Imaging Modalities and Emerging Treatment Options for Geographic Atrophy

Katherine E. Talcott, MD

Assistant Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine

Cole Eye Institute, Cleveland Clinic

February 24, 2024

Cleveland Clinic

Disclosures

- Alimera (consultant), Allergan (consultant), Apellis (consultant), Bausch and Lomb (consultant), Eyepoint (consultant), Genentech (consultant, speaker’s bureau), Iveric Bio (speaker’s bureau), Outlook (consultant), Regeneron (research), Regenxbio (research), Zeiss (speaker, research, consultant)

Overview

- Age-related macular degeneration (AMD) overview
- Imaging modalities and pearls
- Approved treatment for geographic atrophy (GA)

Age-Related Macular Degeneration (AMD)

- One of the most common causes of severe, irreversible vision loss
- Worldwide prevalence:
  - 196 million in 2020
  - Projected to be 288 million in 2040[1]

[1]American Academy of Ophthalmology Preferred Practice Patterns 2019

Risk Factors

- Age is the No. 1 risk factor for AMD[1]
- 1/3 of adults older than 75 years have AMD
- Individuals older than 85 years have a 10-fold higher prevalence of late AMD than those aged 70 to 74
- ~ 50% of individuals with late AMD have GA

1. Jonasson F, Arnarsson A, Eiriksdottir G, et al. Prevalence of age-related macular degeneration in old persons: age, gene/environment susceptibility Reykjavik study. *Ophthalmology.* 2011;118(5):825-830.

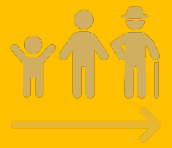
AMD pathogenesis: Complex interaction of many different factors[1]

Genetics

Genes implicated in[2]:

- Drusen formation
- Formation of reactive oxygen species
- Inflammation
- Immune response, including **the complement system**

≈70% contribution[1]



Physiology

Age (greatest risk factor for AMD)[3]

High body mass index[4]

Certain dyslipidemias[5]

Chronic HBV infection[6]

Certain comorbidities and medications[7]

Lifestyle/ Environment

Smoking[4]

Diet[4]

High alcohol intake[8]

High sunlight exposure[4]

≈30% contribution[1]

HBV=hepatitis B virus.

1. Seddon JM. *Arch Ophthalmol.* 2005;123(3):e321-e327. 2. Boyer DS, et al. *Retina.* 2017;37(5):819-835. 3. Jonasson F, et al. *Ophthalmology.* 2011;118(5):825-830. 4. Sobrin L, Seddon JM. *Prog Retin Eye Res.* 2014;40:1-15. 5. Reynolds R, et al. *Ophthalmology.* 2010:117(10):1989-1995. 6. Wu C-M, et al. *Acta Ophthalmol.* 2019;97(5):e713-718. 7. Aldebert G, et al. *JAMA Ophthalmol.* 2018;136(7):770-778. 8. Adams MK, et al. *Am J Epidemiol.* 2012;176(4):289-298. 8.

Risk Factors: Genetic

The key genes linked to AMD/GA involve the immune and complement systems[1,2]

- Most genetic risk factors due to single nucleotide polymorphisms[1,3]
- Genes linked to increased AMD risk implicated in[2]:
  - Drusen formation
  - Formation of reactive oxygen species
  - Inflammation

Genes with confirmed variants associated with AMD[3]

Common Variants		
CFH – Y402H	*LIPC*	*TNFRSF10A*
CFH – rs1410996	*CETP*	*IER3/DDR1*
CFB	*ABCA1*	*SLC16A8*
C2	*TIMP3/SYN3*	*RAD51B*
C3	*VEGFA*	*ADAMTS9*
CFI	*COL10A1*	*B3GALTL*
ARMS2/HTRA1	*COL8A1*	*TGFBR1*
Rare Variants		
CFH – R1210C	*C3* – K155Q	*C9* – P167S

CFI- increased burden of disease with multiple variants.

1. The AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. *Nat Genet.* 2013;45(4):433-439e.
2. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: genetics and biology coming together. *Annu Rev Genomics Hum Genet.* 2014;15:151-171.
3. Sobrin L, Seddon JM. Nature and nurture- genes and environment- predict onset and progression of macular degeneration. *Prog Retin Eye Res.* 2014;40:1-15.

Risk Factors: Physiological

- High body mass index[1]
- Certain dyslipidemias[2]
  - High TC and LDL-C,* low HDL-C
- Chronic HBV infection[3]
- Inflammation (ie, biomarkers linked to systemic inflammation)[1,4]

- Certain comorbidities
  - Cardiovascular disease,[1,5] diabetes (Type 1 and 2),[5] ocular diseases[5]†
- Certain medications
  - Antidiabetic[5] and anticholinergic‡ agents[6]

*Cholesterol is the main component of drusen.
†Glaucoma, retinal disorders, cataracts, and cataract surgery.
‡Anticholinergic drugs increase brain amyloid-β deposition. Amyloid-β is a major component of drusen.
HBV = hepatitis B virus; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; TC = total cholesterol.

1. Sobrin L, Seddon JM. Nature and nurture- genes and environment- predict onset and progression of macular degeneration. *Prog Retin Eye Res.* 2014;40:1-15.
2. Reynolds R, Rosner B, Seddon JM. Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degeneration. *Ophthalmology.* 2010;117:1989-1995.
3. Wu CM, Su F-H, Wang W-C, et al. Association of chronic hepatitis B virus infection with age-related macular degeneration. *Acta Ophthalmol.* 2019;97:713–718.
4. Nielsen MK, Subhi Y, Molbech CR, Falk MK, Nissen MH, Sorensen TL. Systemic levels of interleukin-6 correlate with progression rate of geographic atrophy secondary to age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2019;60:202–208.
5. Vassilev ZP, Ruigómez A, Soriano-Gabarró M, Rodŕiguez LAG. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Invest Ophthalmol Vis Sci.* 2015;56:1585-1592.
6. Aldebert G, Faillie J-L, Hillaire-Buys D, et al. Association of anticholinergic drug use with risk for late age-related macular degeneration. *JAMA Ophthalmol.* 2018;136:770-778.

Risk Factors: Environmental/Lifestyle

- **Smoking**—a factor in ≈30% of cases[1]
- **Diet**
  - High intake of saturated fat and dietary cholesterol[2]*
  - Low intake of antioxidants, vitamins, and minerals[1]
- **High alcohol intake** (>20 g/day)[3]
- **High sunlight exposure**
  (>8 h/day over a working life)[1,4]

*Cholesterol is the main component of drusen.

1. Sobrin L, Seddon JM. Nature and nurture- genes and environment- predict onset and progression of macular degeneration. *Prog Retin Eye Res.* 2014;40:1-15.
2. Khan JC, Thurlby DA, Shahid H, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. *Br J Ophthalmol.* 2006;90:75-80.
3. Adams MKM, Chong EW, Williamson E, et al. 20/20--Alcohol and age-related macular degeneration: The Melbourne Collaborative Cohort Study. *Am J Epidemiol.* 2012;176(4):289-98. Epub 2012 Jul 29.
4. Schick T, Ersoy L, Lechanteur YTE, et al. History of sunlight exposure is a risk factor for age-related macular degeneration. *Retina.* 2016;36:787–790.

AMD Stages[1,2]

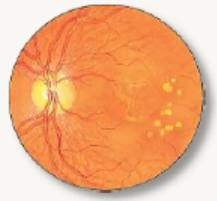
Progression

No AMD

- None or few drupelets (small drusen ≤ 63 µm)
- No AMD pigmentary abnormalities

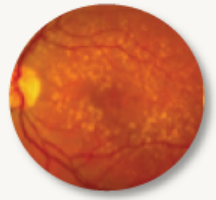
Early AMD

- Medium drusen > 63 µm and ≤ 125 µm
- No AMD pigmentary abnormalities

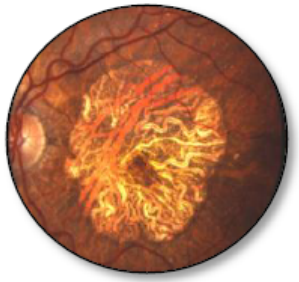


Intermediate AMD

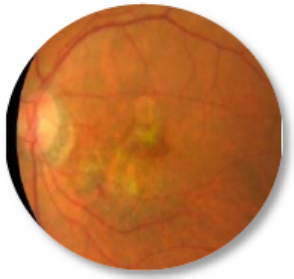
- 1 large drusen > 125 µm and/or
- Any AMD pigmentary abnormalities



Advanced AMD — 2 forms



Geographic atrophy

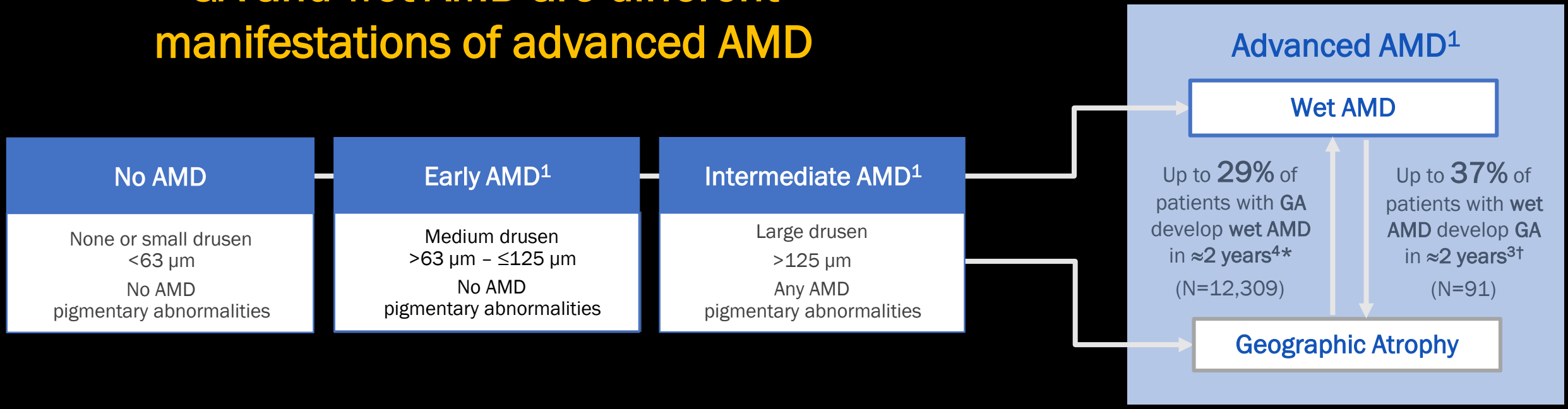


Neovascular AMD

1. Ferris F, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844-851.
2. Ambati J, Atkinson J P, Gelfand BD. Immunology of age-related macular degeneration. *Nat Rev Immunol*. 2013;13:438–451.

AMD has 4 main stages[1-4]

GA and wet AMD are different manifestations of advanced AMD



*Retrospective analysis of the Intelligent Research in Sight (IRIS®) Registry database (n=3606/12,309) in patients with GA in the study eye and wet AMD in the fellow eye.[4]

†Retrospective cohort analysis (N=91) to assess growth of GA in patients with wet AMD treated with anti-VEGF therapy.[3]

anti-VEGF=anti-vascular endothelial growth factor.

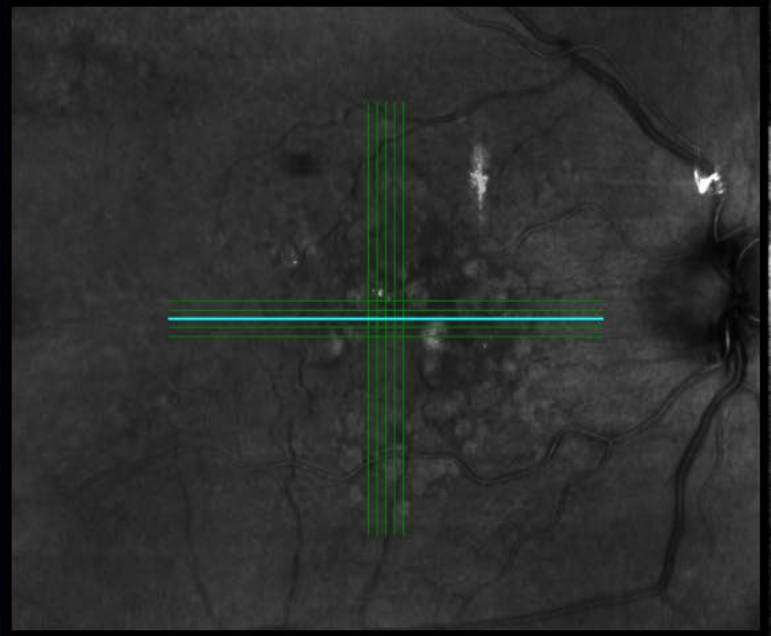
1. Ferris FL 3rd, et al. *Ophthalmology*. 2013;120(4):844-851. 2. Kaszubski P, et al. *Ophthalmic Res*. 2016;55(4):185-193. 3. Xu L, et al. *Retina*. 2015;35(2):176-186. 4. Rahimy E. Presented at: American Academy of Ophthalmology Meeting. November 13-15, 2020. Virtual.

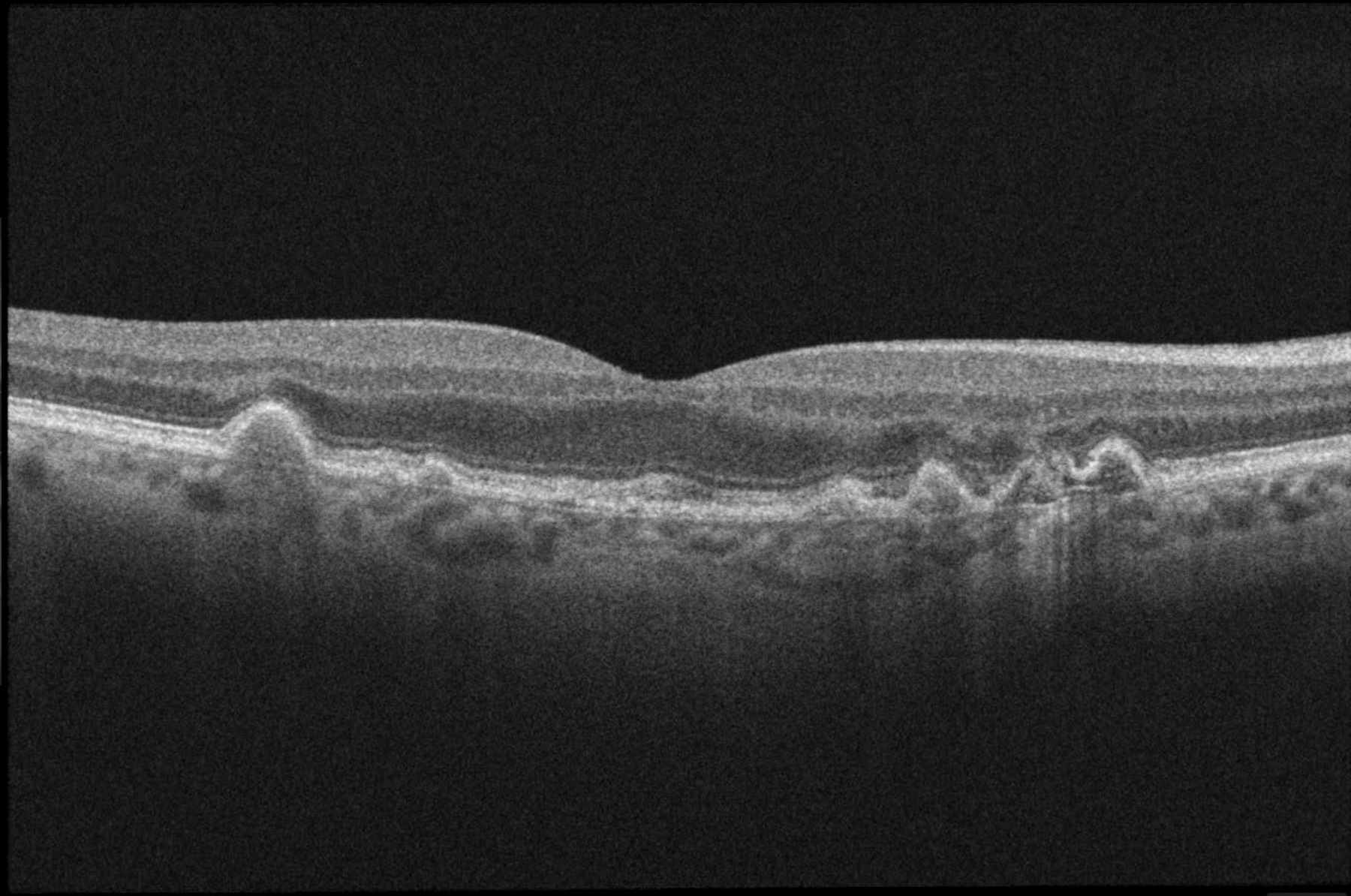
Imaging is critical to the diagnosis and management of AMD

Biomarkers seen through diagnostic imaging, including OCT, OCTA, and FAF, can be used to make clinical decisions

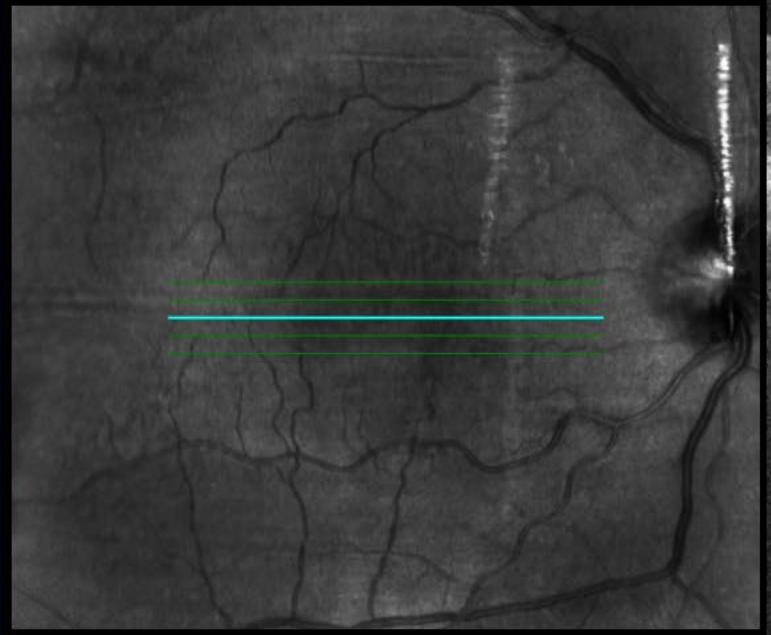
Intermediate AMD

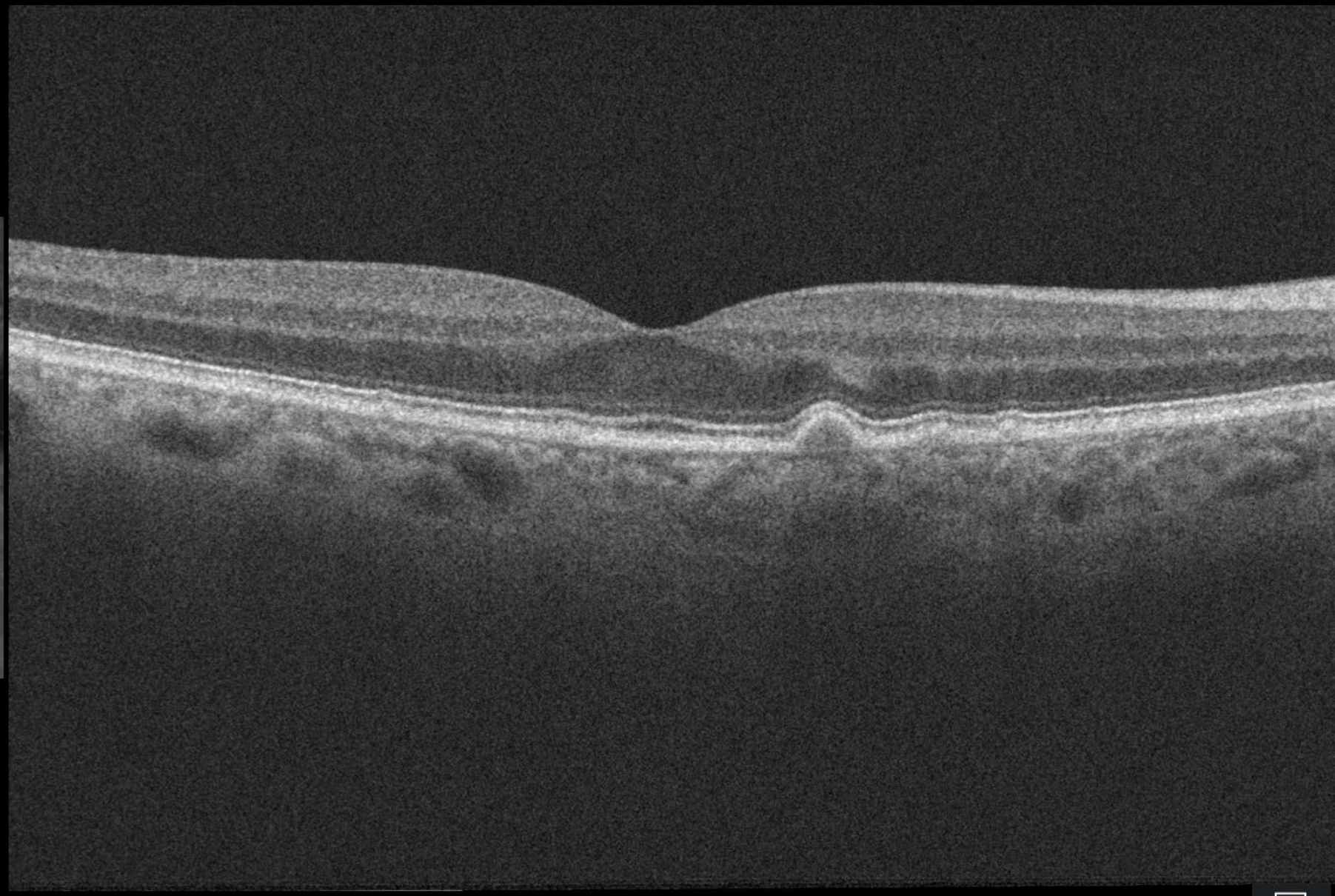
80 year old woman with VA 20/20



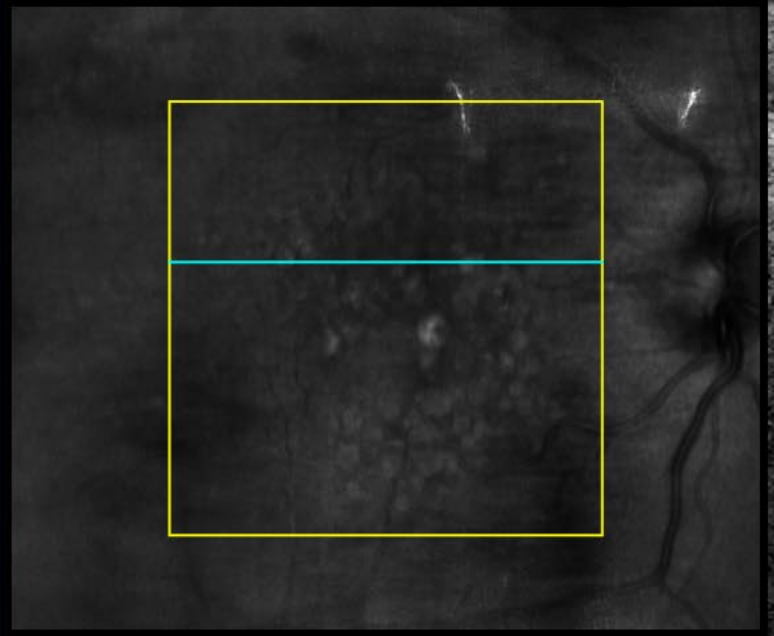


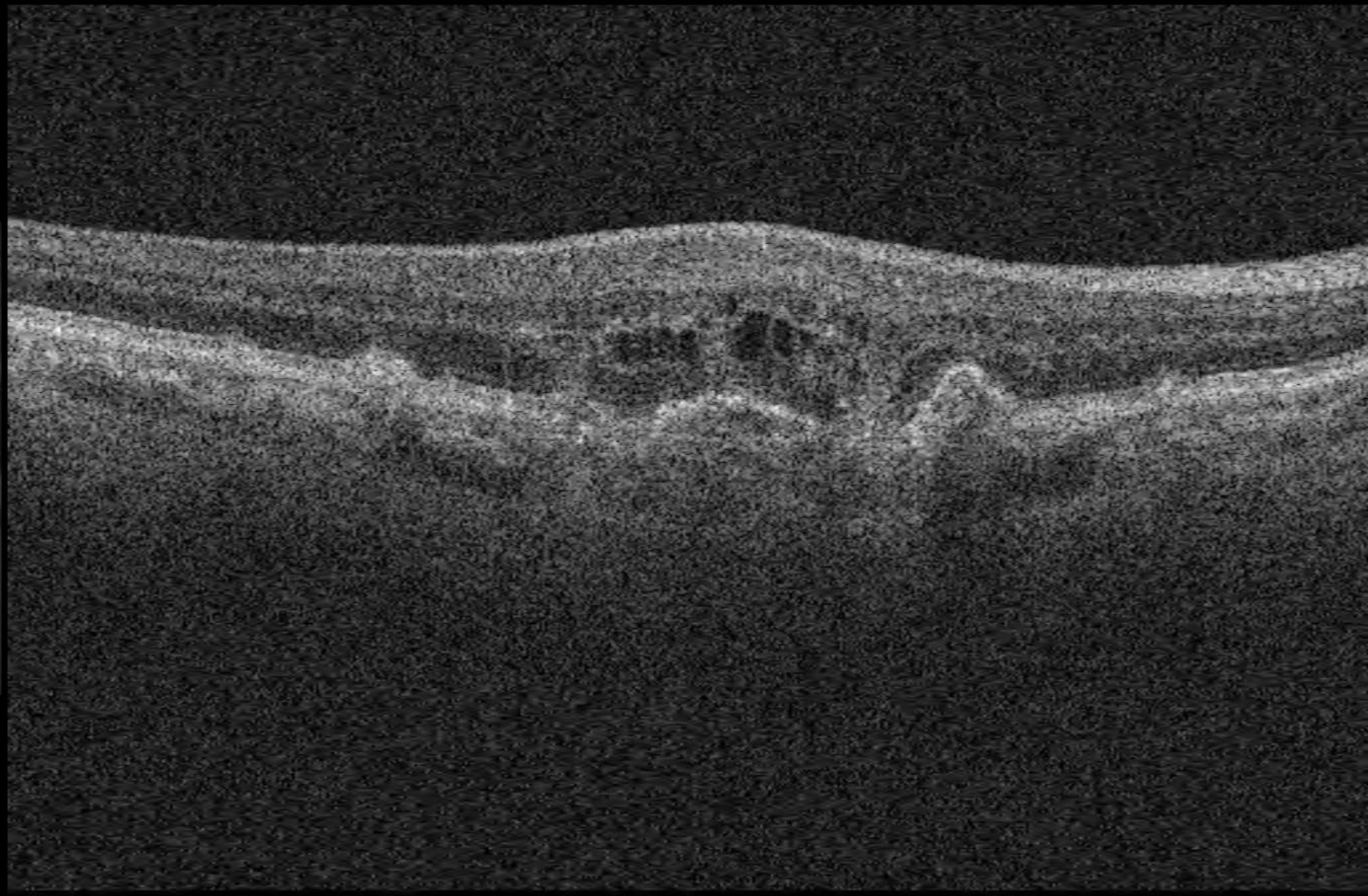
Seven years prior





Two Months after Initial Visit



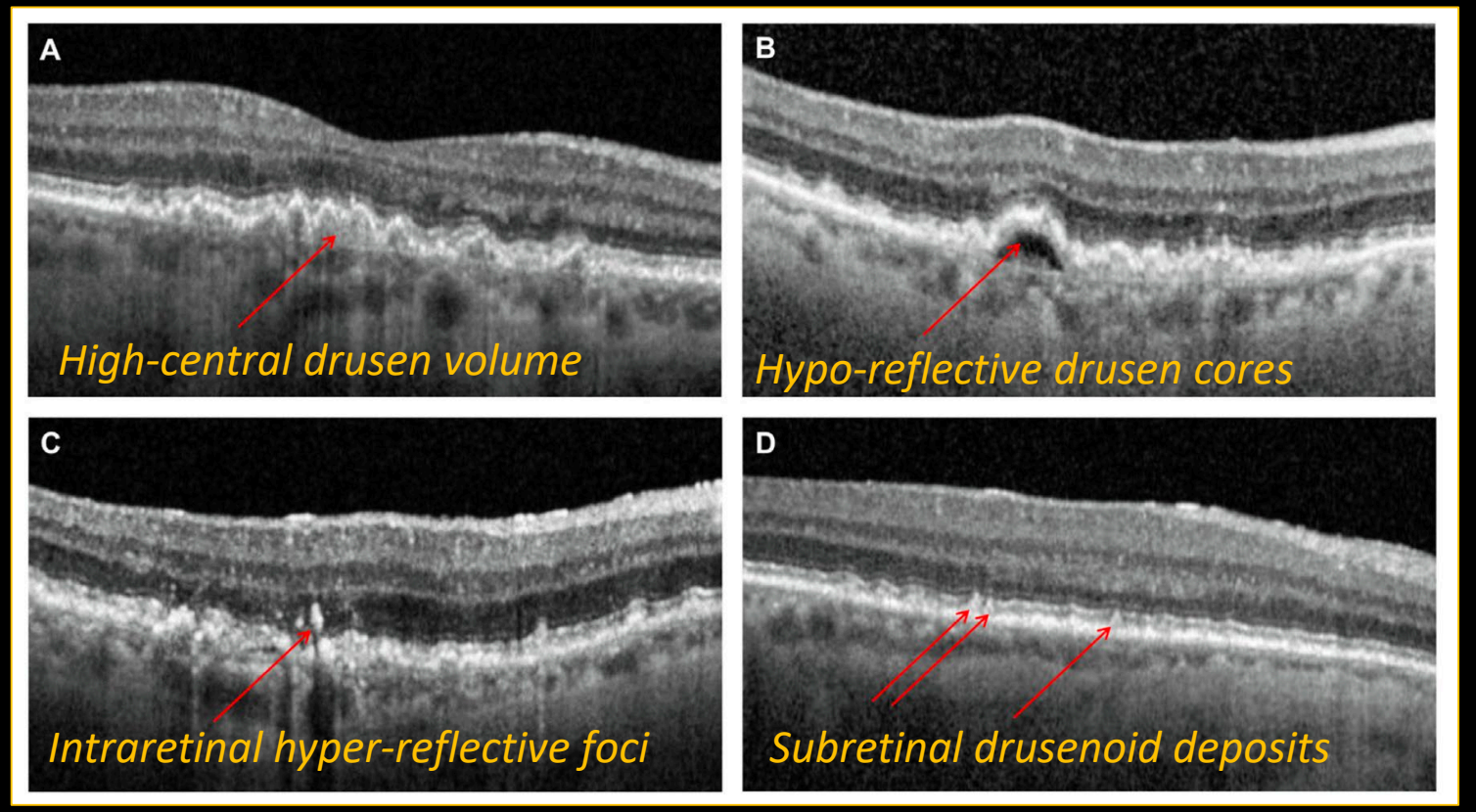


Risk Factors for Developing Atrophy

- Several OCT features at baseline were associated with an increased risk of cRORA at 24 months
  - High-central drusen volume
  - Intraretinal hyper-reflective foci
  - Subretinal drusenoid deposits
  - Hypo-reflective drusen cores
  - Thin double-layer sign
  - cRORA in fellow eye
- May aid in patient prognostication and risk stratification

