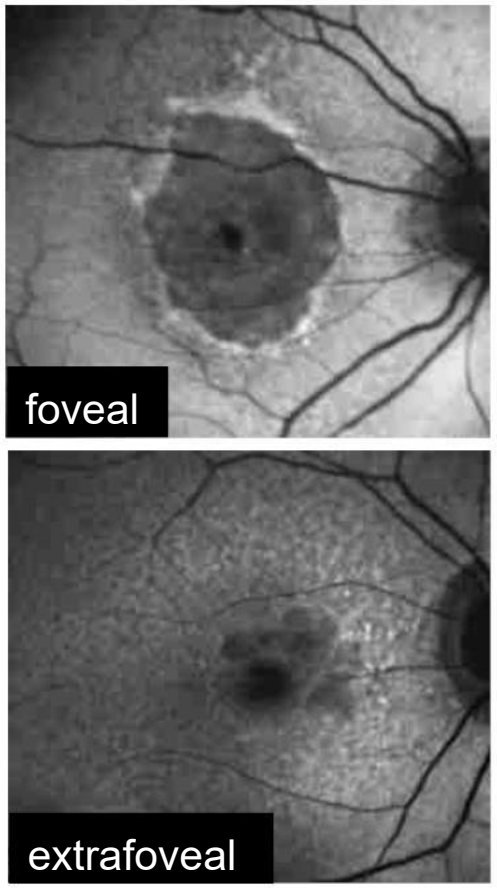

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OCT-> GA Lesions Identified by Loss of Outer Retinal Layers

What to look for

Lesions are identified by

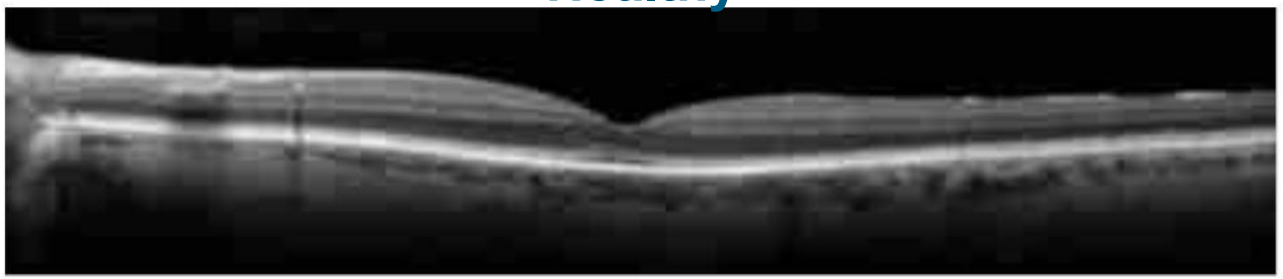
- Loss of RPE and photoreceptor layers[1,2]
- External limiting membrane absence[1,2]
- Increase in choroidal hypertransmission[1,2]

GA, geographic atrophy; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

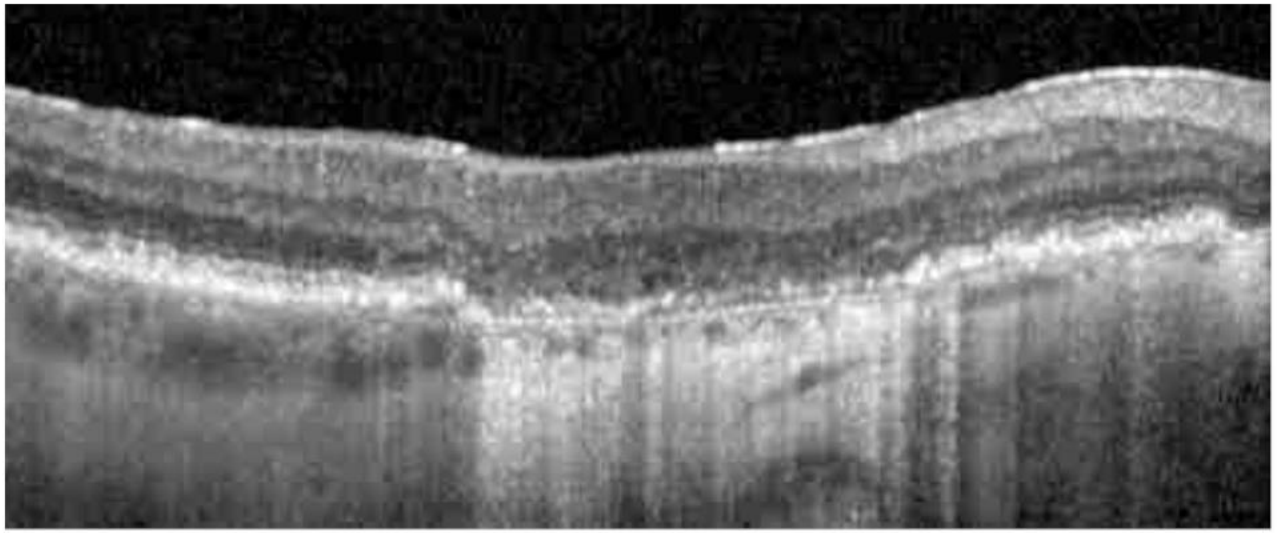
1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Sadda et al. Ophthalmology. 2018;125(4):537-548.
Healthy OCT image from Emmerson Badaró et. al. "Spectral-Domain Optical Coherence Tomography for Macular Edema," The Scientific World Journal.

OCT is emerging as a preferred imaging modality to assess features of lesions in GA[1]

Healthy



GA



AMD Progression Predictors on OCT

Predictive signs detectable on OCT

Reticular pseudodrusen[1]

- Drusenoid deposits located above the RPE
- May represent a risk factor for the development of late AMD

Subsidence "sinking" of INL and OPL[1]

- Retina layers appear to sink towards the RPE in the area of outer atrophy – appear as a hyporeflective wedge
- A finding at high risk to progress to GA

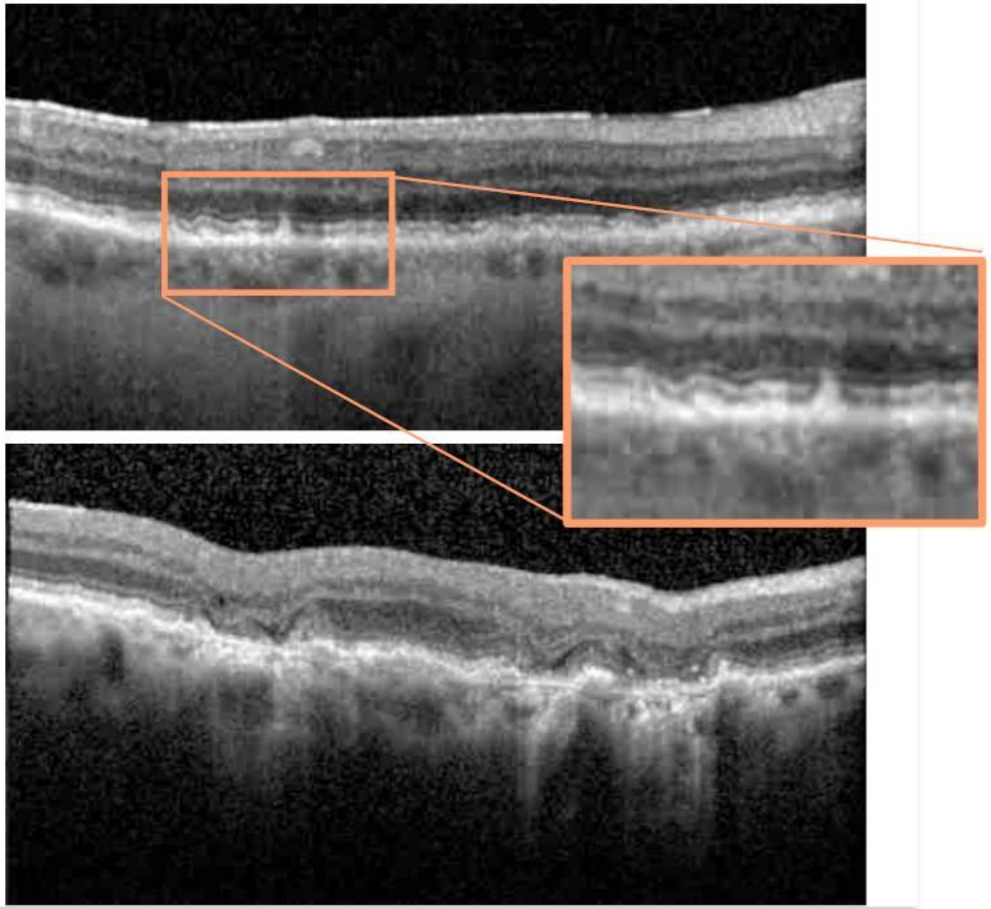
Hyperrefletive Foci[1]

- Appear as discrete well-circumscribed, punctate lesions equal or greater in reflectivity than RPE
- Can indicate higher progression from early to advanced GA

AMD, age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; INL, inner nuclear layer; OPL, outer plexiform layer.

1. Jaffe et al.Ophthalmology Retina 2021;1-13

Predictive signs of Geographic Atrophy (GA)



AMD Progression Predictors on OCT

Predictive signs detectable on OCT

Reticular pseudodrusen[1]

- Drusenoid deposits located above the RPE
- May represent a risk factor for the development of late AMD

Subsidence "sinking" of INL and OPL[1]

- Retina layers appear to sink towards the RPE in the area of outer atrophy – appear as a hyporeflective wedge
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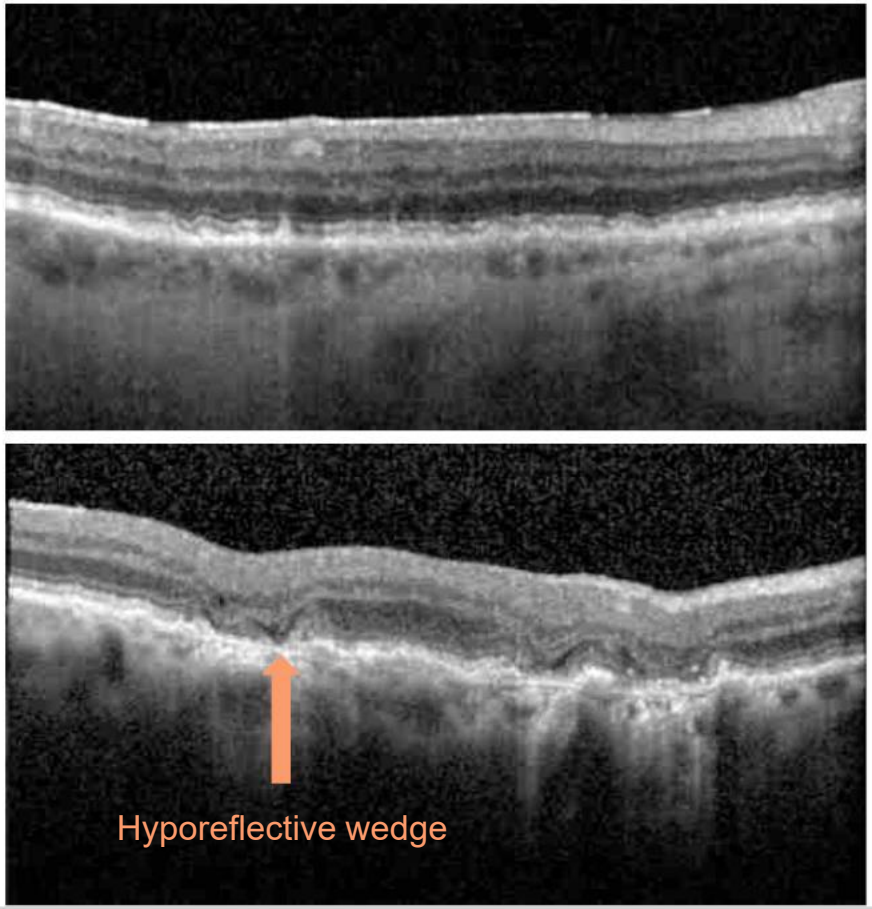

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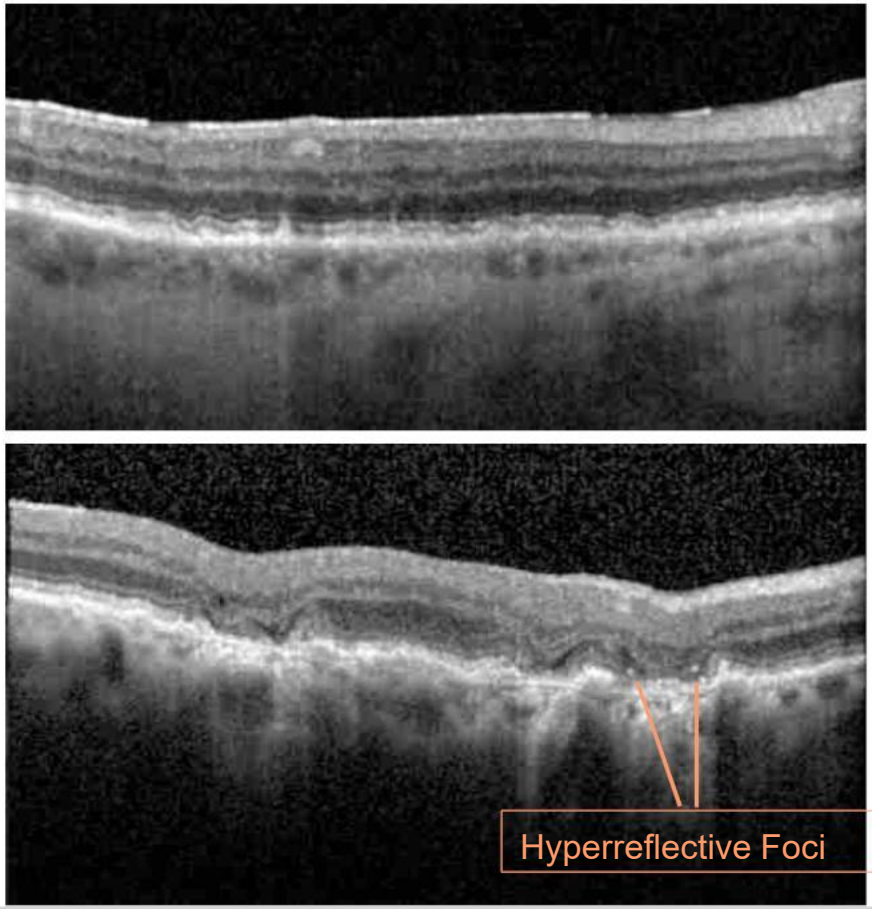
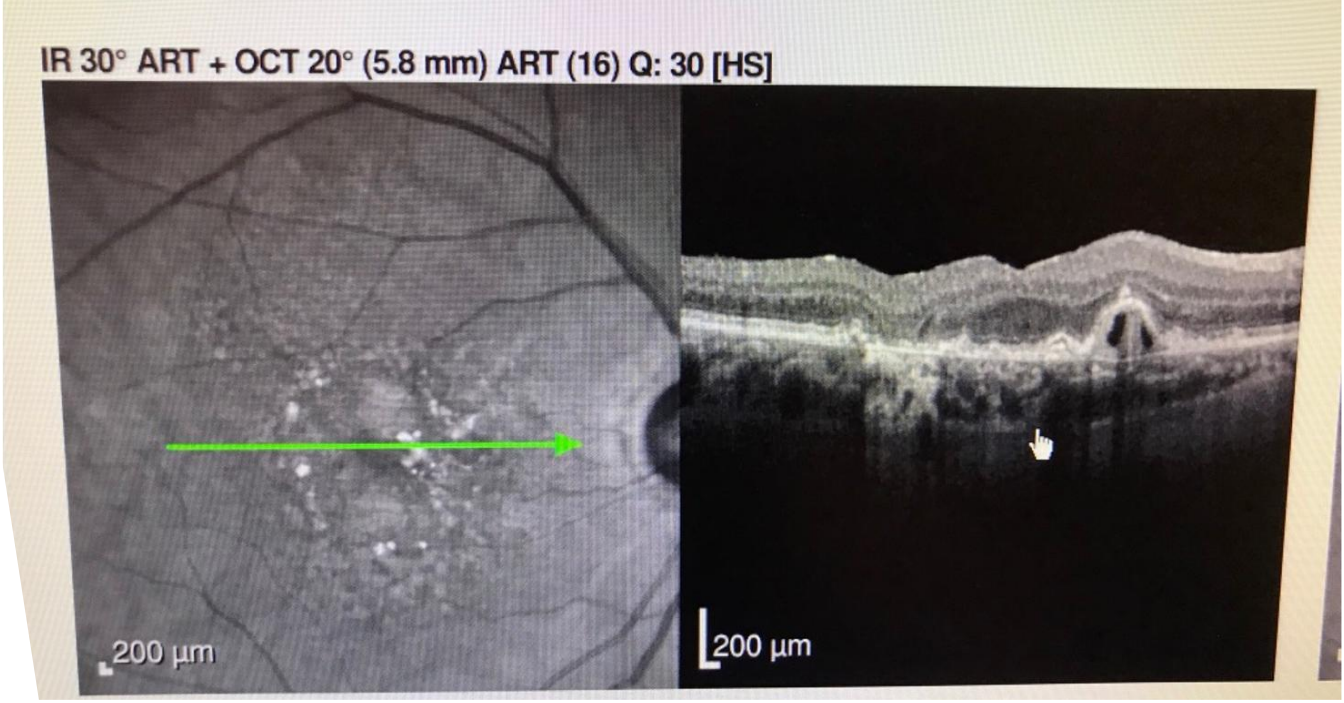
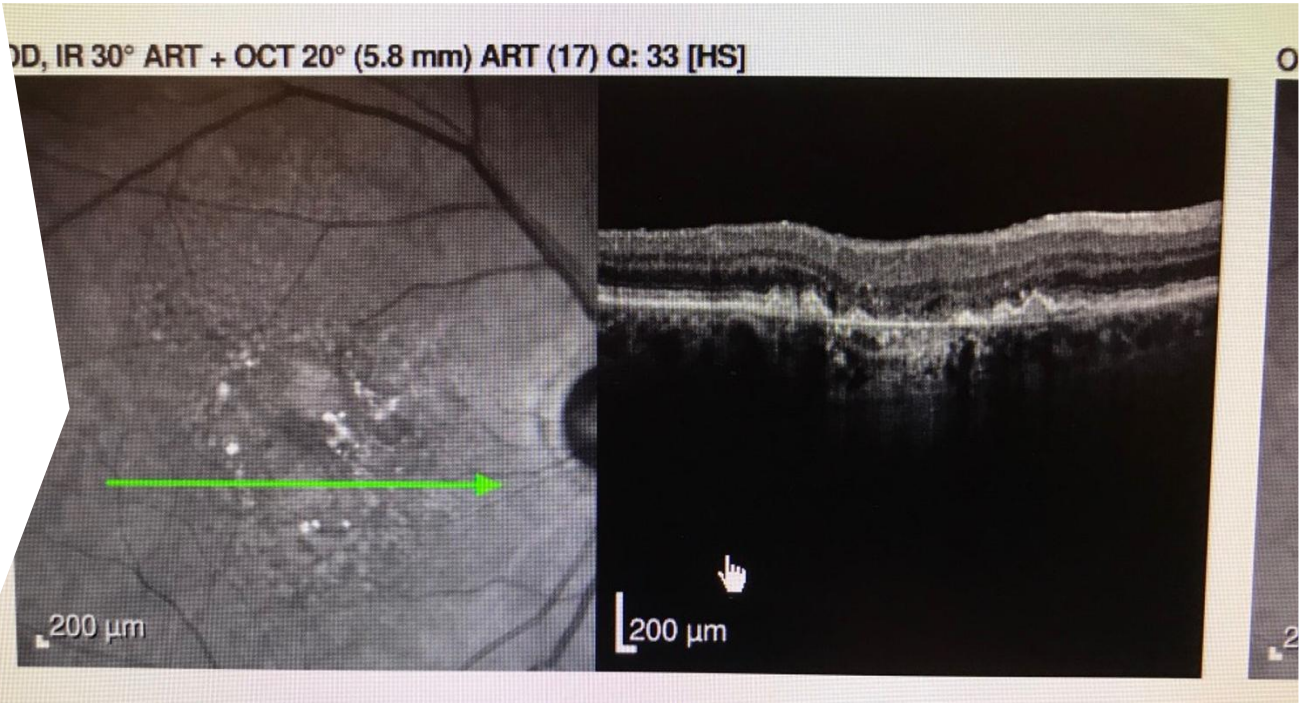


