



GA Treatment: Now & in the future

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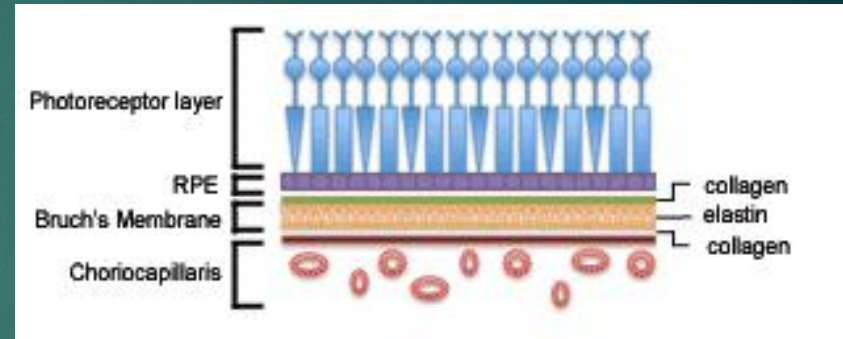
Financial Disclosures

Kori Elkins, MD, FASRS: none

Brandon Runyon, OD, FAAO: none

Normal Anatomy Refresher

- ▶ The PR layer approximates the RPE which overlies the double layered Bruch's membrane and underneath lies the choriocapillaris and choroid
- ▶ As we age, Bruch's membrane tends to accumulate debris in the elastin lamina and also drusen form between the collagen layer and RPE basal lamina
- ▶ Aging is also associated with thinning and breakdown of the central elastin layer within Bruch's membrane
- ▶ This allows blood vessels in the choriocapillaris a potential inlet to grow through



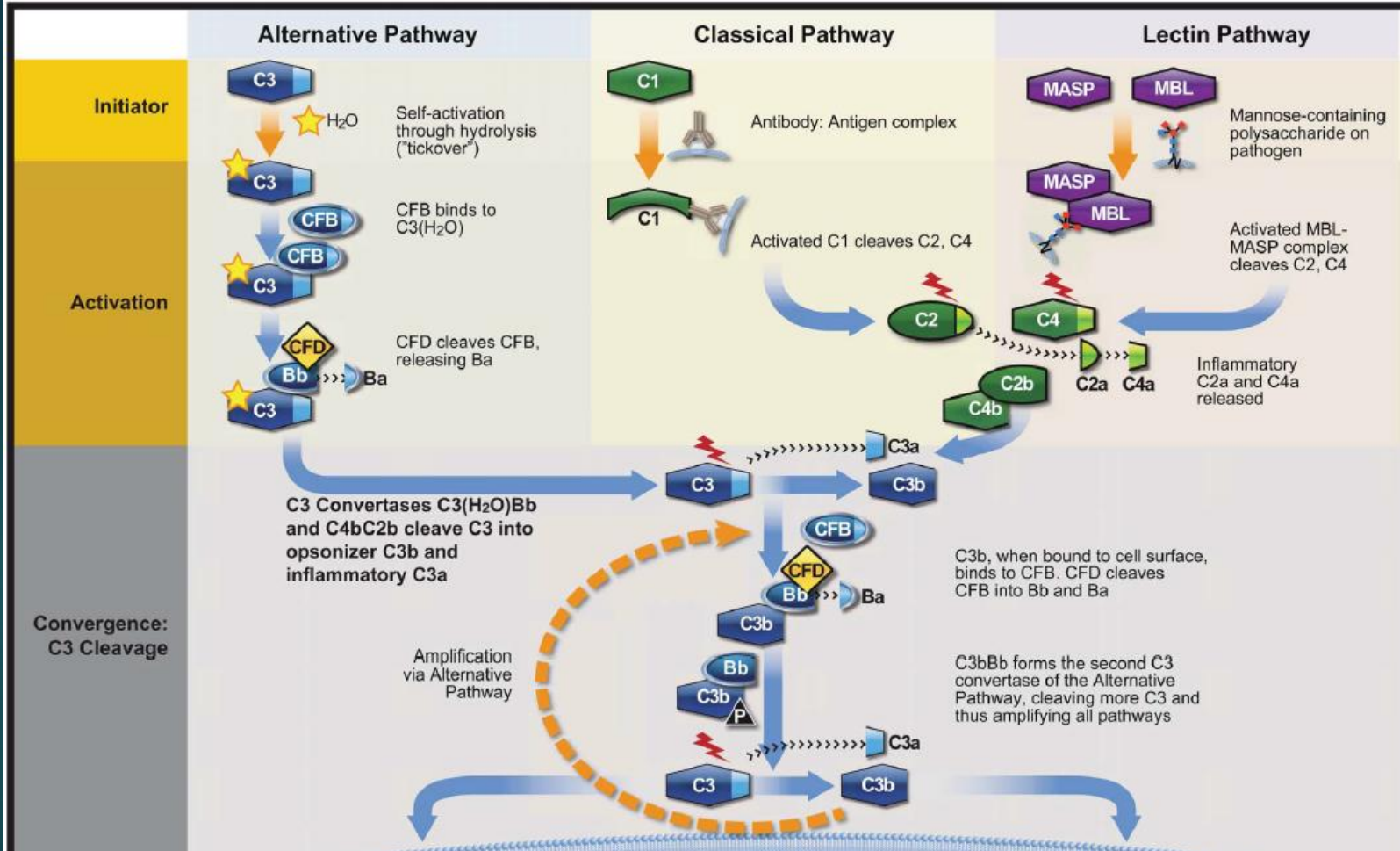
Pathophysiology of GA

Pathophysiology of GA

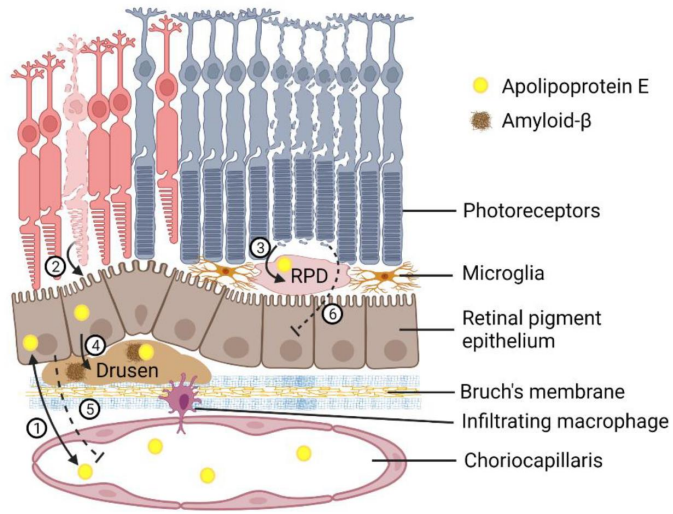
- ▶ Intrinsic and extrinsic stressors of poorly regenerative RPE
 - ▶ Oxidative stress due to high metabolic demand of photoreceptors
 - ▶ Photo-oxidation (constant stimulation by light producing free radicals)
 - ▶ Environmental stressors (i.e. cigarette smoke)
 - ▶ Patient specific factors: age, poor diet, increased BMI, genetic polymorphisms
- ▶ Increasing vs. cumulative damage → drusen and lipofuscin → accumulated components trigger inflammation → GA