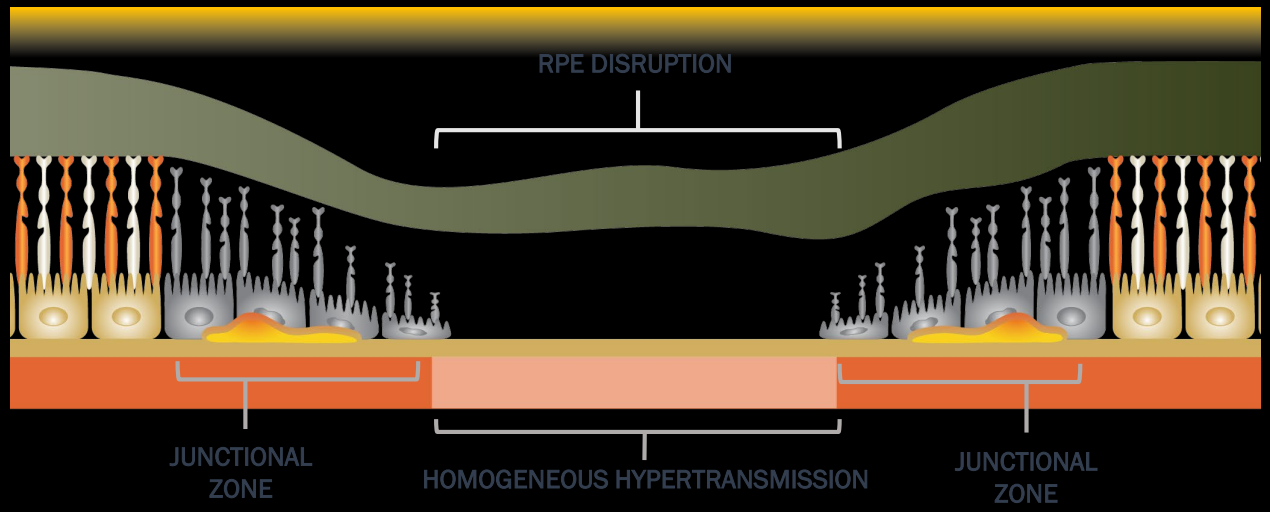
OCT Risk Factors for Development of Atrophy in Eyes with Intermediate Age-Related Macular Degeneration

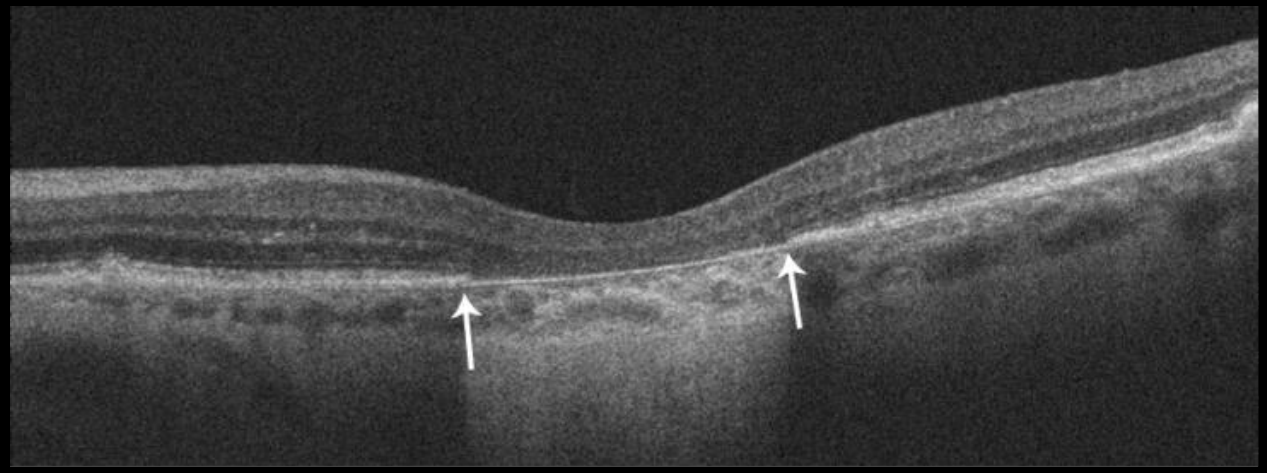
Kazutaka Hirabayashi, MD, PhD,[1] Hannah J. Yu, MD,[2] Yu Wakatsuki, MD, PhD,[1] Kenneth M. Marion, MS, MBA,[1] Charles C. Wykoff, MD, PhD,[2] Srinivas R. Sadda, MD[1]



Hirabayashi K et al, *Ophthalmology Retina* 2023

2018 CAM Classification System is OCT Based





CAM criteria

Incomplete RPE and Outer Retinal Atrophy (iRORA)[2]

- Region of hypertransmission into the choroid
- Zone of RPE attenuation or disruption with or without persistence of BLamD
- Evidence of overlying photoreceptor degeneration*
- Do not meet definition of cRORA
- No signs of RPE tear
- Describes features on OCT imaging previously observed to precede the development of atrophy

Complete RPE and Outer Retinal Atrophy (cRORA)[1]

- Region of hypertransmission ≥250 µm
- Zone of RPE attenuation or disruption ≥250 µm
- Evidence of overlying photoreceptor degeneration (ONL thinning, ELM loss, EZ/IZ loss)
- No signs of RPE tear

*INL subsidence, ONL thinning, ELM disruption, or EZ disintegrity.

OCT image reprinted from Sadda SR, et al. *Ophthalmology*. 2018;125(4):537-548, © 2018, with permission from the American Academy of Ophthalmology.

BLamD=basal laminar deposits; CAM=Classification of Atrophy Meeting; ELM=external limiting membrane; EZ=ellipsoid zone; IZ=interdigitation zone; ONL=outer nuclear layer.

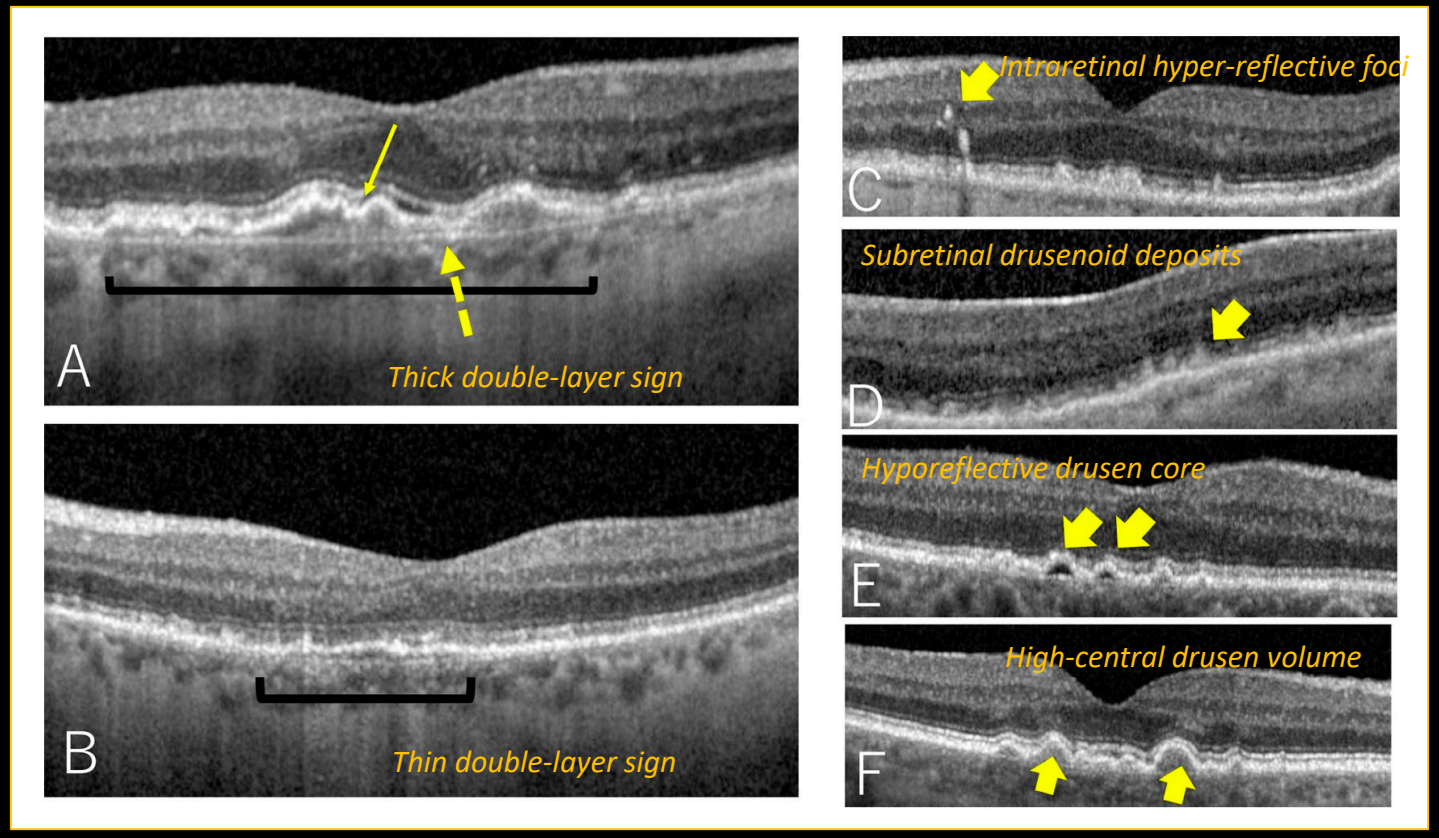
1. Sadda SR, et al. *Ophthalmology*. 2018;125(4):537-548. 2. Guymer RH, et al. *Ophthalmology*. 2020;127(3):394-409.

Risk Factors for Developing Exudation

- Several OCT features at baseline were associated with an increased risk of developing exudative AMD over 24 months
  - Thick double-layer sign
  - Intraretinal hyper-reflective foci
  - Fellow eye macular neovascularization
- May aid in prognostication

Optical Coherence Tomography Biomarkers for Conversion to Exudative Neovascular Age-related Macular Degeneration

YU WAKATSUKI, KAZUTAKA HIRABAYASHI, HANNAH J. YU, KENNETH M. MARION, GIULIA CORRADETTI, CHARLES C. WYKOFF, AND SRINIVAS R. SADDA



Wakatsuki Y et al, *AJO* 2023

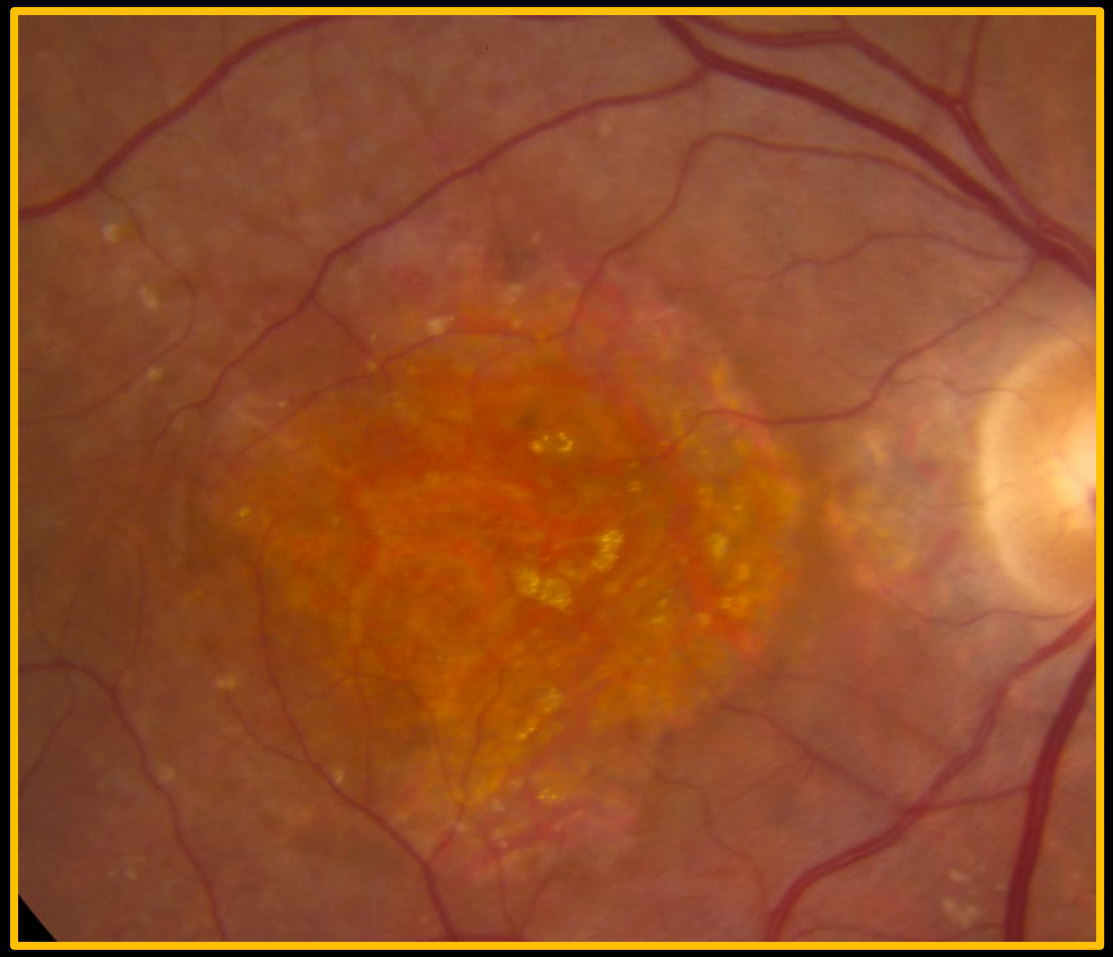
Intermediate AMD Pearls

- Rule out exudative changes
- Compare to baseline
- Look for imaging biomarkers associated with increased risk of progression to atrophy or exudative AMD

Geographic Atrophy

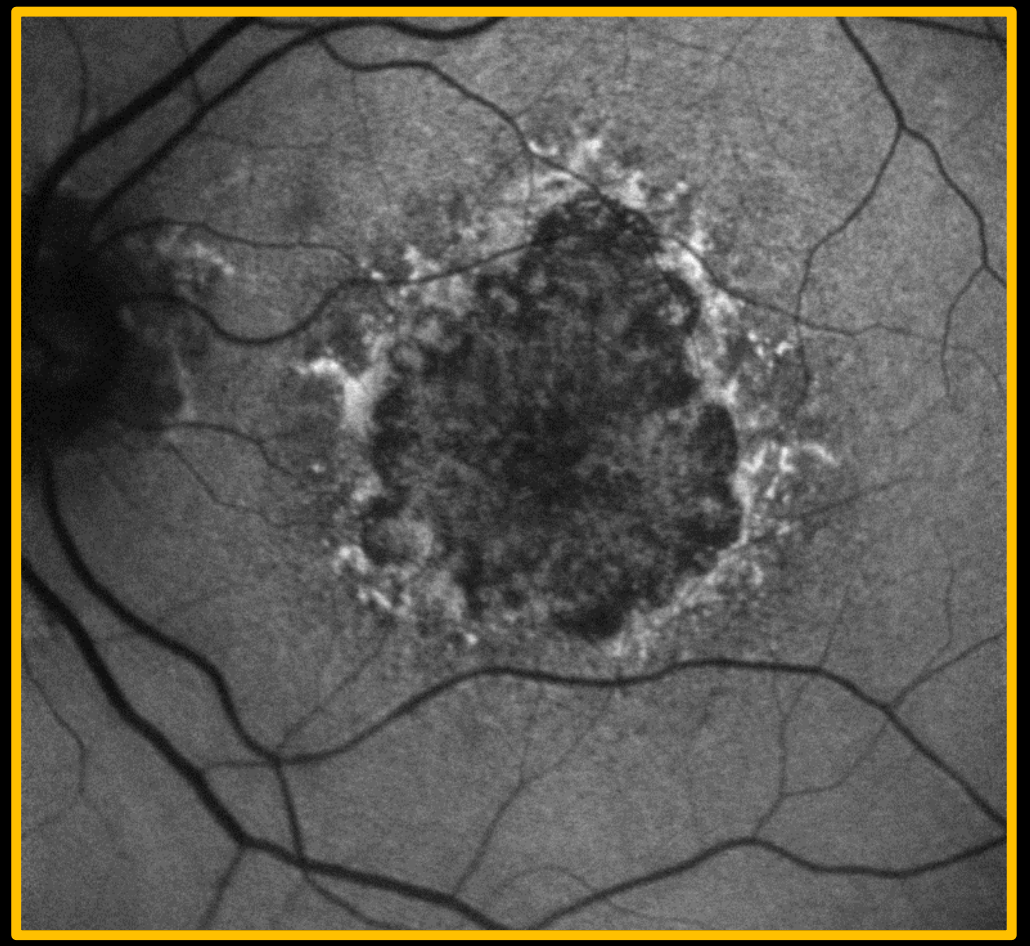
Geographic Atrophy (GA): Advanced Form of Dry AMD

- GA is defined by the presence of sharply demarcated atrophic lesions of the outer retina
- Lesions result from the loss of photoreceptors, retinal pigment epithelium, and underlying choriocapillaris
- Patients with GA develop dense irreversible scotomas



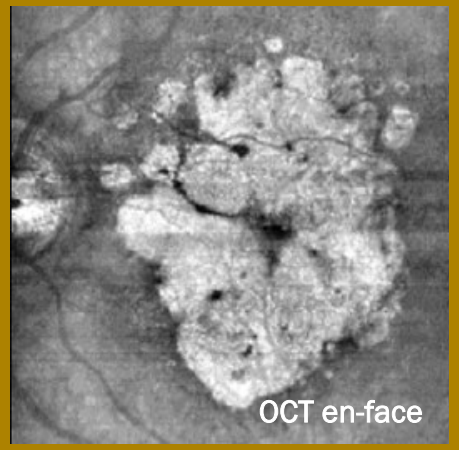
Geographic Atrophy (GA): Advanced Form of Dry AMD

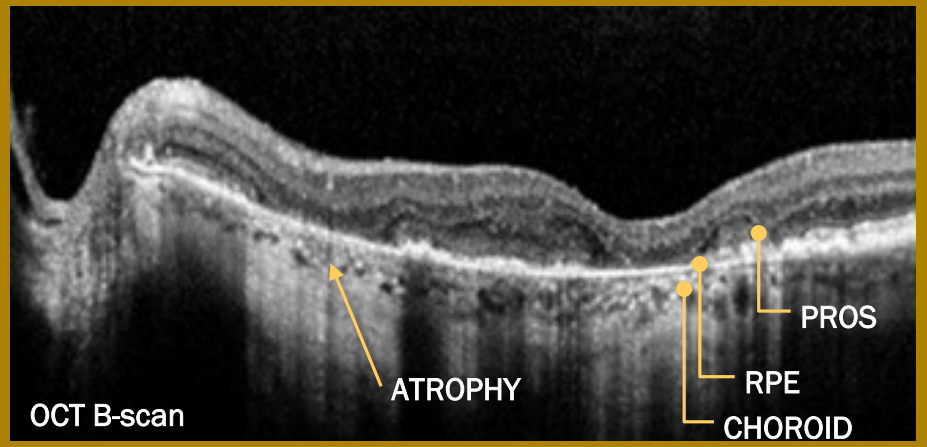
- Significant breakthroughs and continued improvements in therapies for neovascular age-related macular degeneration (nAMD) have occurred
- Despite advances in the treatment of nAMD, treatment for geographic atrophy (GA) remains elusive
  - However, two intravitreal injections were recently approved in the US

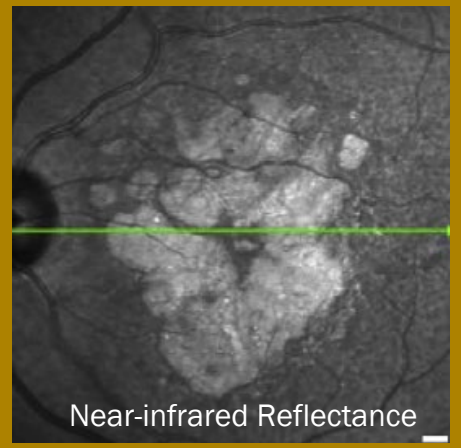


GA can be distinguished from other forms of AMD via imaging, and is characterized as cell layer loss with sharply defined borders[1,2]

Multimodal imaging of GA[1]



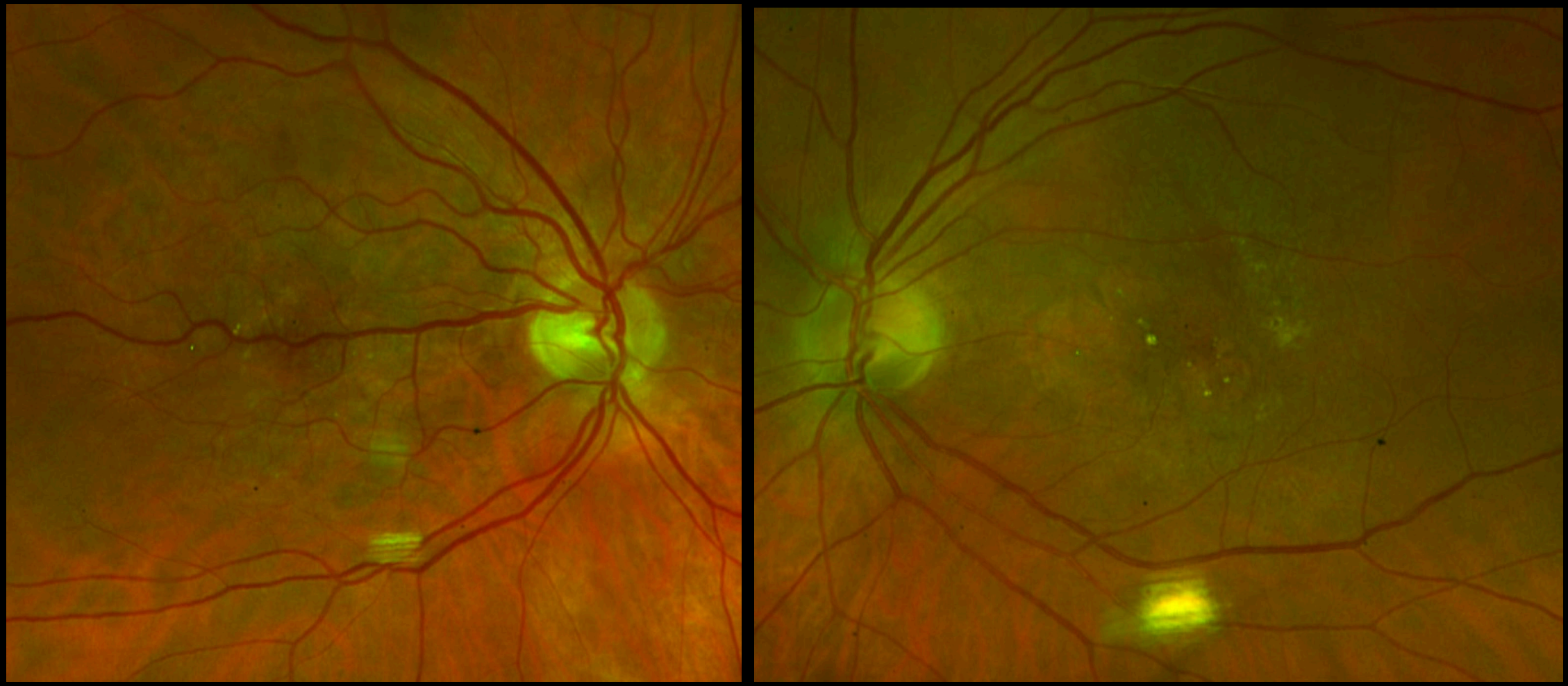


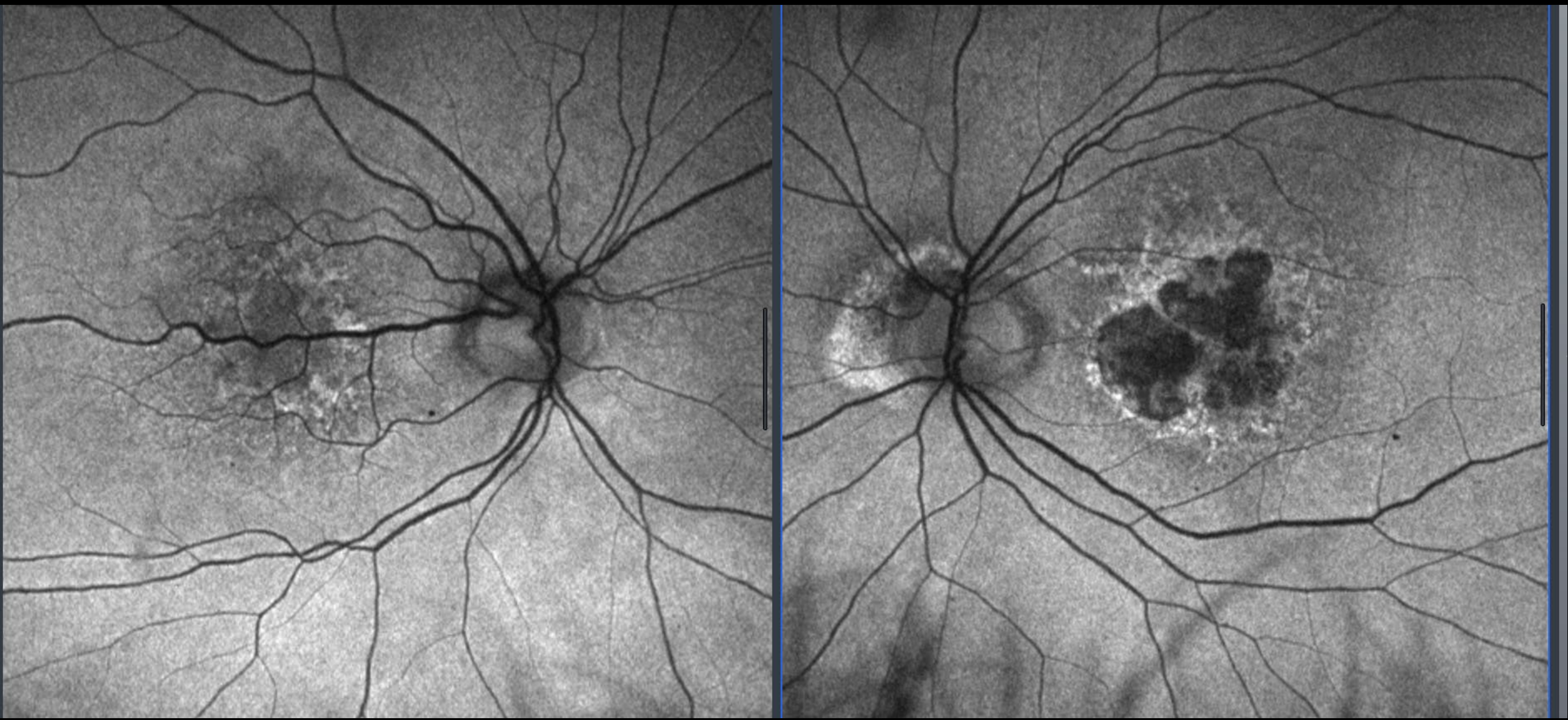


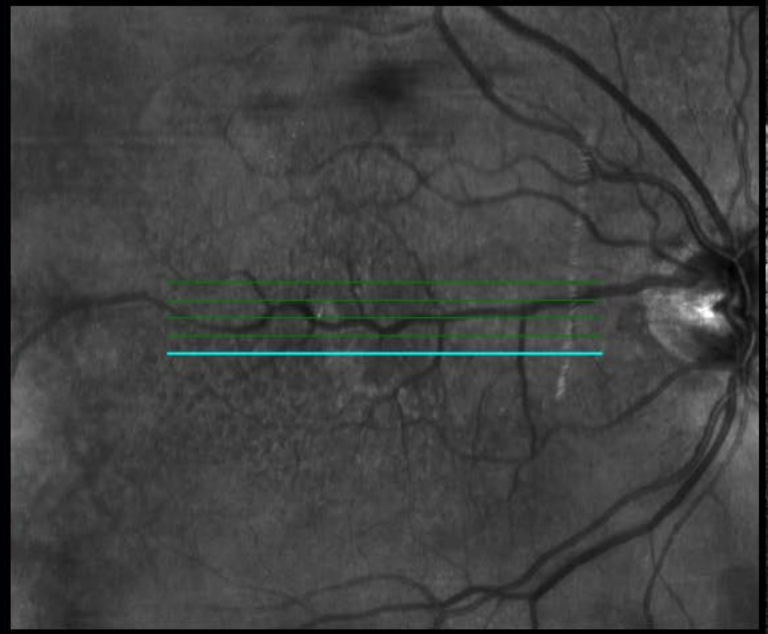
Images reprinted from Fleckenstein M, et al. *Ophthalmology*. 2018;125(3):369-390, © 2018, with permission from the American Academy of Ophthalmology.
CFP=color fundus photography; OCT=optical coherence tomography; PROS=photoreceptor outer segment; NIR=near-infrared reflectance.