AMD, age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; INL, inner nuclear layer; OPL, outer plexiform layer. 1. Jaffe et al. Ophthalmology Retina 2021;1-13

Macular Raster

- Optometrist's assessment:
  - Stage 4 dry AMD OU
- Retina specialist's assessment:
  - nAMD with active CNV OD



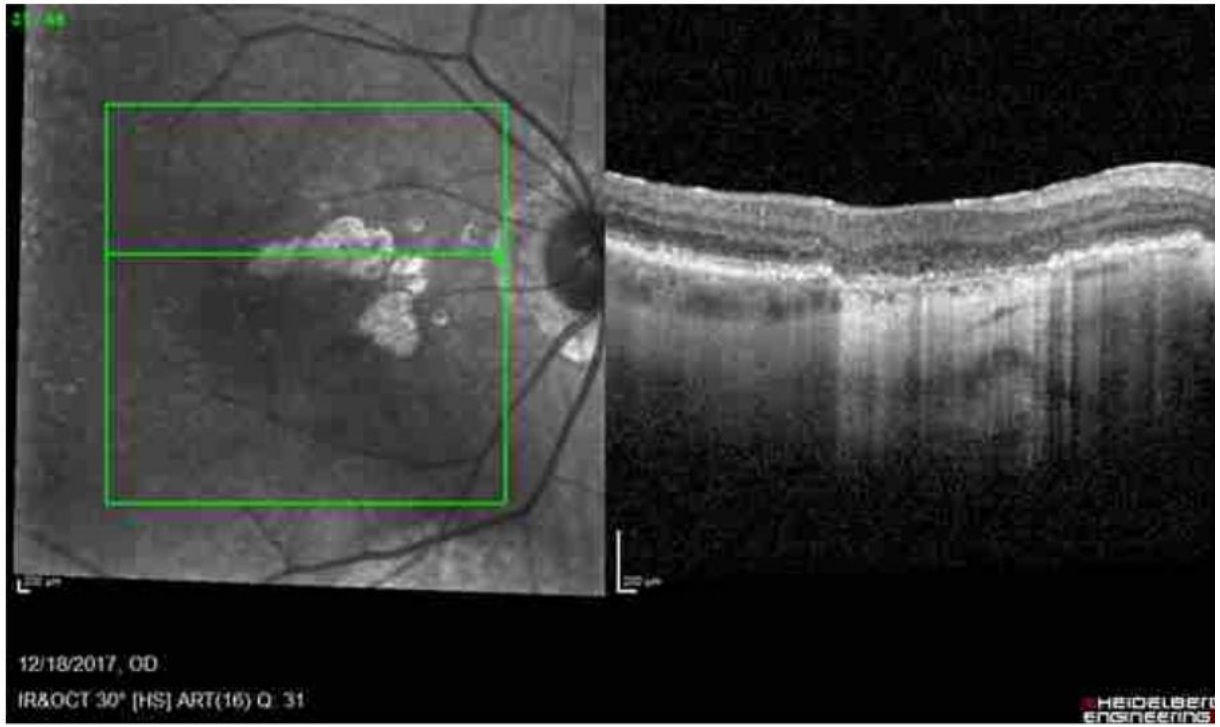


ART, automatic real-time tracking; CNV, choroidal neovascularization; IR, infrared; OCT, optical coherence tomography; OU, both eyes

Images courtesy of Cecelia Koetting, OD, FAAO, DipABO

Near-infrared Reflectance (NIR)

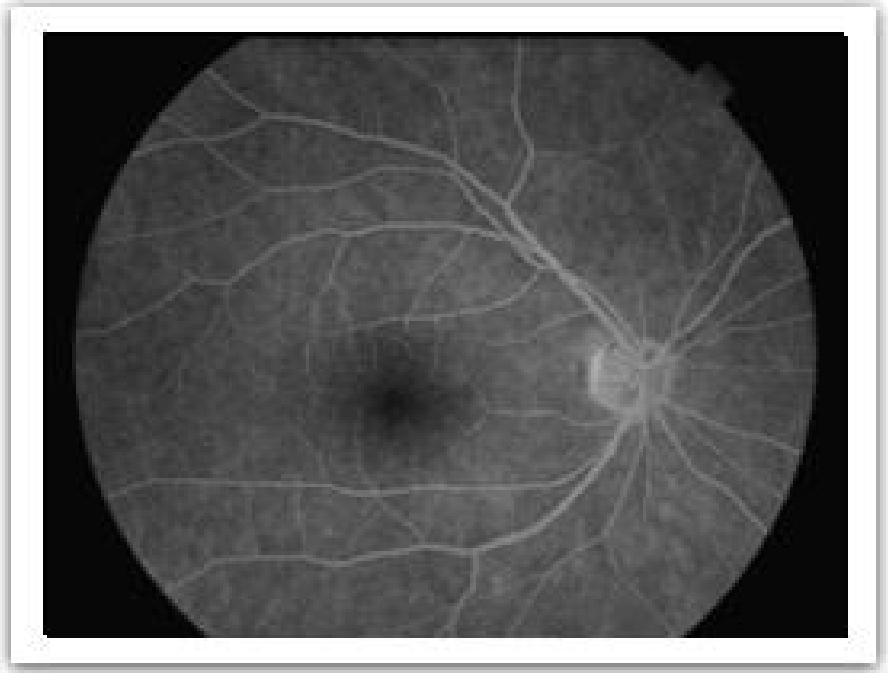
- Fundus images acquired simultaneously with SD-OCT
- Drusen/pigmentary changes and areas of GA appear hyperreflective compared to surrounding retinal structures
- More comfortable for patients as compared to the bright flash of fundus photography or the intense blue light of FAF
- Benefit of NIR over many other imaging modalities is minimal light scattering through a hazy media[1]



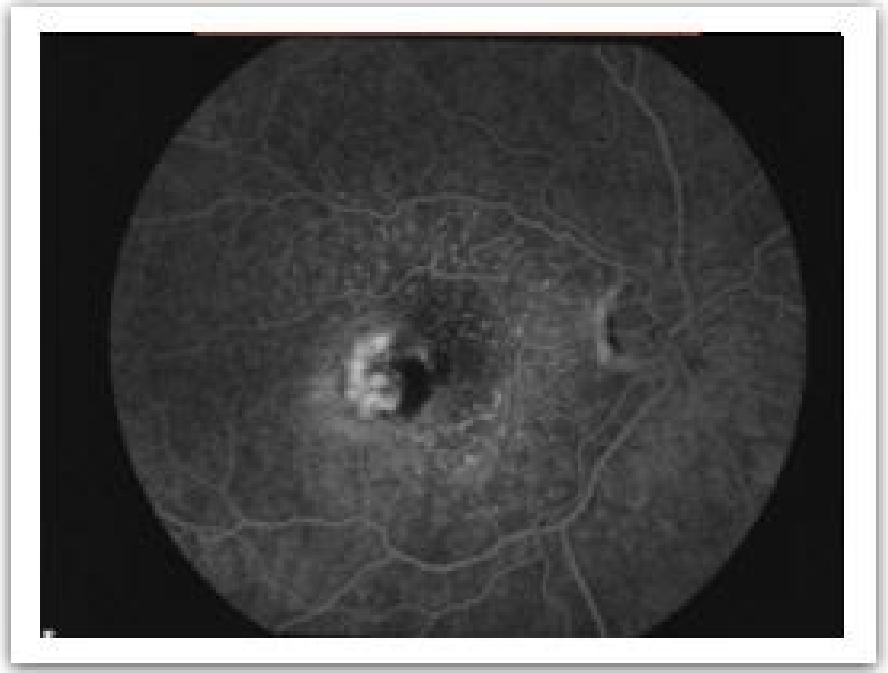
1. Dolz-Marco et al; Ophthalmol. Vis. Sci. 2016;57(14):6440-6446. doi: https://doi.org/10.1167/iovs.16-20265.

Fluorescein Angiography

- Analyzing retinal blood flow, retinal perfusion, and choroidal vasculature
- Helps to identify neovascularization and leakage



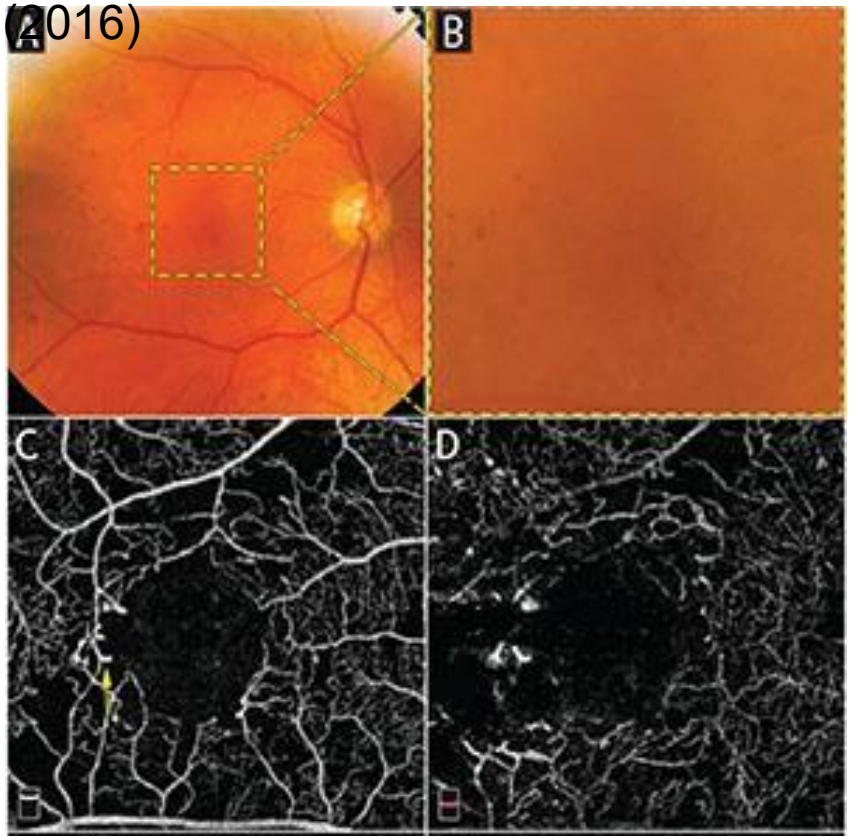
FA Normal Macula



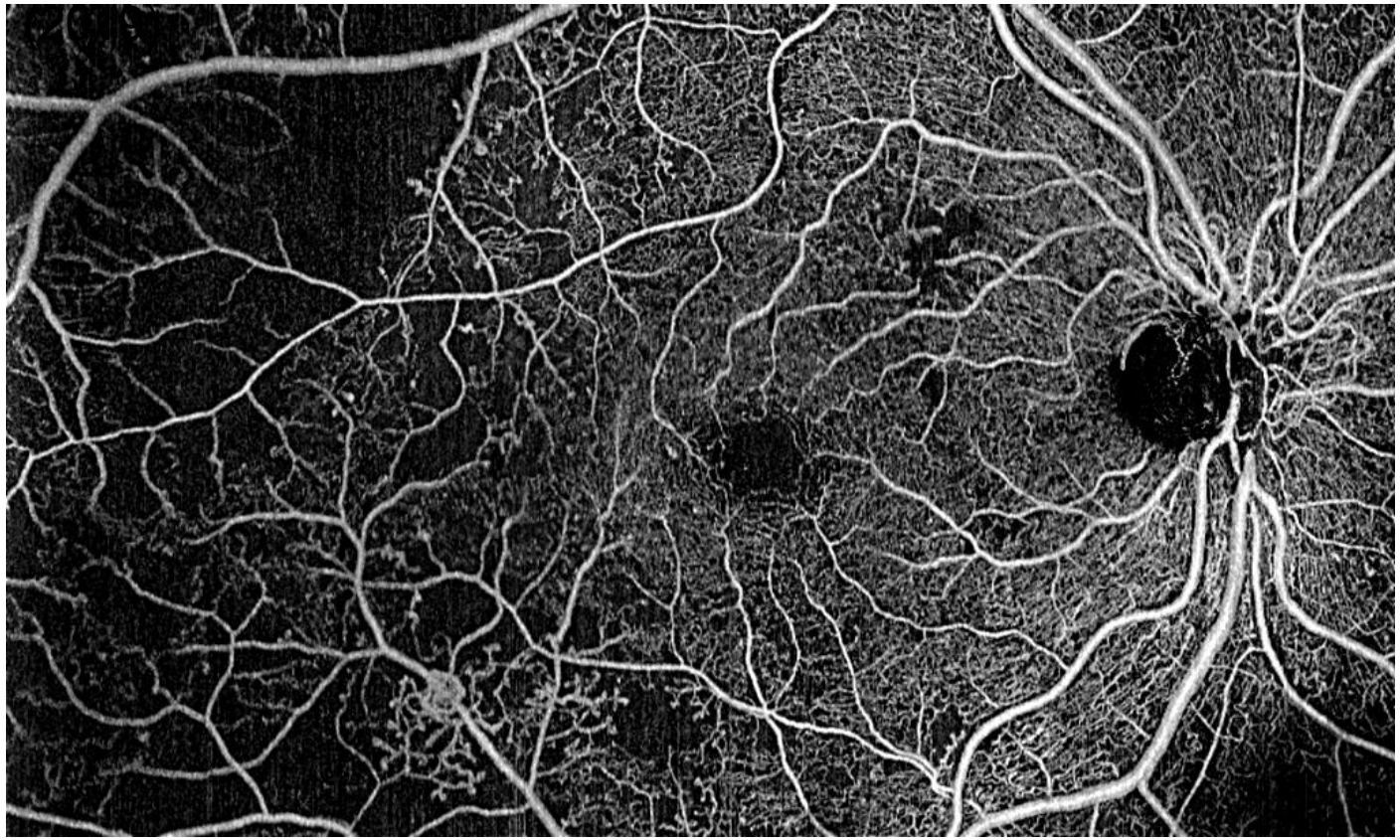
FA Wet AMD

OCTA improving rapidly

3x3 mm superficial and deep plexus (2016)

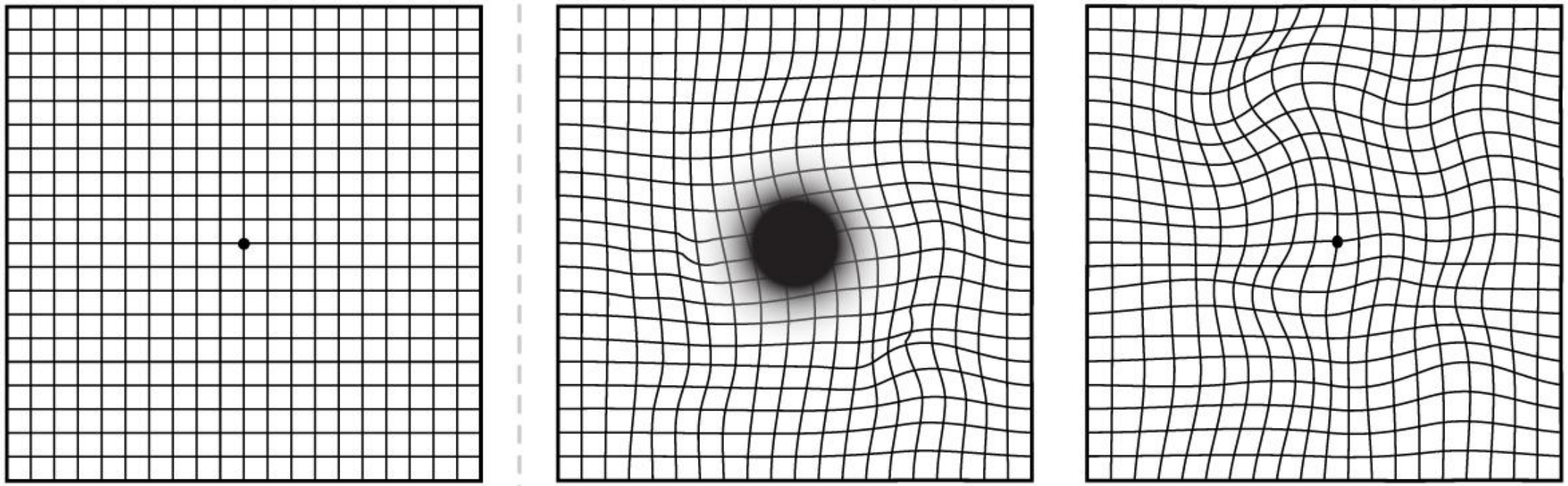


15 x 9 mm 200kHz SS OCTa



Novais E, Baumal C. The Clinical Utility of OCT Angiography. Review of Ophthalmology, Jan 2017.

At Home Monitoring : Amsler Grid



Normal

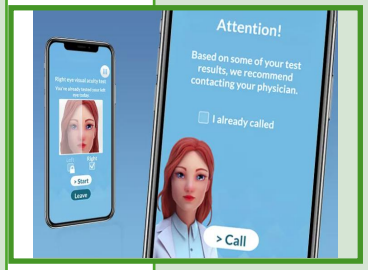
Missing area/blind spot

Distortion/wavy lines

Next Generation: FDA-Cleared Digital Retina Home Monitoring

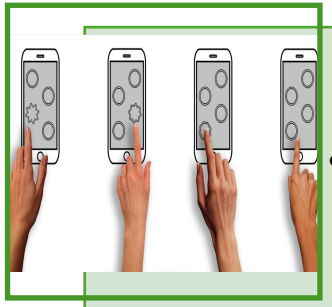
ForeseeHome

- Detects conversion from dry AMD to nAMD early
- Data from each daily test sent to monitoring center, then to doctor



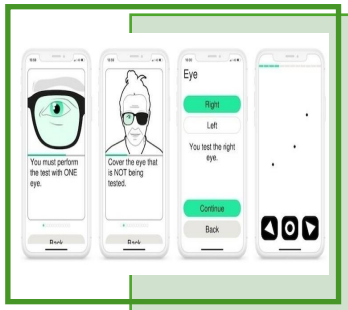
OdySight Care

- App for home VA testing in patients with retinal disease
- Alerts notify physicians and patients when significant change in VA detected



Home Vision Monitor

- Smartphone app that monitors vision in patients with neovascular retinal diseases



Alleye

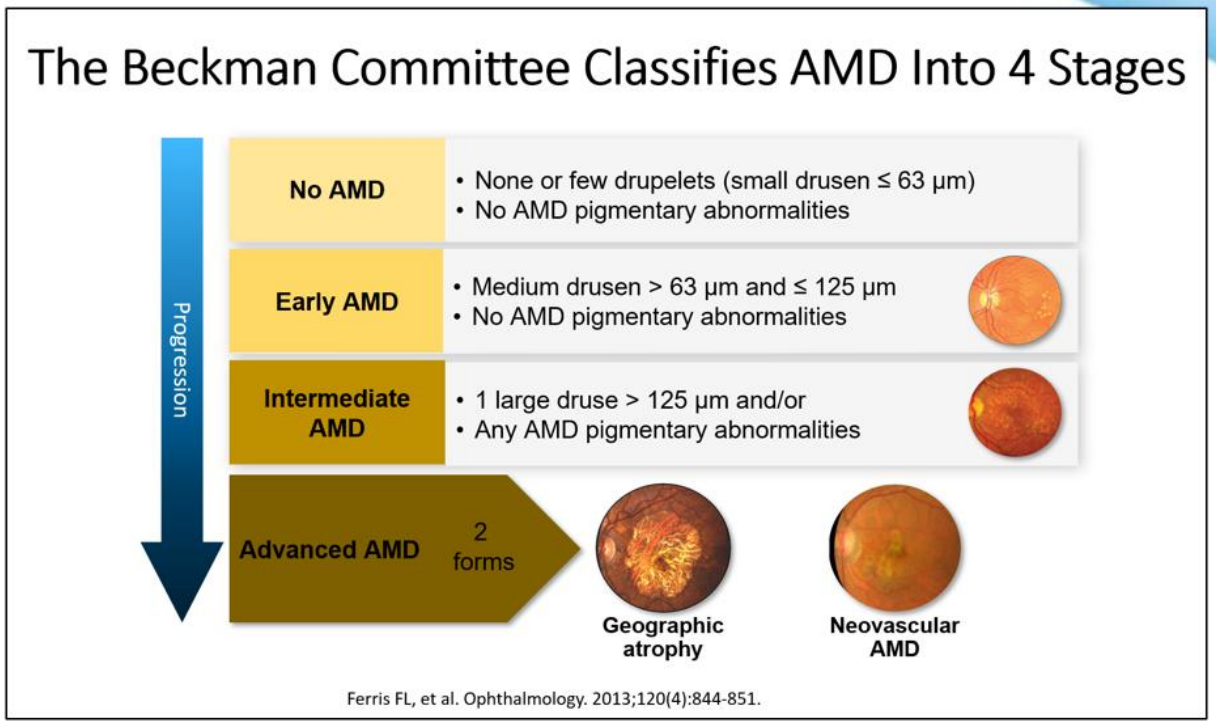
- Smartphone app enabling early detection of worsening pathology or need for IVT in patients with neovascular retinal diseases