Complement System Activation

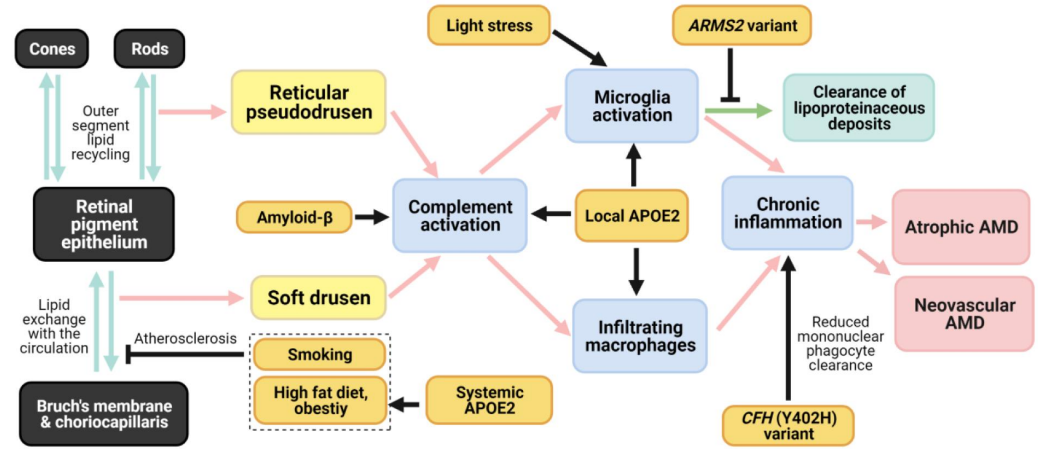
- ▶ Antigen-antibody complexes (IgM / IgG) → Classical Complement System
- ▶ Mannose-binding lectin (MBL) → Lectin Complement System
- ▶ Low level spontaneous hydrolysis of C3 → Alternative Complement System → amplifies C1



(a)



(b)



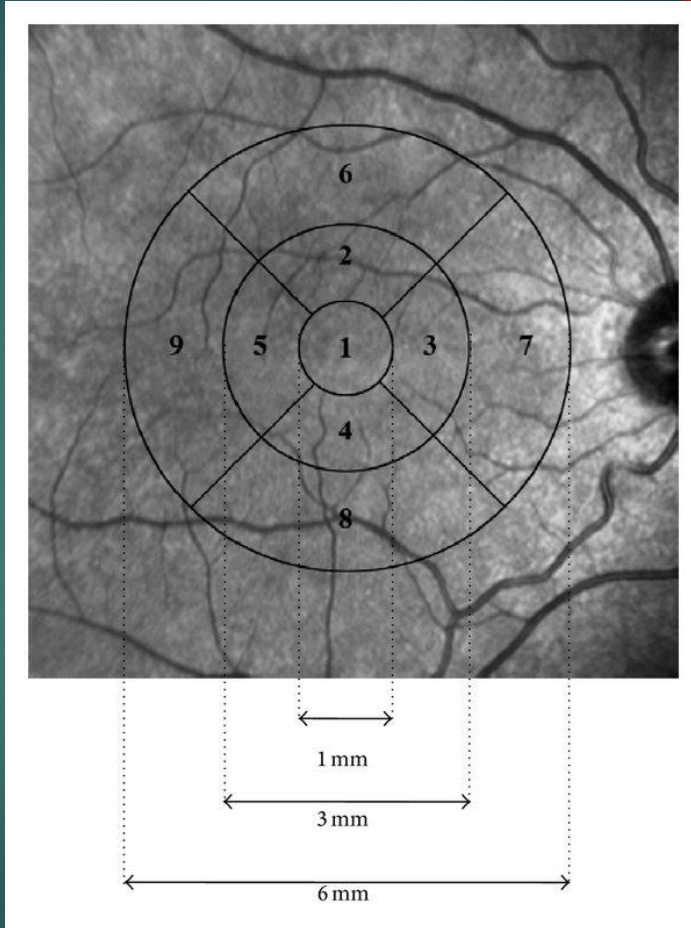
Hu ML, Quinn J, Xue K. Interactions between Apolipoprotein E Metabolism and Retinal Inflammation in Age-Related Macular Degeneration. *Life*. 2021; 11(7):635. <https://doi.org/10.3390/life11070635>

Defining GA

- ▶ Multiple systems have defined GA with various size constraints and there is no international consensus
 - ▶ Wisconsin Age-Related Maculopathy Grading system defines the minimum area of RPE loss to “qualify” as GA is 175 microns in size
 - ▶ Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) specified a diameter $>250\ \mu\text{m}$ for definition of GA
 - ▶ AREDS2 study defined minimum diameter as $433\ \mu\text{m}$
- ▶ Additionally, GA can be foveal involving or extrafoveal/juxtafoveal

ETDRS Grid Sizing

- ▶ The retinal veins as they exit the optic nerve head are between 125 - 140 microns in width
- ▶ The optic nerve, on average, measures 1500 microns



AMD: Extra/juxtafoveal GA



AMD: Foveal-involving GA



Historical Treatment Paradigm

- ▶ AREDS (Age Related Eye Disease Study) Vitamins
 - ▶ Intermediate AMD or advanced AMD in only one eye had a 25% lower risk of progressing to advanced AMD in one or both eyes, when treated with zinc plus antioxidants
 - ▶ Patients categorized as having no or early AMD did not show a benefit with the high dose supplementation
- ▶ AREDS2 formulation are as follows:
 - ▶ 500 milligrams (mg) of vitamin C
 - ▶ 400 international units (IU) of vitamin E
 - ▶ 10 mg lutein
 - ▶ 80 mg of zinc oxide
 - ▶ 2 mg of copper (as cupric oxide) – to prevent copper deficiency anemia from zinc intake
- ▶ Smoking is the most important modifiable risk factor to prevent/reduce morbidity from AMD so smoking cessation should be discussed
 - ▶ For active or former smokers AREDS (original) increases the risk of lung cancer

Which AREDS/AREDS2 formula is right for me?

Consult your doctor or eye care professional about which supplement, if any, is right for you.

Commercially available formulas based on AREDS/AREDS2

Nutrient	AREDS formula*	AREDS2 fomula
Vitamin C	500 mg	500 mg
Vitamin E	400 IU	400 IU
Beta-carotene	15 mg	-
Copper (cupric oxide) **	2 mg	2 mg
Lutein	-	10 mg
Zeaxanthin	-	2 mg
Zinc	80 mg	80 mg