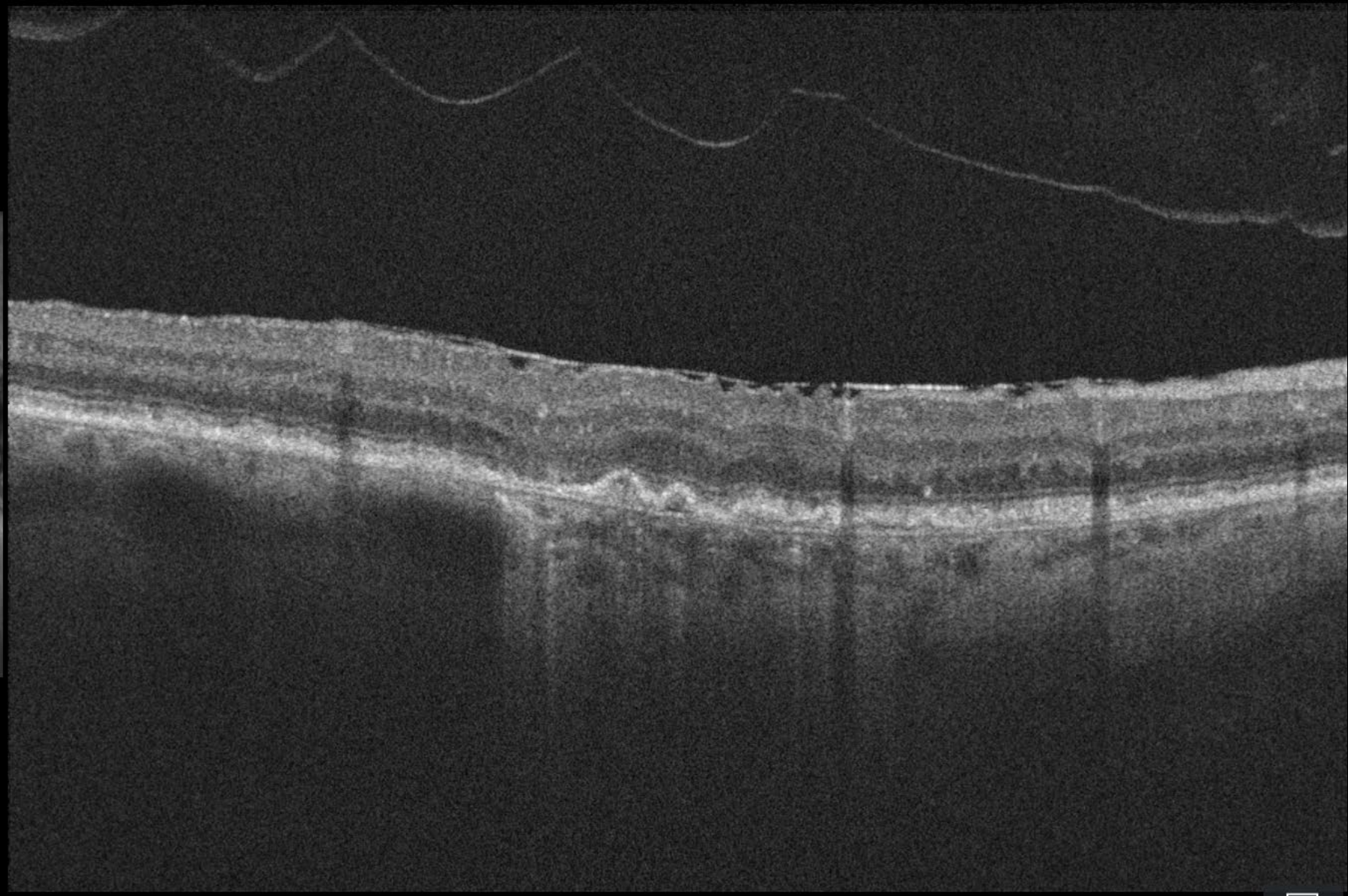
1. Fleckenstein M, et al. *Ophthalmology*. 2018;125(3):369-390. 2. Sadda SR, et al. *Ophthalmology*. 2018;125(4):537-548.

76 yo woman with VA OD 20/30 and OS 20/400

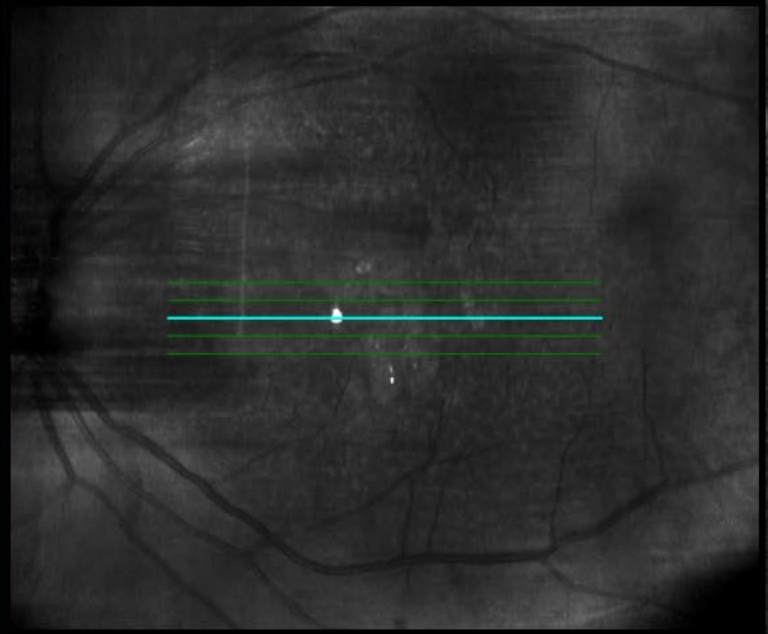


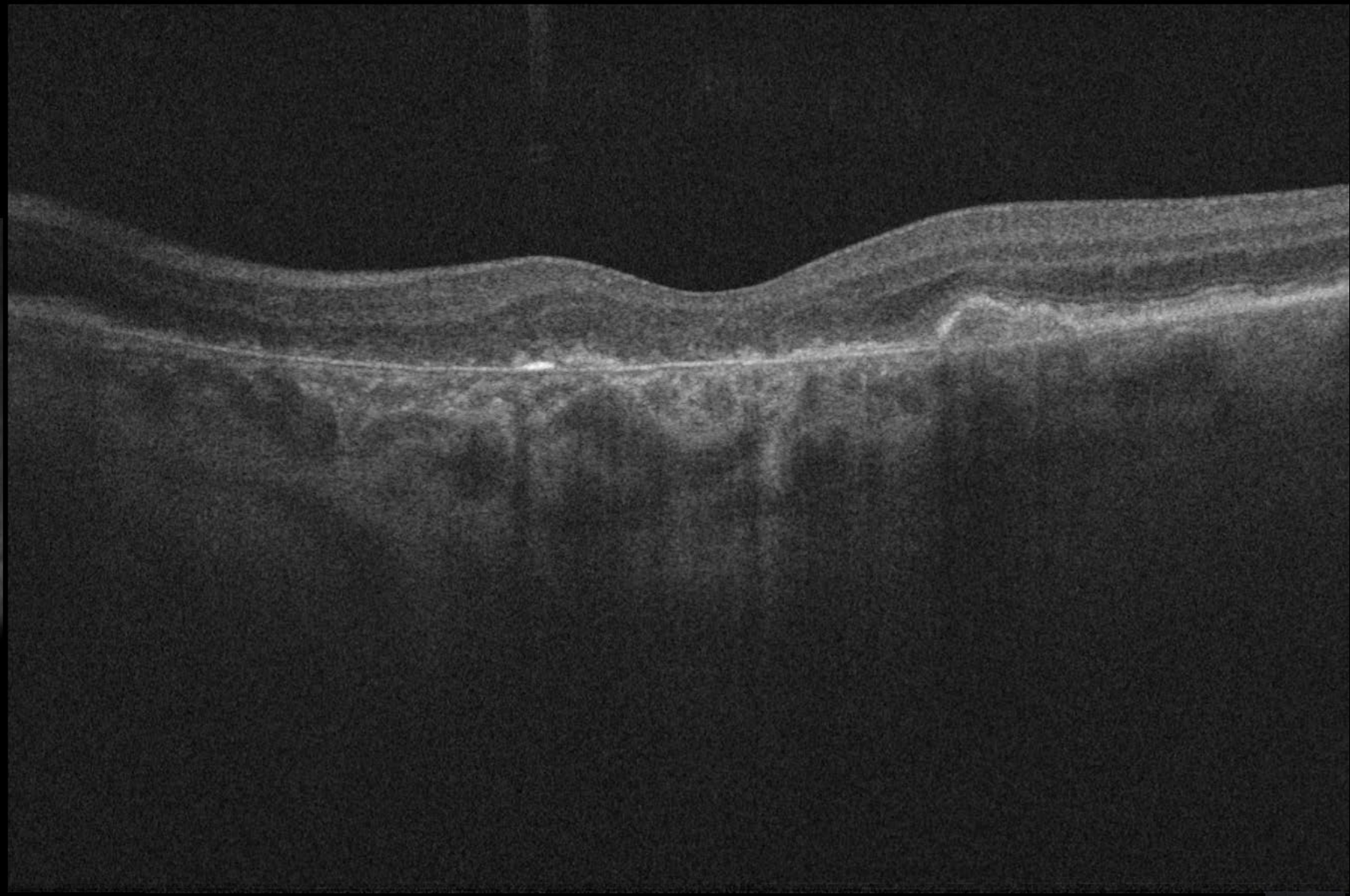






T N

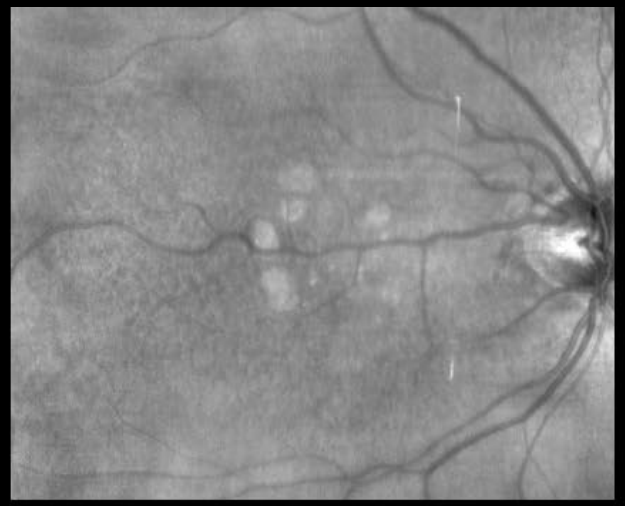


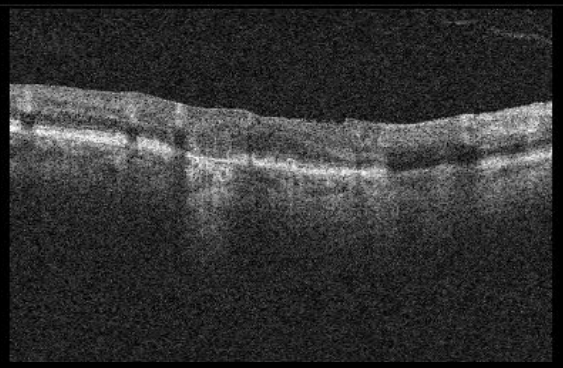


N T

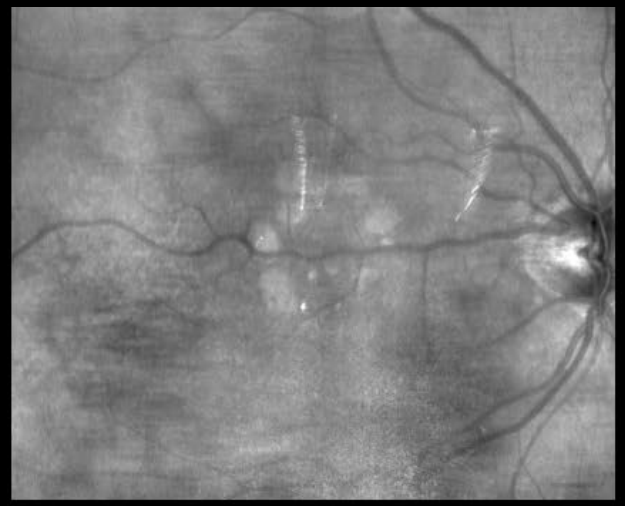
Worsening extrafoveal atrophy over 12 months

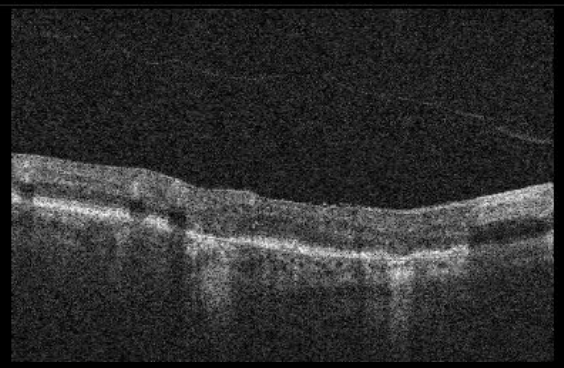
Baseline



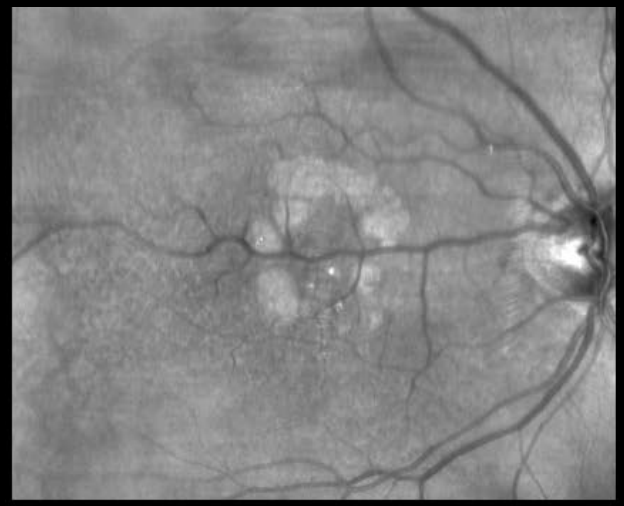


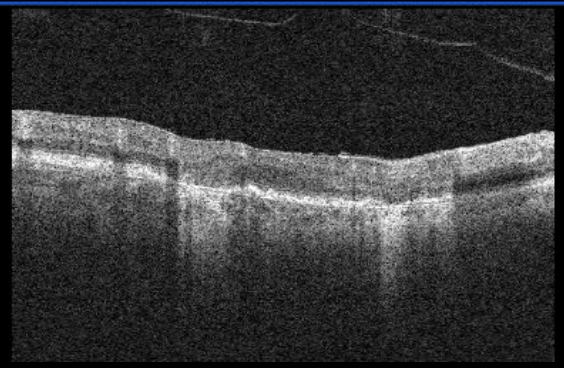
6 months



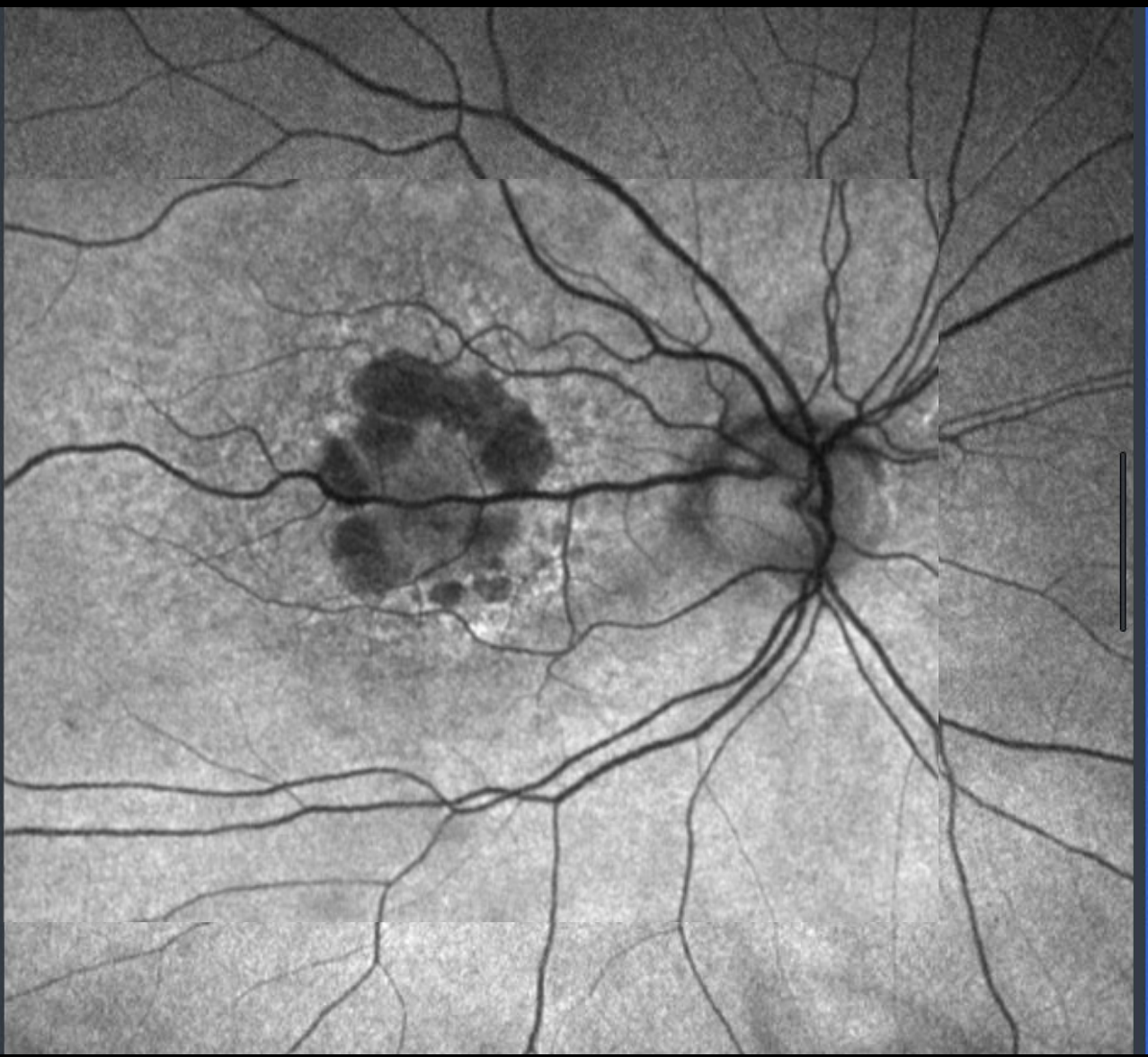


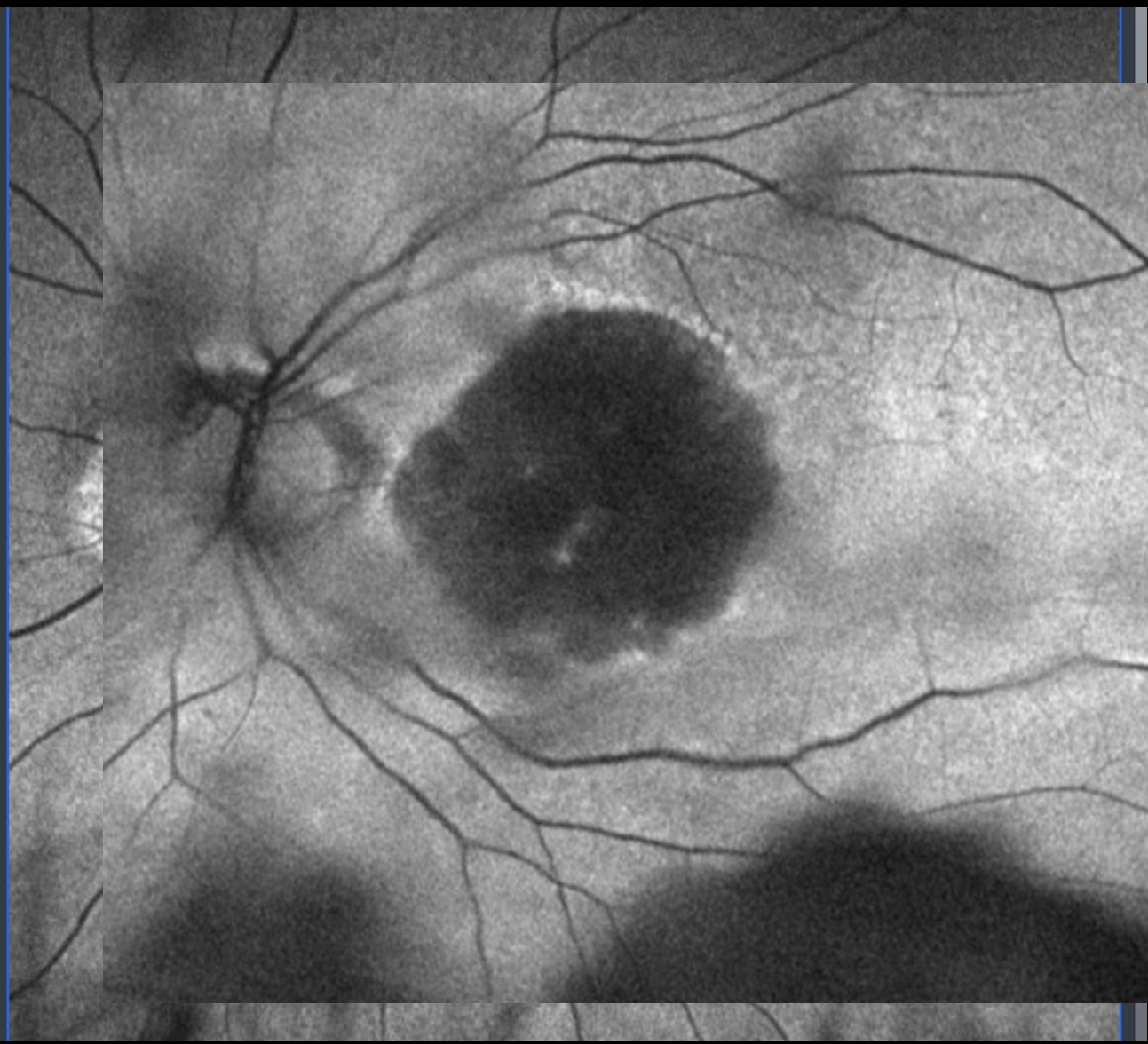
12 months



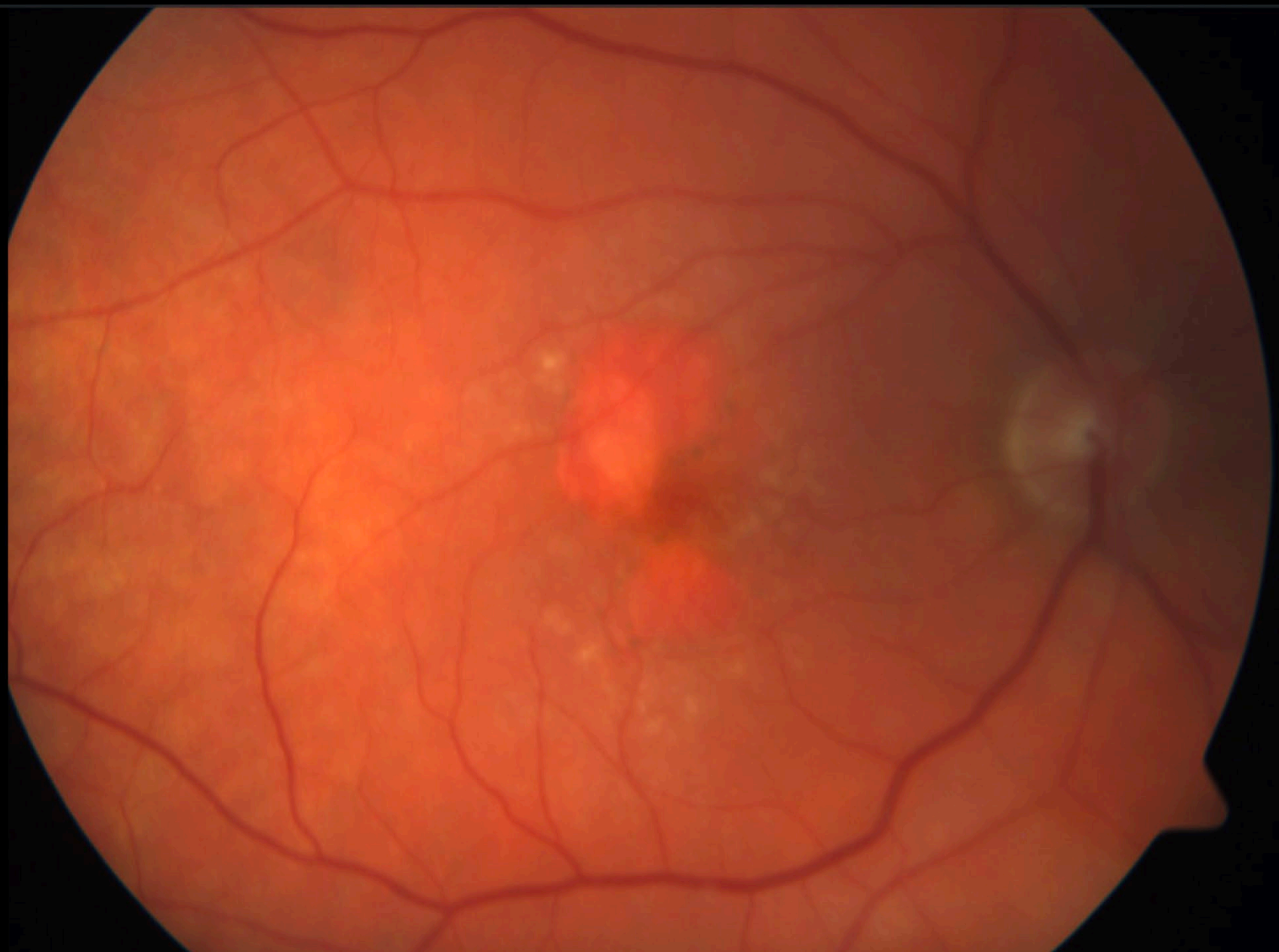


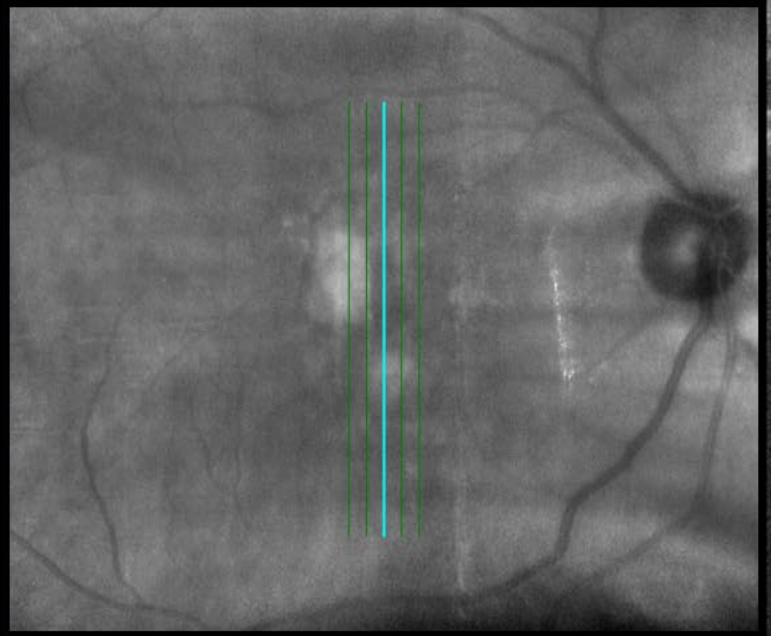

Application
Patient
System
Help
retina
Logout
OD
OS
Close all
52%
Synchronize
30%
Mar 15, 2022 | 8:13:43 AM | ARPE
Sep 20, 2022 | 8:27:14 AM | ARPE
Apr 4, 2023 | 8:41:31 AM | ARPE
512 × 128
200 µm
T → N
Closest distance to fovea (mm)
Show clinical events
Show All
Illumination area in 5 mm circle (mm²)
Apr 4, 2023 | 512x128 | OD
Illumination area in 5 mm circle
5.7 mm²
Jan 2021
Apr 2021
Jul 2021
Oct 2021
Jan 2022
Apr 2022
Oct 2022
Jan 2023
Apr 2023
Jul 2023
Oct 2023
Jan 2024
Patient Directory