Geographic Atrophy

Treatment and Comanagement

Risk Reduction Strategies – AMD

- Smoking cessation
- Diet
- Nutritional supplements
- HTN/cholesterol control
- Exercise/weight control
- UV/blue light protection



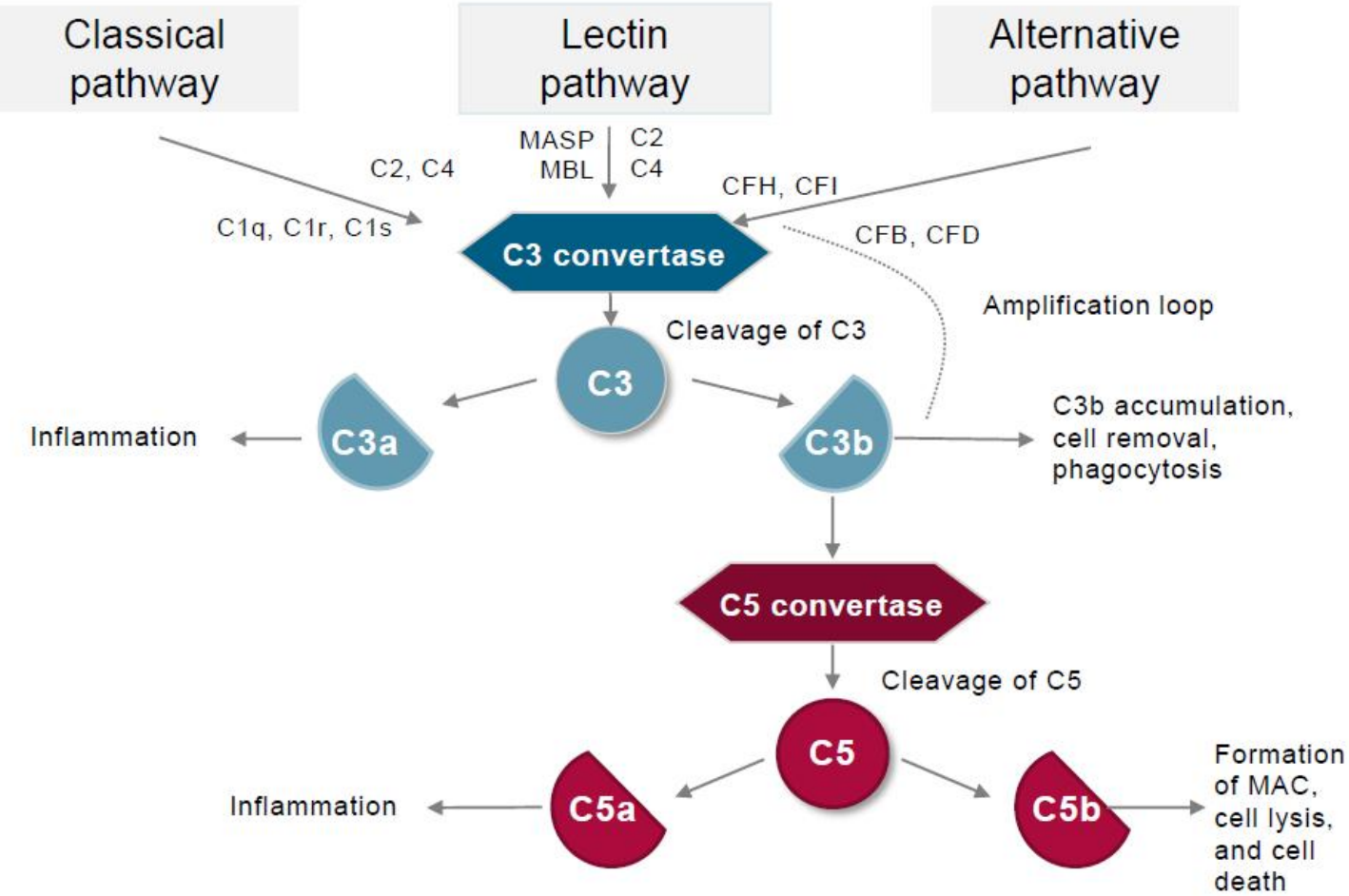
A Leading Contributor to Inflammation in GA Pathogenesis Is Dysregulation of the Complement System

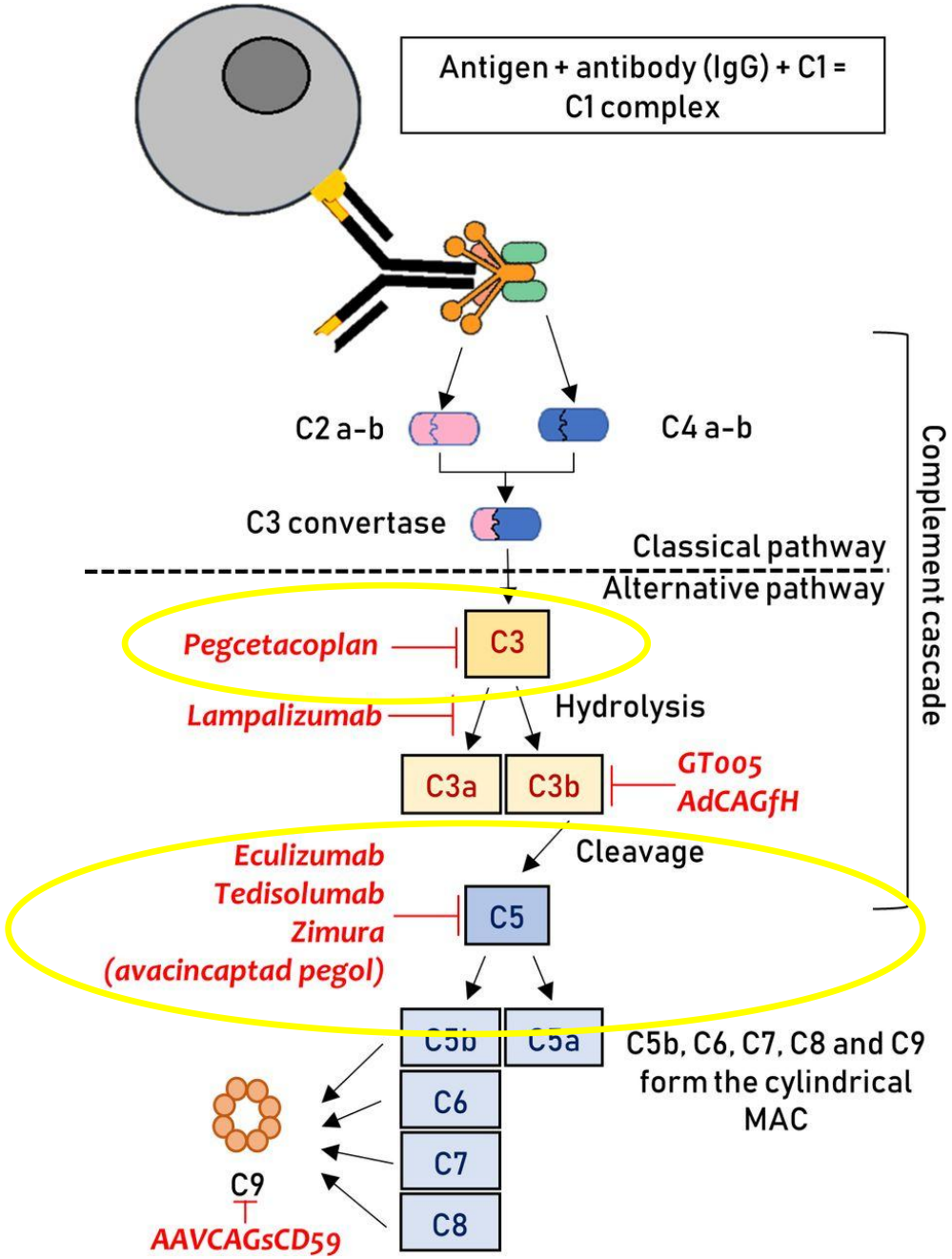
- The complement cascade is controlled by **regulator proteins** and is primarily responsible for **removal of pathogens**[1,2]
- Patients with AMD have been shown to have **increased levels** of activated complement components[3]
- Dysregulation can lead to **excess phagocytosis, inflammation, and cell lysis,** potentially **contributing to lesion growth in GA**[1,2]

AMD, age-related macular degeneration; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; GA, geographic atrophy; MAC, membrane attack complex; MASP, MBL-associated protease; MBL, mannose-binding lectin.

1. Boyer et al. *Retina*. 2017;37(5):819-835. 2. Katschke et al. *Sci Rep*. 2018;8(1):13055. 3. Smailhodzic et al. *Ophthalmology*. 2012;119(2):339-346. 4. Mastellos et al. *Trends Immunol*. 2017;38(6):383-394.

The complement cascade consists of 3 distinct pathways[1,4]





Newly Approved Complement Inhibition Therapy for GA

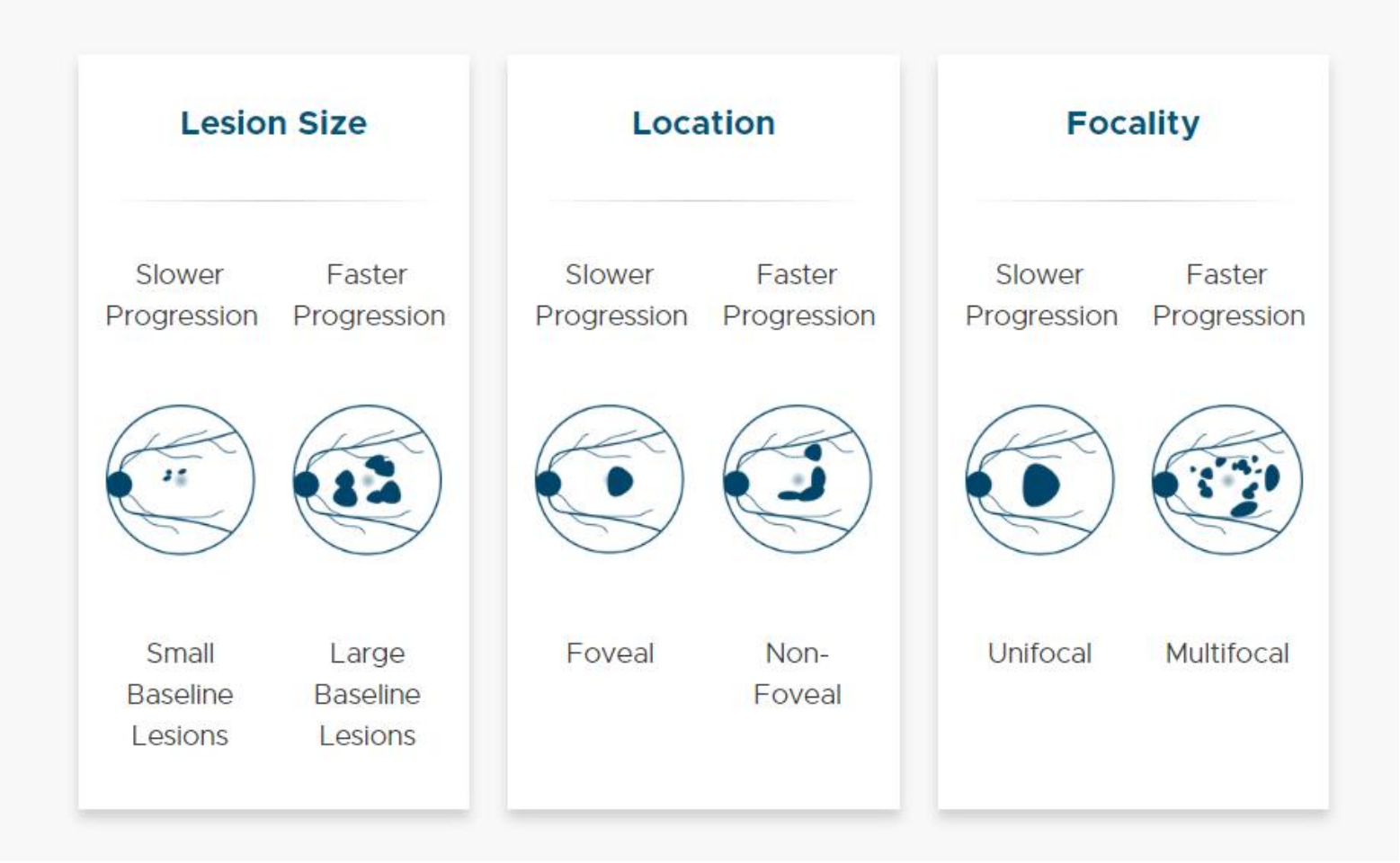
- **Pegcetacoplan (SYFOVRE®)**
  - Approved February 2023
  - Indication: GA secondary to AMD
  - MOA/Target: C3
  - Clinical Trials: OAKS/DERBY/GALE
  - 15 mg intravitreal injection every 25-60 days

- **Avacincaptad Pegol (IZERVAY®)**
  - Approved August 2023
  - Indication: GA secondary to AMD
  - MOA/Target: C5
  - Clinical Trials: GATHER1/GATHER2
  - 2 mg intravitreal injection monthly for up to 12 months

Cabral de Guimaraes TA, Daich Varela M, Georgiou M, *et al*
Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. *BJO* 2022;106:297-304.

Complement Inhibition Therapy Slows Progression of GA

What Should We Be Looking For When Considering Referral?



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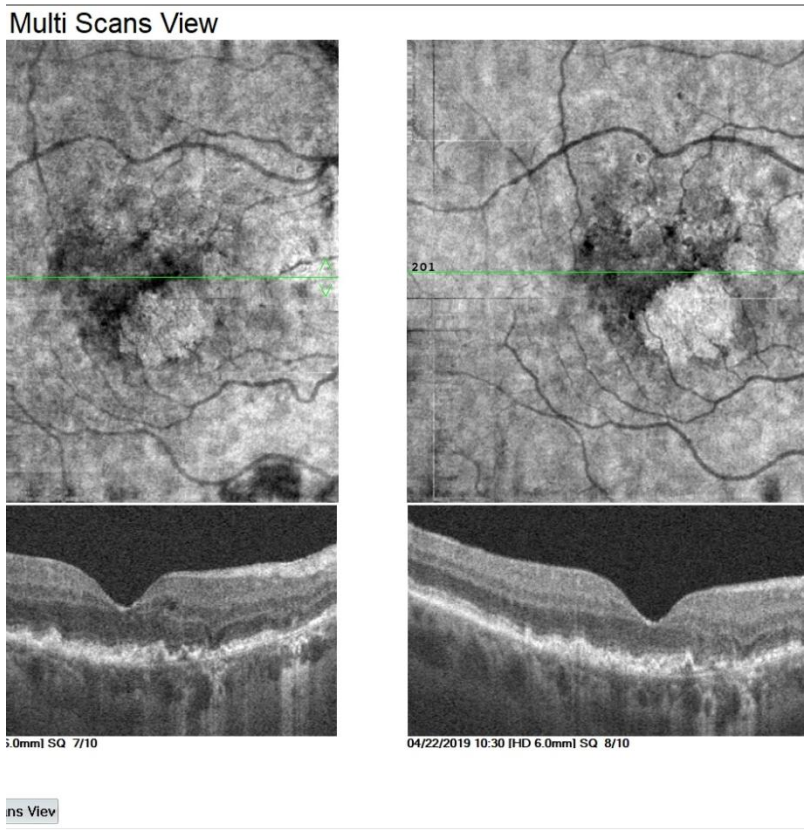
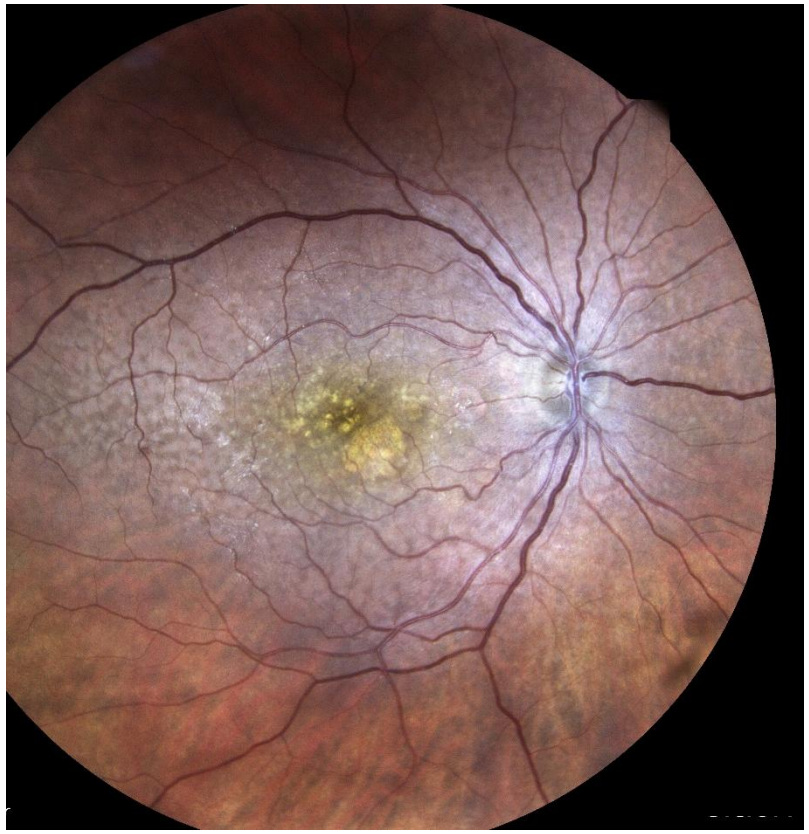
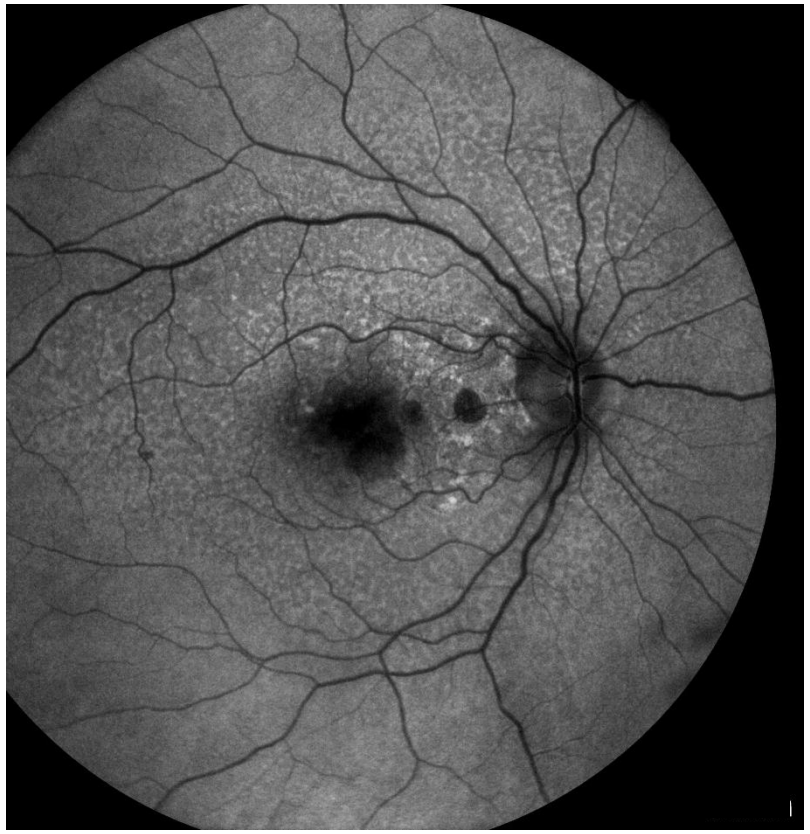
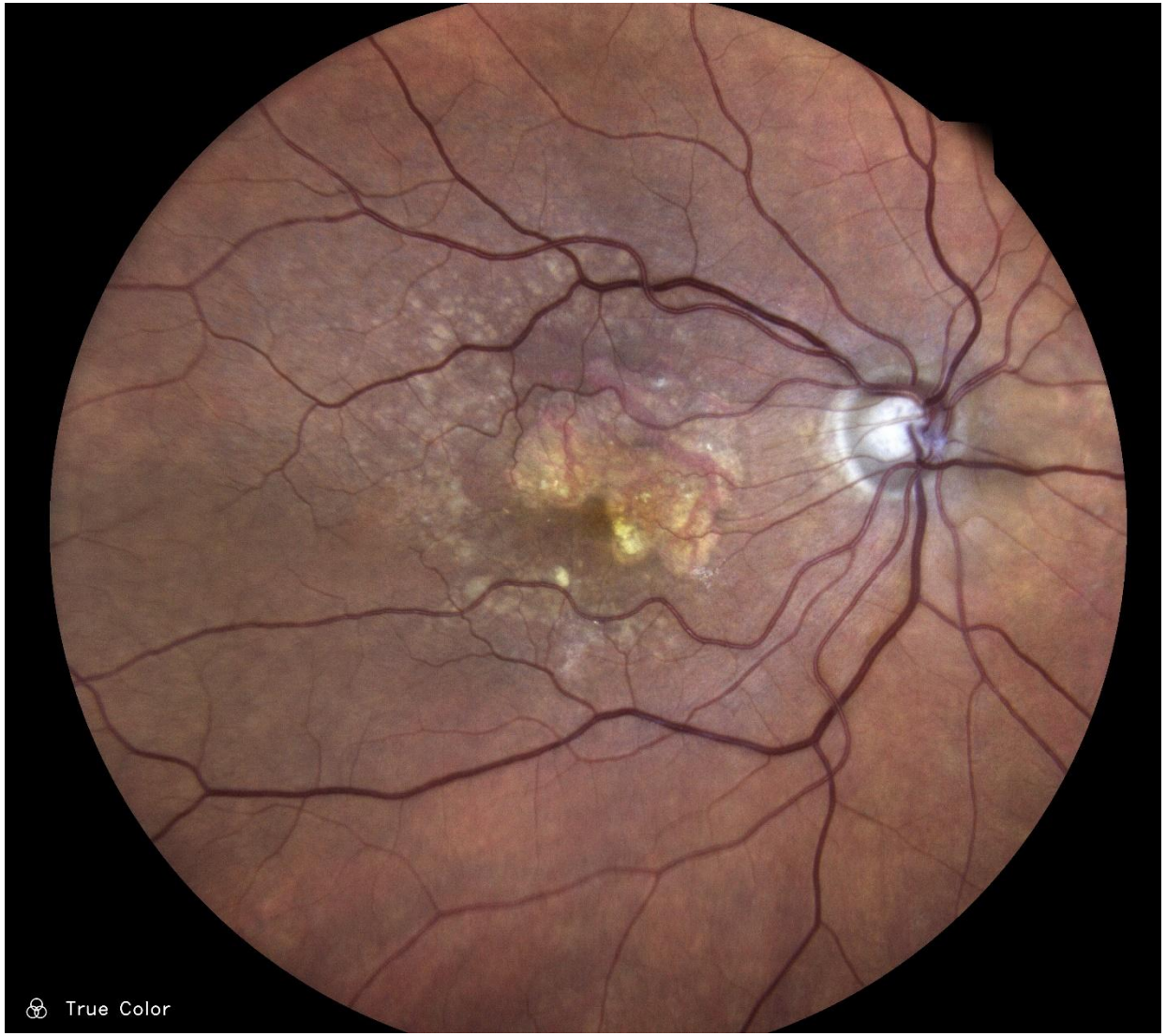
1.Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819-835.
2.Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.