*Not recommended for current or former smokers

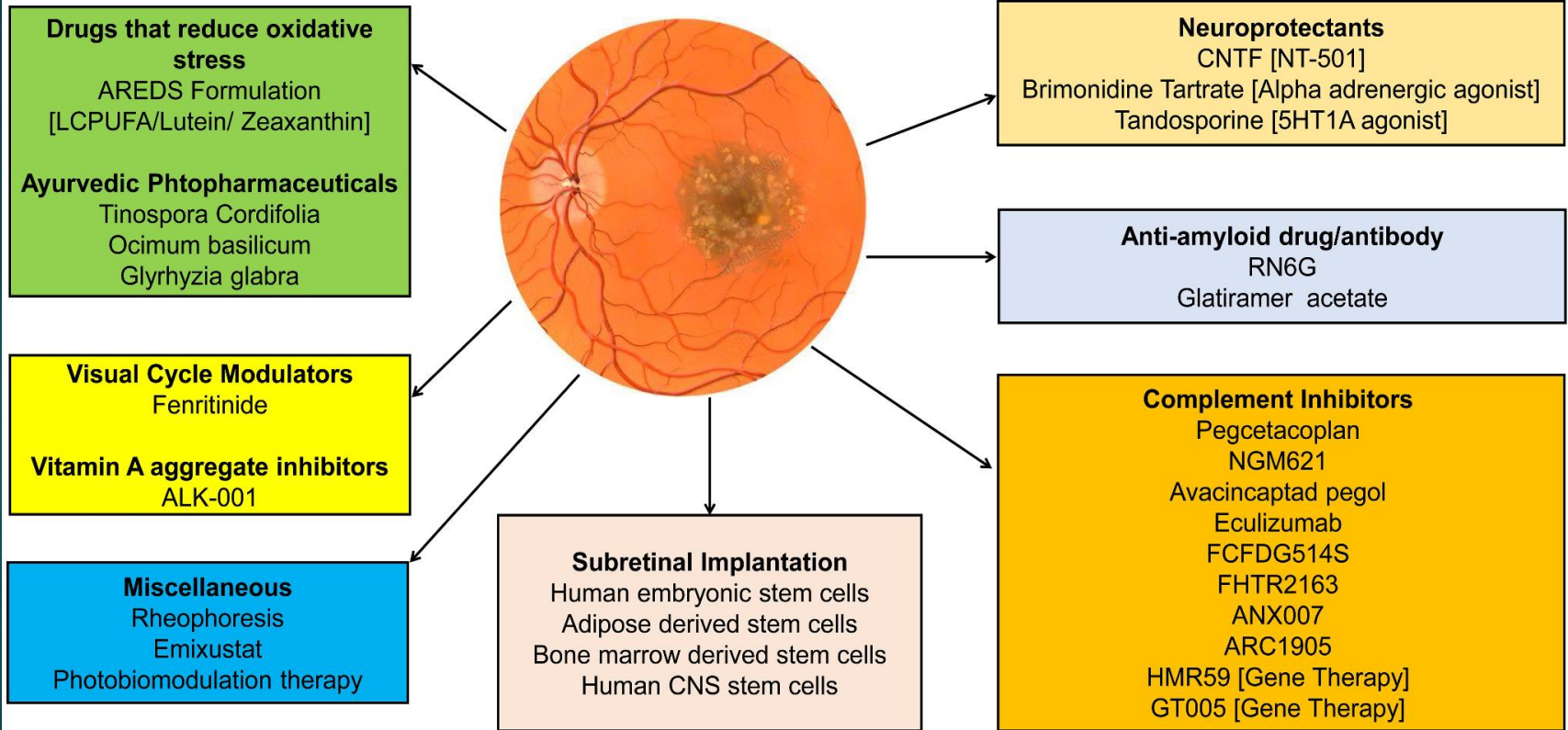
**Added to avoid zinc-related copper deficiency

mg = milligrams

IU = international units

Source: National Eye Institute
AREDS/AREDS2 FAQ's

HUMAN RETINA WITH AGE RELATED MACULAR DEGENERATION AND DRUSEN DEPOSITS



Geographic Atrophy Trials



- ▶ There are currently around 20 NIH registered studies evaluating geographic atrophy treatments
- ▶ Many studies never make it past phase I for various reasons
 - ▶ Lack of efficacy
 - ▶ Complications limiting use
- ▶ European/Asian studies are not registered through NIH

Geographic Atrophy Trials

Treatment Modality	Trial Name
Complement System	FILLY (Phase 2): NCT02503332 CATALINA (Phase 2): NCT04465955 OPH2001 (Phase 2): NCT00950638 OPH2003/GATHER1 (Phase 2/3): NCT02686658 GATHER2 (Phase 3): NCT04435366 DERBY (Phase 3): NCT03525613 OAKS (Phase 3): NCT03525600 GALE (Phase 3): NCT04770545
Neuroprotective Agents	Brimonidine IVT Implant (Phase 2): NCT00658619 BEACON (Phase 2): NCT02087085
Ocular Gene Therapy	HMR-1001 (Phase 1): NCT03144999 FOCUS (Phase 1/2): NCT03846193 EXPLORE (Phase 2): NCT04437368 HORIZON (Phase 2): NCT04566445
Stem Cell Therapy	OpRegen (Phase 1/2): NCT02286089

Geographic Atrophy Trials



Trial Name
FILLY (Phase 2): NCT02503332
CATALINA (Phase 2): NCT04465955
OPH2001 (Phase 2): NCT00950638
OPH2003/GATHER1 (Phase 2/3): NCT02686658
GATHER2 (Phase 3): NCT04435366
DERBY (Phase 3): NCT03525613
OAKS (Phase 3): NCT03525600
GALE (Phase 3): NCT04770545
Brimonidine IVT Implant (Phase 2): NCT00658619
BEACON (Phase 2): NCT02087085
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OpRegen (Phase 1/2): NCT02286089

Pegcetacoplan

NGM621 - humanized IgG1 antibody to C3

Avacincaptad pegol

Pegcetacoplan

400 mcg Brimonidine IVT implant

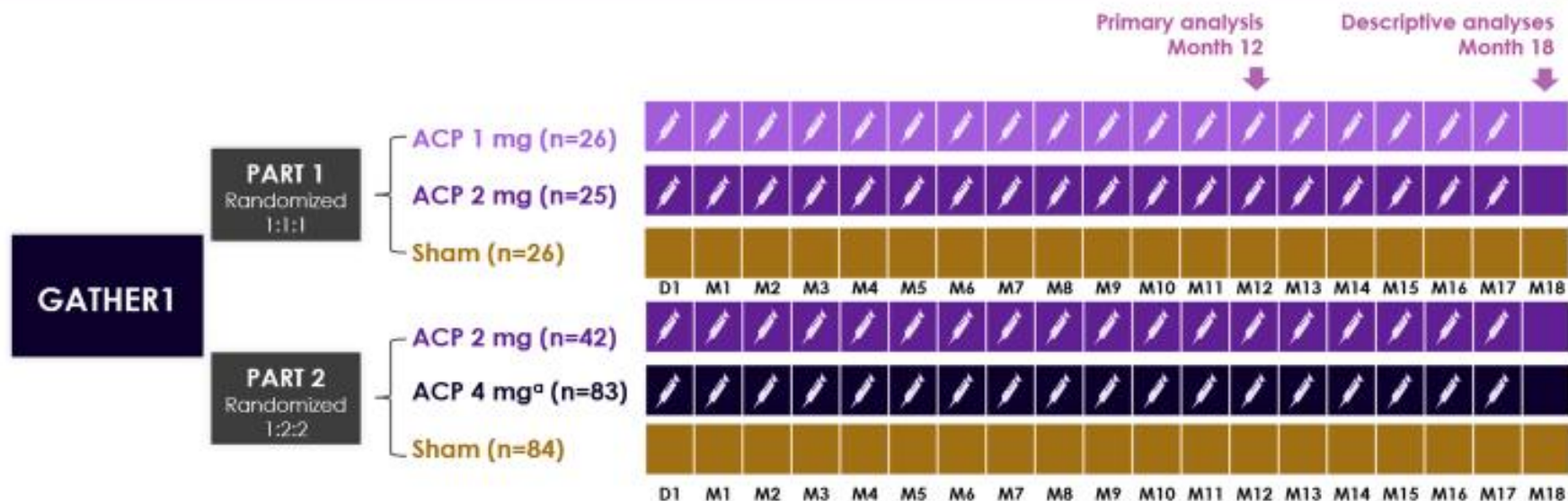
AAVCAGsCD59 - AAV2 gene tx for CD59 to block membrane attack complex (MAC)

GT005 - subretinal injection of AAV gene product to increase CFI

Subretinal delivery of allogenic RPE cells (OpRegen)

Avacincaptad pegol (Zimura)

- ▶ Avacincaptad pegol (known as Zimura) is a pegylated RNA aptamer that acts as a potent and specific inhibitor of complement C5
- ▶ Two part prospective, randomized, double-masked, sham-controlled phase 2/3 clinical trial
 - ▶ Part 1 - pts randomized in a 1:1:1 ratio to the following dose groups: avacincaptad pegol 1 mg, avacincaptad pegol 2 mg, and sham
 - ▶ Part 2 - 1:2:2 ratio to the following dose groups: avacincaptad pegol 2 mg, avacincaptad pegol 4 mg, and sham
- ▶ Primary efficacy endpoint was the mean rate of change in GA area over 12 months measured by FAF at 3 timepoints: baseline, month 6, and month 12
- ▶ Secondary endpoints included the mean change in BCVA (ETDRS letters) from baseline to month 12 and the mean change in low luminance BCVA (ETDRS letters) from baseline to month 12