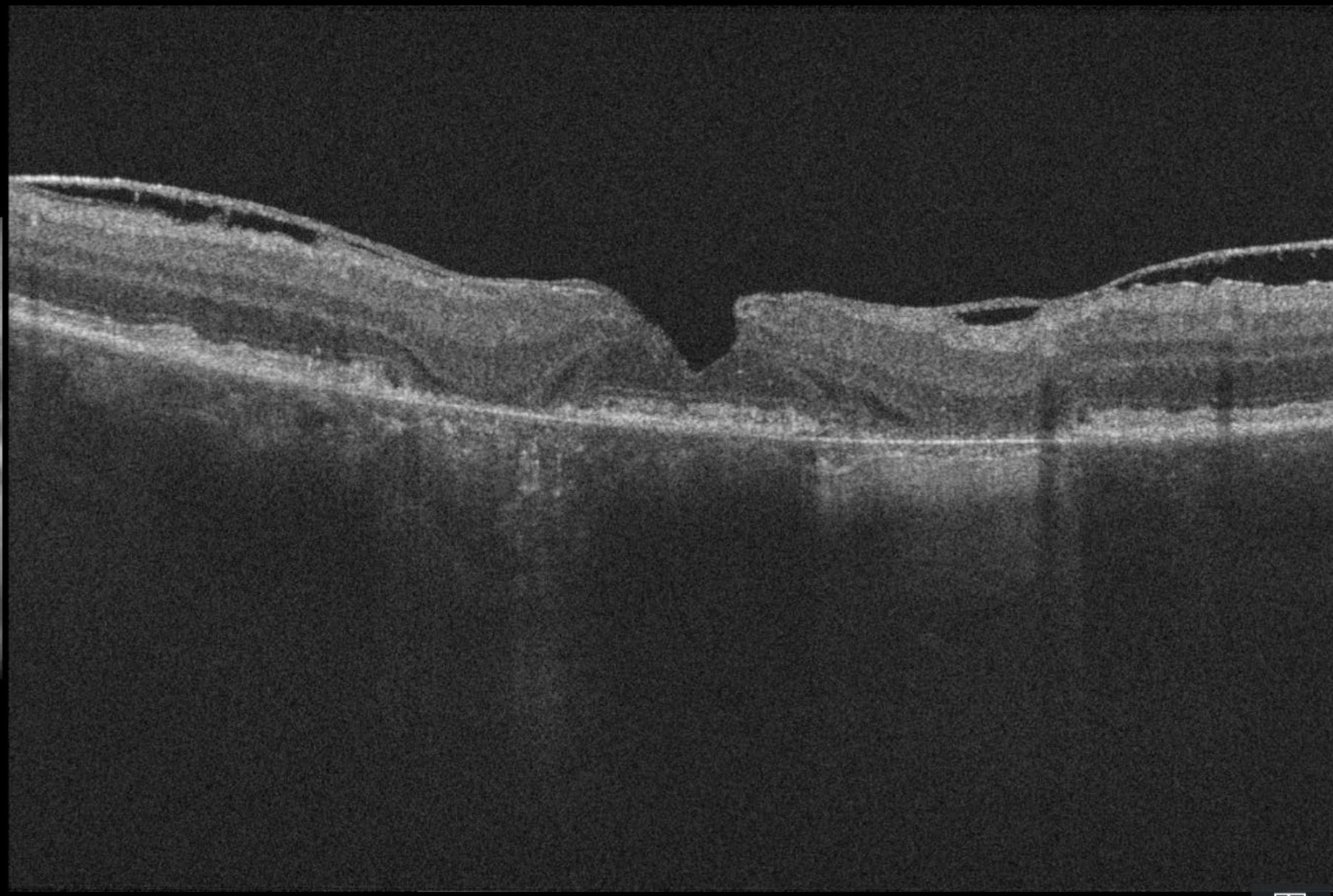




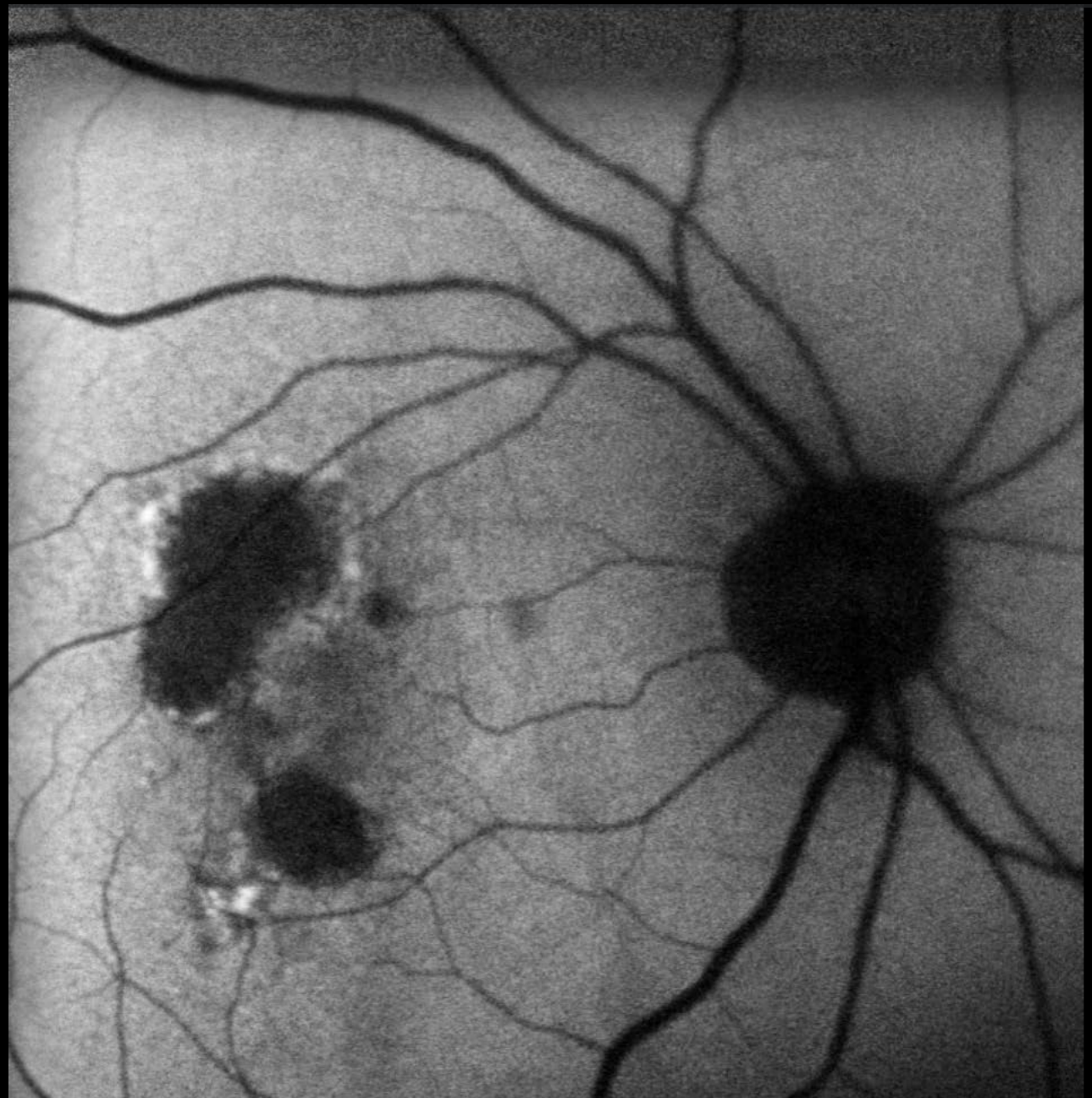
78 yo man with VA 20/50



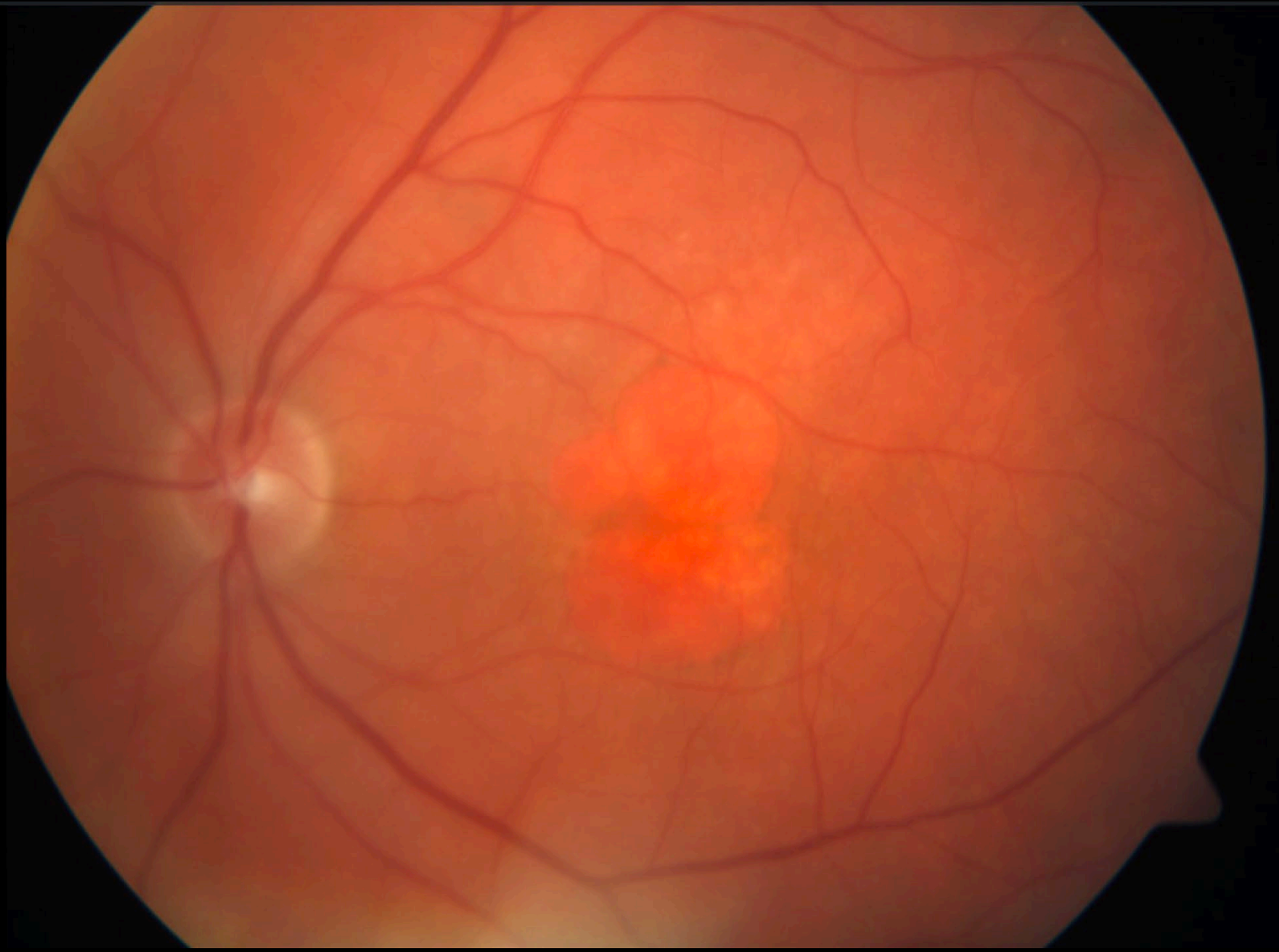


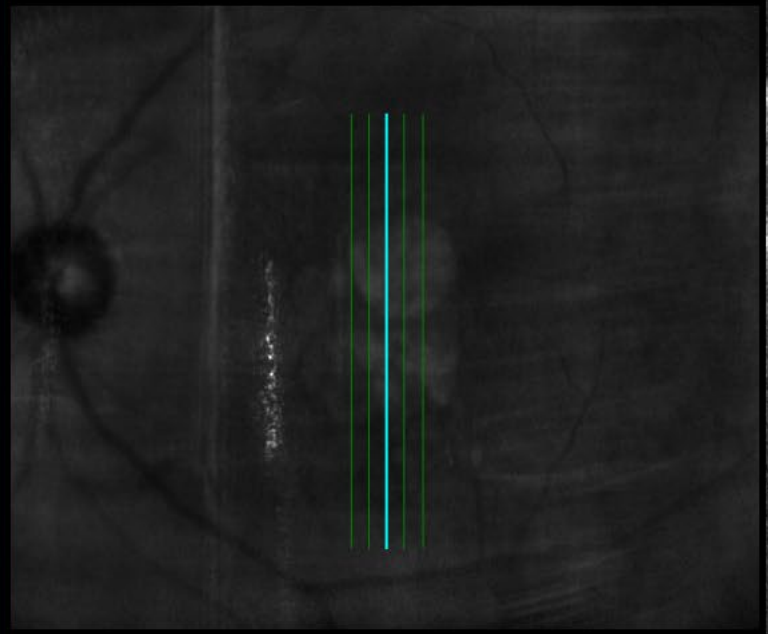


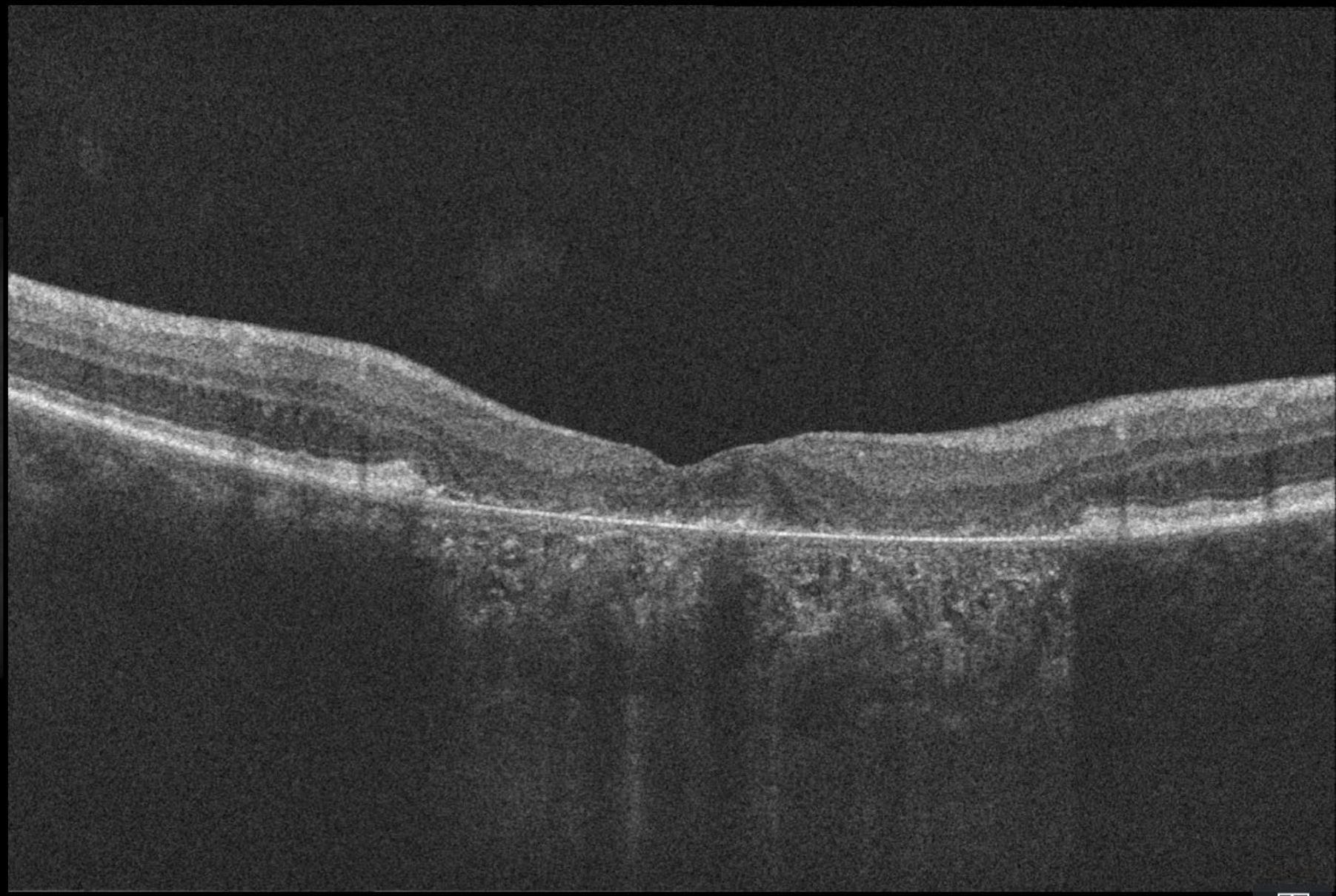
T N



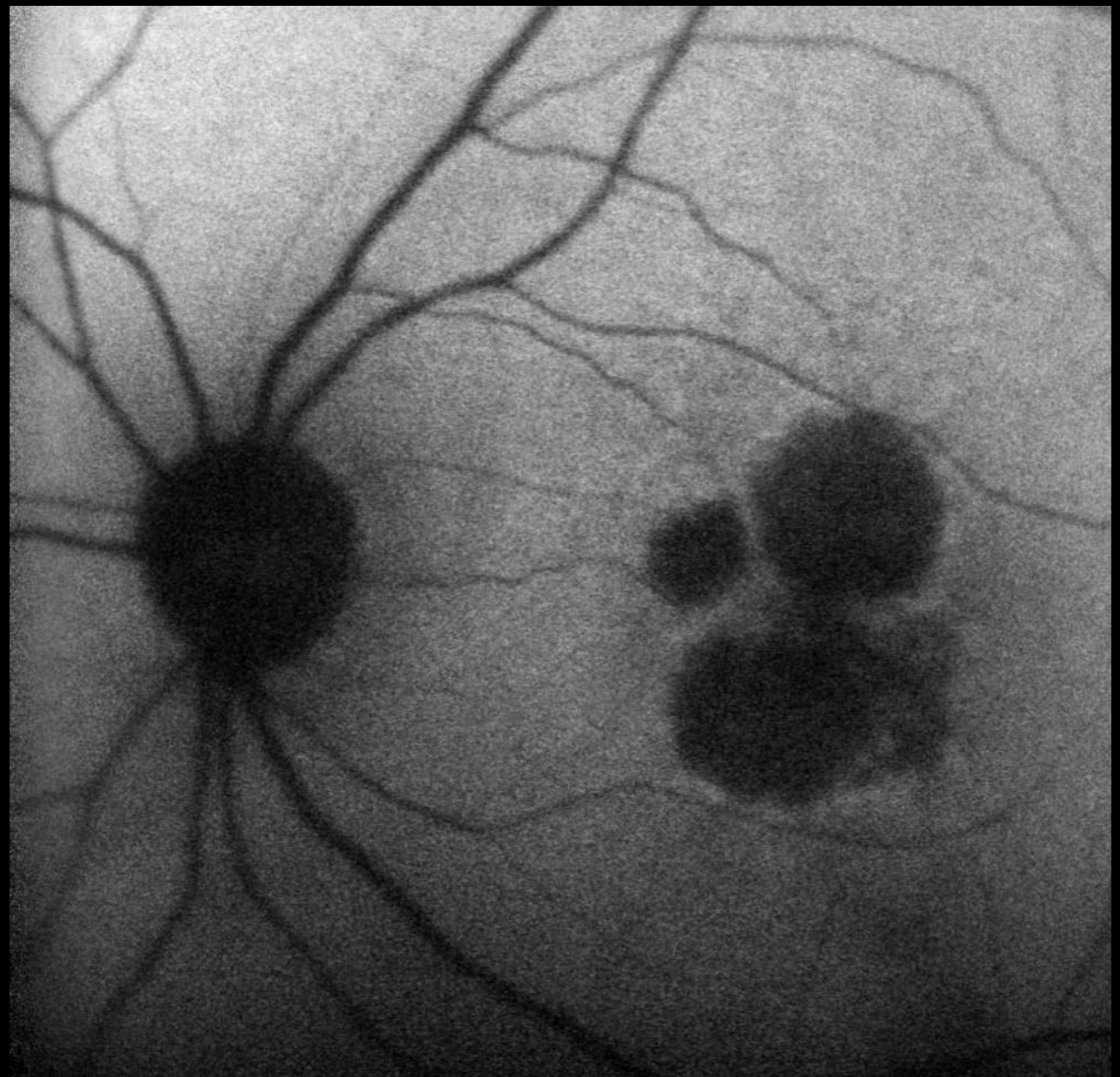
78 yo man with VA 20/50



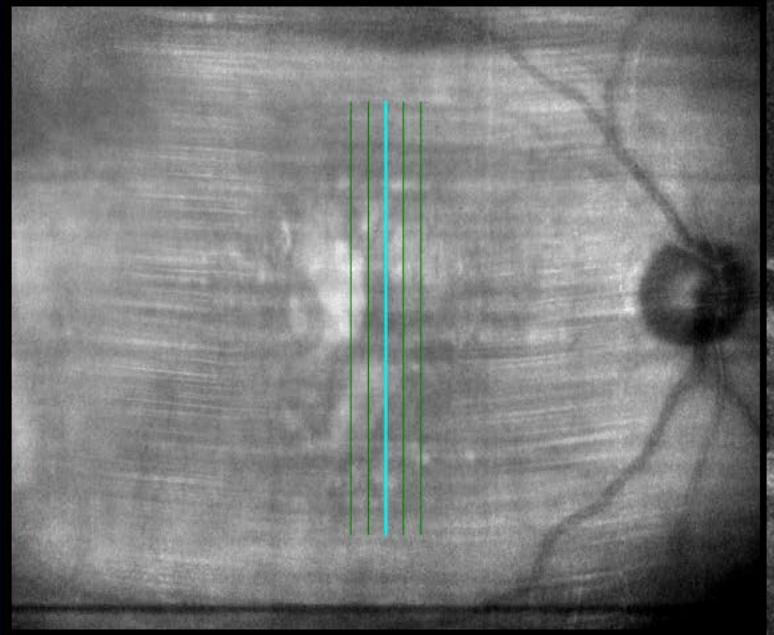


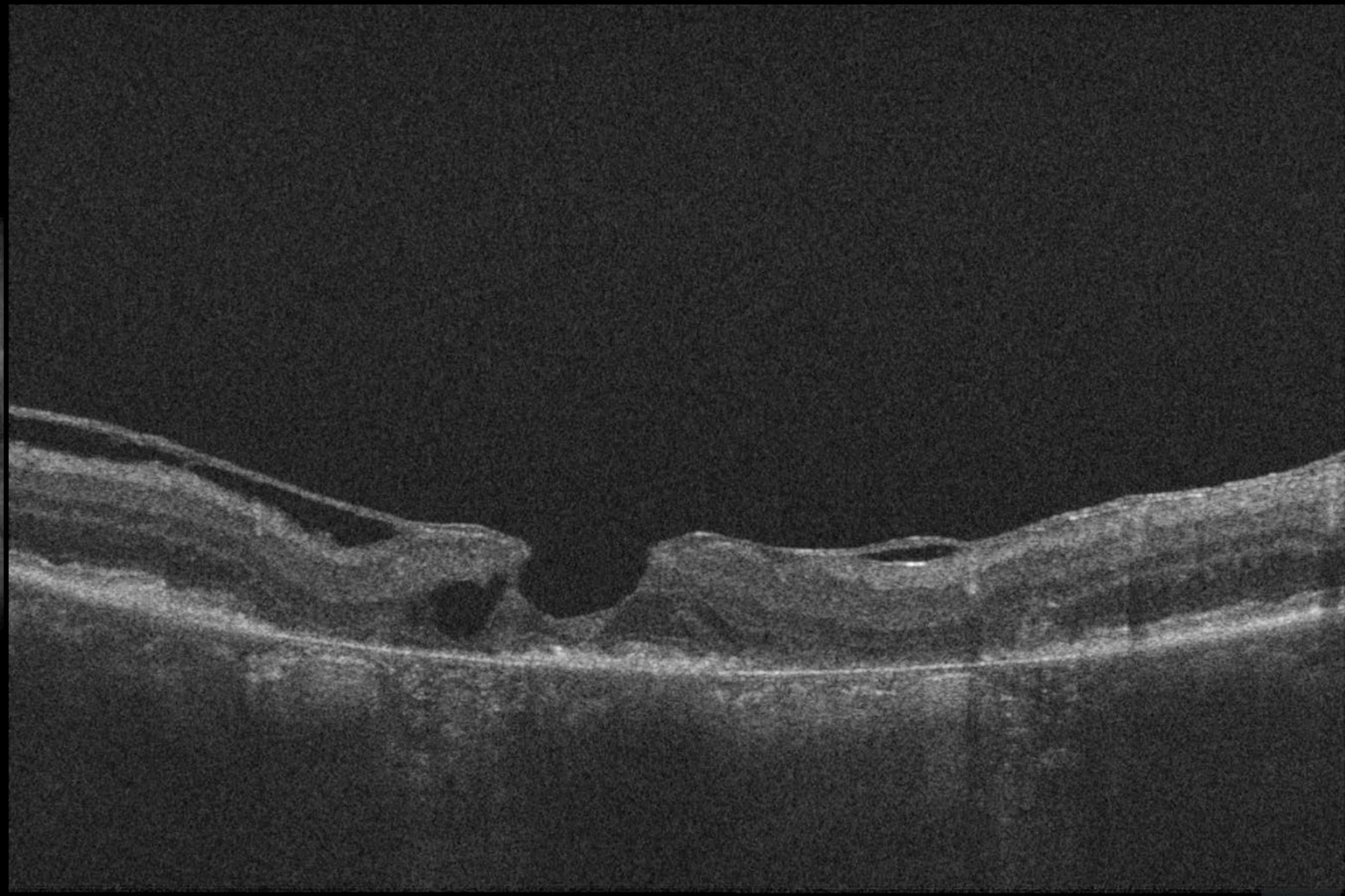


N T

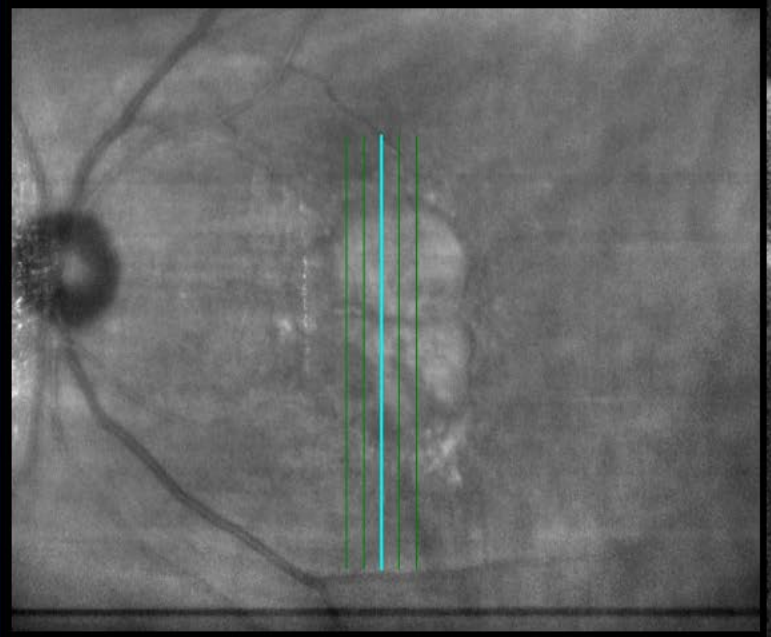


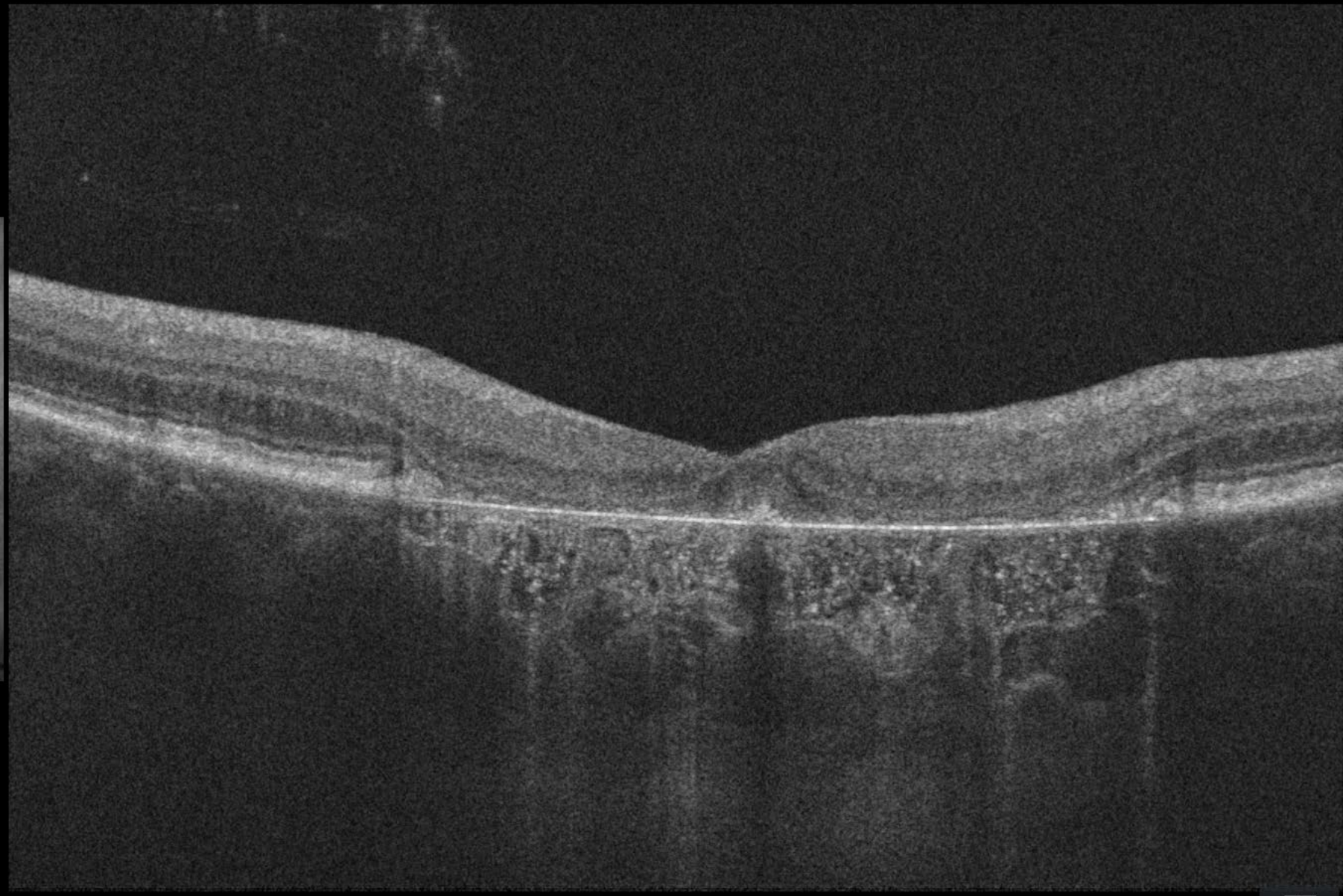
Three years later, vision still 20/50



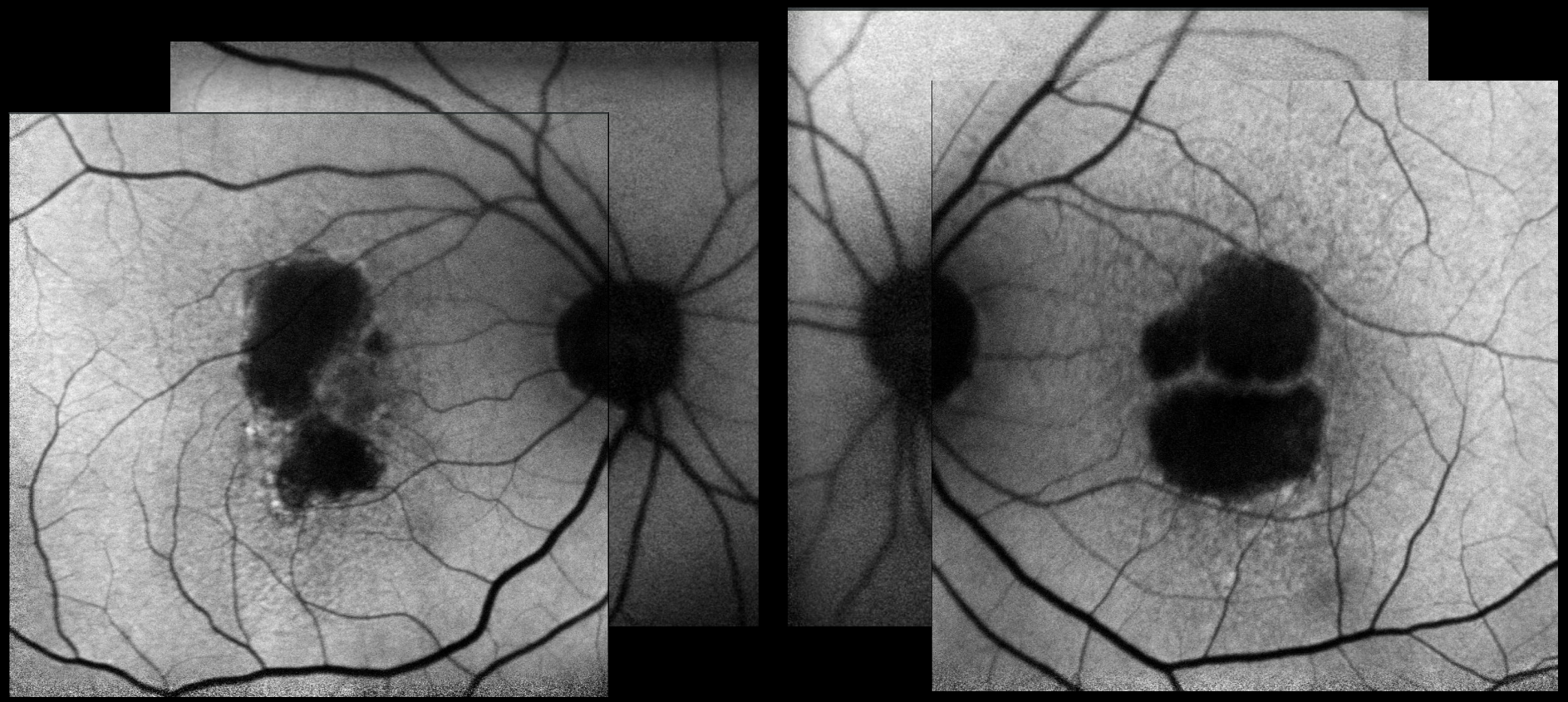


Three years later, vision still 20/50





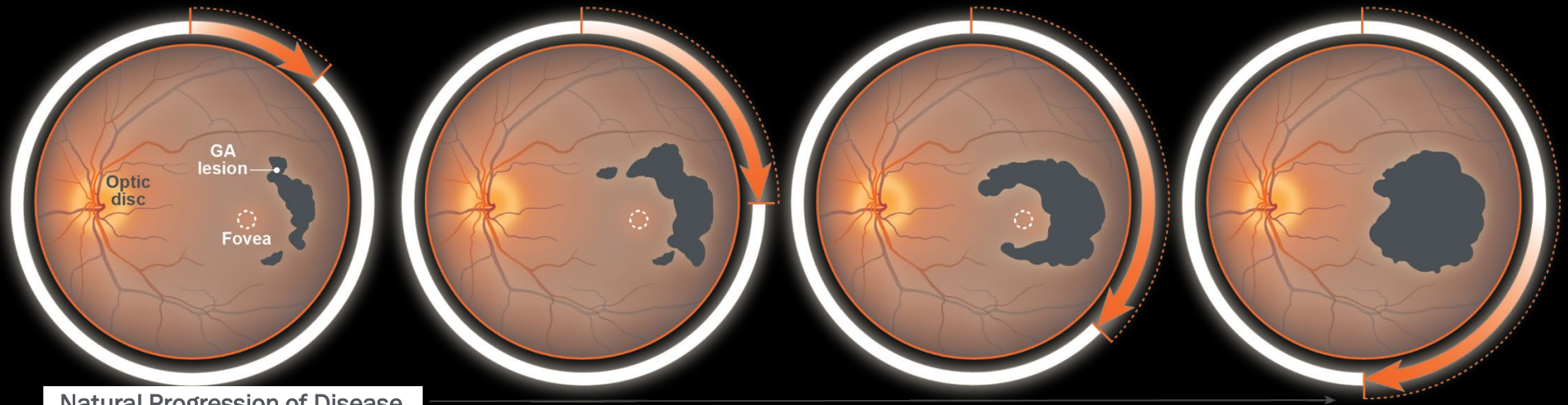
Geographic Atrophy (GA)



Progressive Geographic Atrophy Over Three Years

The rate of GA progression is highly variable

GA progression rates range from **≤0.8 TO 10.2 MM²/YEAR** (mean 2.5 mm²/year)[2*]



(Median 2.5 years from first non-central GA to central GA)[3†]
Data from patients who had lesions impacting the fovea (n=397) from the Age-Related Eye Disease Study (AREDS)

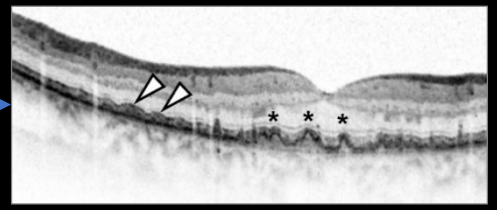
*Two-year enlargement rates, defined as the enlargement rate over the first follow-up interval of between 1.5 and 2.5 years.[2]

†Data from the Age-Related Eye Disease Study (AREDS) #26, a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.[3]

1. Holz FG, et al. *Ophthalmology*. 2014;121(5):1079-1091. 2. Sunness JS, et al. *Ophthalmology*. 2007;114(2):271-277. 3. Lindblad AS, et al. *Arch Ophthalmol*. 2009;127(9):1168-1174.

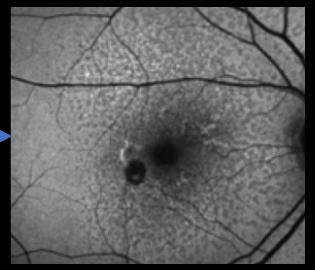
Factors that affect the rate of GA progression[1]

Reticular pseudodrusen[1]

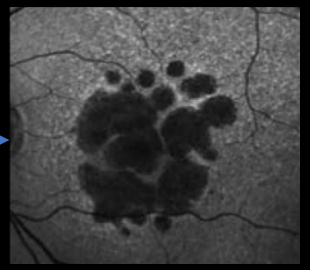


*Soft drusen. ▷ Reticular pseudodrusen.

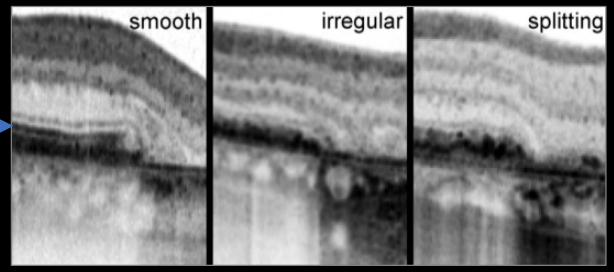
Non-subfoveal location[1]



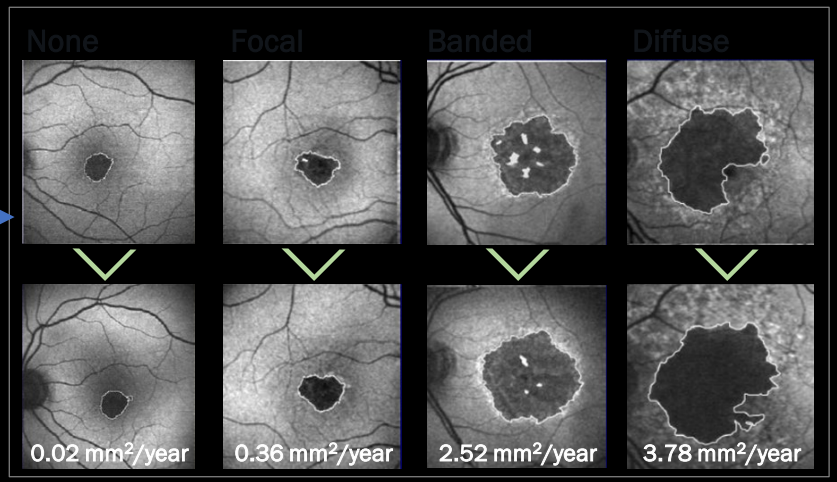
Medium/ Large size[1]



Junctional zone abnormalities[1,2]

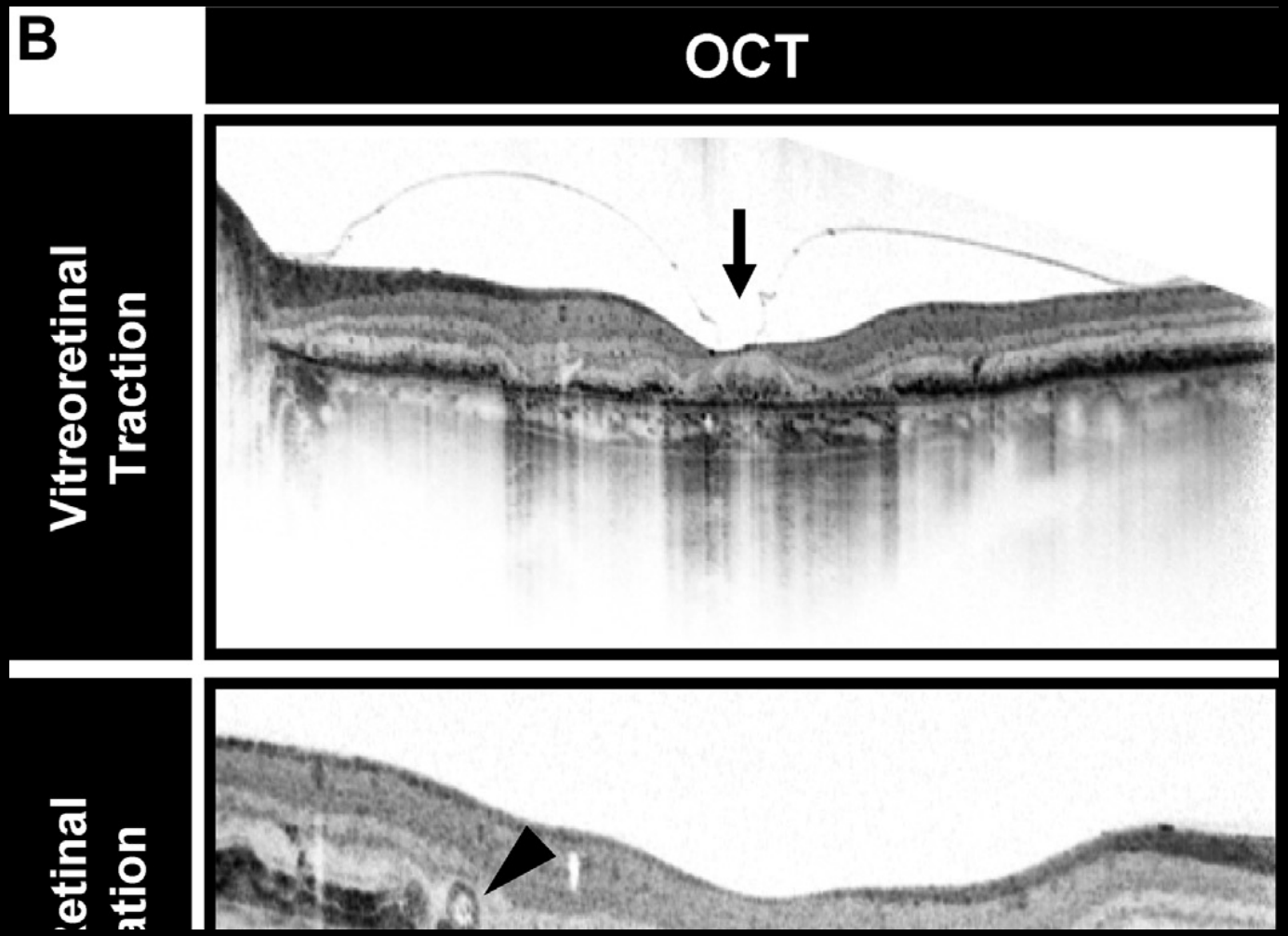


Multifocal, banded, and diffuse presentations on FAF[2,3]



1. Fleckenstein M, et al. *Ophthalmology.* 2018;125(3):369-390. 2. Holz FG, et al. *Am J Ophthalmol.* 2007;143(3):463-472. 3. Jeong YJ, et al. *Eye (Lond).* 2014;28(2):209-218.

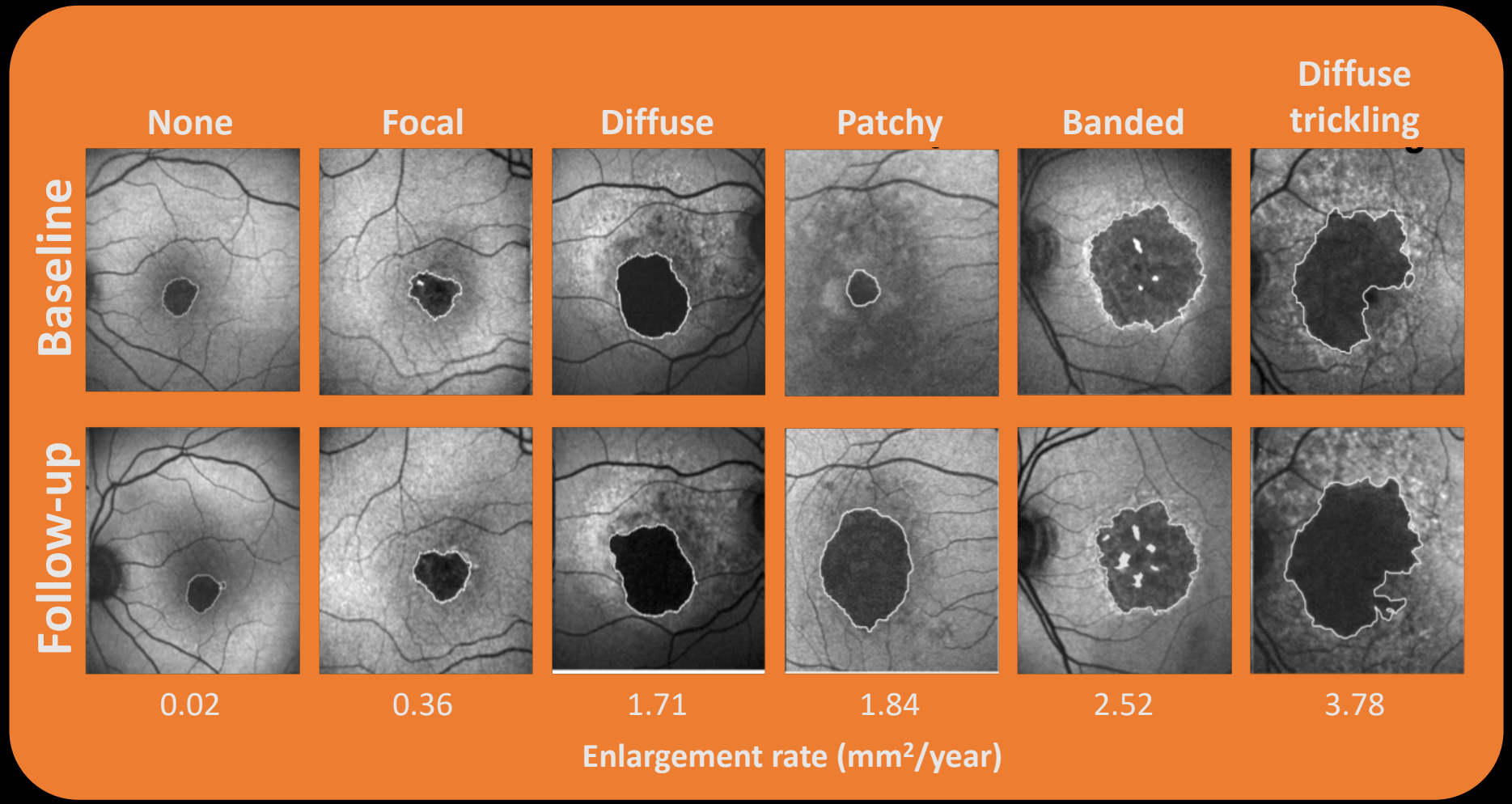
Subretinal Drusenoid Deposits and Thin Choroid



- Reticular pseudodrusen = subretinal drusenoid deposits (SDD)
- Associated with thin choroid
- Faster GA progression

Fleckenstein, *Ophthalmology* 2018.

FAF Imaging Can Identify GA Subtypes that Predict Rate of Lesion Enlargement



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

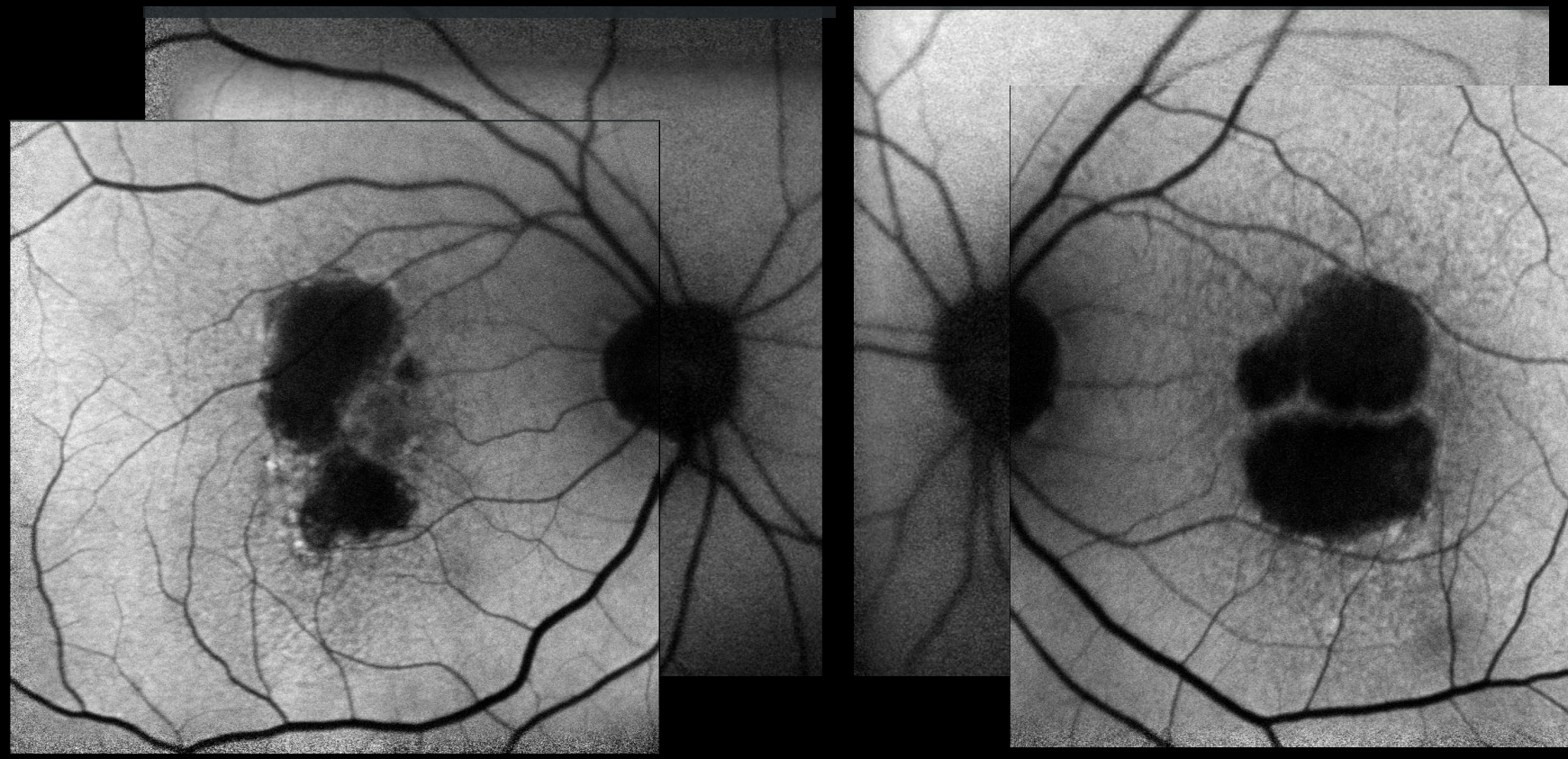
Geographic Atrophy Pearls

- OCT is important to rule out concurrent exudative changes
- Infrared images from OCT can be used to follow atrophy
- The rate of GA progression is highly variable
  - Patterns of surrounding RPE on FAF predict growth rate
  - Small round lesions grow slowest
  - GA grows faster toward the periphery
  - High concordance between eyes in growth rates

Geographic Atrophy and Treatment

Geographic Atrophy (GA)

- Significant breakthroughs and continued improvements in therapies for neovascular age-related macular degeneration (nAMD) have occurred
  - Multiple intravitreal anti-VEGF injections
  - Recent approval of surgical implant with refillable reservoir of anti-VEGF medication