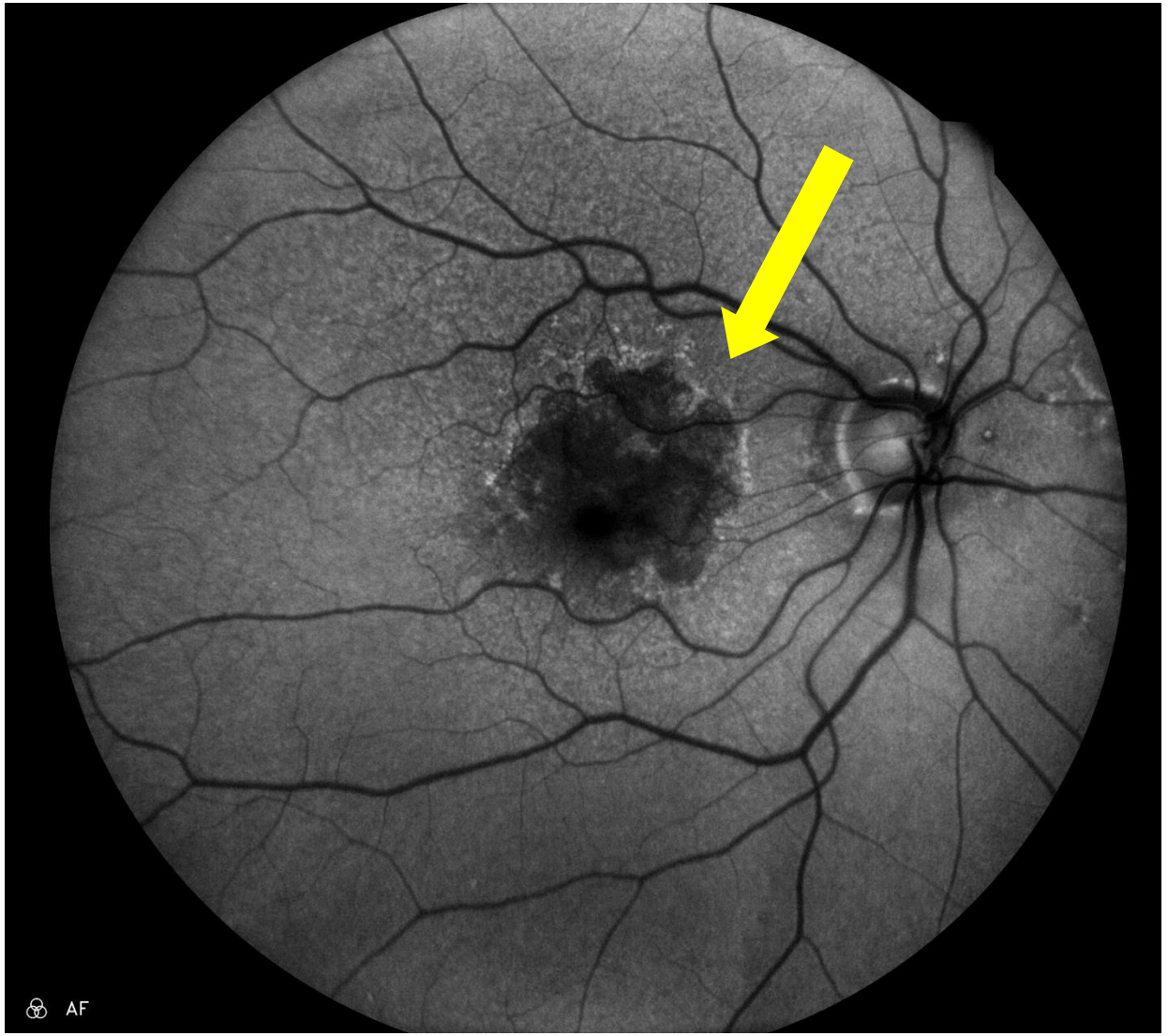






Management of all but early stage AMD now requires multimodal imaging as best practice





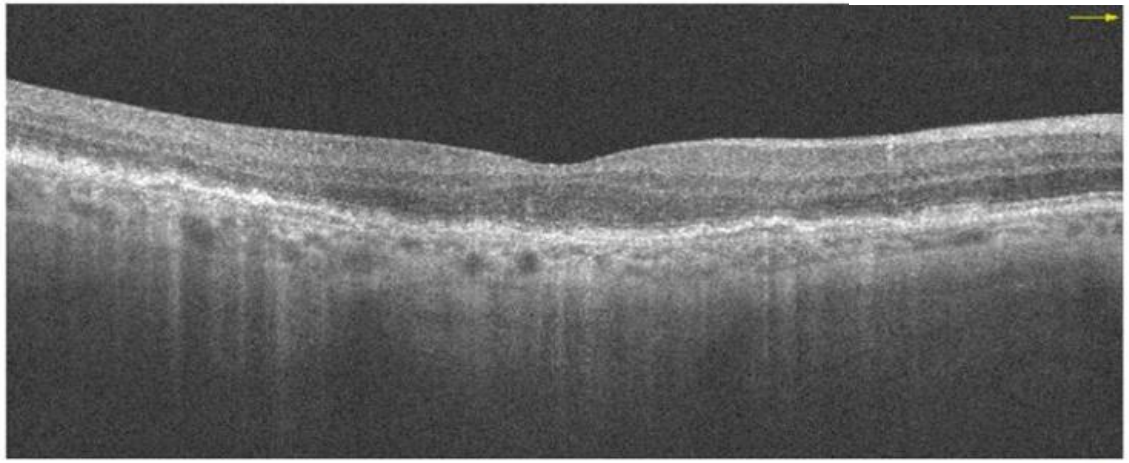
Hyperautofluorescent borders = high risk of progression

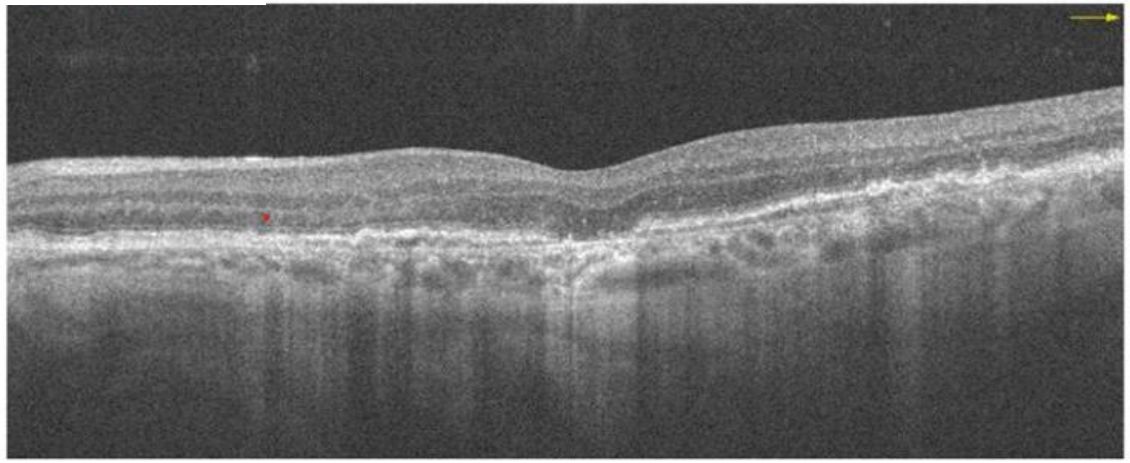
Holz FG, et al. *Am J Ophthalmol.* 2007;143:463-72.

Case #1

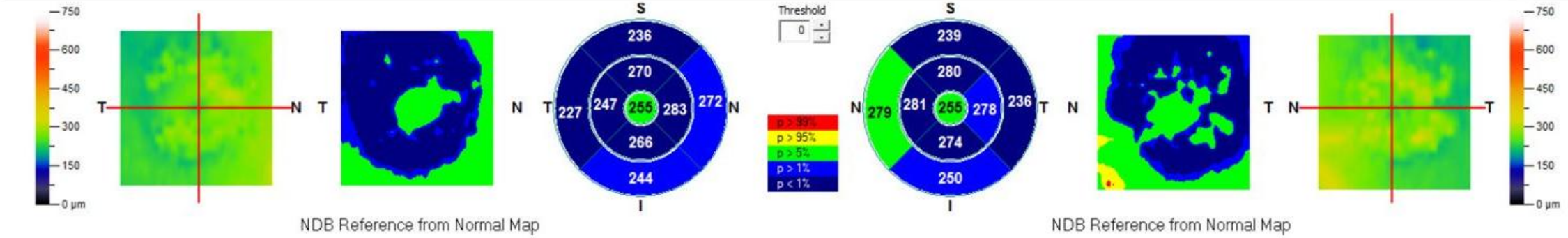
Right / OD

Left / OS

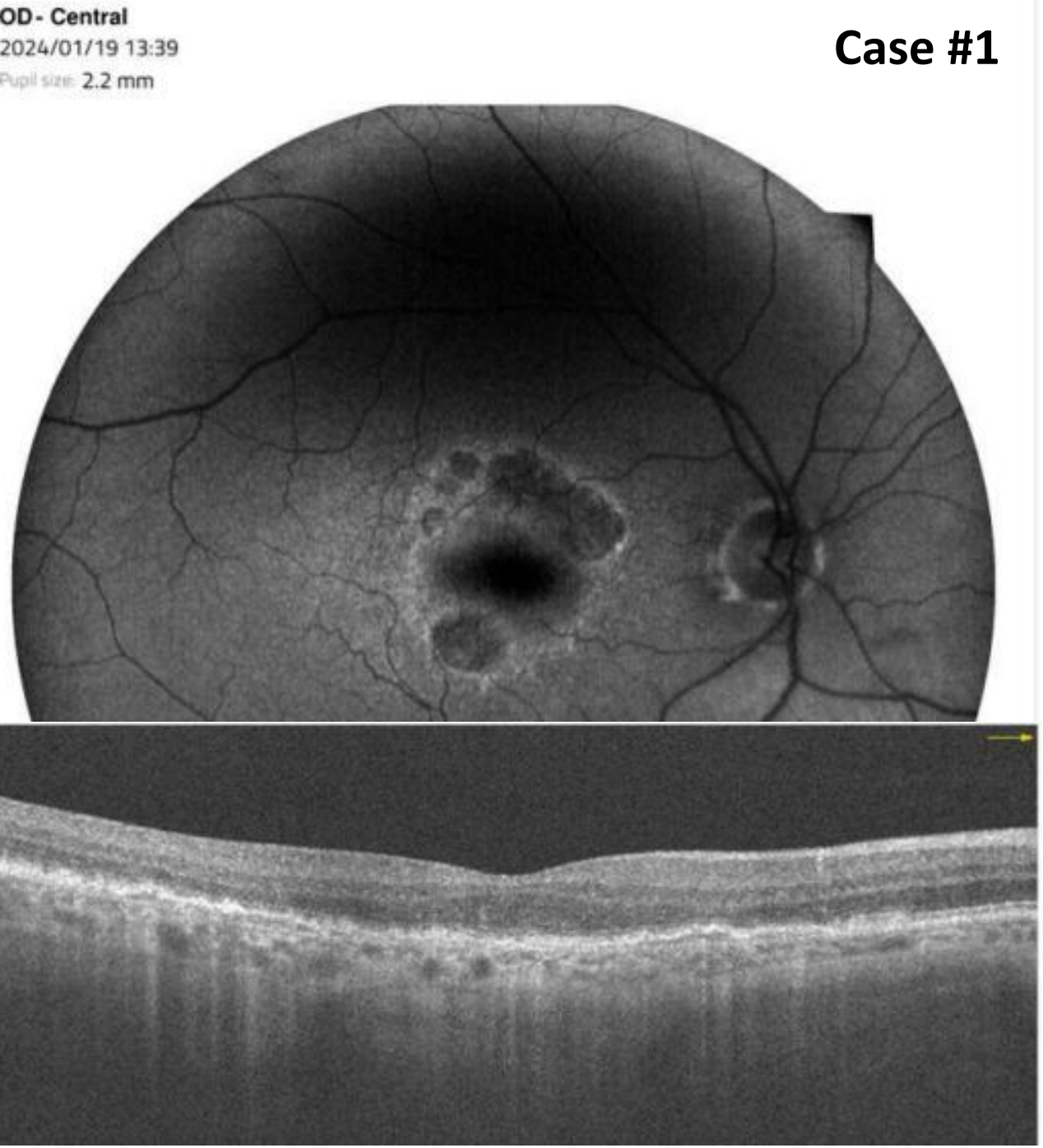


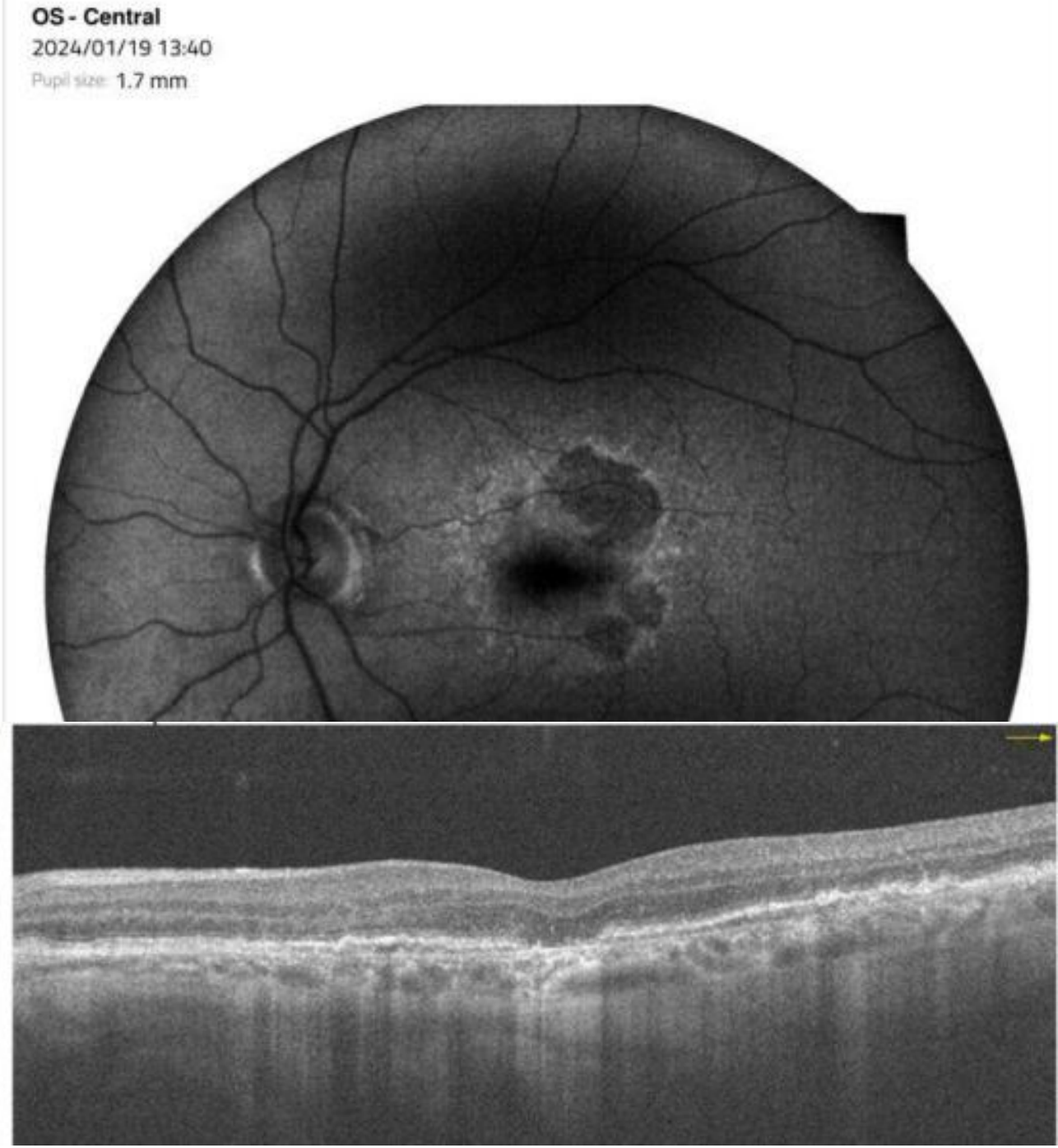


- 77 yo WM presents for comprehensive exam c/o blurry vision OU
- Has been told that he had “start of AMD” LEE ~1 year ago
- h/o cataract surgery in 2019
- BCVA 20/25 OD, 20/25 OS