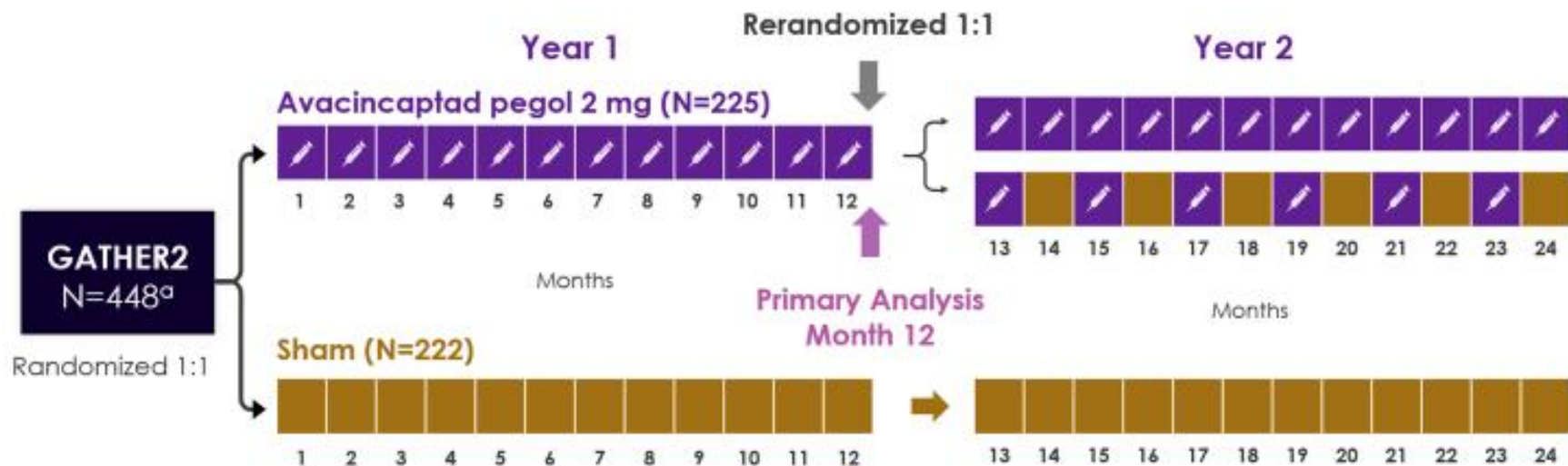
Primary Endpoint/Analysis

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

^a2 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.



Primary Endpoint/Analysis

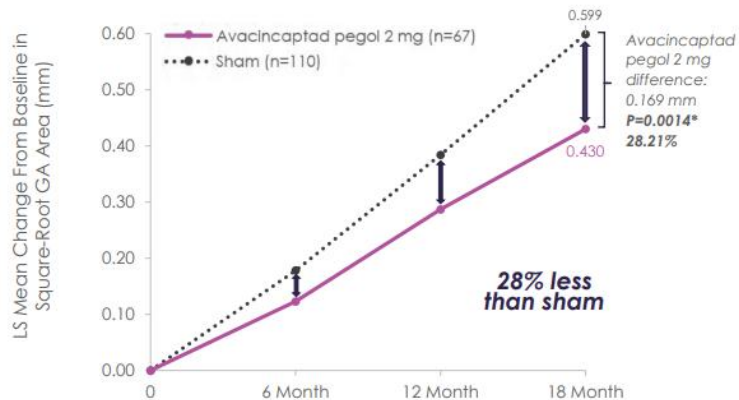
Mean rate of growth (slope) in geographic atrophy area from baseline to month 12 (square root transformation)

^a448 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.

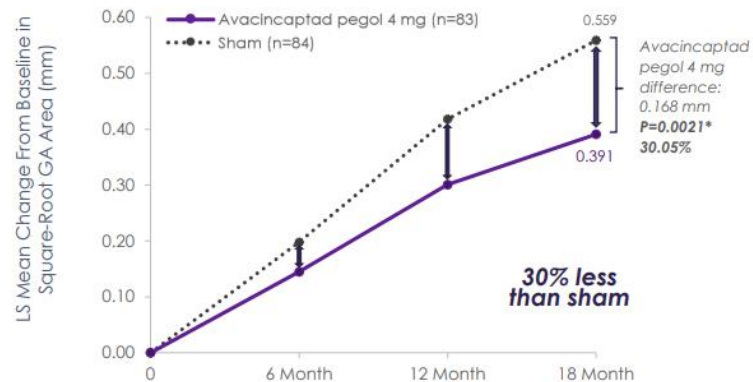
Avacincaptad pegol (Zimura)

MEAN CHANGE FROM BASELINE IN SQUARE-ROOT GA LESION AREA OVER 18 MONTHS

Avacincaptad pegol 2 mg vs sham



Avacincaptad pegol 4 mg vs sham



Based on LSMEANS from MRM model; ITT population Hochberg procedure was used for significance testing; prespecified and descriptive analysis. These least squares means are estimates of the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data. *18-month P values are descriptive in nature.

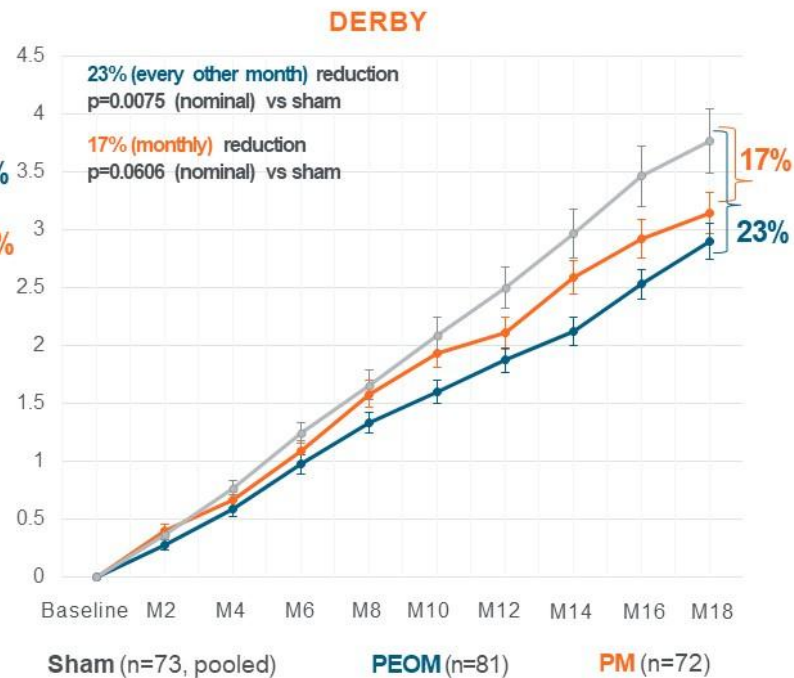
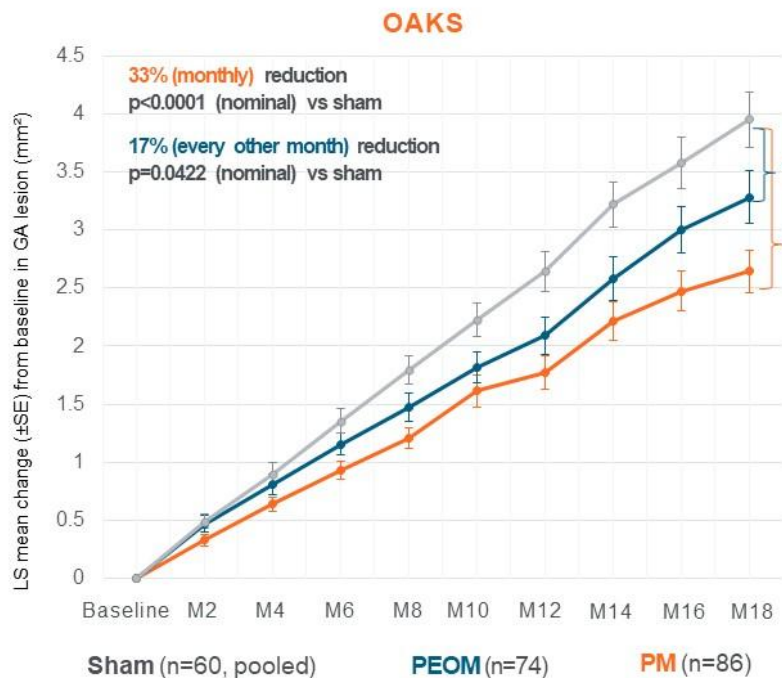
Pegcetacoplan (Syfovre)