- Despite advances in the treatment of nAMD, treatment for geographic atrophy (GA) remains elusive
  - GA is an advanced form of dry AMD characterized by the loss of photoreceptors and retinal pigment epithelial (RPE) cells in the macula



Progressive Geographic Atrophy Over Three Years

Major cause of vision loss worldwide[1-4]

5M Currently **GA affects more than 5 million people** worldwide[5]

1M **GA affects approximately 1 million people** in the United States[6]

4x From age 50, **prevalence quadruples every 10 years**

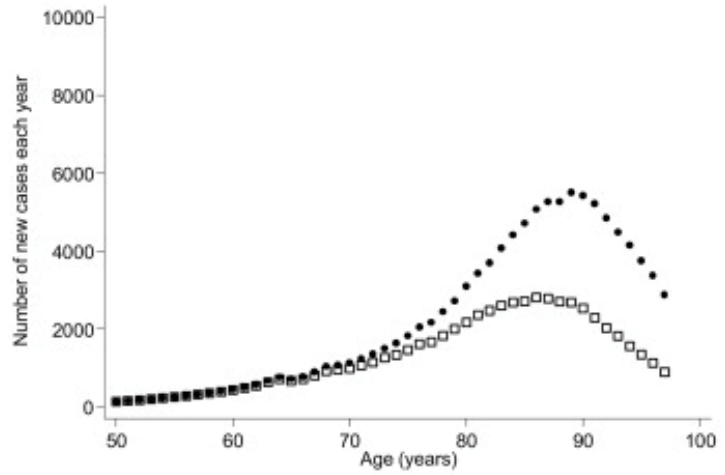
20% **GA accounts for 20% of all legal blindness attributed to AMD**; AMD is the leading cause of blindness in the elderly worldwide[1,8]

1. Biarnés M, et al. *Optom Vis Sci.* 2011;88(7):881-889. 2. Holz FG, et al. *Ophthalmology*. 2014;121(5):1079-1091. 3. Rees A, et al. *Eye*. 2014;28:832-837. 4. Klein R, et al. *Invest Ophthalmol Vis Sci*. 1995;36:182-191. 5. Boyer DS, et al. *Retina*. 2017;37(5):819-835. 6. Friedman DS, et al. *Arch Ophthalmol.* 2004;122(4):564-572. 7. Rudnicka AR, et al. *Ophthalmology*. 2012;119(3):571-580. 8. Gehrs KM, et al. *Ann Med*. 2006;38(7):450-471.

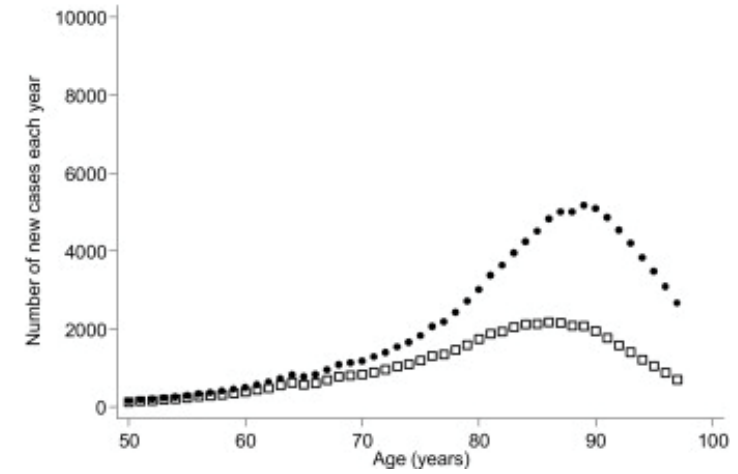
GA Incidence Among White Population in US[1]

- 160,000 new cases per year among Caucasians
- Incidence rate for late AMD (GA and neovascular AMD) triples per decade increase in age
- Annual incidence rate of GA – 1.9 per 1,000 Caucasians aged ≥50 y of age
- Slightly higher than incidence of neovascular AMD (1.8 per 1000)
- Incidence of GA and neovascular AMD comparable through age 69; thereafter, GA incidence is higher

GA



nvAMD



1. Rudnicka AR, Kapetanakis VV, Jarrar Z, et al. Incidence of late-stage age-related macular degeneration in American whites: systematic review and meta-analysis. *Am J Ophthalmol*. 2015;160(1):85-93.

Visual Impairment Impacts Daily Life

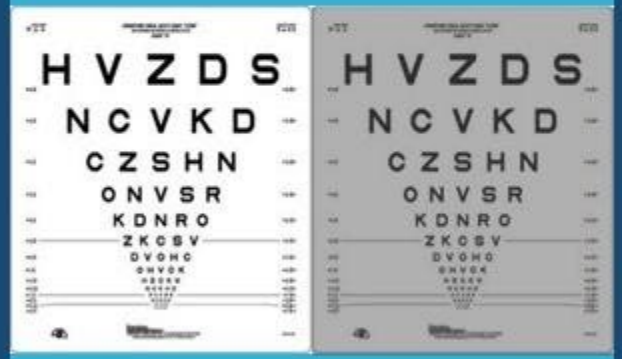
Normal

Extra-foveal GA

Fovea-involving GA

Visual Impairment Impacts Every Day Life

Reduced **low-luminance vision**



Reduced **contrast sensitivity**

Reduced **reading speed**

Sunness JS, et al. *Ophthalmology*.1997;104:1677–91

Quality of Life Affected by Dry AMD and GA

Sports

- Less exercise
- Less engagement with friends

Household Chores

- Less social interactions, unsure of a clean house

Personal Hygiene

- Too much effort to prepare for outing; social isolation

Reading

- Loss of reading as a hobby

Transportation

- Isolation from family and friends
- Reliance on others

Need for Aids

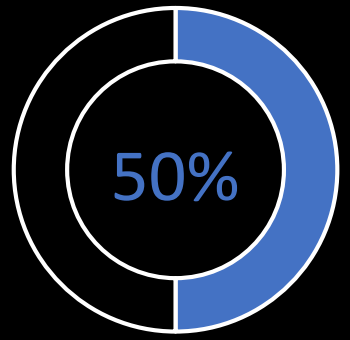
- Need to carry magnifiers at all times

Nielsen JS, Singh RP, Patel SS, et al. How much do we know about the economic and patient-reported burden of geographic atrophy? Talk presented at EURETINA 2016, Copenhagen, September 11, 2016. Accessed November 29, 2016.

Patients with GA

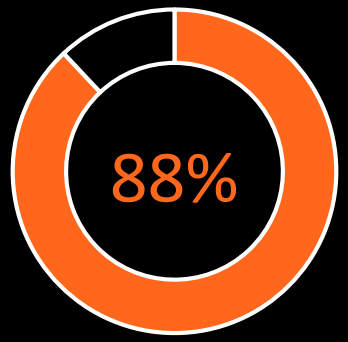
Poor Vision-Related Quality of Life

Among patients with GA who had a driver's license:

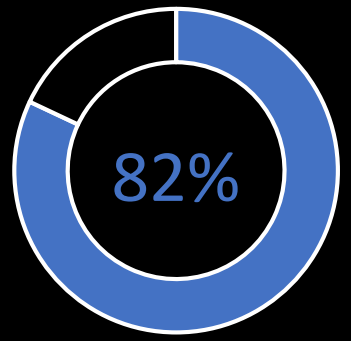


said they did not feel confident driving during the day

AND

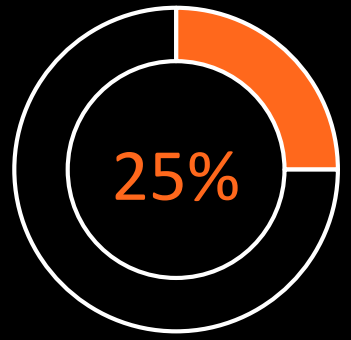


said they did not feel confident driving at night



of those with GA reported a worsening of vision

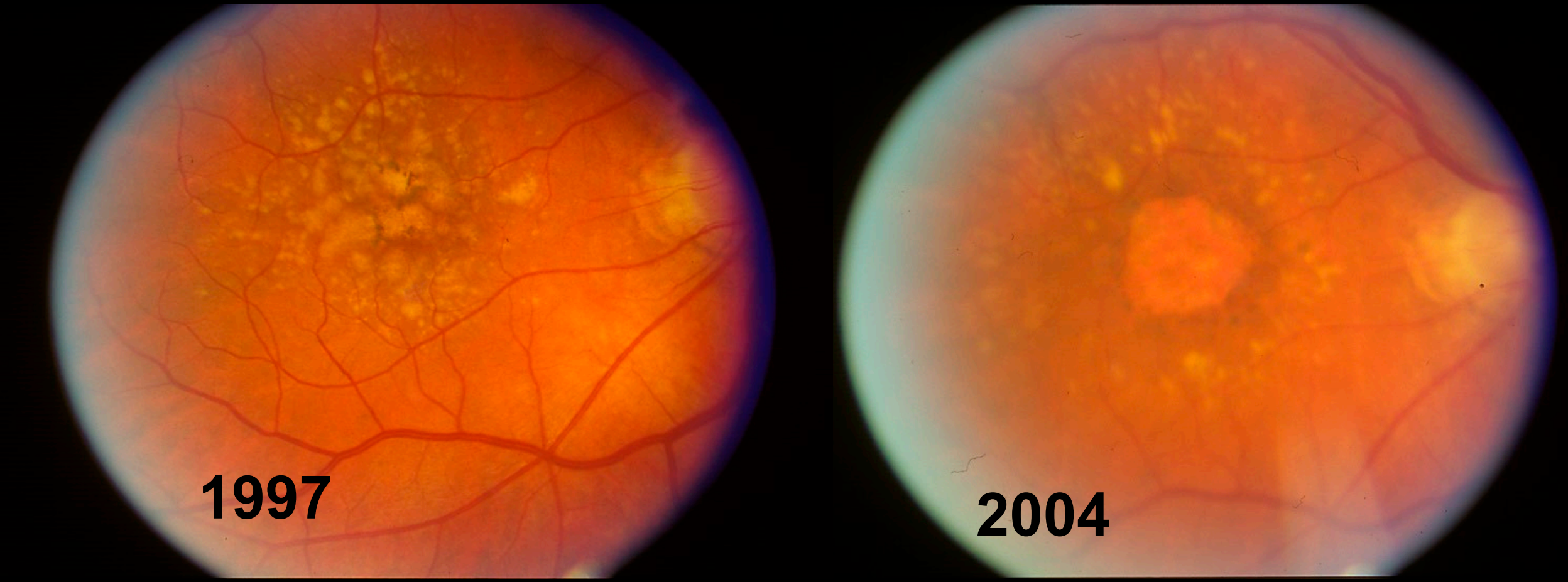
VS



of controls
(OR 13.55; $P < .001$)

Patel PJ, et al. *Clin Ophthalmol*. 2020;14:15.