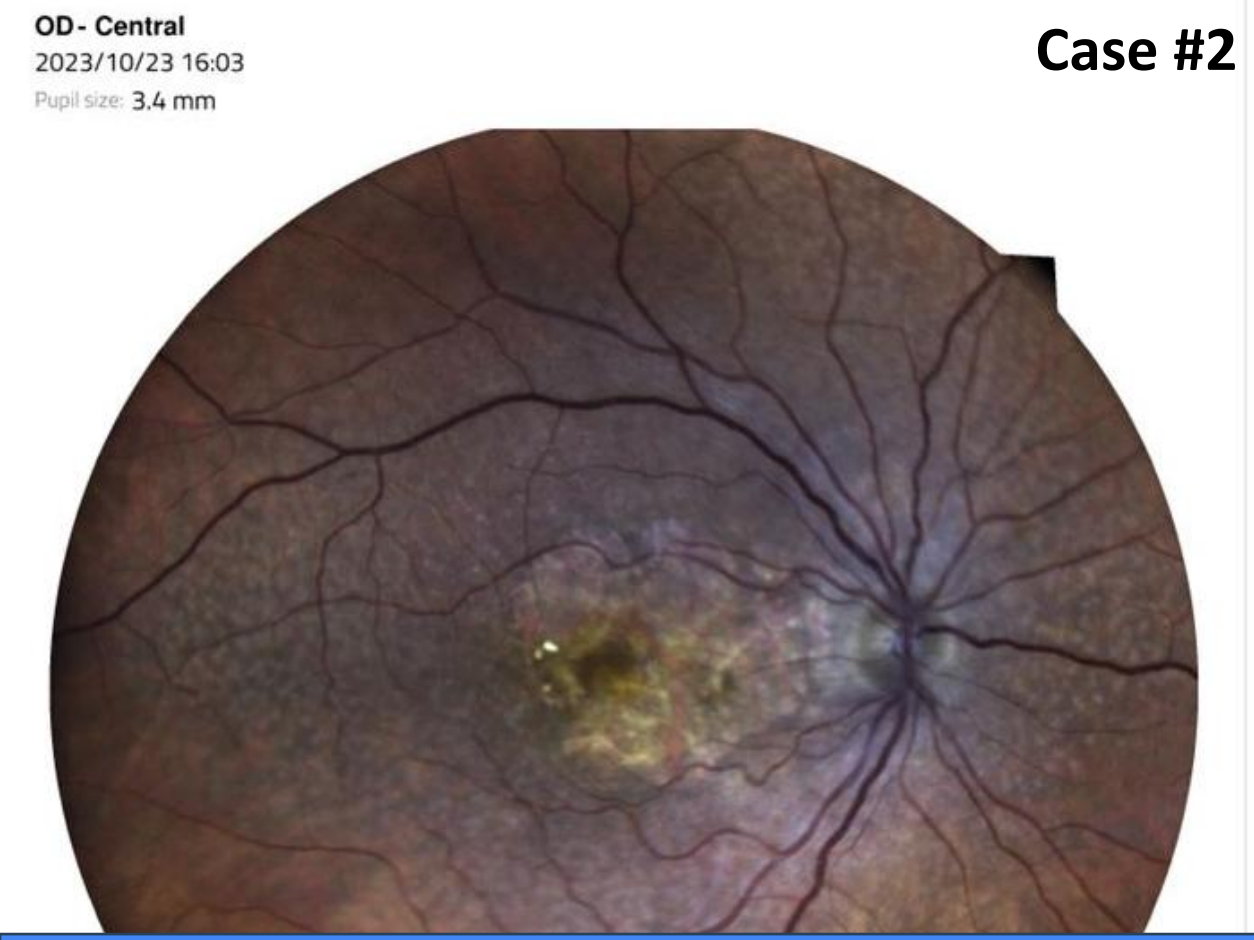


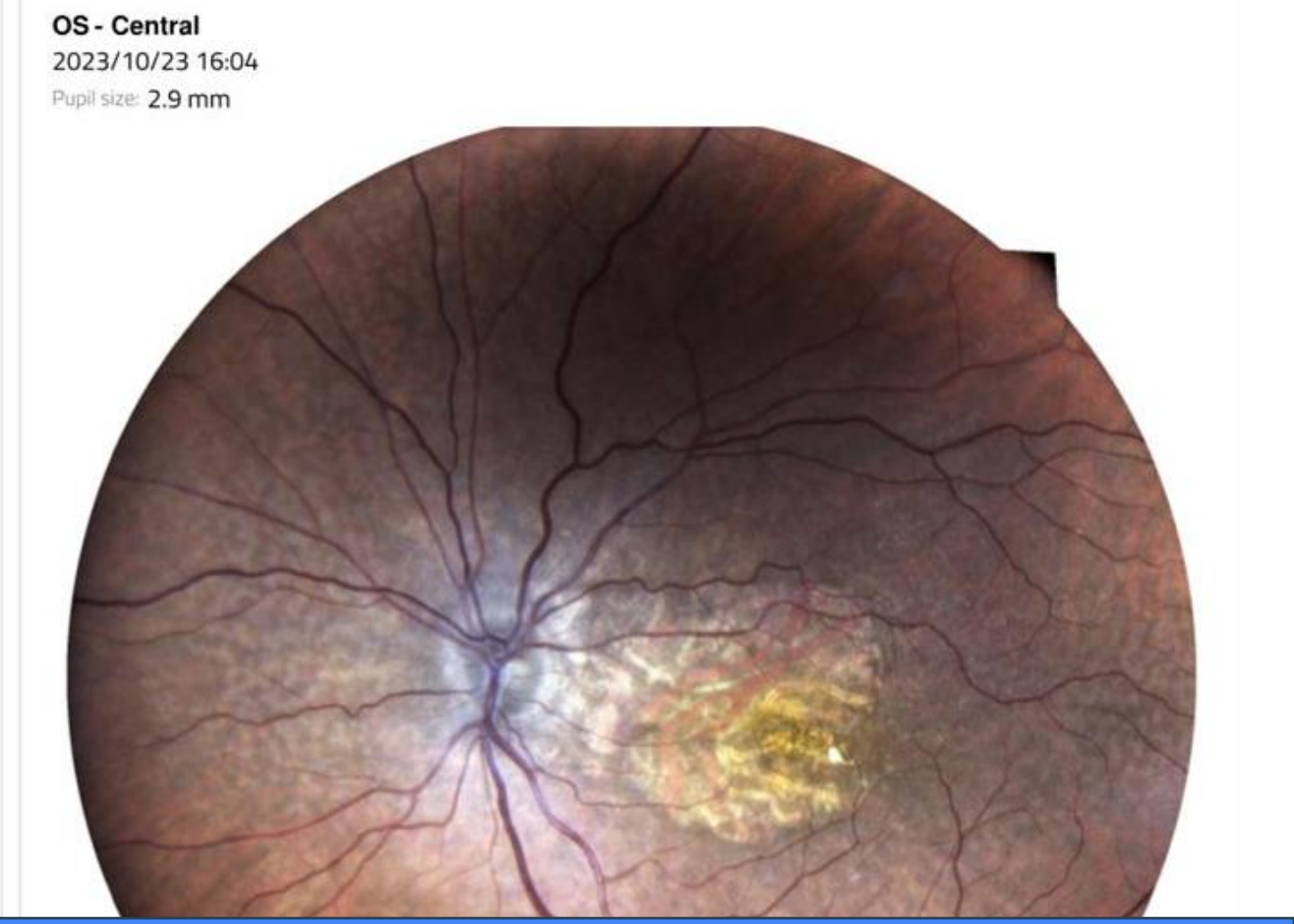
Case #1


OD - Central
2024/01/19 13:39
Pupil size: 2.2 mm


OS - Central
2024/01/19 13:40
Pupil size: 1.7 mm

Case #2

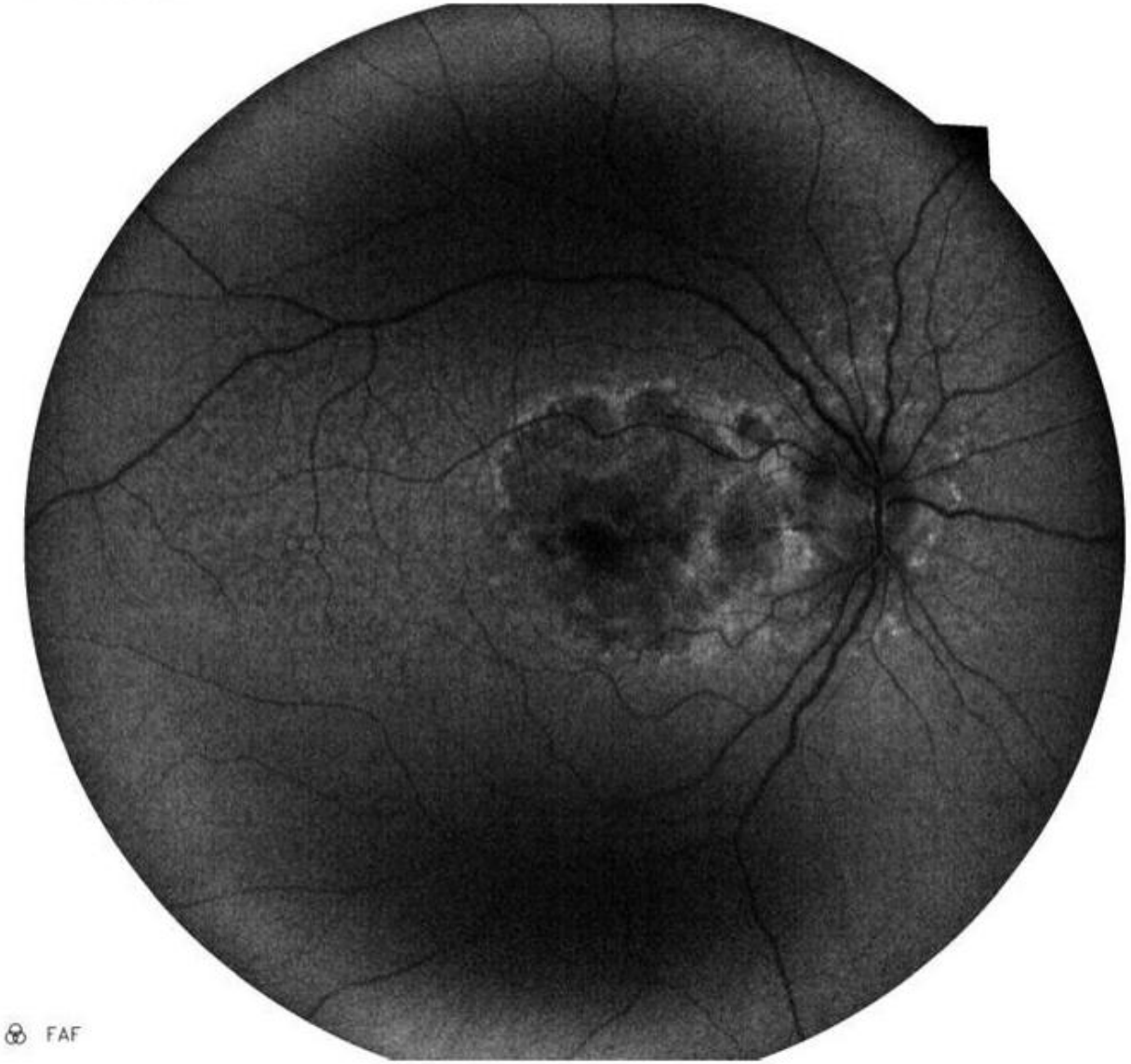




- 82 yo WF presents for 6 month AMD F/U
- Diagnosed w/ GA years ago and was referred for clinical trial consideration
- c/o worsening vision OS>OD x several months
- BCVA 20/50 OD, 2/200 OS (was 20/40 OD and 20/70 OS last visit)