Pegcetacoplan - Apellis



- ▶ Pegcetacoplan (Syfovre) is a pegylated complement C3 inhibitor peptide
- ▶ Approved for intravitreal injection given every 25-60 days



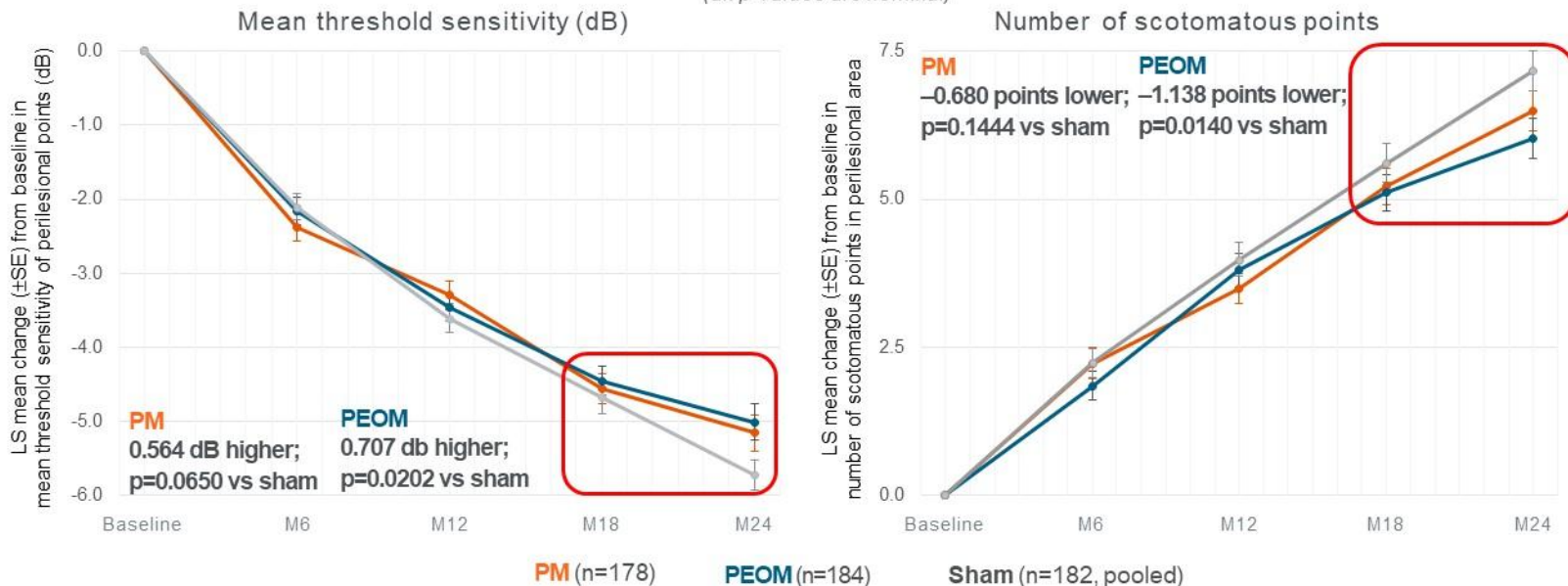
Extrafoveal is defined as lesion with distance >0 to foveal center point.

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Post hoc analyses of microperimetry data showed positive trends with both monthly and every-other-month pegcetacoplan near the GA lesion border

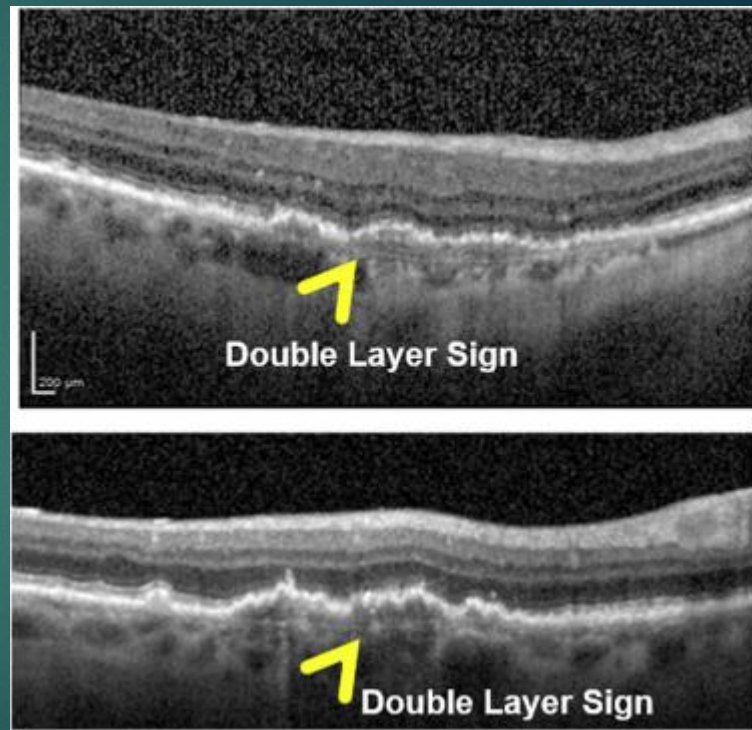
(all p-values are nominal)



LS means estimated from an MMRM. Subjects in the mITT population who had a baseline and at least one post-baseline value for perilesional mean threshold sensitivity or perilesional number of scotomatous points were included in the analysis. Perilesional area defined as $-250 \mu\text{m}$ inside baseline atrophy border to $+250 \mu\text{m}$ outside atrophy border. dB=decibel; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan - Apellis

- ▶ FALLY study (phase 2) showed around 10-11% of patients in the study developed nAMD
- ▶ All but 1 patient was in one of the two drug arms and 92% were in the monthly group
- ▶ Post-hoc analysis of entry OCTs showed evidence of a double-layer sign before developing nAMD
- ▶ Highlights the need for careful screening prior to starting therapy





Case Studies: Treat or Observe?