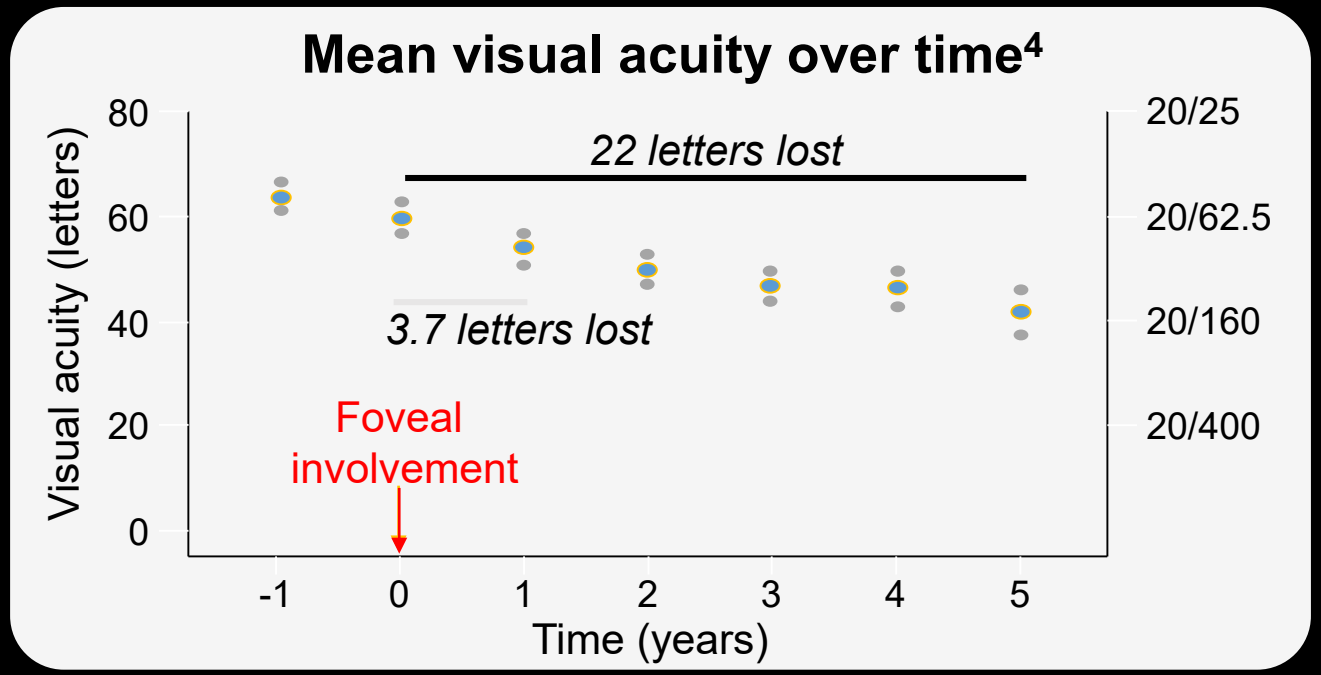
Geographic Atrophy : Development



Visual Decline from GA

- 31% of patients experience ≥3-line vision loss in 2 years[1]
- 29% of patients experience ≥6-line loss in 4 years[1]

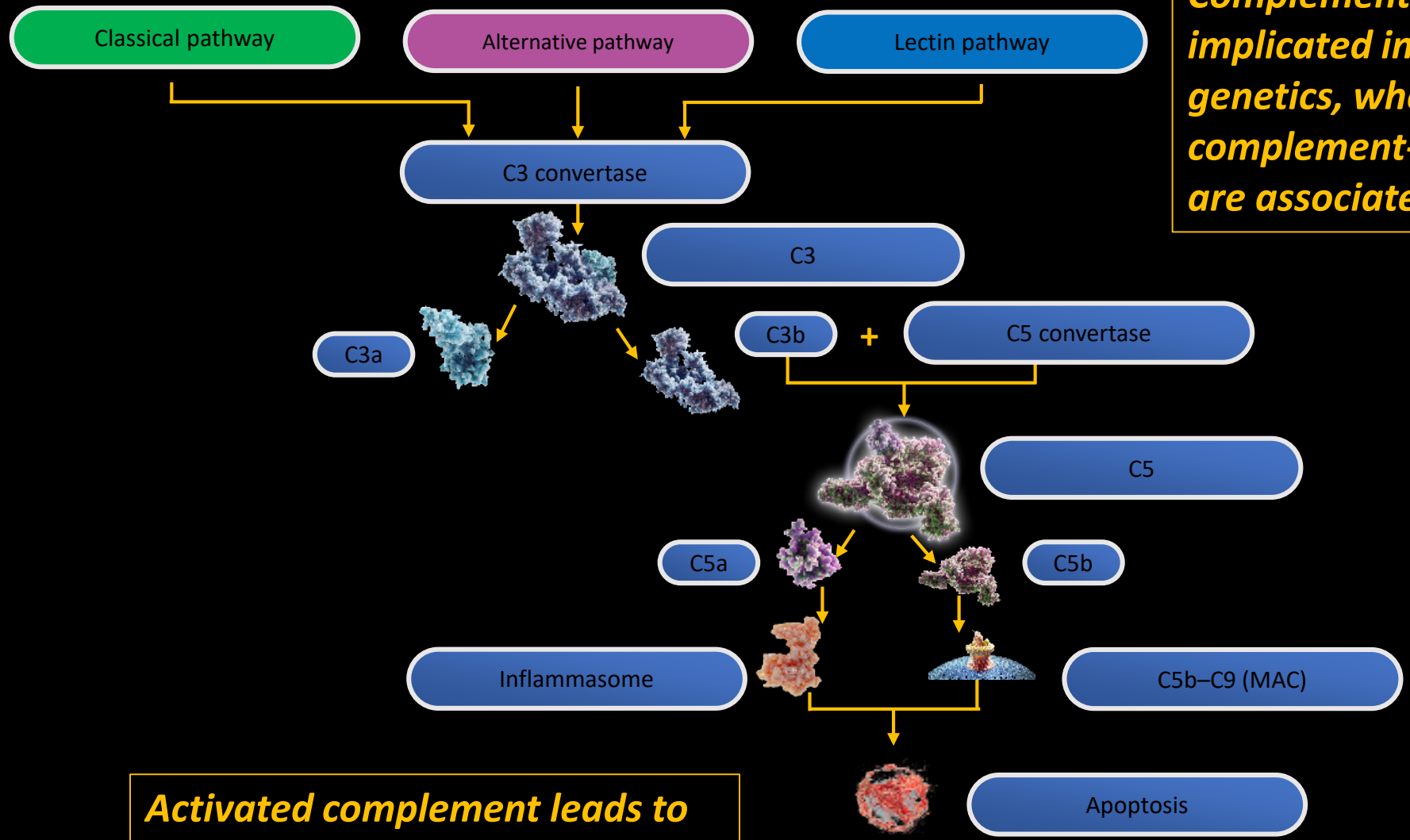
- High variability in visual decline[2]
- Modelling of progression[2]
- One-third of patients with advanced AMD have clinical depression[3]



Sunness JS, et al. Ophthalmology. 1999;106:1768–79; 2. Fleckenstein M, et al. ARVO 2015; manuscript submitted;
3. Brody BL, et al. Ophthalmology. 2001;108:1893–901; 4. AREDS Research Group. Arch Ophthalmol. 2009;127:1168–74

Complement Inhibition

Complement Inhibition



Complement system has been implicated in GA by human genetics, where variants in complement-related genes are associated with GA

Activated complement leads to inflammation and cell death

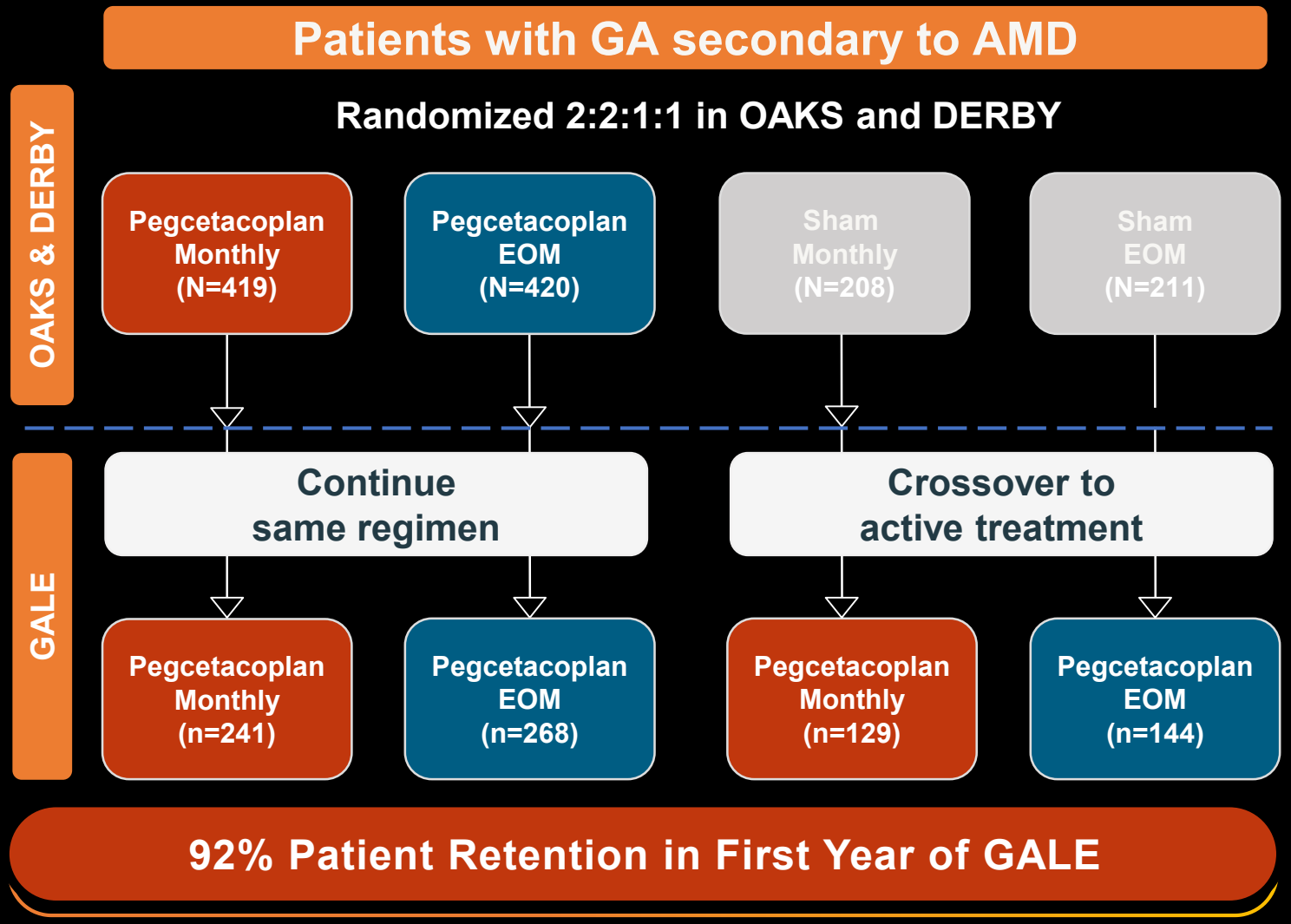
Pegcetacoplan

Pegcetacoplan (Syfovre, Apellis)

- Pegylated cyclic peptide inhibitor of complement C3
- Approved in February 2023 for geographic atrophy; shown to slow tissue loss
- Treatment consists of intravitreal injections given every 1 to 2 months

Liao DS et al. Ophthalmology. 2020.

OAKS & DERBY 24-Month Phase 3 Trials[1] Followed by GALE 36-Month, Open-Label Extension Study[2]



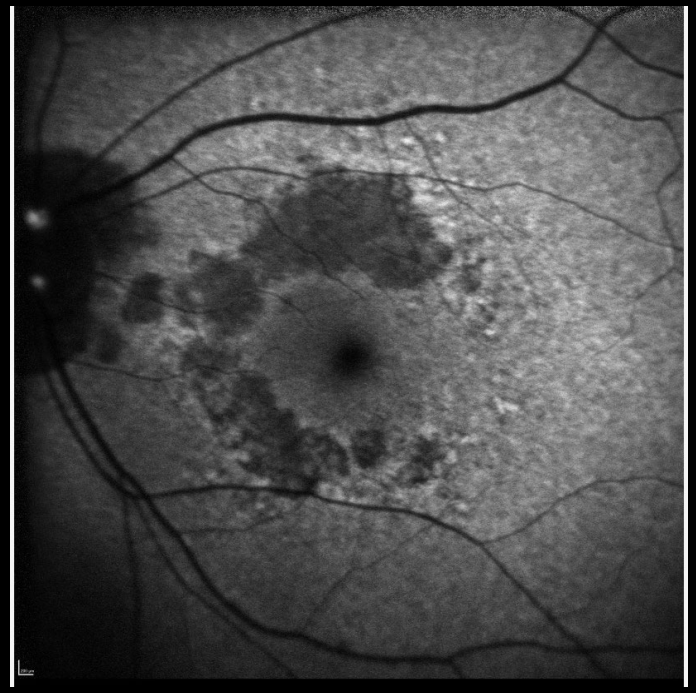
AMD, age-related macular degeneration; **EOM,** every other month; **GA,** geographic atrophy; **IOI,** intraocular inflammation; **ION,** ischemic optic neuropathy.

1. Heier JS, et al. *Lancet*. 2023; 402: 1434–48. 2. GALE ClinicalTrials.gov identifier: NCT04770545.

GA Location Affects Growth Rate

- Nonsubfoveal GA grows more rapidly than subfoveal GA[1]

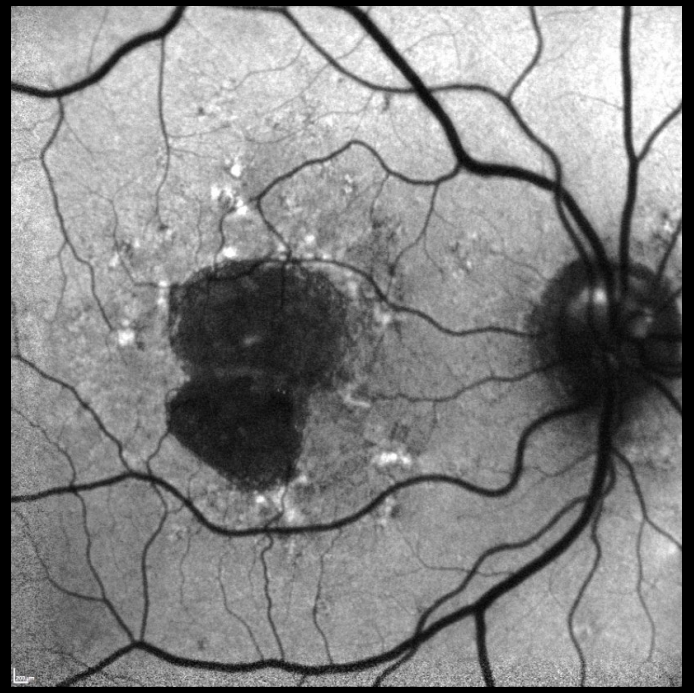
Nonsubfoveal



GA border ≥ 1 micron from foveal center point

~35% of OAKS & DERBY population (n=446)

Subfoveal



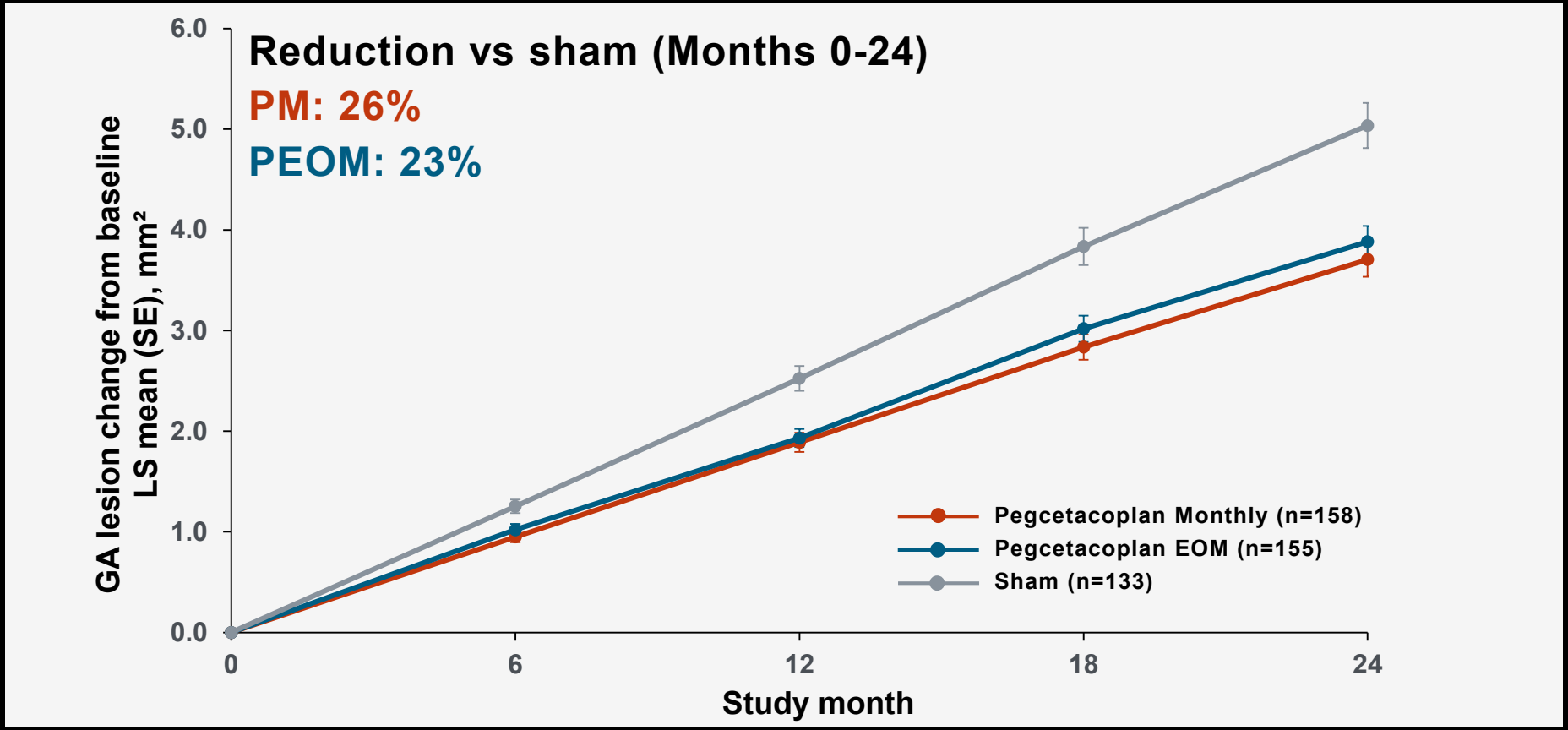
GA present at the center point of fovea

~65% of OAKS & DERBY population (n=765)

Images from OAKS and DERBY.
FAF, fundus autofluorescence; **GA,** geographic atrophy; **OCT,** optical coherence tomography.
1. Fleckenstein M, et al. *Ophthalmol.* 2018;125:369–90.

Non-subfoveal GA

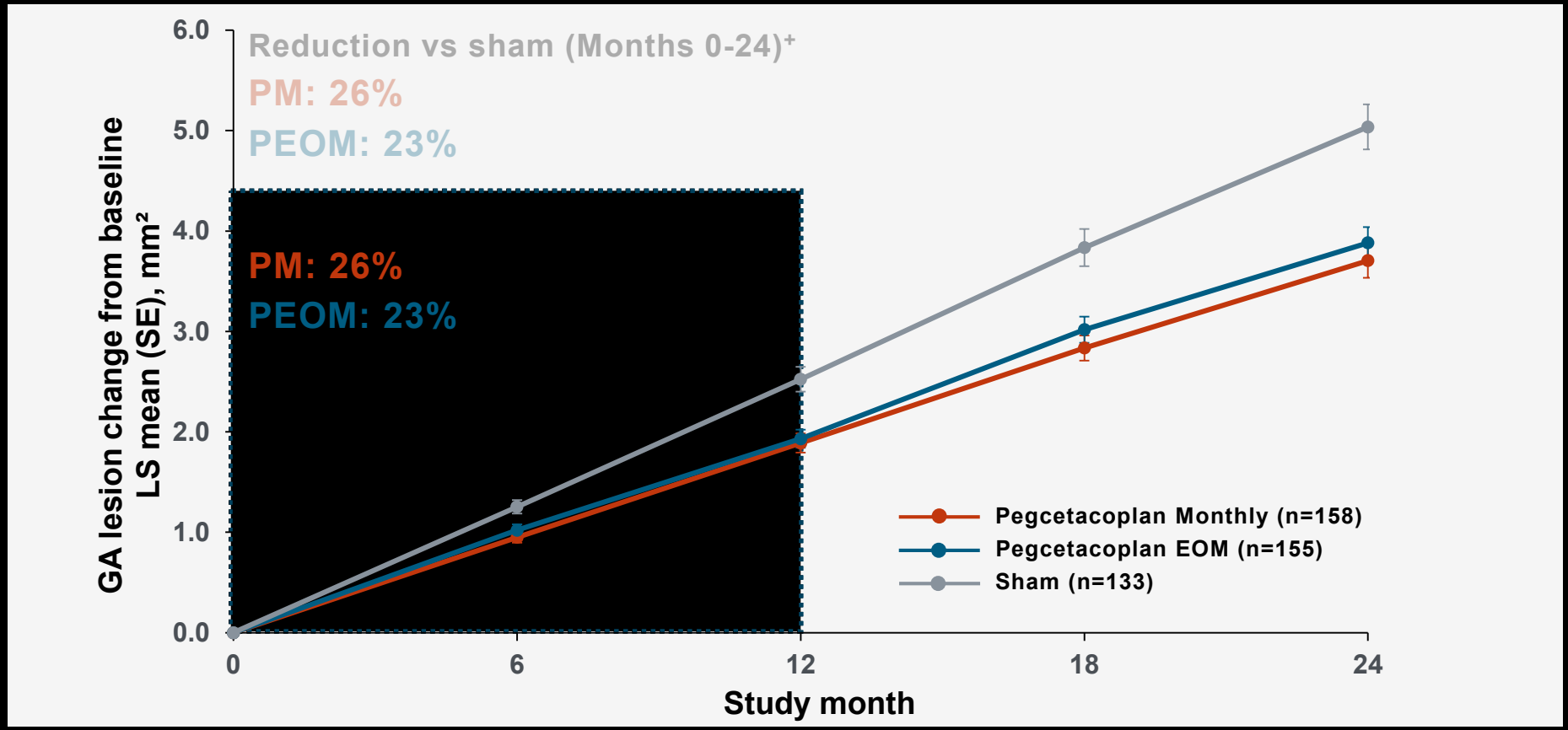
OAKS & DERBY: Nonsubfoveal (n=446 eyes)
Meaningful Reductions in NSF GA Growth Through Month 24



1.30 mm² (PM) & 1.11 mm² (PEOM) of Retinal Tissue Preserved Over 24 Months

[a]Estimated based on macular RPE density[1] range of 5082 cells/mm² to 7728 cells/mm².
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 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). Analyses performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups who had their first postbaseline GA lesion assessment after month 12.[2]
EOM, every other month; **GA,** geographic atrophy; **LS,** least squares; **mITT,** modified intent-to-treat; **PM,** pegcetacoplan monthly; **PEOM,** pegcetacoplan every other month; **SE,** standard error.
1. Ach T, et al. *Invest Ophthalmol Vis Sci*. 2014;55:4832–4841. 2. Heier JS, et al. *Lancet*. 2023; 402:1434–48.

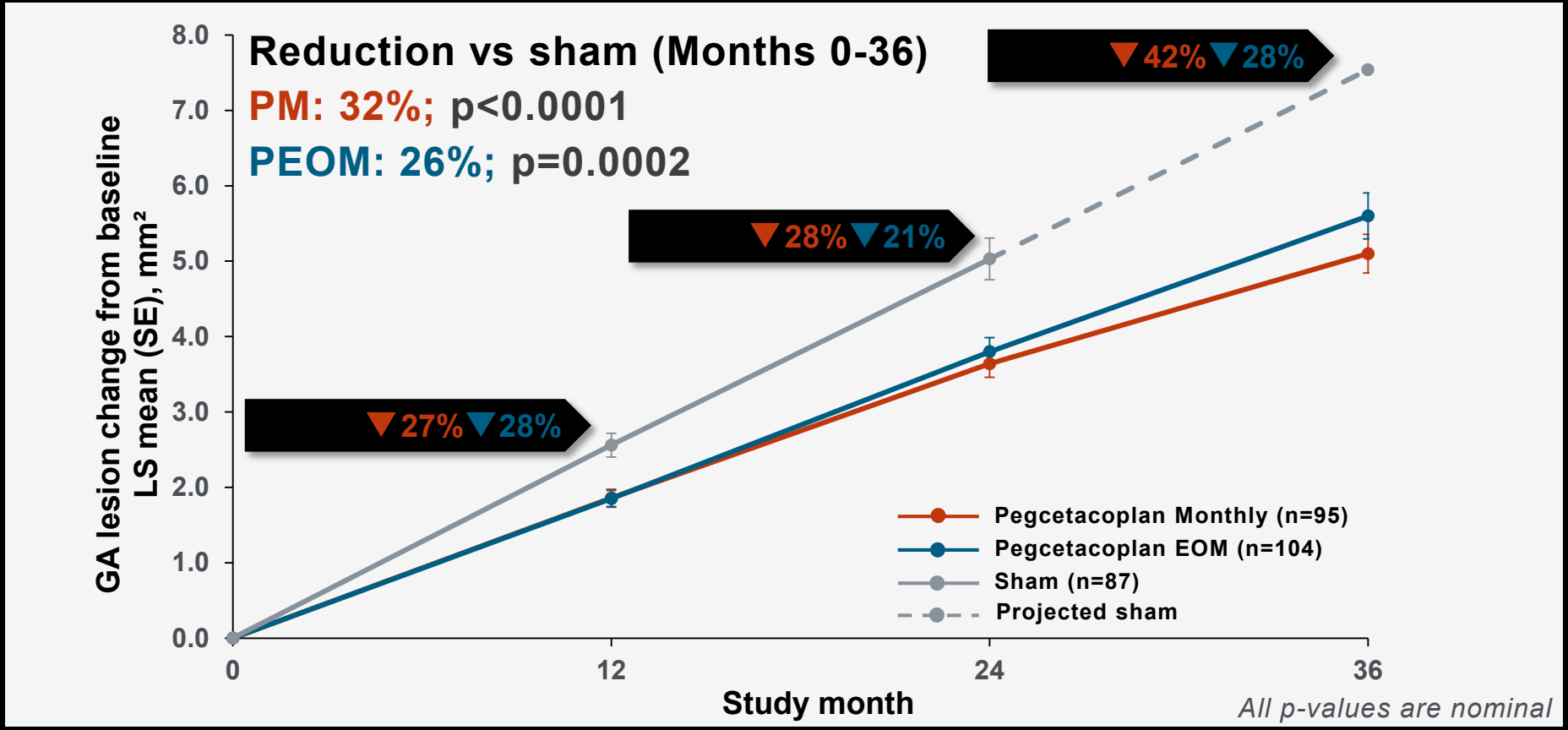
OAKS & DERBY: Nonsubfoveal (n=446 eyes)
Meaningful Reductions in NSF GA Growth at Months 12 & 24



0.64 mm² (PM) & 0.59 mm² (PEOM) of Retinal Tissue Preserved Over 12 Months

[a]Estimated based on macular RPE density[1] range of 5082 cells/mm² to 7728 cells/mm².
*LS means estimated from a mixed-effects model for repeated measures. +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 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis).[2]
Analyses performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value.
Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups who had their first postbaseline GA lesion assessment after month 12.[2]
EOM, every other month; **GA,** geographic atrophy; **LS,** least squares; **mITT,** modified intent-to-treat; **PM,** pegcetacoplan monthly; **PEOM,** pegcetacoplan every other month; **SE,** standard error.
1. Ach T, et al. *Invest Ophthalmol Vis Sci*. 2014;55:4832–4841. 2. Heier JS, et al. *Lancet*. 2023; 402:1434–48.