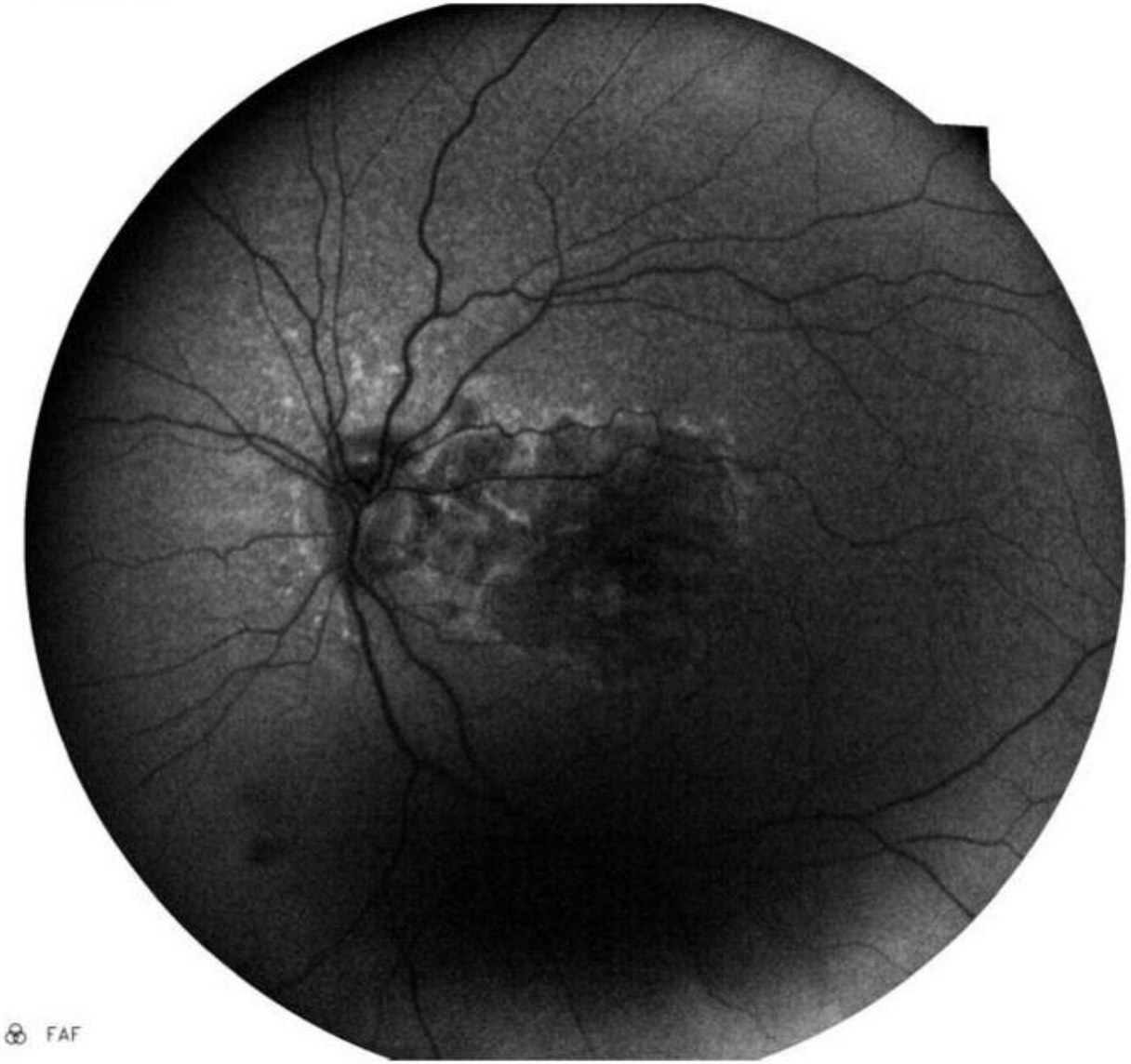
Case #2

OD - Central
2023/10/23 16:06
Pupil size: 1.8 mm



FAF

OS - Central
2023/10/23 16:04
Pupil size: 2.1 mm

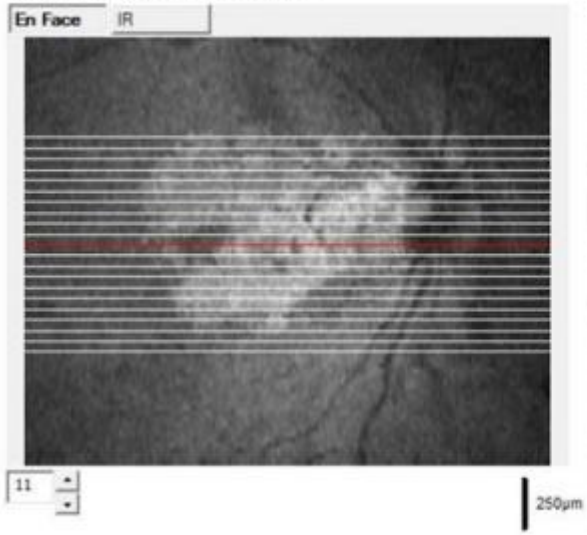


FAF

Case #2 Raster OU Report

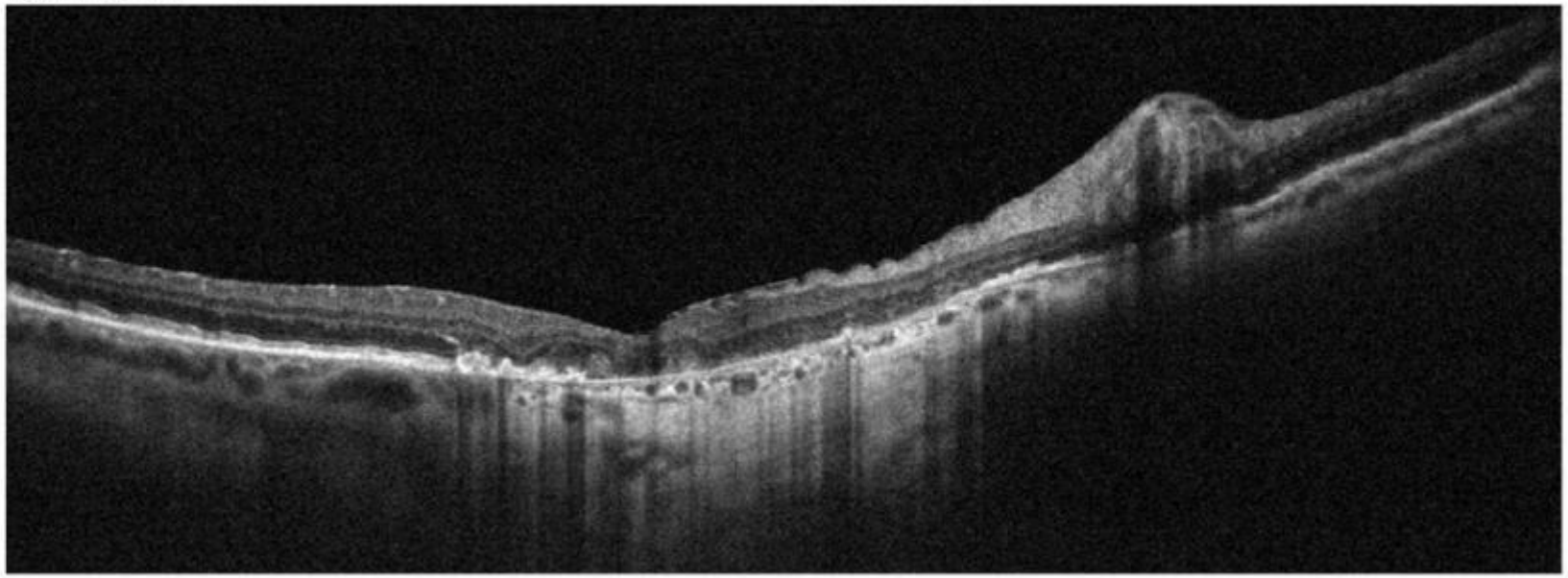
Right / OD

Scan 10/23/2023 15:53:43

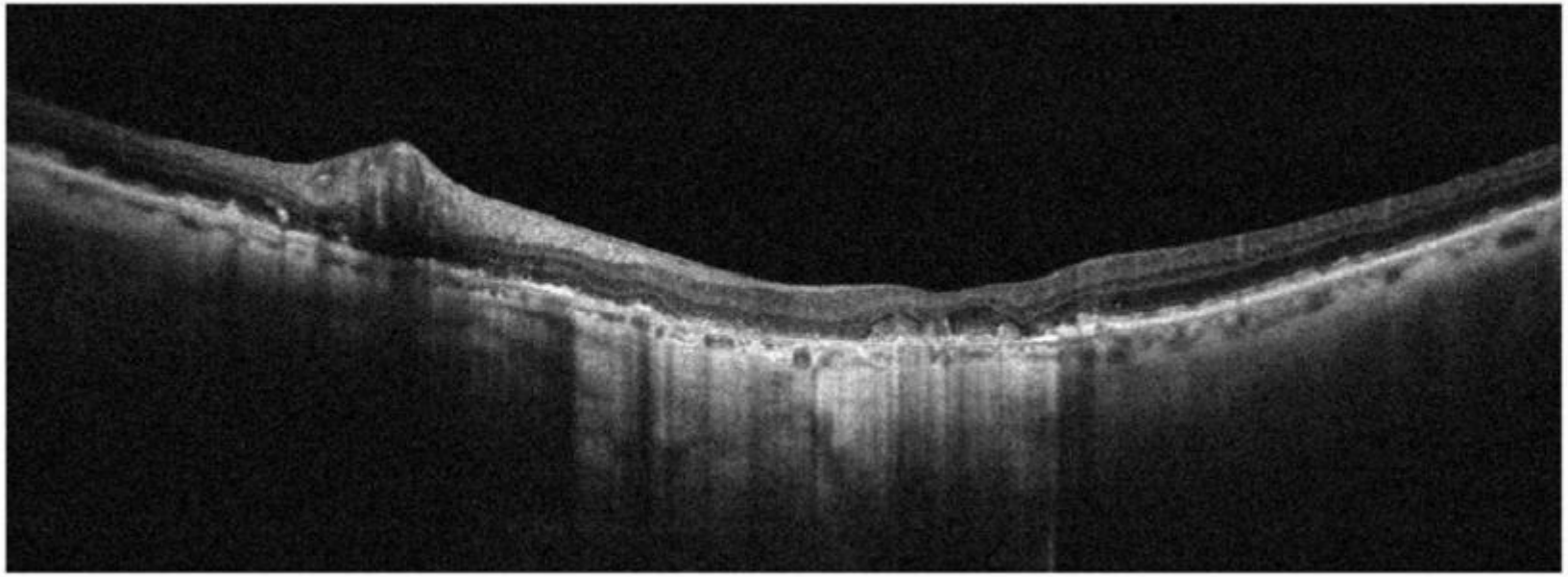


Signal Strength Index 39

12.00 x 4.00 Scan Size (mm)

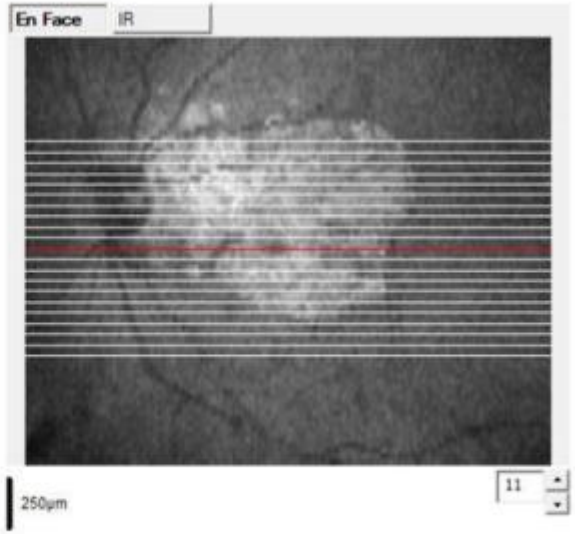


Auto Zoom



Signal Strength Index 43

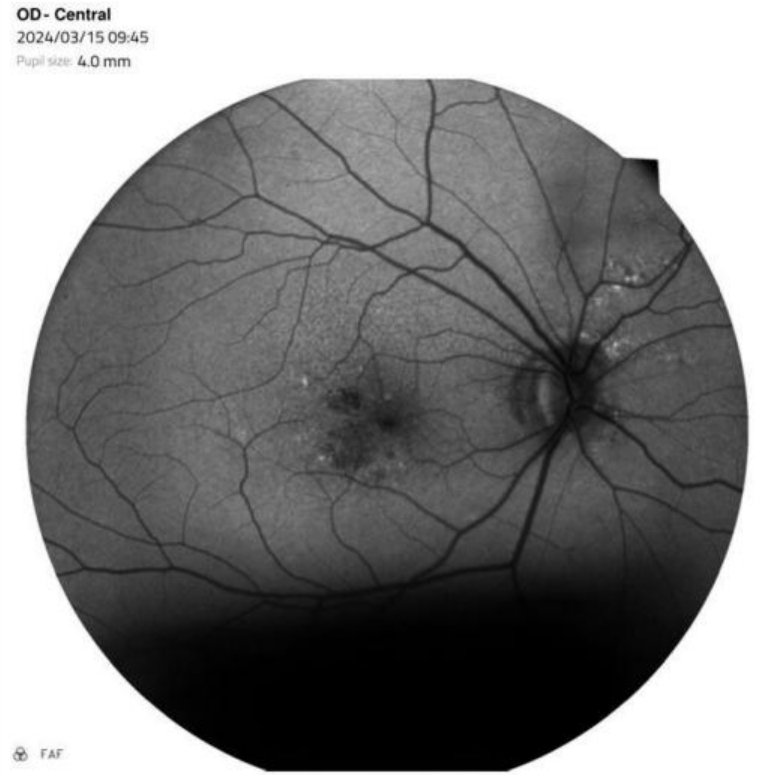
12.00 x 4.00 Scan Size (mm)



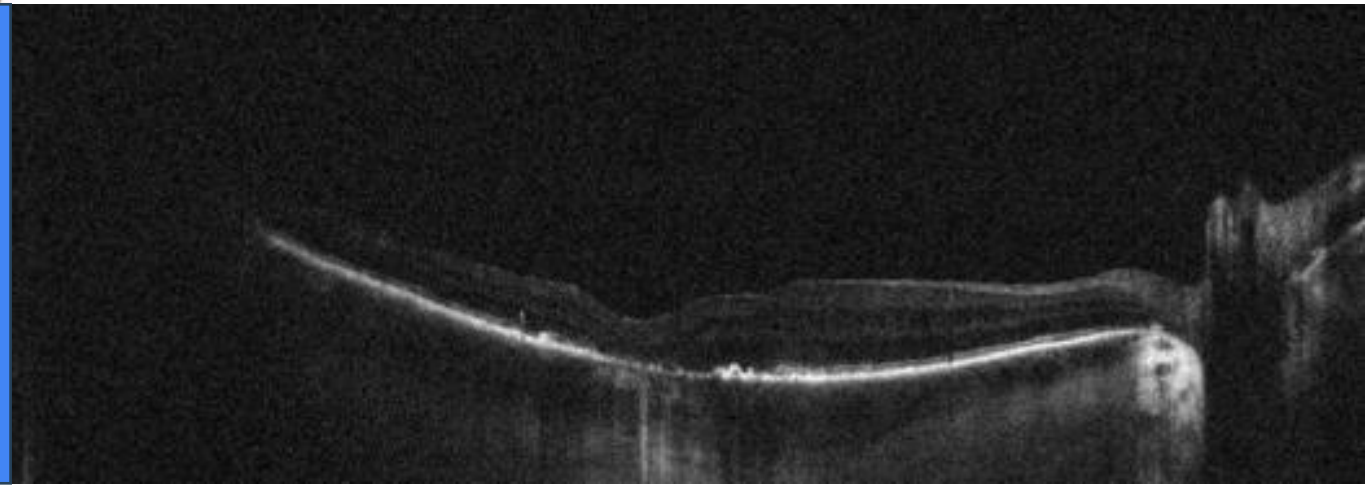
Scan 10/23/2023 15:54:24

Left / OS

Case #3

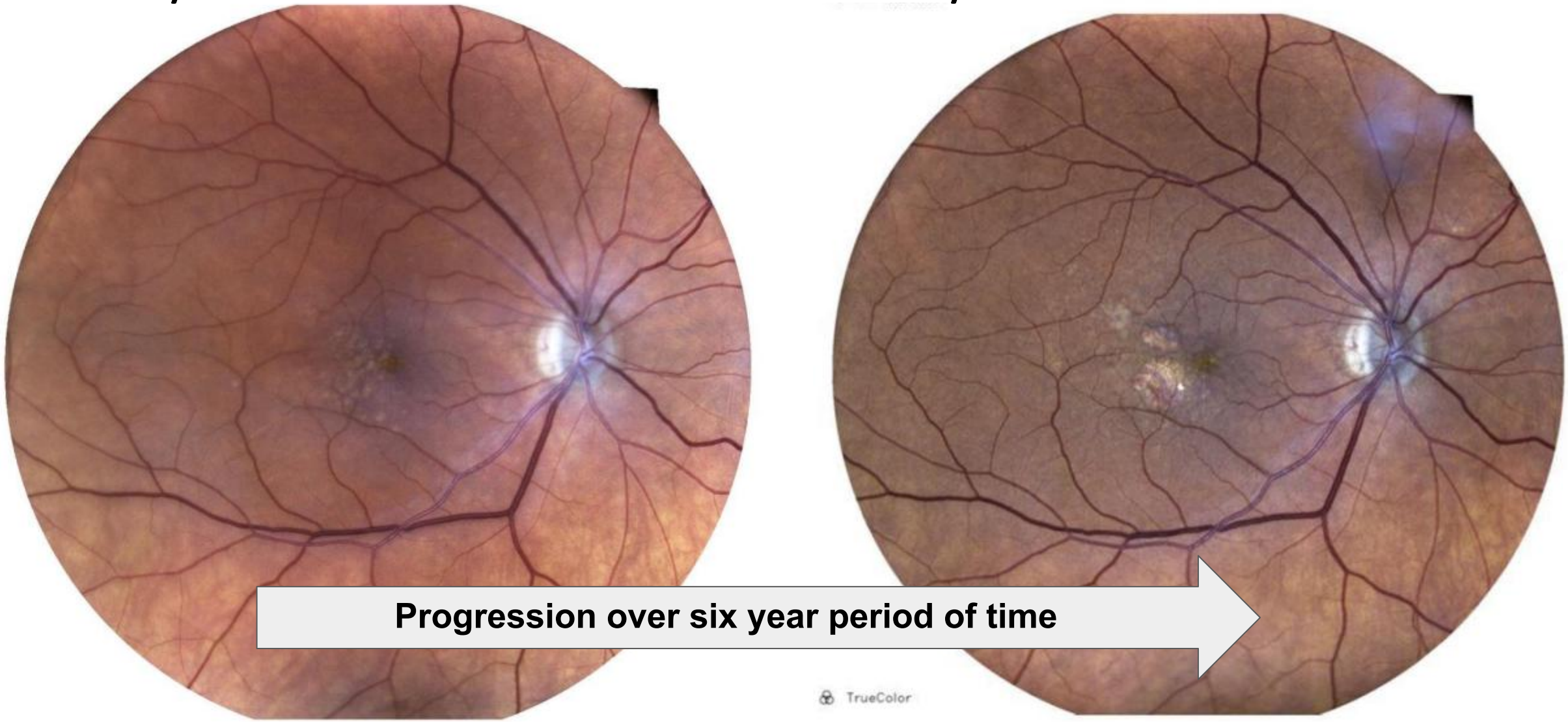


- 73 yo WF presents for AMD F/U
- LEE 18 months ago
- c/o slowly worsening night VA OU
- BCVA 20/25 OD, 20/25 OS



Case #3 2018
BCVA 20/20

Case #3 2024
BCVA 20/25



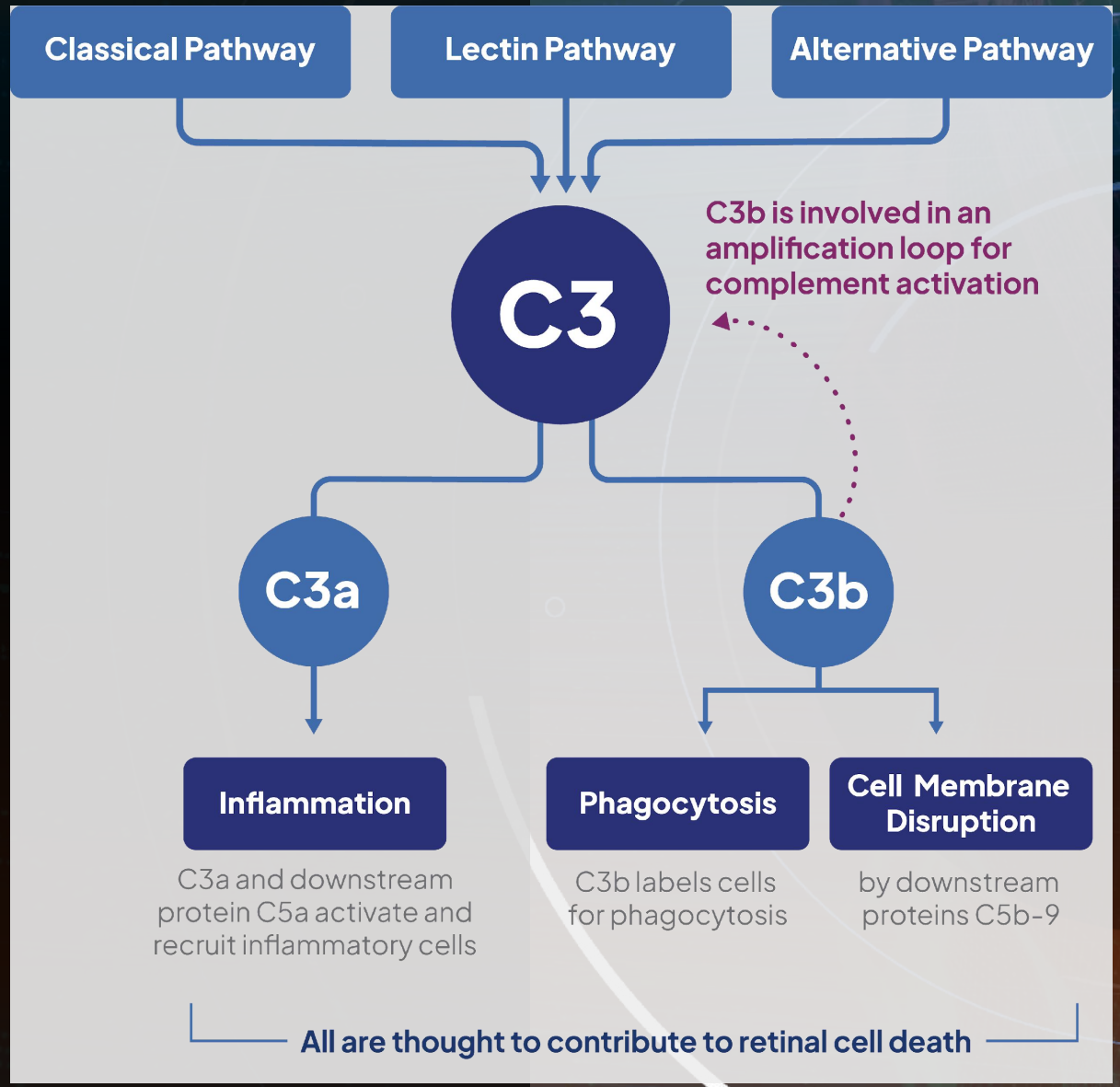
Comanagement of GA – Setting Expectations

- Educate patient that GA is a progressive, irreversible form of AMD
- Available treatment options can slow progression of GA but don’t reverse it
- Vision may continue to worsen, with or without treatment
- Current treatment administered by intravitreal injection every 1-2 months
- Considerations when referring for possible GA treatment:
    - Patient specific - symptoms, age, motivation, comorbidities
    - Imaging specific - progression rate, risk factors for progression
- Don’t forget about referral to low vision specialist when appropriate
- Patient will still require primary eyecare services

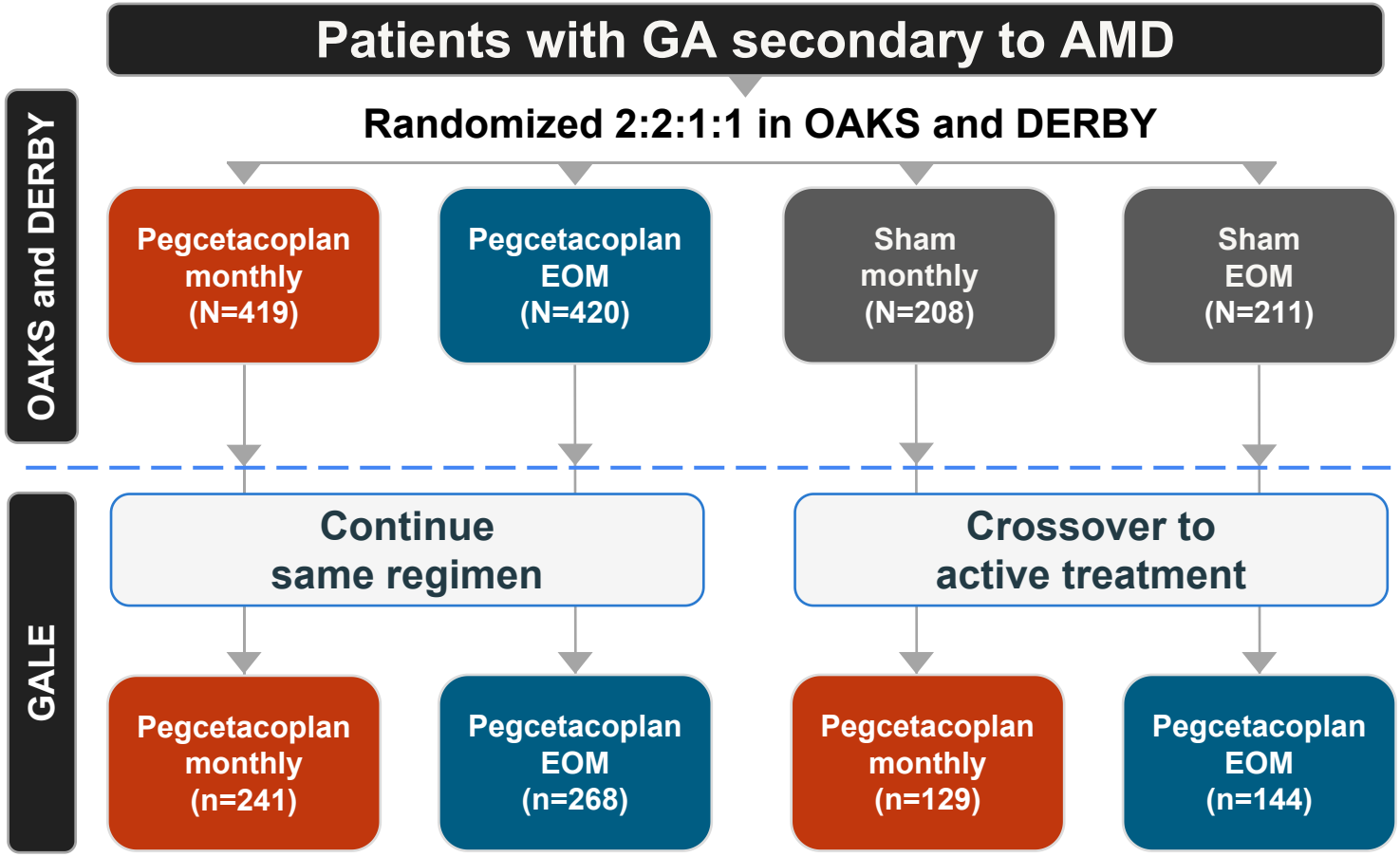
SYFOVRE- Apellis

Pegcetacoplan Intravitreal Injection

- FDA Approved February 2023
- Increased levels of complement activity have in GA lesions and surrounding areas including photoreceptors.
- C3 is the central protein in the complement cascade.
- Three complement activation pathways converge with the cleavage of C3 to C3a and C3b.
- SYFOVRE Targets C3 and C3b to help regulate complement overactivation in GA



GALE: 36-Month, Open-Label Extension Study



83% who completed OAKS or DERBY continued in GALE (n=782)

Efficacy analysis: Change in GA lesion area based on 6-month GALE data

- 30-month continuous pegcetacoplan treatment compared with sham[a]
  - Pegcetacoplan was compared with sham (actual sham [24 months OAKS and DERBY] + projected sham [6 months GALE])
  - Piecewise linear slope analysis with 6-month segments
- 6-month pegcetacoplan treatment for sham crossover group

Safety data through 30 months

- Exudative AMD, IOI, ION

OAKS, DERBY, GALE ClinicalTrials.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively.
[a]Projected sham was estimated by calculating the average of the mean rate of change of each 6-month period of sham treatment.
AMD, age-related macular degeneration; **EOM,** every other month; **GA,** geographic atrophy; **IOI,** intraocular inflammation; **ION,** ischemic optic neuropathy.