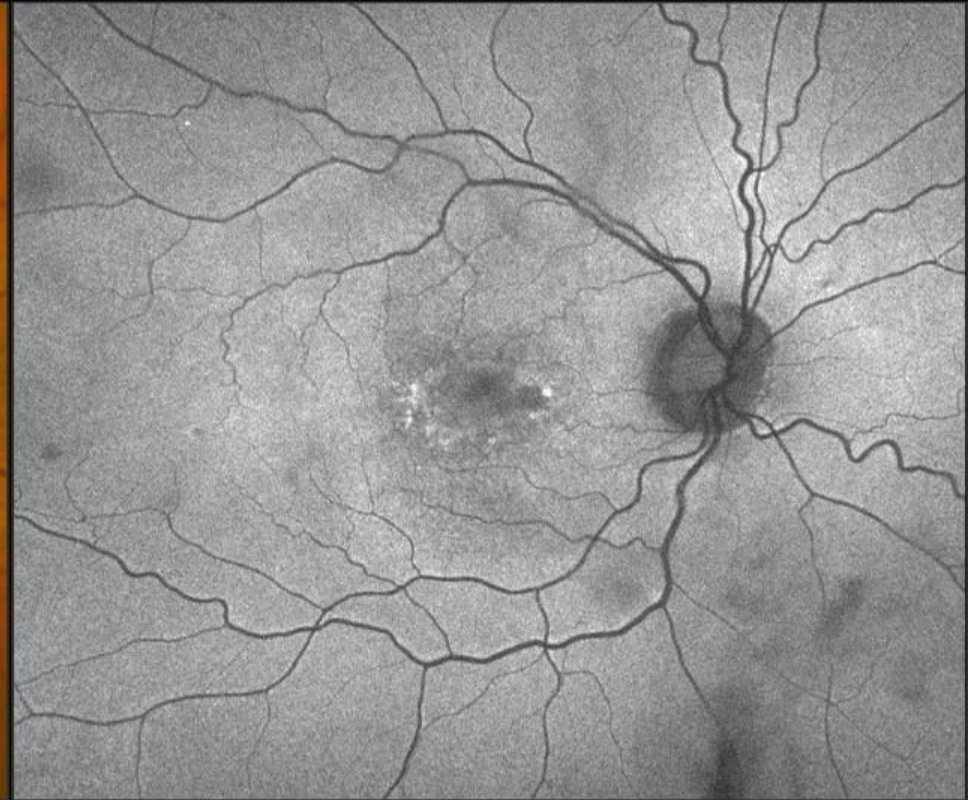
Case 1 - 67 YO WM

In 07/2019:

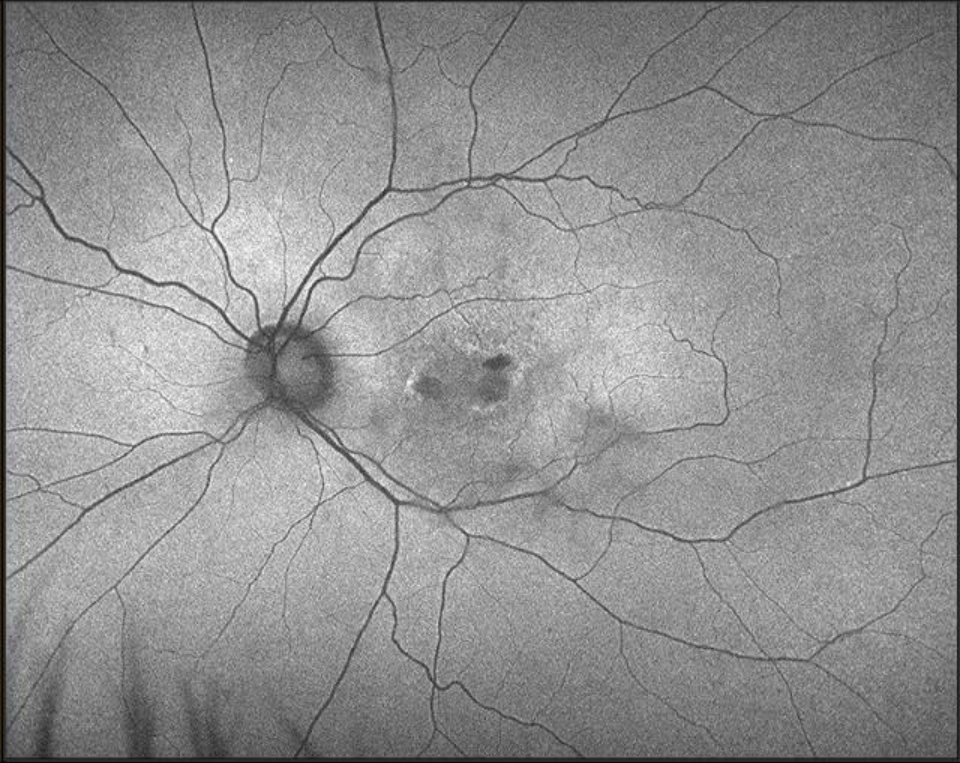
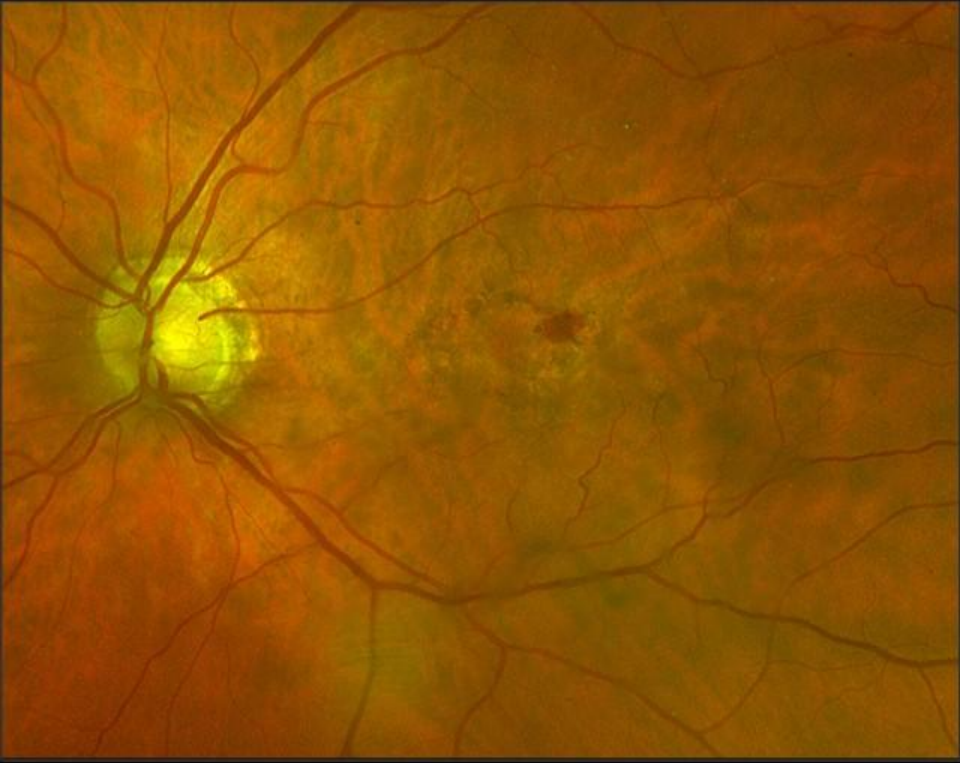
- ▶ Initially referred for wet AMD eval OS
- ▶ (+) Former smoker, (-) FHx of AMD/retinal disease/blindness
- ▶ Med Hx: HTN, Hyperlipidemia