GALE: Nonsubfoveal (n=286 eyes)
Reductions in GA Growth with 36 Months of Continuous Pegcetacoplan

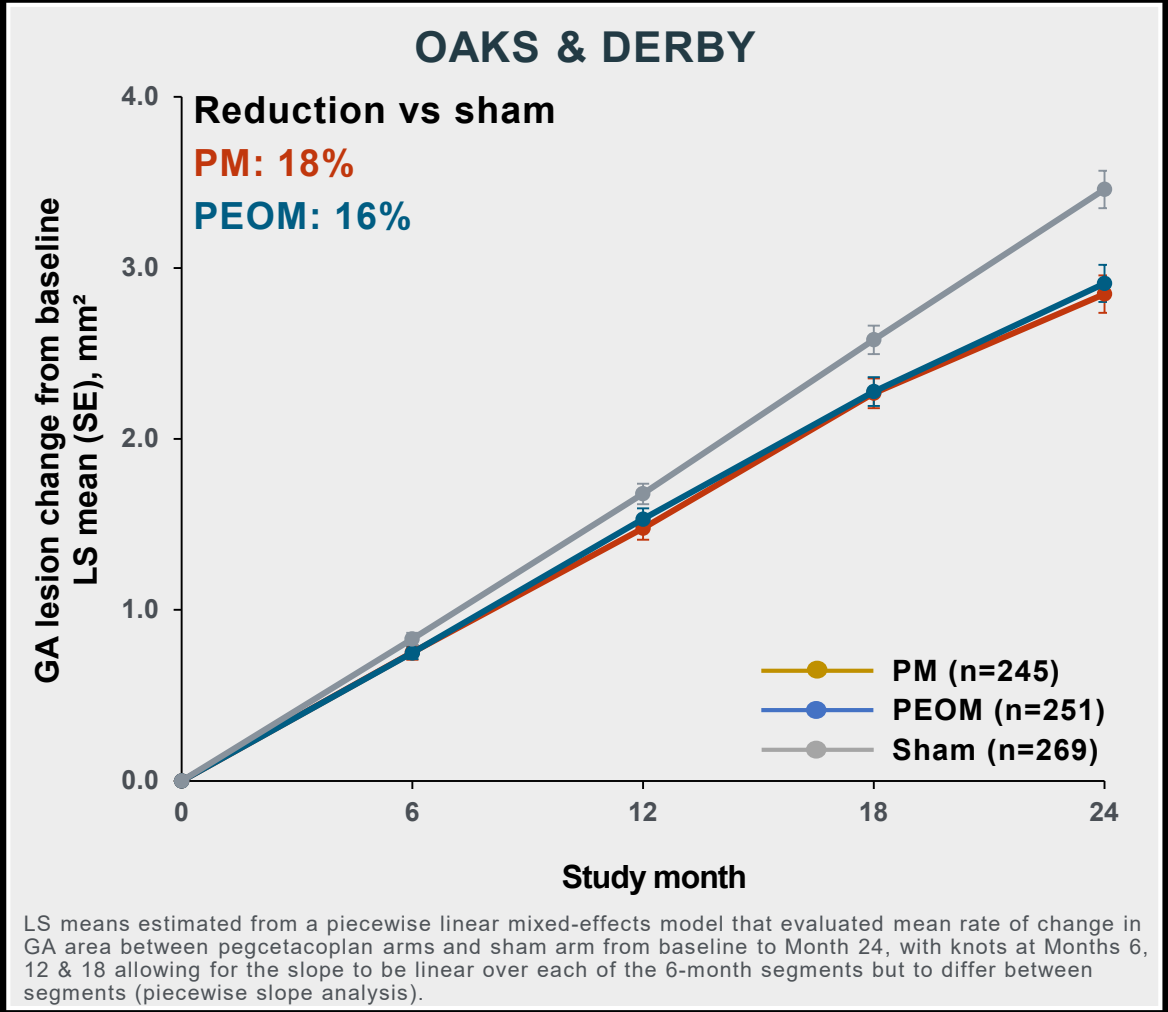


2.44 mm² (PM) & 1.94 mm² (PEOM) of Retinal Tissue Preserved Over 36 Months

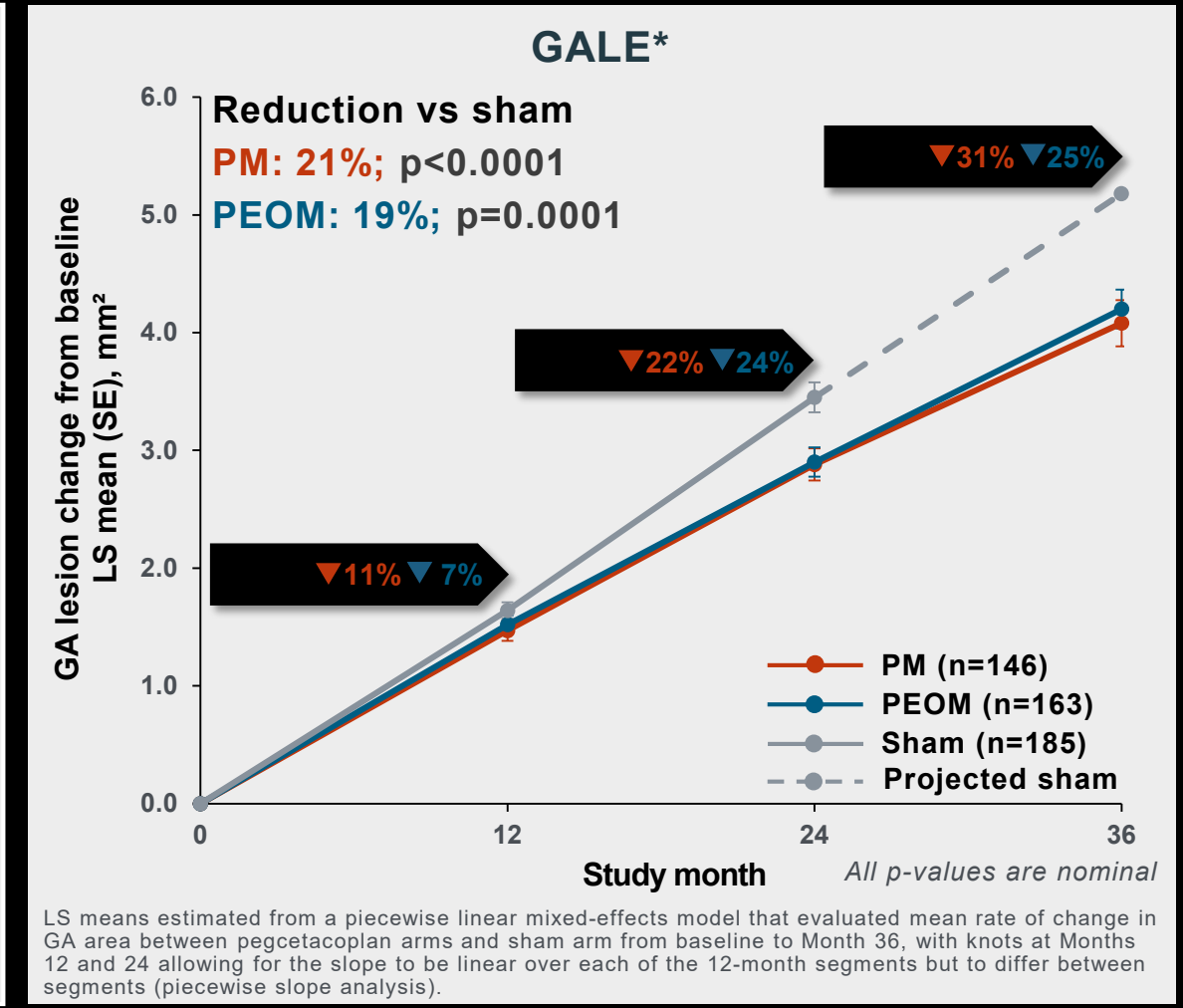
[a]Estimated based on macular RPE density[1] range of 5082 cells/mm² to 7728 cells/mm².
LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each 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 & 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.
1. Ach T, et al. *Invest Ophthalmol Vis Sci*. 2014;55:4832–4841.

Subfoveal GA

OAKS, DERBY & GALE: Subfoveal GA
Reductions in GA Growth Over 24 & 36 Months with Continuous Pegcetacoplan



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 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis).



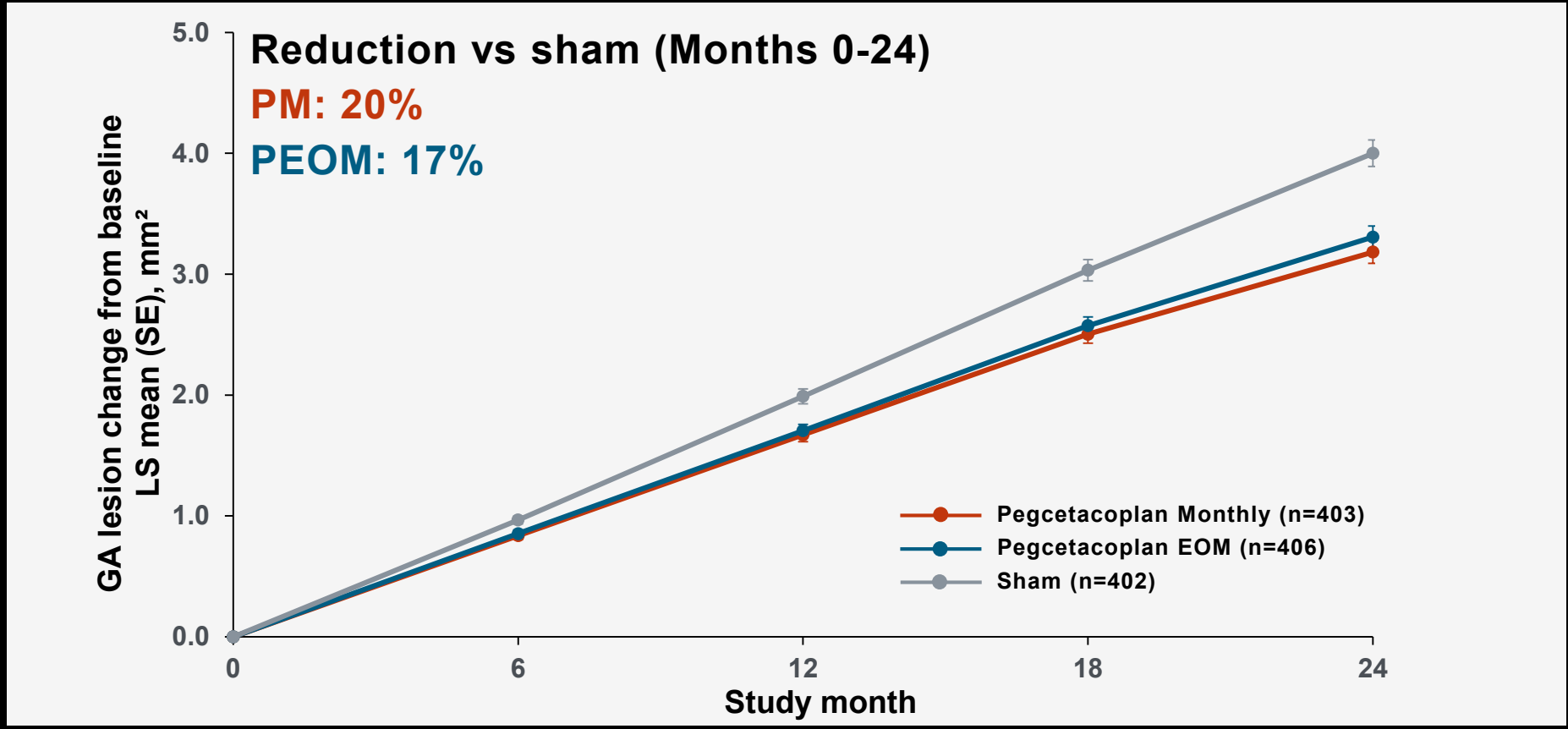
LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis).

*Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each 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 & DERBY.

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

Total Population

OAKS & DERBY Total Population (Nonsubfoveal + Subfoveal): Pegcetacoplan Reduced GA Growth Through Month 24

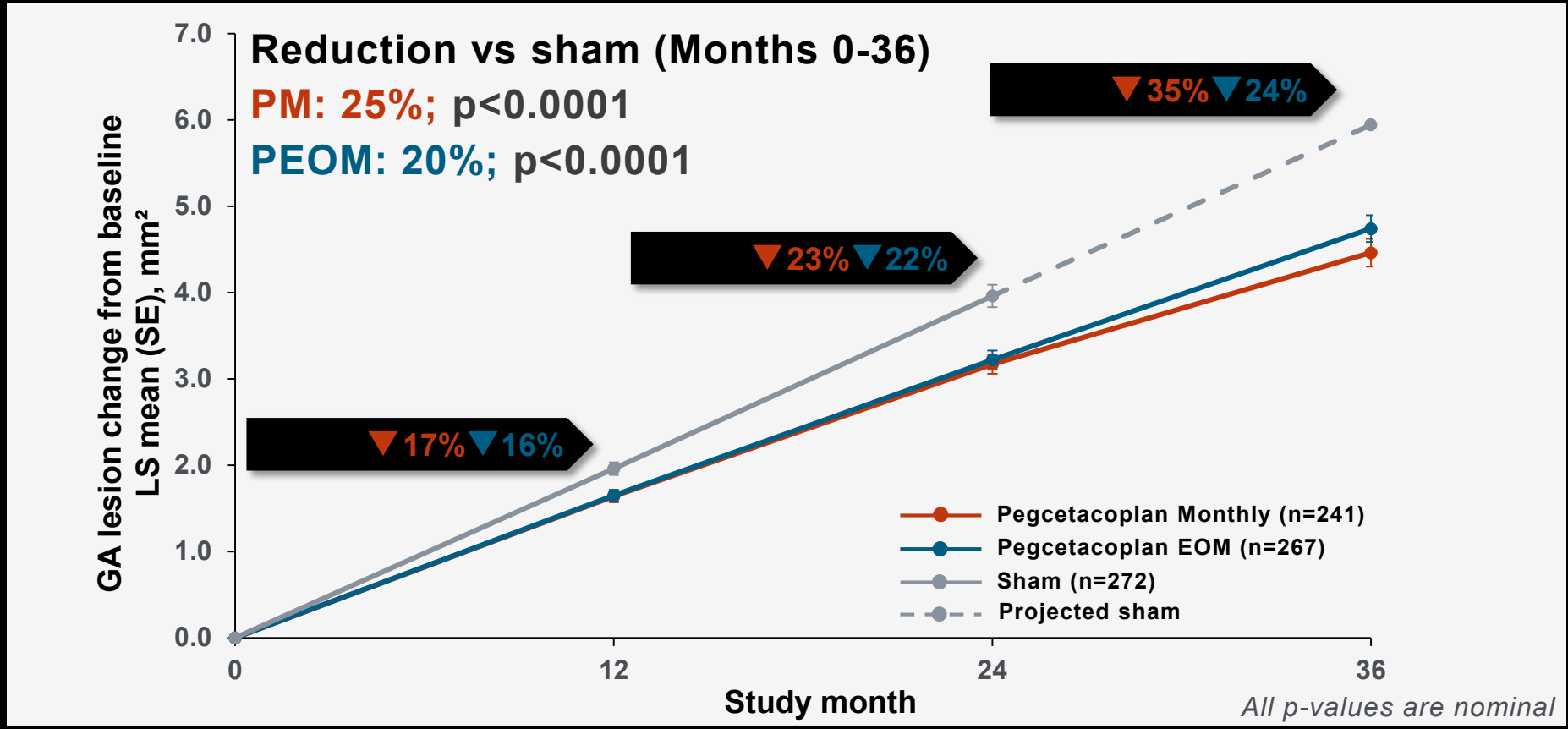


Similar Reductions in GA Growth with PM and PEOM Dosing

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 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). Analysis performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups who had their first postbaseline GA lesion assessment after month 12.

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

GALE Total Population (Nonsubfoveal + Subfoveal): Reductions in GA Growth Rate Following 36 Months of Continuous Pegcetacoplan Increased Over Time

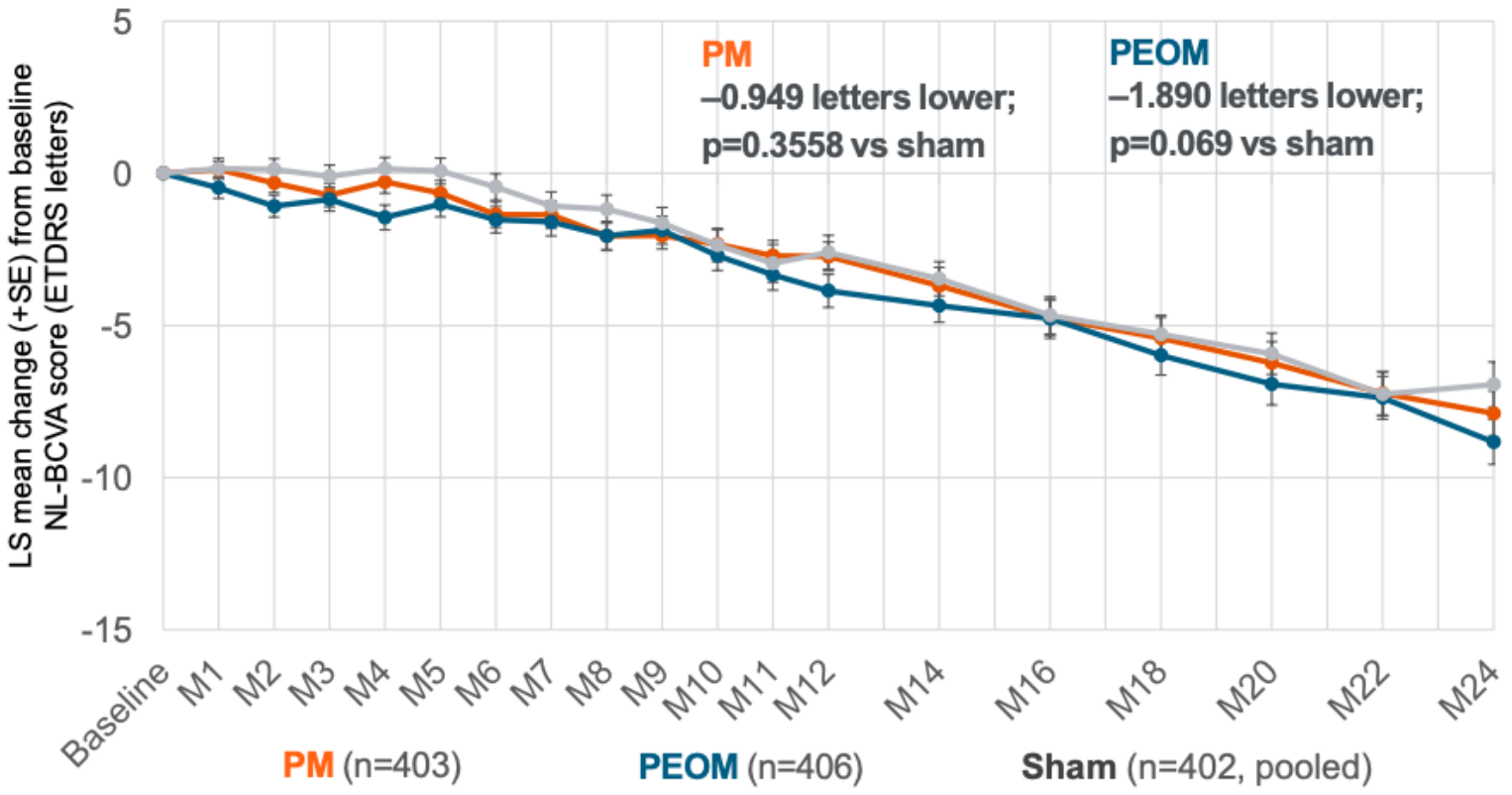


1.49 mm² (PM) & 1.21 mm² (PEOM) of Retinal Tissue Preserved Over 36 Months

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 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each 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 & 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.

OAKS and DERBY combined

BCVA in the study eye over 24 months



Visual function endpoints:

No statistically significant differences across study arms on key secondary endpoints at 24 months

- BCVA
- Maximum reading speed
- Functional Reading Independence Index
- Microperimetry: Mean threshold sensitivity (OAKS only)

In nonsubfoveal subgroup, lesion distance to foveal center at baseline was larger in sham pooled (370 microns) than in PM (337 microns) and PEOM (340 microns)

LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye. BCVA=best-corrected visual acuity; ETDRS=Early Treatment of Diabetic Retinopathy Study; GA=geographic atrophy; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; NL=normal luminance; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

TEAEs in OAKS and DERBY Over 24 Months

	OAKS			DERBY		
	PM (N=213)	PEOM (N=212)	Sham pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham pooled (N=206)
All TEAEs, n (%)	192 (90.1%)	187 (88.2%)	175 (82.9%)	178 (86.4%)	180 (86.5%)	169 (82.0%)
Ocular TEAEs in study eye, patients, n (%)	133 (62.4%)	123 (58.0%)	98 (46.4%)	125 (60.7%)	108 (51.9%)	95 (46.1%)
Non-ocular TEAEs, patients, n (%)	174 (81.7%)	165 (77.8%)	154 (73.0%)	163 (79.1%)	142 (68.3%)	146 (70.9%)
Serious ocular TEAEs in the study eye, n (%) M	5 (2.3%) 7	4 (1.9%) 4	1 (0.5%) 1	4 (1.9%) 4	2 (1.0%) 4	2 (1.0%) 2
Endophthalmitis	2 (0.9%) 2	3 (1.4%) 3	0	0	0	0
Optic ischemic neuropathy	2 (0.9%) 2	0	0	1 (0.5%) 1	0	0
Retinal detachment	1 (0.5%) 1	1 (0.5%) 1	0	0	0	0
Uveitis	0	0	0	0	2 (1.0%) 2	0
Vitritis	0	0	0	2 (1.0%) 2	0	0
Visual acuity reduced	0	0	1 (0.5%) 1	0	1 (0.5%) 1	0
Papilledema	1 (0.5%) 1	0	0	0	0	0
Iridocyclitis	0	0	0	0	1 (0.5%) 1	0
Retinal tear	0	0	0	1 (0.5%) 1	0	0
Dry AMD	0	0	0	0	0	1 (0.5%) 1
Macular hole	0	0	0	0	0	1 (0.5%) 1
Hyphema	1 (0.5%) 1	0	0	0	0	0

Safety set. Note that n indicated the number of patients. M indicates cumber of events. The events of endophthalmitis include infectious and noninfectious endophthalmitis. Sham patients do not receive injections. PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; TEAE = treatment-emergent adverse event. Singh R, et al. Presented at: AAO 2022; September 30-October 3, 2022; Chicago, IL. Wycoff C, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

New-onset eAMD in Study Eye at Months 12 and 24: OAKS and DERBY Combined

OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)[b]	Sham Pooled (N=417)
New-onset investigator-determined eAMD in study eye, n (%)	**51 (12.2%)**	**28 (6.7%)**	**13 (3.1%)**
Confirmed by reading center, N (%) At time of investigator-reported eAMD, 100% of patients had available SD-OCT and 82% had available FA for reading center evaluation	**37 (8.8%)**	**23 (5.5%)**	**11 (2.6%)**
Reading center-determined CNV cases on protocol-specified FA, not reported as AEs by investigators, n (%)	9 (2.1%)	4 (1.0%)	8 (1.9%)

- Patients who developed eAMD continued treatment with study drug and received on-label anti-VEGF therapy at the discretion of the investigator
- No patients in the pegcetacoplan study arms discontinued the studies due to eAMD

CNV = choroidal neovascularization; eAMD = exudative age-related macular degeneration; FA = fluorescein angiography; SD-OCT = spectral-domain optical coherence tomography; VEGF = vascular endothelial growth factor. Singh R, et al. Presented at: AAO 2022; September 30-October 3, 2022; Chicago, IL; Wycoff C, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

Avacincaptad pegol

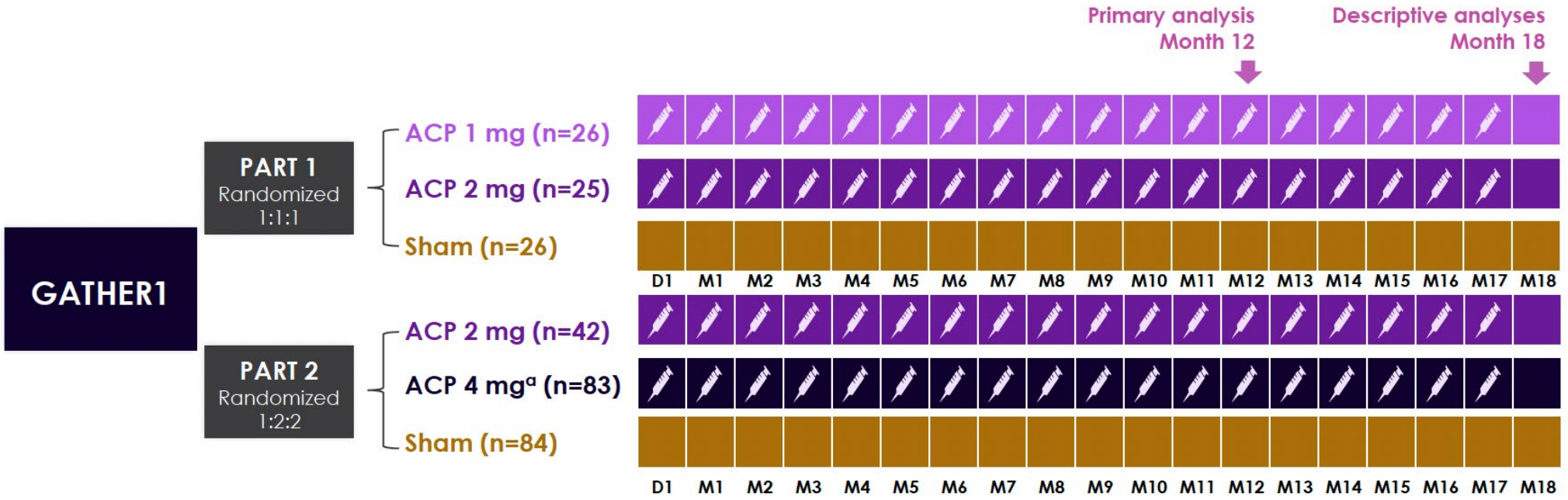
Avacincaptad pegol (Izervay, Iveric Bio)

- Pegylated cyclic peptide inhibitor of complement C5
- Approved in August 2023 for geographic atrophy; shown to slow tissue loss
- Treatment consists of intravitreal injections

https://www.astellas.com/en/news/28281

Jaffe G et al. Ophthalmology 2021

GATHER1 Study



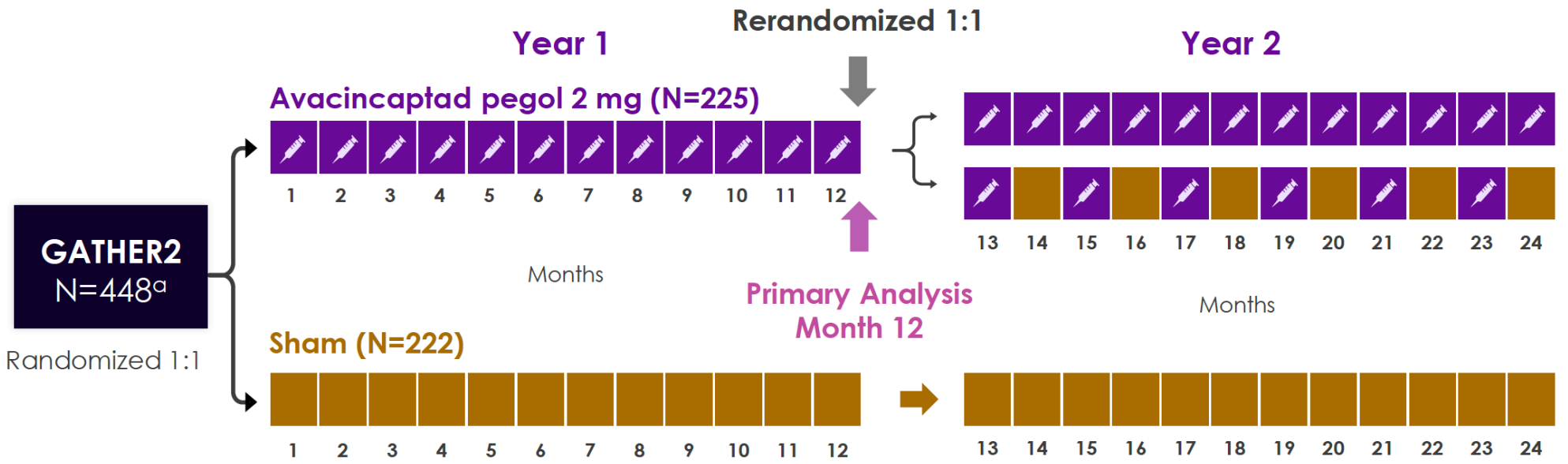
Primary Endpoint/Analysis

Mean change in GA area from baseline to Month 12 (square root transformation)

[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.