GALE: Baseline Demographics and Study Eye Characteristics at OAKS and DERBY Enrollment[a]

Characteristic	PM to PM (n=241)	PEOM to PEOM (n=267)	Sham Pooled to Pegcetacoplan (n=272)
Age, mean (SD), years	77.4 (6.89)	77.5 (7.23)	77.4 (7.28)
Female, n (%) Male, n (%)	140 (58.1) 101 (41.9)	159 (59.6) 108 (40.4)	166 (61.0) 106 (39.0)
Geographic region, n (%) United States Rest of world	 159 (66.0) 82 (34.0)	 169 (63.3) 98 (36.7)	 177 (65.1) 95 (34.9)
White, n (%)	213 (88.4)	244 (91.4)	251 (92.3)
GA lesion size, mean (SD), mm^2	8.30 (4.04)	8.21 (3.89)	8.12 (3.99)
GA lesion size <7.5 mm^2, n (%)	117 (48.5)	128 (47.9)	139 (51.1)
Nonsubfoveal or extrafoveal lesion, n (%)	95 (39.4)	104 (39.0)	87 (32.0)
Unifocal lesion, n (%)	62 (25.7)	77 (28.8)	93 (34.2)
Intermediate or large drusen >20, n (%)	121 (50.2)	127 (47.6)	146 (53.7)
NL-BCVA, mean (SD), ETDRS letters	60.5 (15.9)	58.4 (16.7)	59.0 (16.4)

Baseline characteristics consistent with OAKS and DERBY

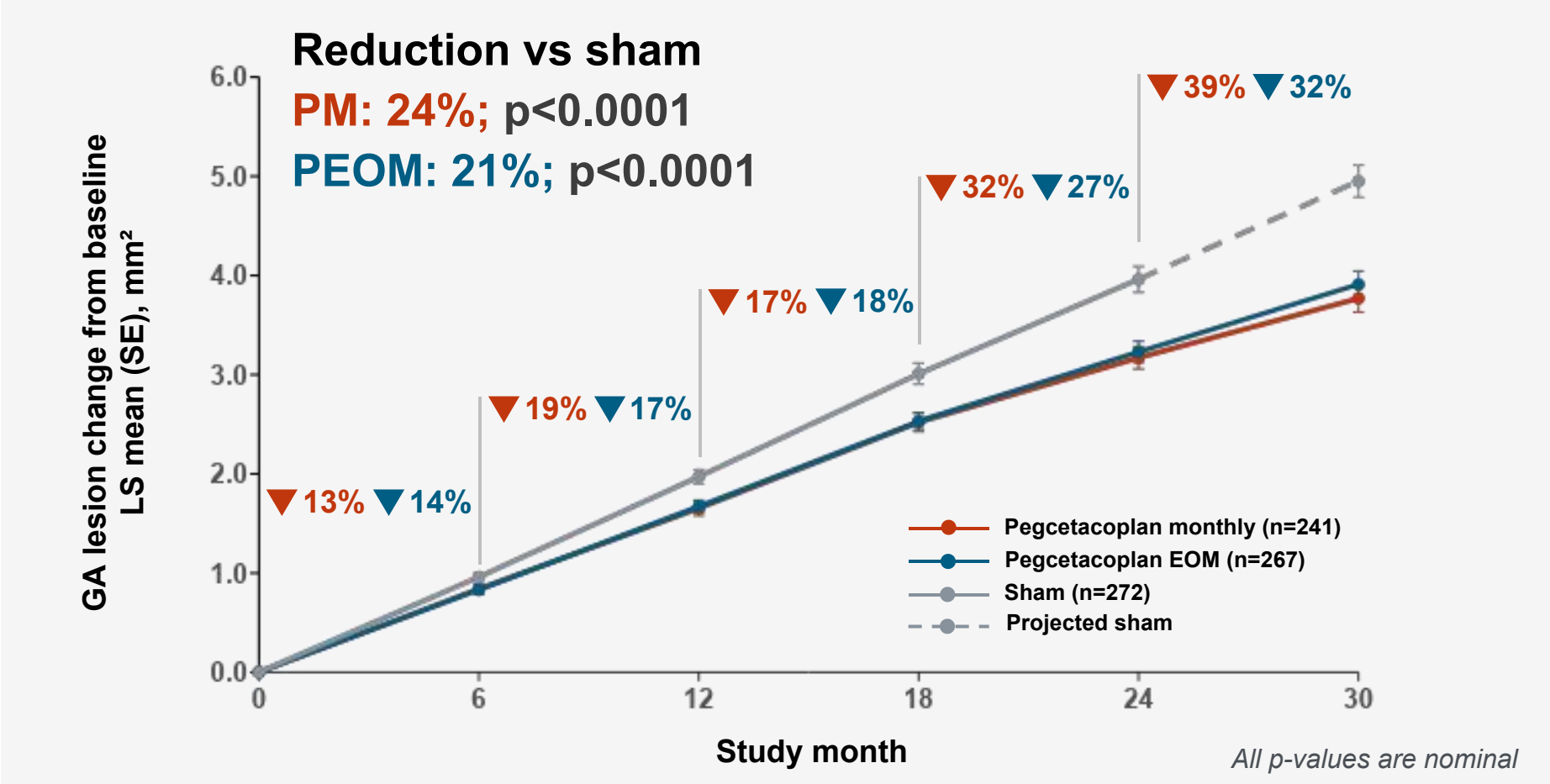
[a]Modified full analysis set, included all randomized patients entering GALE from either OAKS or DERBY who received ≥1 injection and had ≥1 post-baseline GA measure.
ETDRS, Early Treatment Diabetic Retinopathy Study; **GA**, geographic atrophy; **NL-BCVA**, normal luminance best-corrected visual acuity; **PEOM**, pegcetacoplan every other month; **PM**, pegcetacoplan monthly; **SD**, standard deviation.

GALE: Reduction in GA Lesion Growth in the First 6 Months of Pegcetacoplan Treatment (Sham Crossover)

	Statistics	Sham Pooled to Pegcetacoplan (N=272)
GA growth rate with pegcetacoplan (GALE, Months 24–30) vs previous sham average 6-month change (OAKS and DERBY, Months 0–24)	Estimate (SE)	-0.14 (0.051)
	95% CI of estimate	-0.24, -0.04
	Reduction in GA lesion growth	**15%**
	p-value	0.0050[a]

[a]Nominal p-value.
Assuming a piecewise linear trend in time with a knot at integrated Month 6, Month 12, Month 18, and Month 24.
CI, confidence interval; **GA,** geographic atrophy; **SE,** standard error.

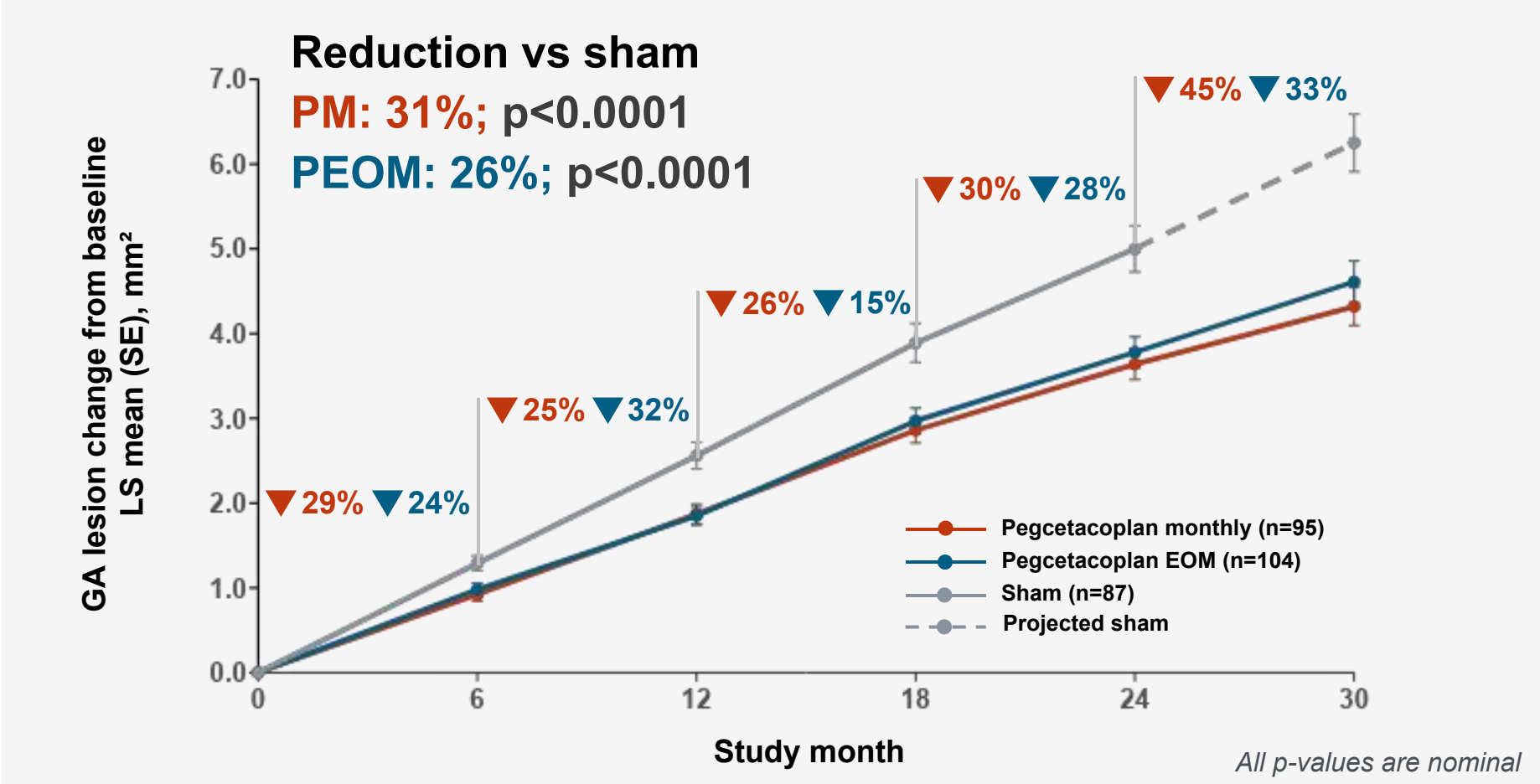
GALE: Reductions in GA Lesion Growth Following 30 Months of Continuous Treatment With Pegcetacoplan Increased Over Time



LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 30, with knots at Months 6, 12, 18, and 24 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 30 was estimated from the mean rate of change in each 6-month period from Month 0 to Month 24.The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS and DERBY.

GA, geographic atrophy; **ITT,** intent to treat; **LS,** least-squares; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SE,** standard error.

GALE: Reductions in GA Lesion Growth Following 30 Months of Continuous Treatment With Pegcetacoplan in Patients With Nonsubfoveal Lesions



LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 30, with knots at Months 6, 12, 18, and 24 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 30 was estimated from the mean rate of change in each 6-month period from Month 0 to Month 24.The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS and DERBY.

EOM, every other month; **GA,** geographic atrophy; **ITT,** intent to treat; **LS,** least-squares; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SE,** standard error.

GALE: New-Onset eAMD[a]

	PM		PEOM[b]	
	24 months	30 months	24 months	30 months
Study eye, safety set,[c] %	12.2%	16.6%	6.7%	8.6%
Events per 100 patient-years	7.5	7.2	3.9	3.6
Fellow eye,* %	4.2%	5.2%	4.1%	4.6%
Events per 100 patient-years	2.5	2.1	2.4	1.9

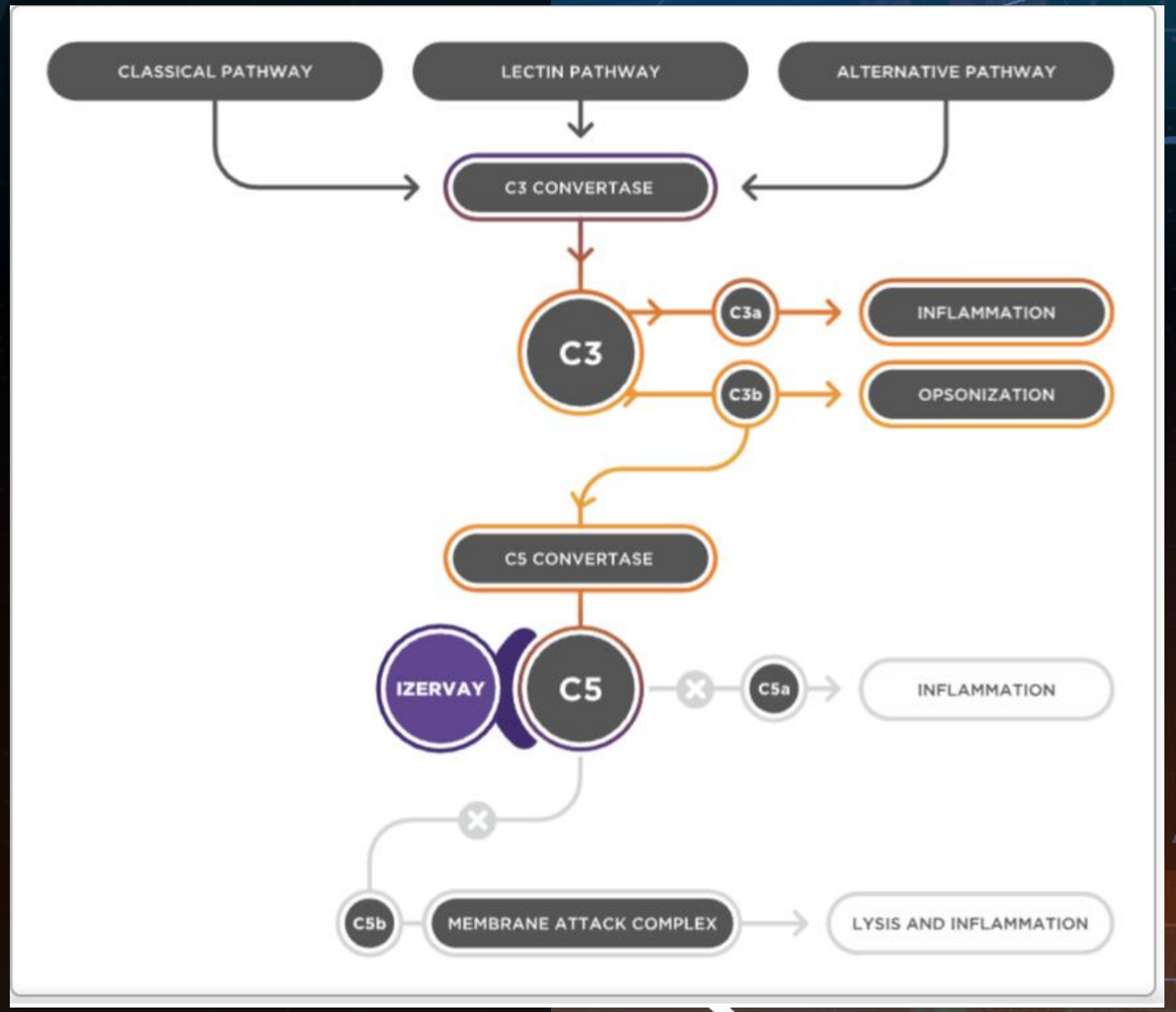
**Fellow eye analysis includes patients at risk for new-onset eAMD.*

[a]Events include preferred terms of CNV and neovascular AMD.
[b]Number of patients at risk for new-onset eAMD in PEOM arms from OAKS and DERBY combined was 419.
[c]10 patients from Study 103 enrolled in GALE and were included in the safety analysis.
AMD, age-related macular degeneration; **CNV,** choroidal neovascularization; **eAMD,** exudative age-related macular degeneration; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly.

Izervay-Iveric Bio

Avacincaptad Pegol Intravitreal Injection

- FDA Approved August 2023
- Pegylated RNA aptamer molecule that targets C5
- Helps preserve upstream benefits of C3 and may prevent formation of membrane attack complex which initiates retinal cell death
- Helps to reduce inflammation, retinal cell death and loss of PR associated with development and progression of GA



GATHER1 – A phase 2/3, international, prospective, randomized, double-masked, sham-controlled study

GATHER1

[a]2 injections of 2 mg per eye.