- ▶ VA (cc): OD: 20/25
 OS: 20/50 PHNI

Case 1 - 67 YO WM



Case 1 - 67 YO WM



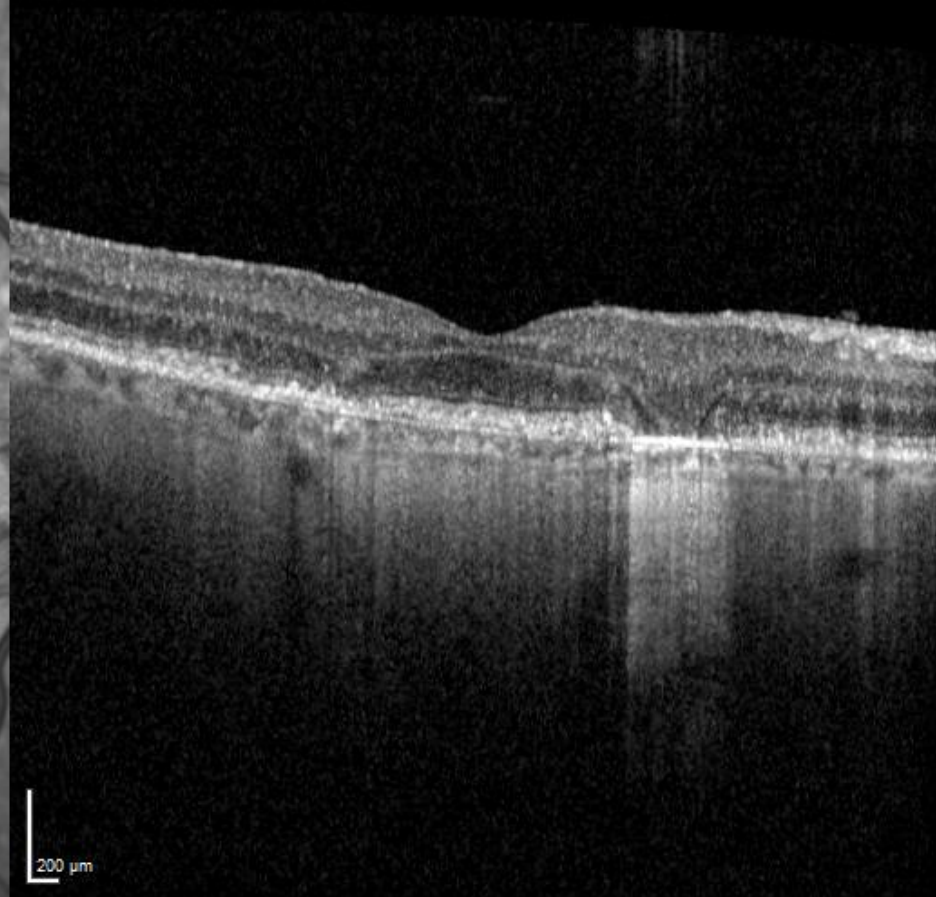
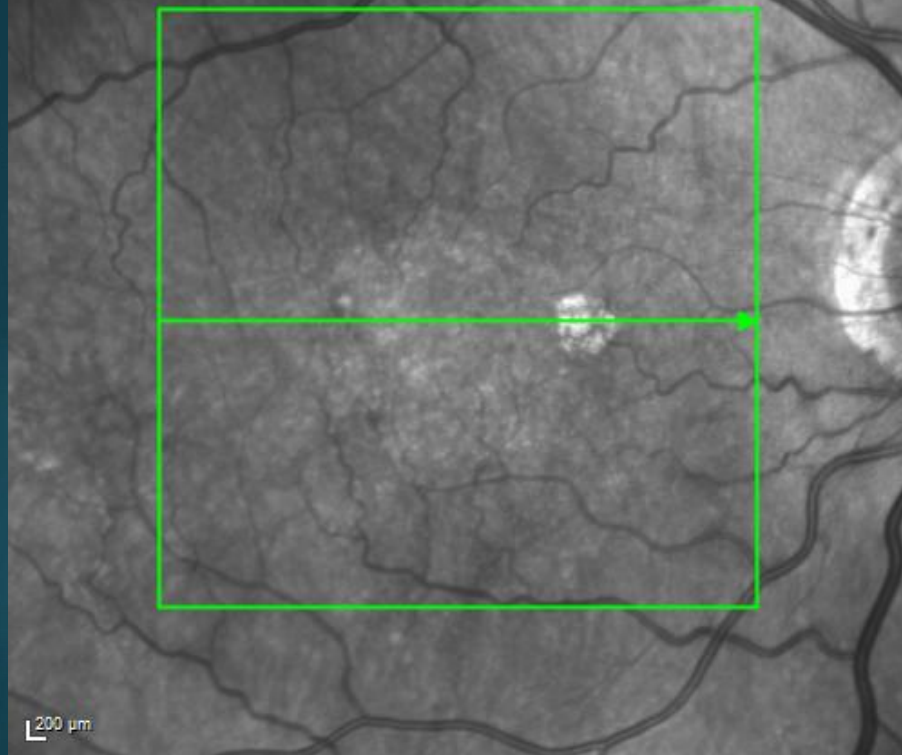
Case 1 - 67 YOM

Diagnosis:

- ▶ Intermediate Dry AMD OD
- ▶ Wet AMD OS

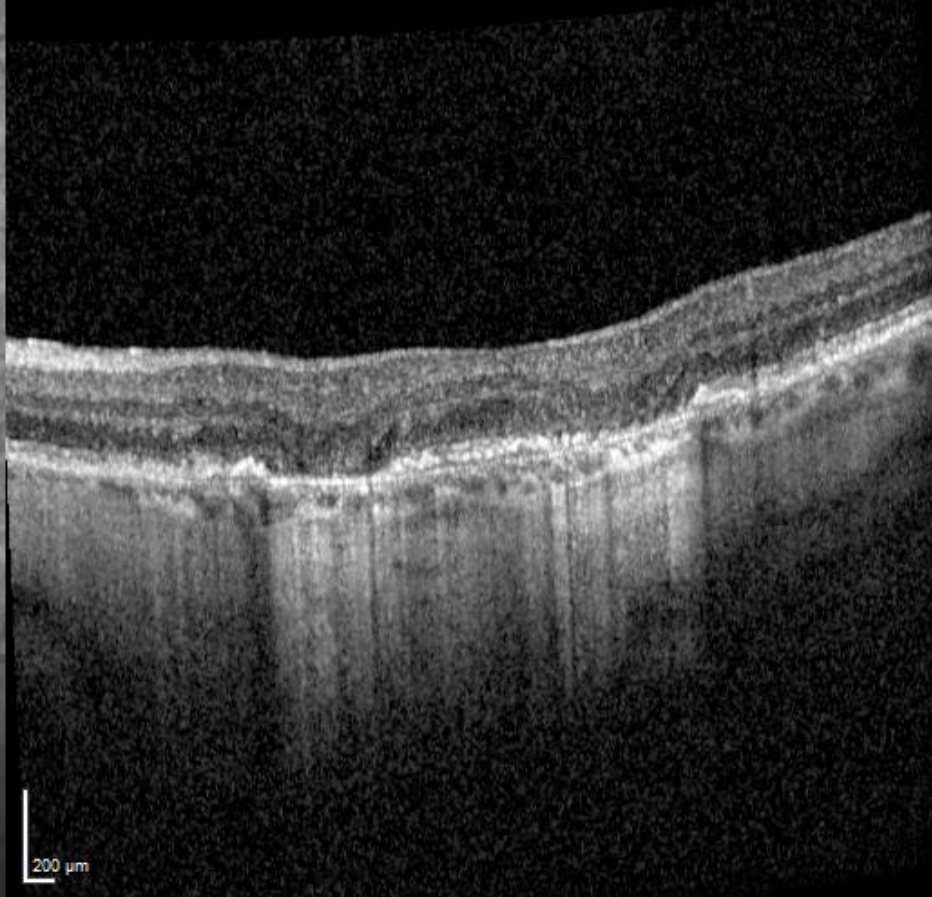
Treatment:

- ▶ Avastin injections OS
 - ▶ Good initial response
 - ▶ treat and extend → eventually inactive wet AMD
-
- ▶ Later developed progressive GA OU