Jaffe G et al. Ophthalmology 2021

GATHER2



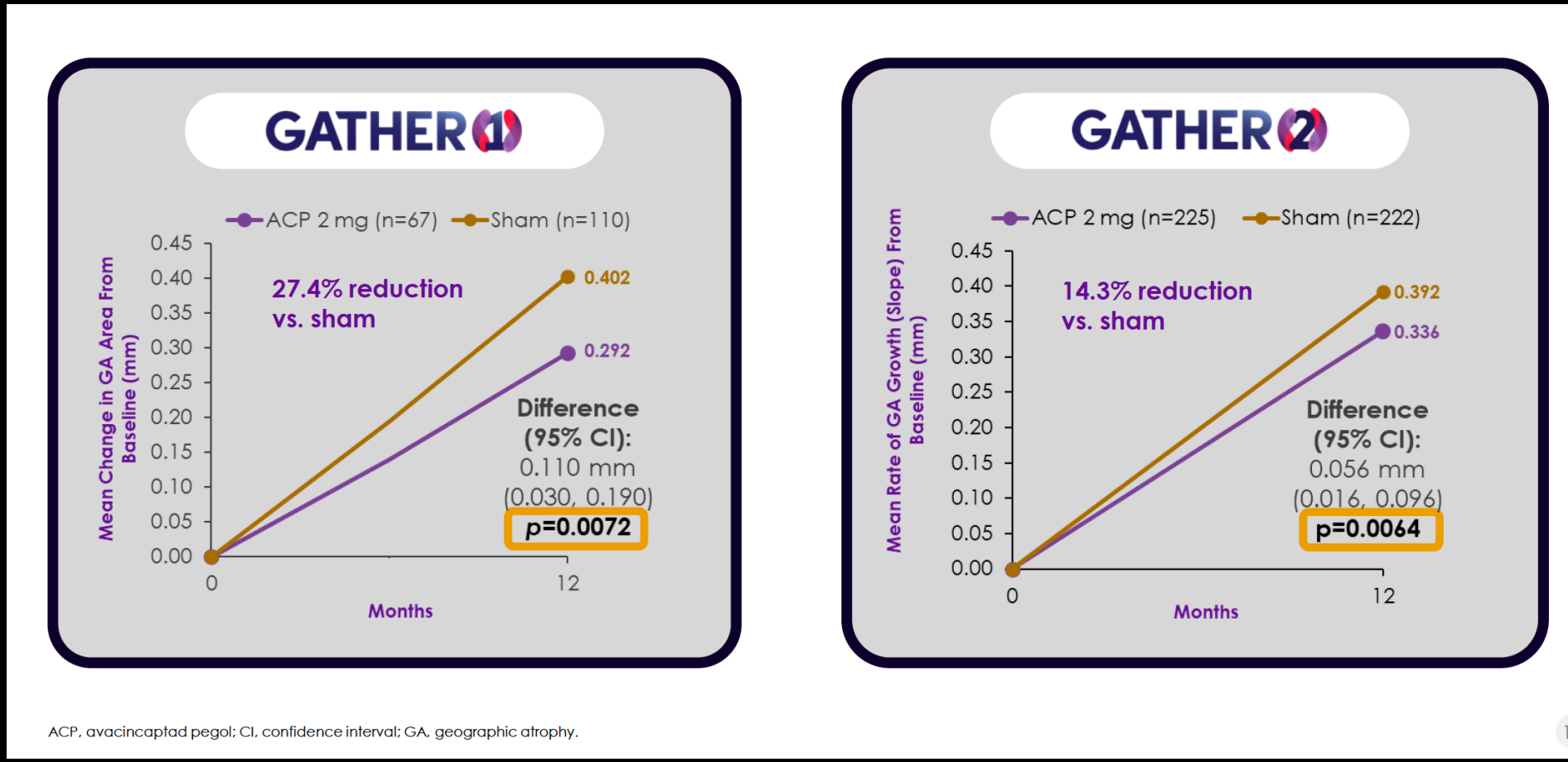
Primary Endpoint/Analysis

Mean rate of growth (slope) in geographic atrophy area from baseline to month 12 (square root transformation)

[a]448 randomized, with 447 treated (one patient in sham not receiving treatment after randomization).
Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022.

Khanani AM et al. Retina Society 2022

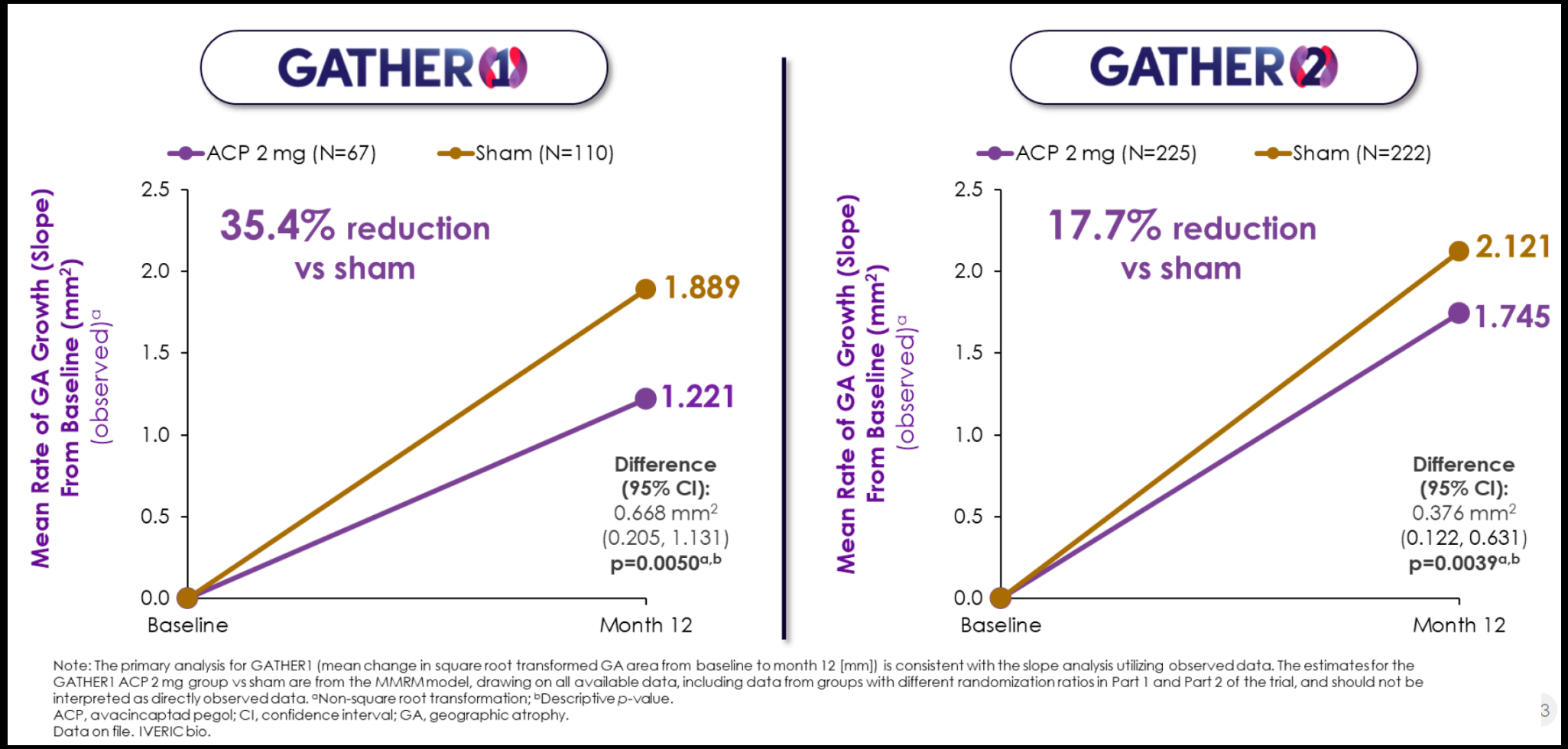
Pre-specified primary endpoint met in GATHER1 and GATHER2



ACP, avacincaptad pegol; CI, confidence interval; GA, geographic atrophy.

Khanani AM et al. Retina Society 2022

Mean Rate of Observed GA Growth (Slope Analysis) Reduced in GATHER1 and GATHER2



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. [a]Non-square root transformation; [b]Descriptive *p*-value.
ACP, avacincaptad pegol; CI, confidence interval; GA, geographic atrophy.
Data on file. IVERIC bio.

Khanani AM et al. Retina Society 2022

Safety in GATHER1 and GATHER2

Ocular TEAEs, n (%)	GATHER2 12 months[1] ACP 2 mg (N=225)	GATHER2 12 months[1] Sham (N=222)	GATHER1 12 months[2,3,a] ACP 2 mg (N=67)	GATHER1 12 months[2,3,a] Sham (N=110)
Conjunctival hemorrhage	27 (12.0)	17 (7.7)	10 (14.9)	13 (11.8)
Punctate keratitis	11 (4.9)	14 (6.3)	4 (6.0)	8 (7.3)
Conjunctival hyperemia	12 (5.3)	13 (5.9)	3 (4.5)	4 (3.6)
Choroidal neovascularization	**15 (6.7)**	**9 (4.1)**	**6 (9.0)**	**3 (2.7)**
Dry eye	8 (3.6)	8 (3.6)	0	2 (1.8)
Eye pain	9 (4.0)	6 (2.7)	2 (3.0)	3 (2.7)
Vitreous detachment	7 (3.1)	6 (2.7)	2 (3.0)	5 (4.5)
Visual acuity reduced	3 (1.3)	5 (2.3)	2 (3.0)	4 (3.6)
Vision blurred	6 (2.7)	2 (0.9)	1 (1.5)	2 (1.8)
Visual impairment	6 (2.7)	2 (0.9)	0	0
Intraocular pressure increased	**21 (9.3)**	**2 (0.9)**	**4 (6.0)**	**1 (0.9)**
Vitreous floaters	6 (2.7)	1 (0.5)	1 (1.5)	1 (0.9)
Visual acuity reduced transiently	6 (2.7)	1 (0.5)	---	---
Blepharitis	6 (2.7)	0	0	1 (0.9)
Ocular hypertension	5 (2.2)	0	---	---

[a]Both ACP and sham groups are a combination of Part 1 and Part 2.
Note: N = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once; --- indicates data not collected.
ACP, avacincaptad pegol; TEAE, treatment emergent adverse event.
1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio. 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

Kaiser PK et al. Retina Society 2022

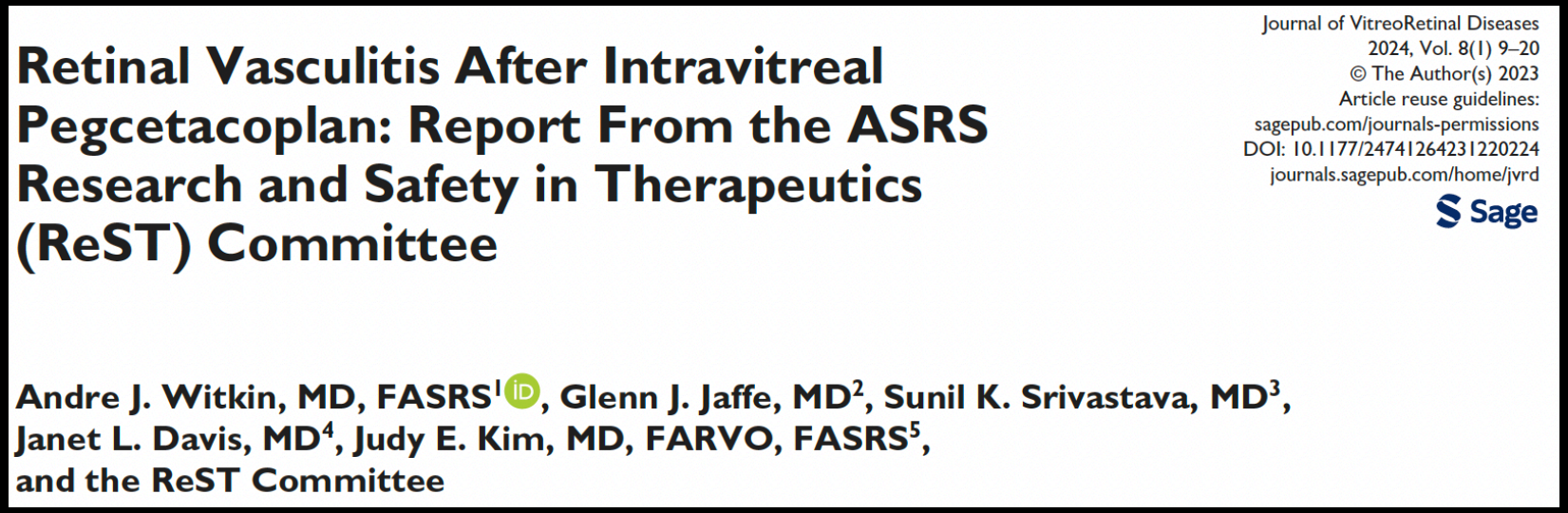
Safety in GATHER1 and GATHER2

	GATHER2 12 months[1]		GATHER1 12 months[2,3,a,b]	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Intraocular inflammation, n	0	0	1 (1.5)	0
Endophthalmitis, n	0	0	0	0
Ischemic optic neuropathy, n	0	0	0	0

[a]Both ACP and sham groups are a combination of Part 1 and Part 2.
[b]There was 1 case of ischemic optic neuropathy in the ACP 2 mg group in GATHER1 at 18 months.
ACP, avacincaptad pegol.
1. Heier JS, et al. Presented at: AAO; September 30-October 3, 2022; Chicago, IL; 2. Data on file. IVERIC bio; 3. Jaffe GJ, et al. Ophthalmology. 2021;128(4):576-586.

Kaiser PK et al. Retina Society 2022

Safety Concerns with GA Treatment



Retinal Vasculitis After Intravitreal Pegcetacoplan: Report From the ASRS Research and Safety in Therapeutics (ReST) Committee

Journal of VitreoRetinal Diseases
2024, Vol. 8(1) 9–20

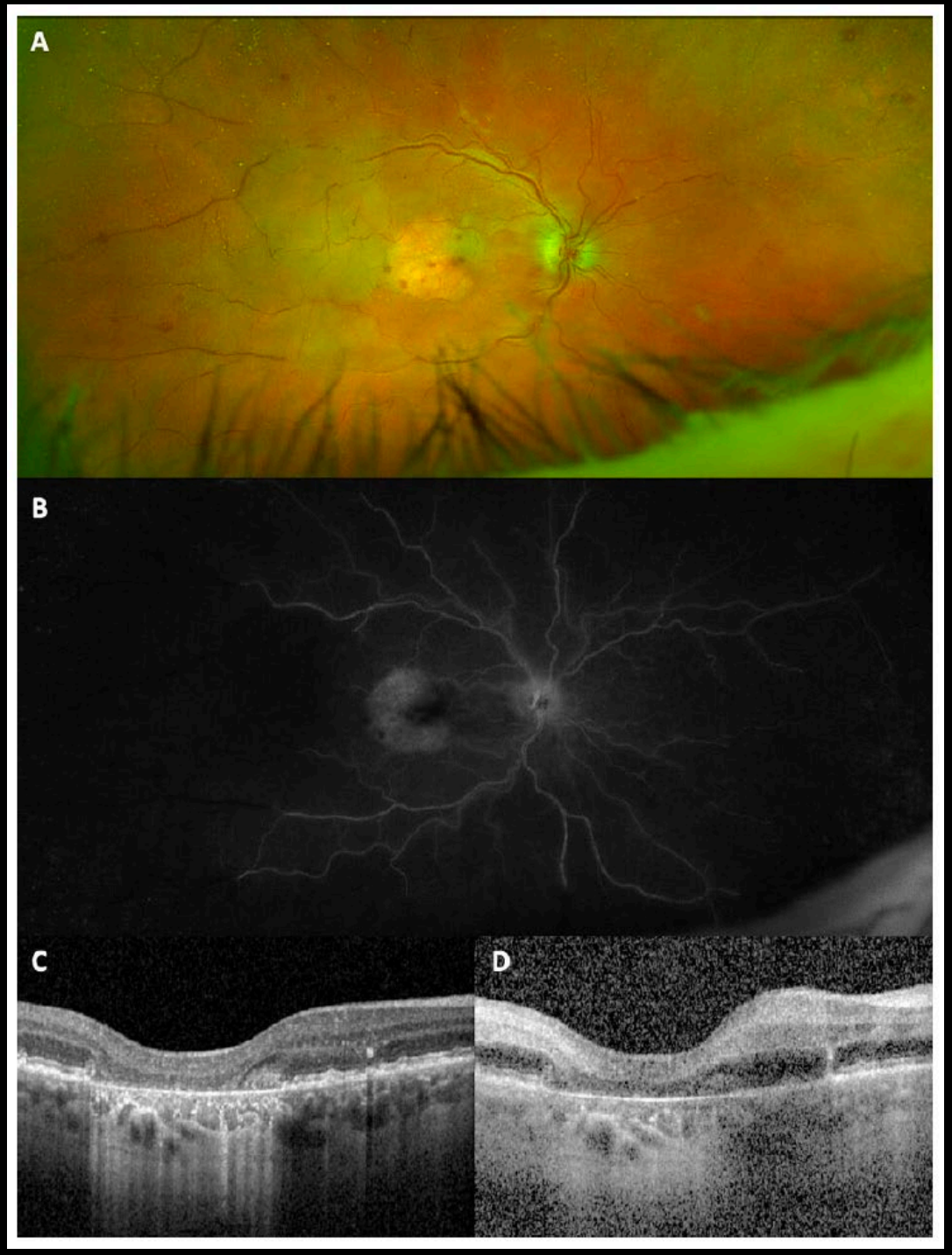
DOI: 10.1177/24741264231220224
journals.sagepub.com/home/jvrd
Sage

Andre J. Witkin, MD, FASRS[1], Glenn J. Jaffe, MD[2], Sunil K. Srivastava, MD[3], Janet L. Davis, MD[4], Judy E. Kim, MD, FARVO, FASRS[5], and the ReST Committee

- Retrospective review of post-marketing cases of retinal vasculitis following intravitreal pegcetacoplan reported to the ASRS ReST committee
  - Also reviewed by uveitis experts
- 14 eyes of 13 patients confirmed to have retina vasculitis, all following first injection
  - Occlusive retinal vasculopathy was confirmed in 11 eyes (79%)
- Patients presented a median of 10.5 days after injection

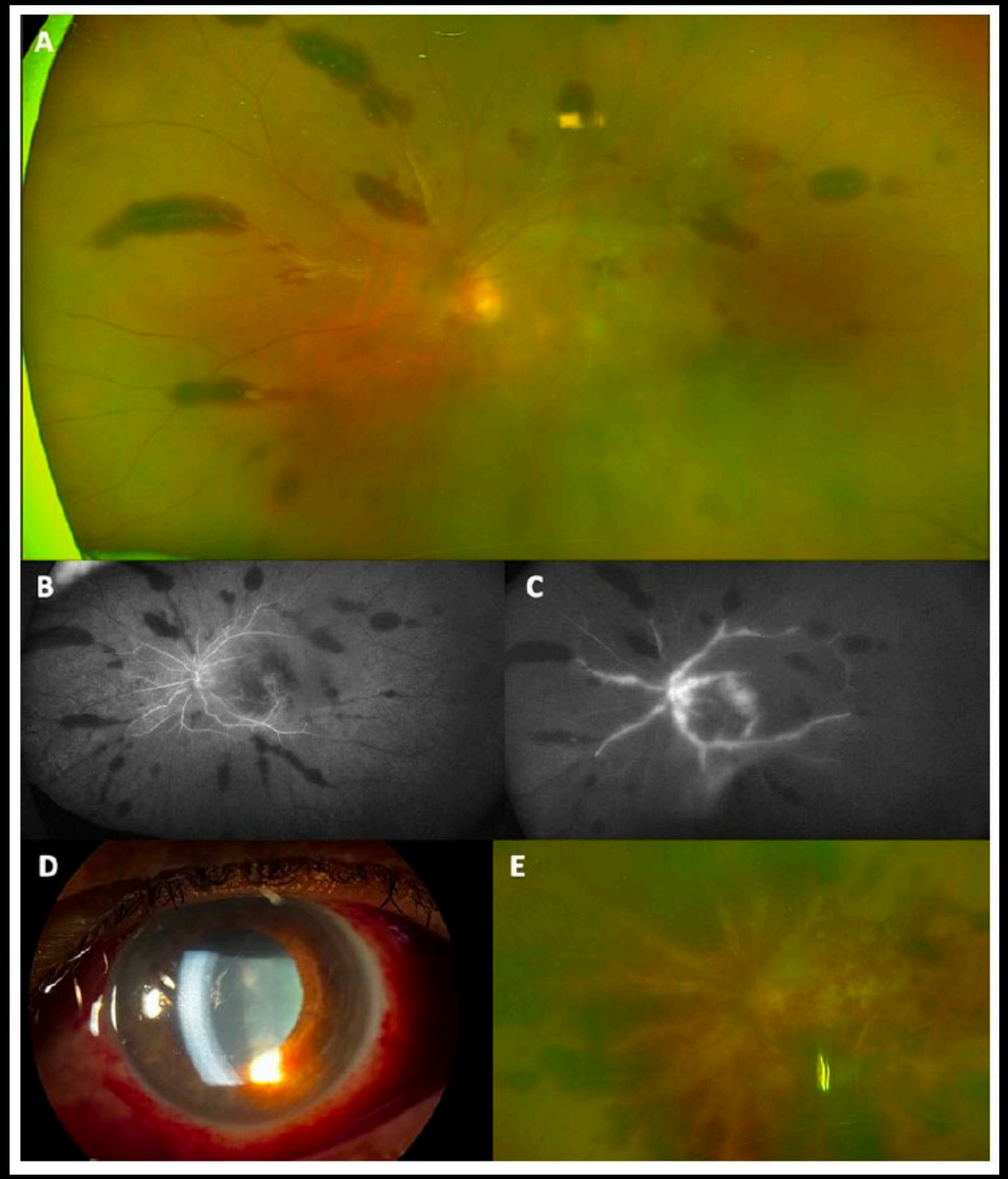
Witkin AJ et al. *JVRD* 2023

70-year old man with bilateral GA received pegcetacoplan in the right eye and developed blurry vision, eye pain, and redness in the right eye 10 days later with VA CF (from 20/30)



Witkin AJ et al. *JVRD* 2023

67-year old with bilateral GA received pegcetacoplan in the left eye and developed pain and decreased vision 10 days later with VA 20/400 (from 20/100)



Witkin AJ et al. *JVRD* 2023

Safety Concerns from ReST Report

- Visual outcomes
  - Median VA at baseline was 20/60, 20/300 at vasculitis presentation, and 20/200 at last follow-up
  - Eight eyes (57%) had more than a 3-line decrease in VA
  - 6 eyes (435) had more than a 6-line decrease in VA from baseline to follow-up, including 2 eyes that were enucleated
- Conclusions
  - Report states that there is currently no known etiology for vasculitis and optimum treatment strategies unknown
  - Infectious etiologies should be considered, and corticosteroid treatments may hasten resolution of inflammatory findings
  - Continued treatment of affected patients were pegcetacoplan should be avoided

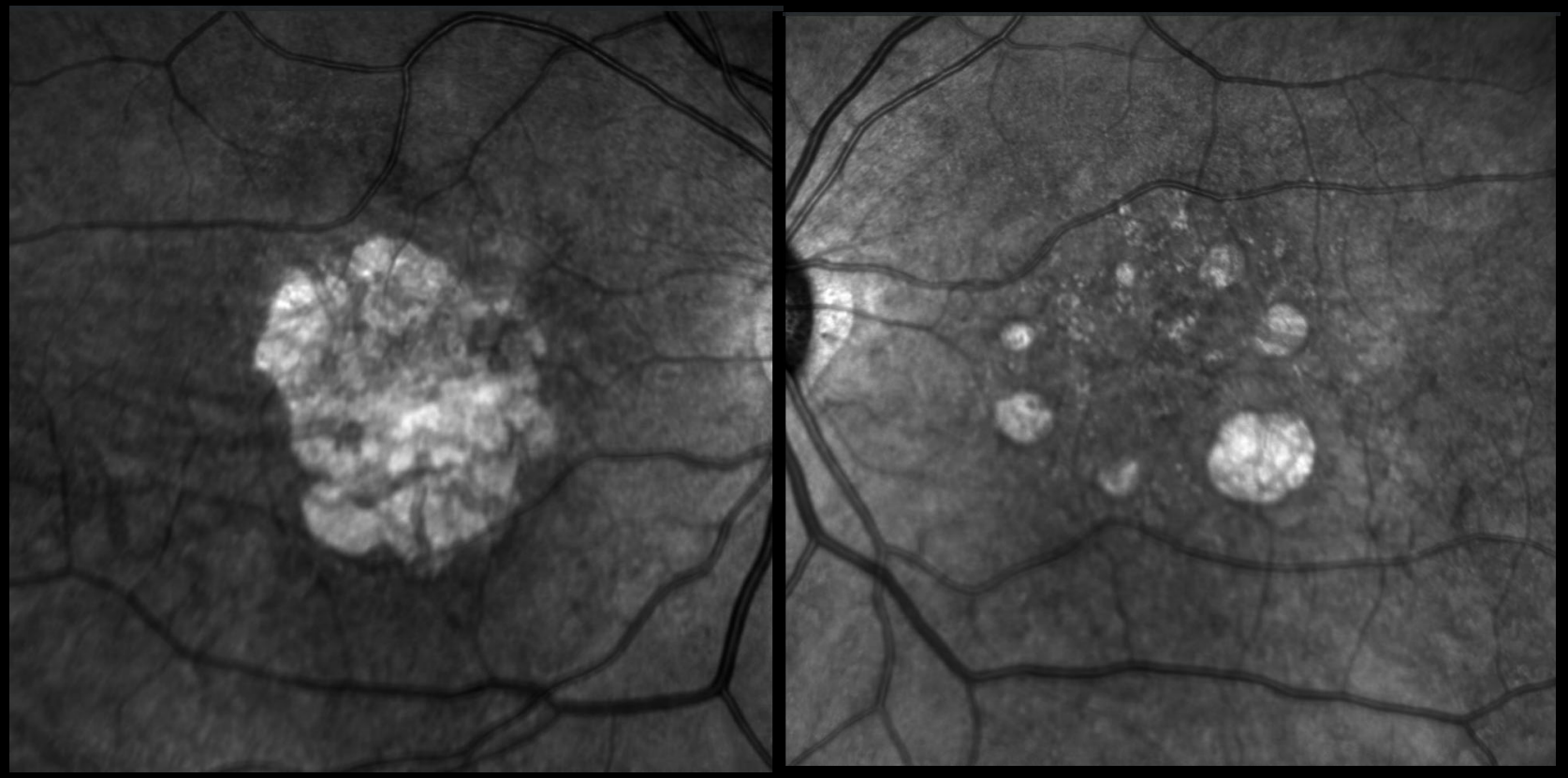
Witkin AJ et al. *JVRD* 2023

What Do GA Treatment Look Like?

- Intravitreal injections every 1 to 2 months
  - OCT every visit, likely fundus imaging every 6 months
  - Can be burdensome to patient and caregivers
- Important to understand that goal is to slow tissue loss
  - Patients will continue to get worse, even if treatment is “working”
  - No metrics in clinic to show that patient is improving (unlike OCT for neovascular AMD)
- Discussion of risks with patient
  - Endophthalmitis, conversion to neovascular AMD, inflammation/vasculitis

Who Are Ideal Candidates for GA Treatment?

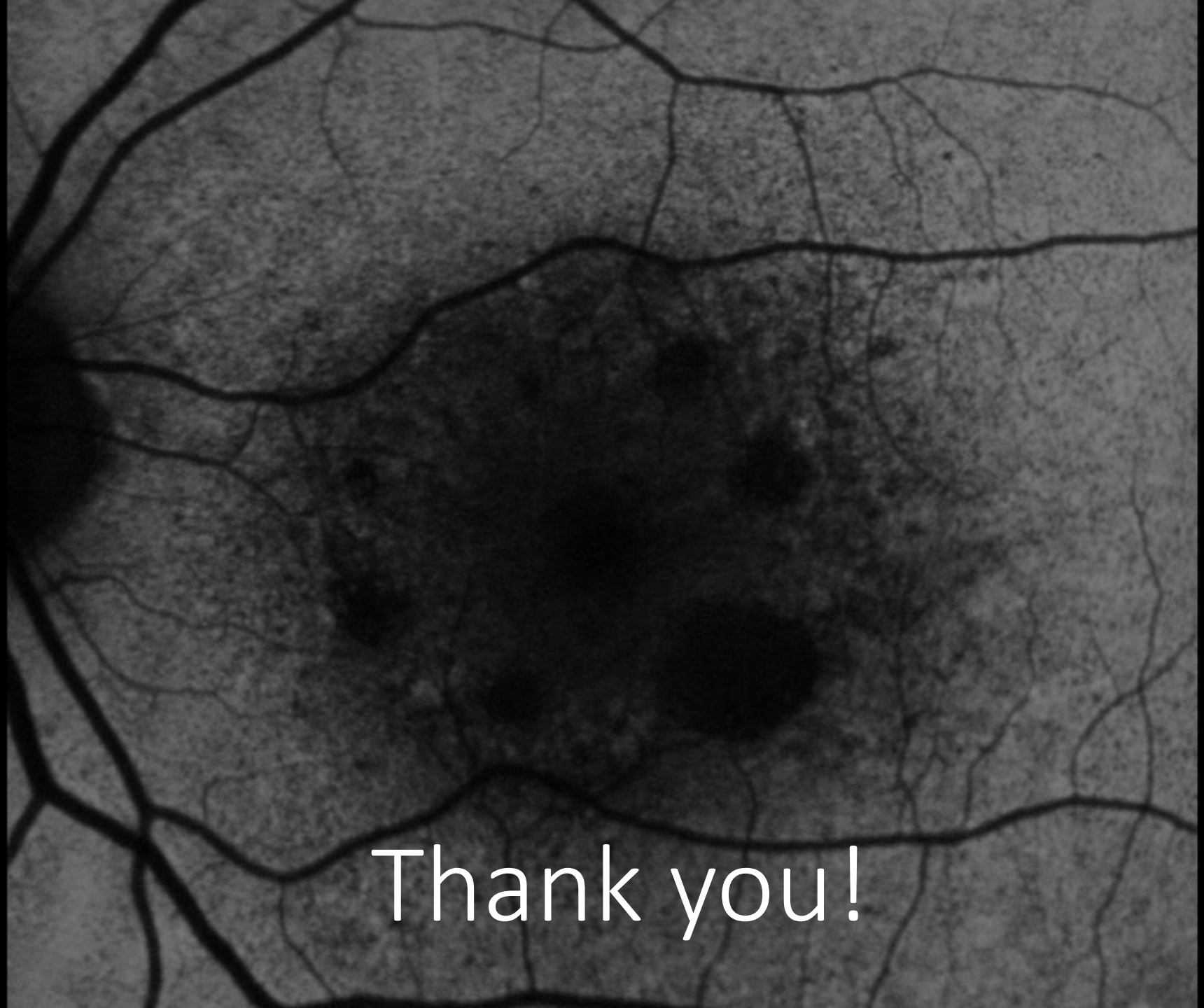
- Should there be a vision criteria?
- Extrafoveal GA in one eye, center-involving in fellow eye
- Early extrafoveal GA, strong family history
- Patients on anti-VEGF injections for neovascular AMD with progressive atrophy?



61 yo patient with center-involving GA OD and extra foveal GA OS

Conclusions

- AMD is a progressive disease that can result in irreversible vision loss, including from exudative AMD and GA
  - Careful review of multimodal imaging is critical to help monitor for complications as well to help with prognostication and risk stratification
- Effective treatments are needed to reduce individual and societal burdens
  - Coupled with an aging population and an increasing prevalence of disease
- New therapeutic options are emerging
  - Intravitreal injections for GA
  - Important to have a nuanced conversation with patients regarding expectations and risks to starting injections



Thank you!