ACP, avacincaptad pegol; D, day; FAF, fundus autofluorescence; GA, geographic atrophy; M, month

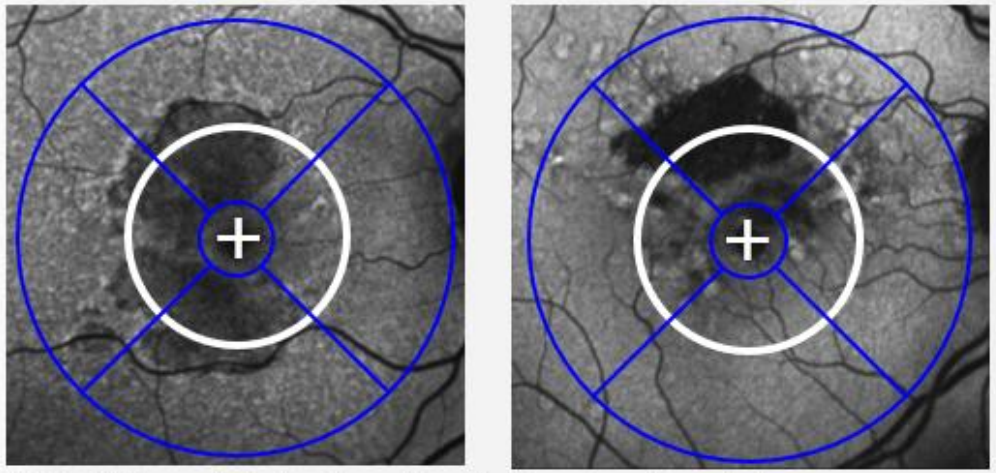
1. Jaffe GJ, et al. Ophthalmology. 2021;128:576-586; **2.** Data on file. IVERIC Bio. **3.** Zimura in Subjects With Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration. ClinicalTrials.gov Identifier: NCT02686658. Updated March 21, 2022. https://clinicaltrials.gov/ct2/show/study/NCT02686658

GA had to be in part within 1500 µm, but not involving the center point

GATHER1 + GATHER2

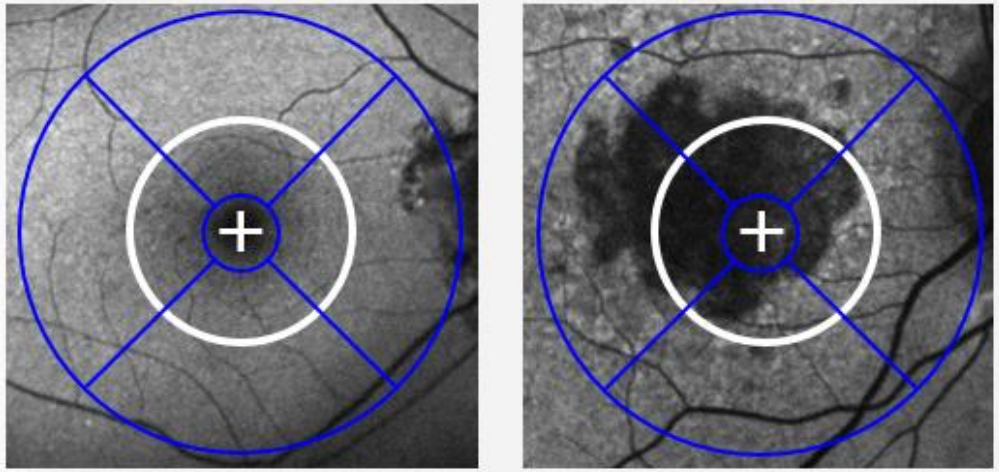
Center point involvement was determined by the Duke Reading Center using multimodal imaging

Included[a]



Within 1500 µm of, but not involving the foveal center point

Excluded[a]



Outside of 1500 µm from the foveal center point

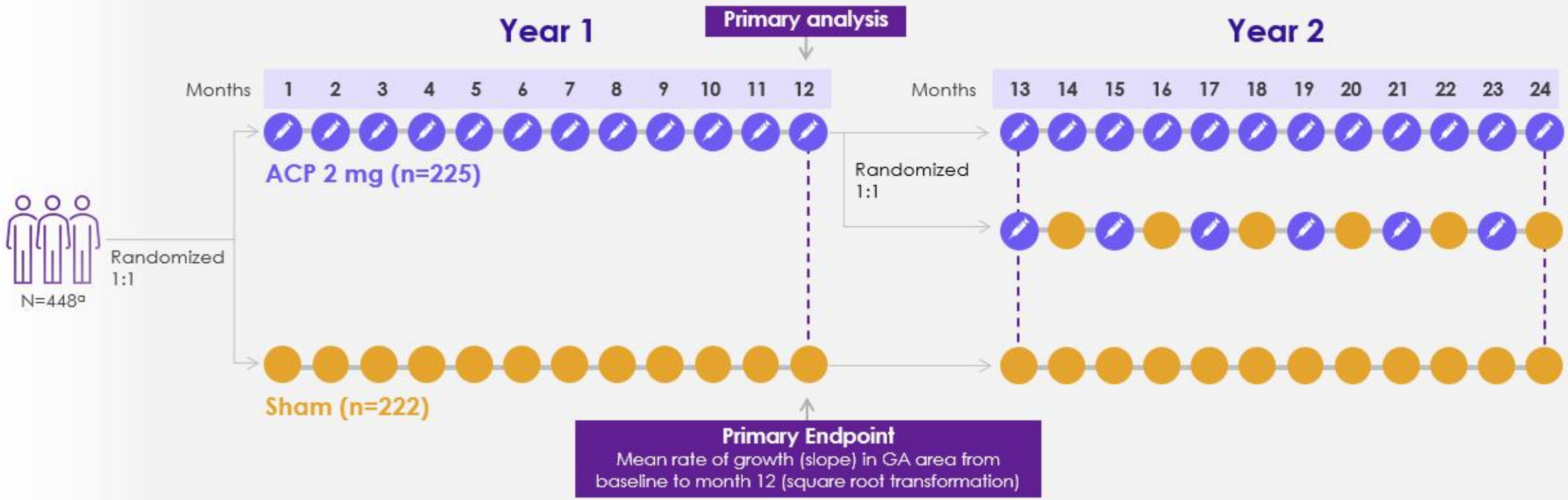
Foveal center point involvement

[a]Unifocal lesion for example only, patients could have had multi-focal lesions. GA, geographic atrophy

Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022.

GATHER2 – A phase 3, international, multicenter, prospective, randomized, double-masked, sham-controlled study

GATHER 2

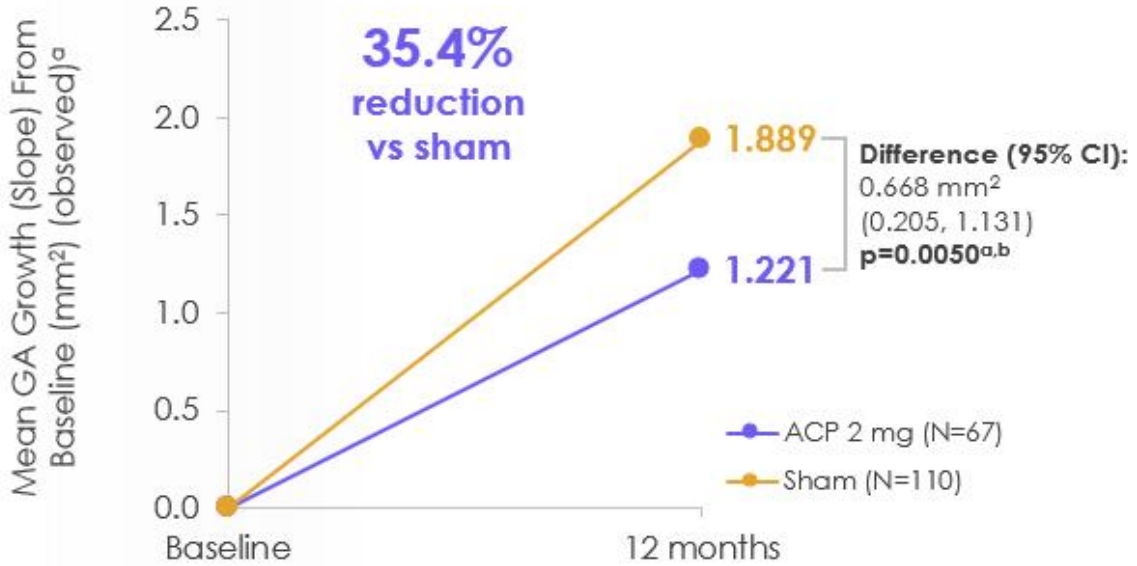


[a]448 randomized, with 447 treated (one patient in sham not receiving treatment after randomization).
ACP, avacincaptad pegol; GA, geographic atrophy.

1. Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022. **2.** A Phase 3 Safety and Efficacy Study of Intravitreal Administration of Zimura (Complement C5 Inhibitor). ClinicalTrials.gov Identifier: NCT04435366. Updated September 28, 2022. https://clinicaltrials.gov/ct2/show/NCT0443

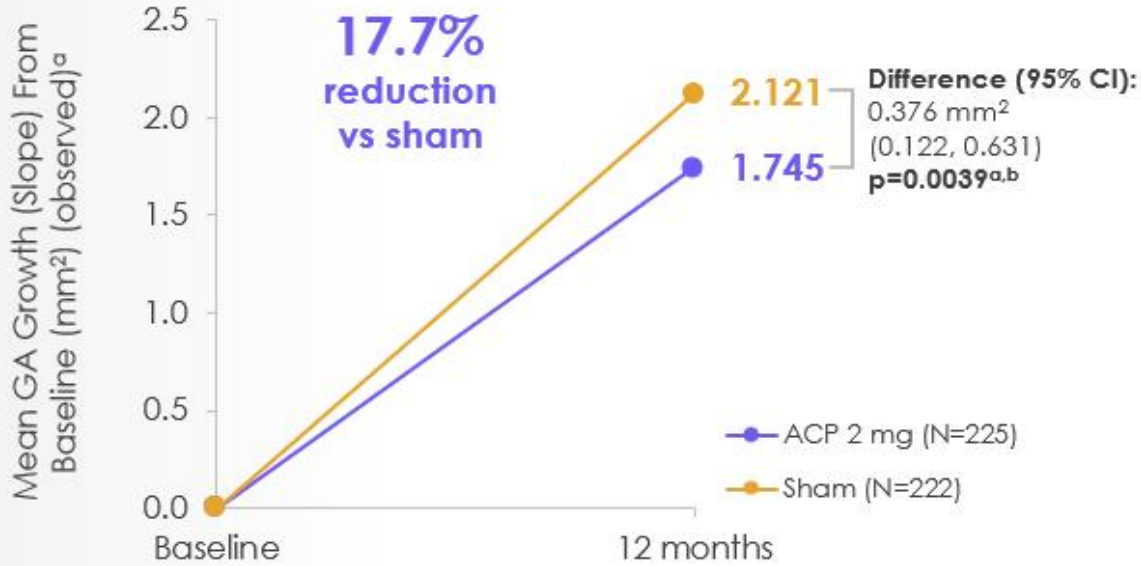
Mean observed GA growth demonstrated consistent efficacy results between the two studies

GATHER1



Note: The primary analysis for GATHER1 (mean change in square root transformed GA area from baseline to month 12 [mm]) is consistent with the slope analysis utilizing observed data. The estimates for the GATHER1 ACP 2 mg group vs sham are from the MMRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2 of the trial, and should not be interpreted as directly observed data.

GATHER2



ªNon-square root transformation; ᵇDescriptive *p*-value. ACP, avacincaptad pegol; CI, confidence interval; GA, geographic atrophy
Data on file. IVERIC bio

Key inclusion and exclusion criteria[1,2]

GATHER1 + GATHER2

Inclusion criteria

- Age ≥50 years
- BCVA between 20/25 and 20/320
- GA lesion:
  - Non-center point involving
  - GA in part within 1500 µm from the foveal center
  - Total area between 2.5 mm^2 and 17.5 mm^2 (1 – 7 DA, respectively)
  - If multifocal lesions, at least 1 lesion had to be ≥1.25 mm^2 (0.5 DA)

Exclusion criteria

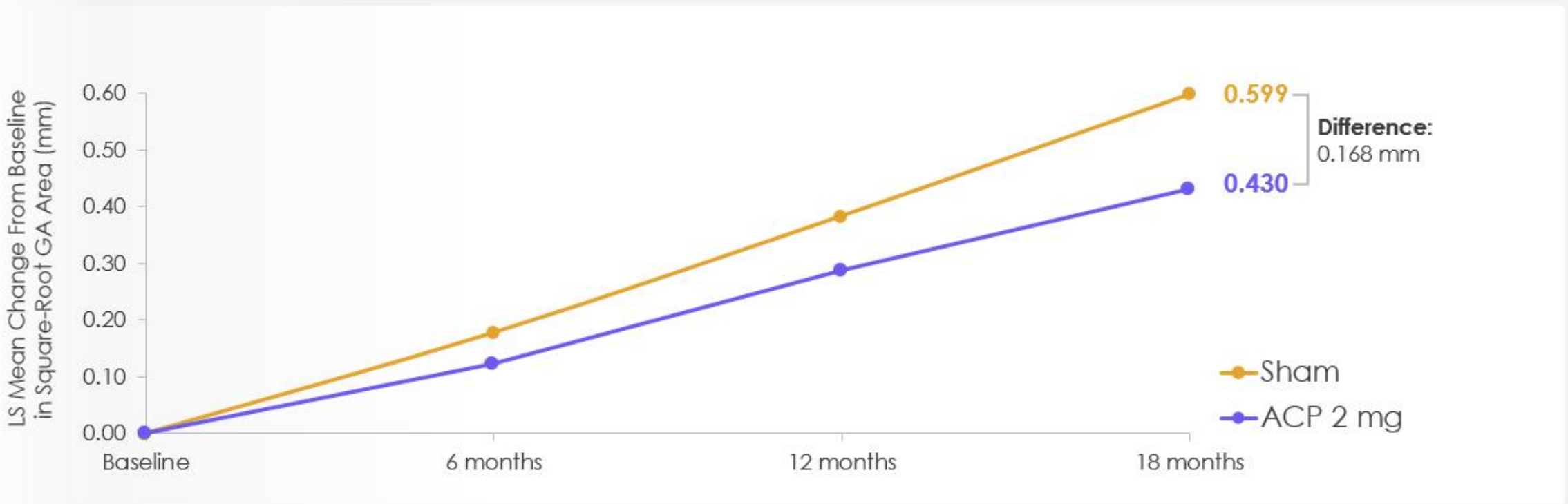
- Evidence of CNV in either eye at baseline
- GA secondary to any condition other than AMD in either eye
- Any prior treatment for AMD or any prior intravitreal treatment for any indication in either eye (except oral vitamin or mineral supplements)
- Any ocular condition in study eye that could progress during the study and potentially affect central vision or otherwise act as a confounding factor
- Any sign of diabetic retinopathy in either eye

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; DA, disc area; GA, geographic atrophy

1. Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022; **2.** Jaffe GJ, et al. Ophthalmology. 2021;128:576-586.

Reduction in growth of GA lesion area observed through Month 18 in GATHER1

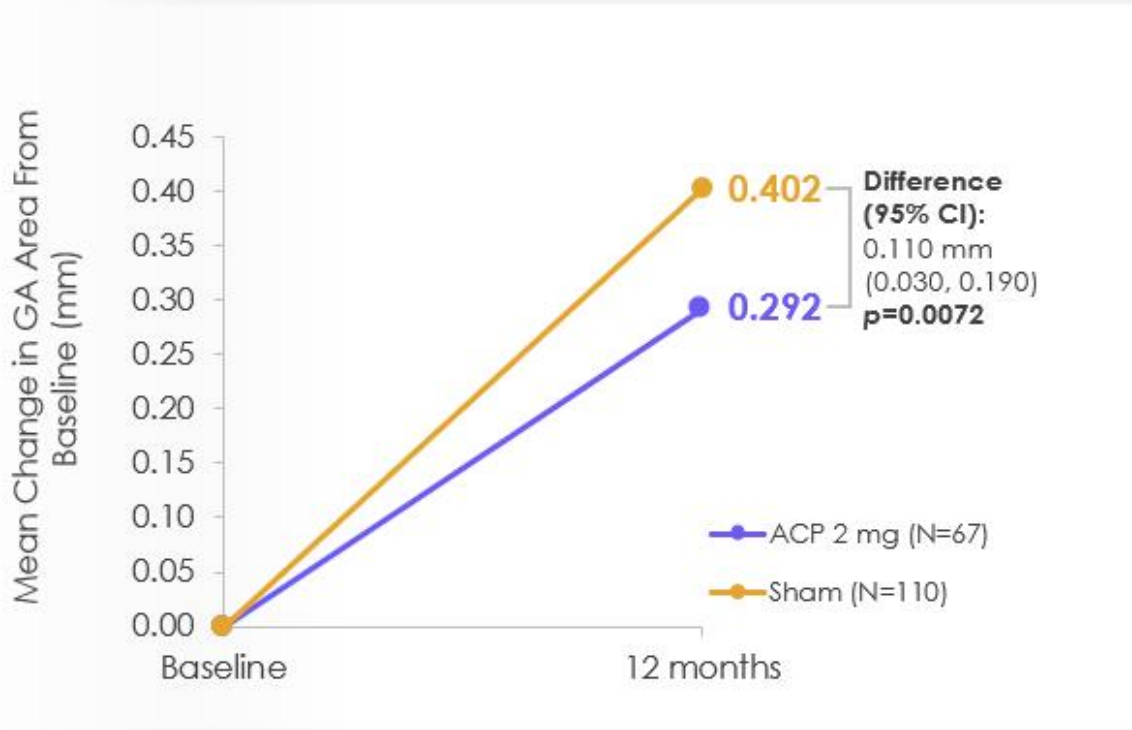
GATHER1



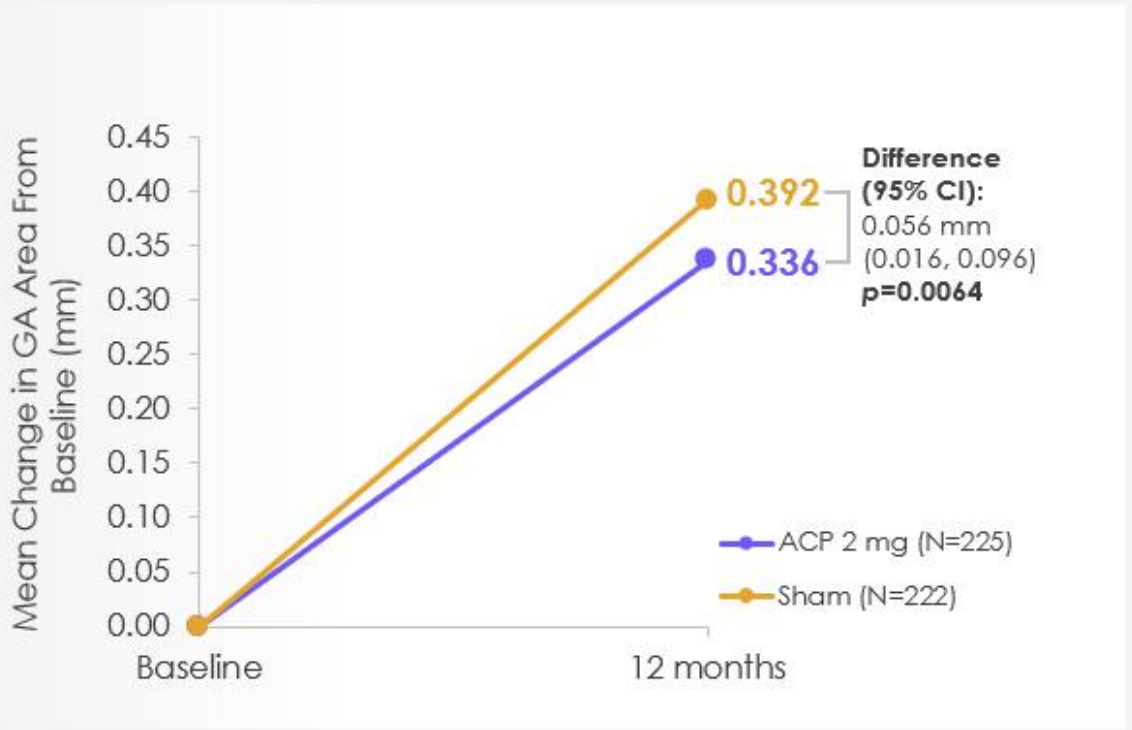
Note: Subgroup analysis based on square root transformation data (mm).
ACP, avacincaptad pegol; GA, geographic atrophy; LS, least squares.
Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022.

Avacincaptad pegol is the first investigational therapy in GA to achieve the 12-month prespecified, primary endpoint, in two pivotal, phase 3 studies

GATHER1



GATHER2



Avacincaptad pegol is under review with the FDA, and safety and efficacy have not been established. There is no guarantee that avacincaptad pegol will become commercially available.

Summary

Primary endpoint

GATHER1 + GATHER2

Avacincaptad pegol is the first investigational therapy in GA to achieve the 12-month, prespecified, primary objective vs. sham, coupled with a consistent safety profile, in two pivotal, phase 3 studies

Adverse events

GATHER1

Results were similar to GATHER2 at 12 months, except for 1 case of intraocular inflammation

GATHER2

No cases of intraocular inflammation, endophthalmitis and ischemic optic neuropathy in study eyes treated with avacincaptad pegol 2 mg at Month 12

The most common ocular TEAEs (≥5%) in the study eye for both studies were conjunctival hemorrhage, increased IOP, and CNV

CNV rates

GATHER1

CNV rates were 9.0% in the avacincaptad pegol 2 mg group and 2.7% in the sham group

GATHER2

CNV rates were 6.7% in the avacincaptad pegol 2 mg group and 4.1% in the sham group

CNV, choroidal neovascularization; GA, geographic atrophy