8/9/2019, OD

IR&OCT 30° ART [HS] ART(6) Q: 40

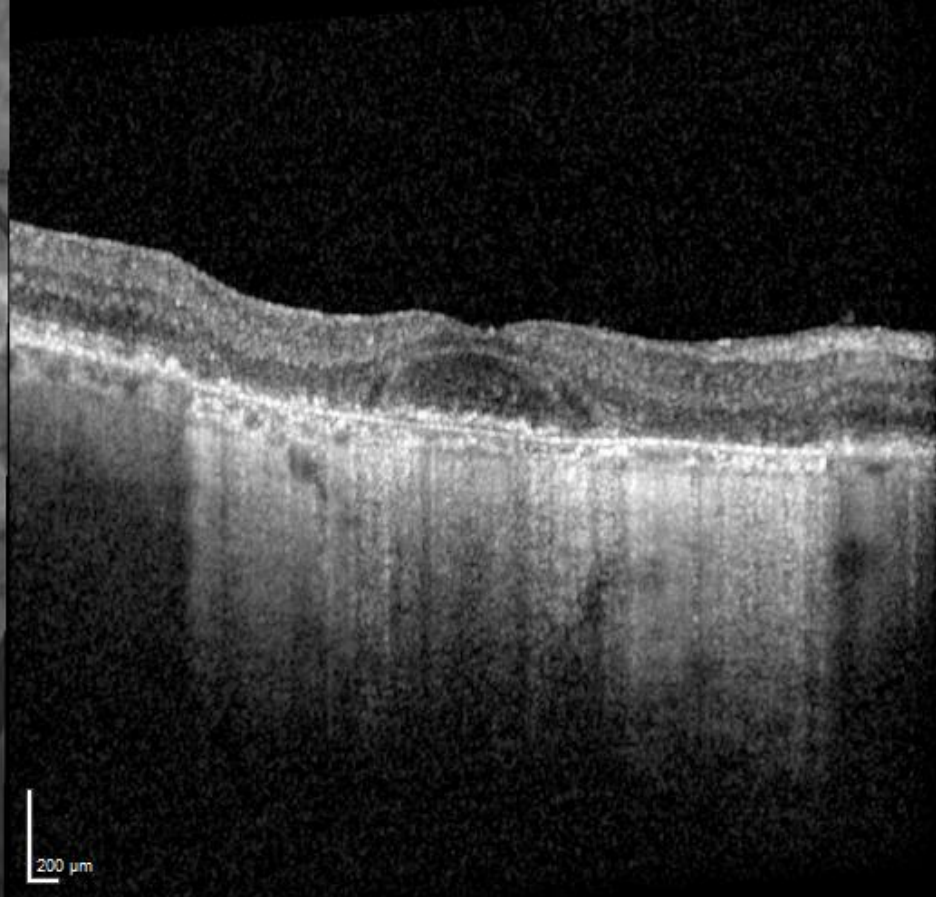


8/9/2019, OS

IR&OCT 30° ART [HS] ART(5) Q: 27

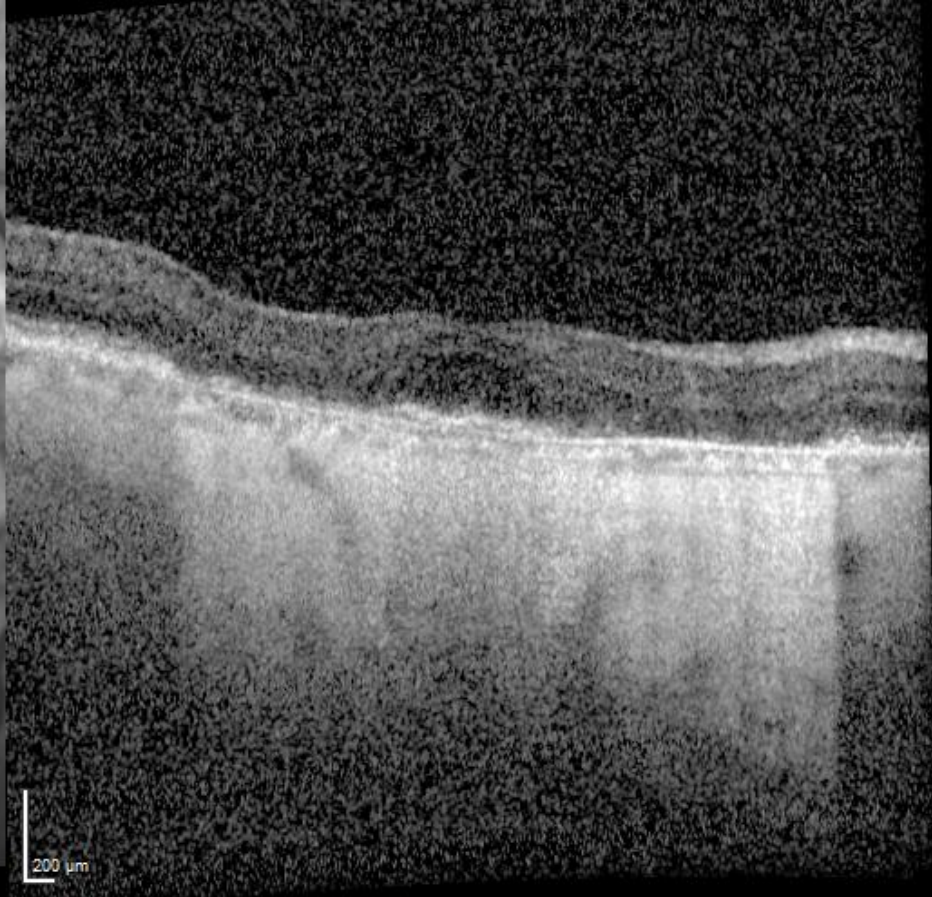
Syfovre?





11/11/2022, OD

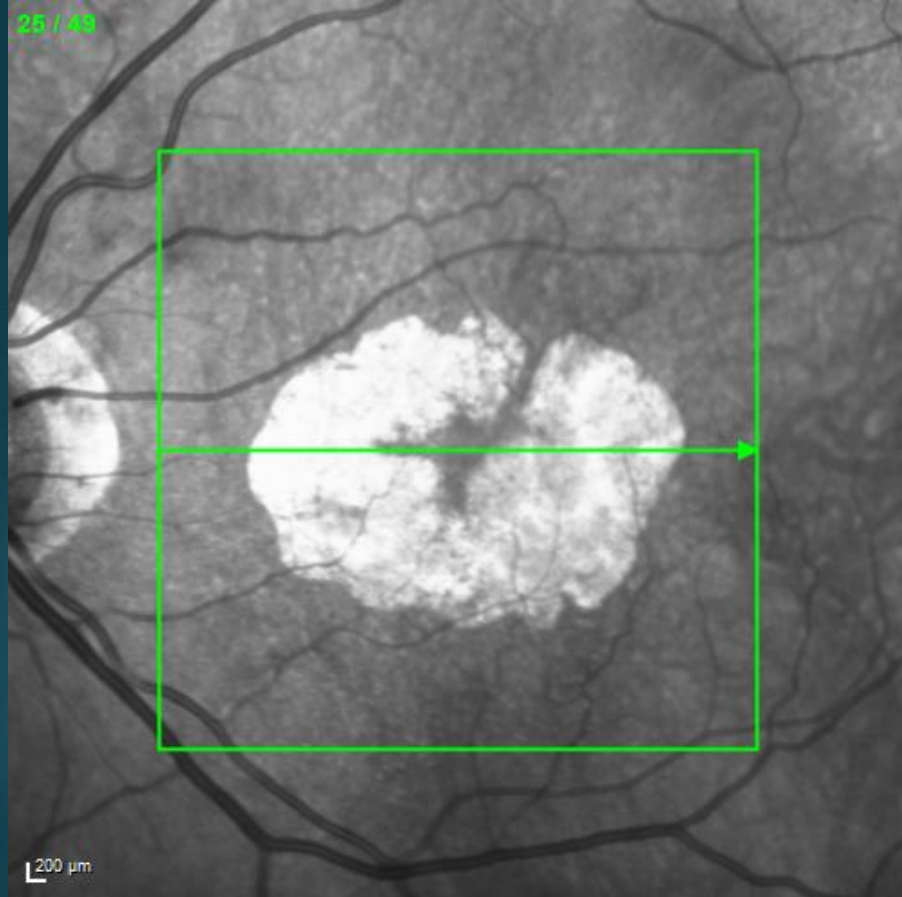
IR&OCT 30° ART [HS] ART(6) Q: 31



2/22/2023, OD

IR&OCT 30° ART [HS] ART(6) Q: 21

25/1/23

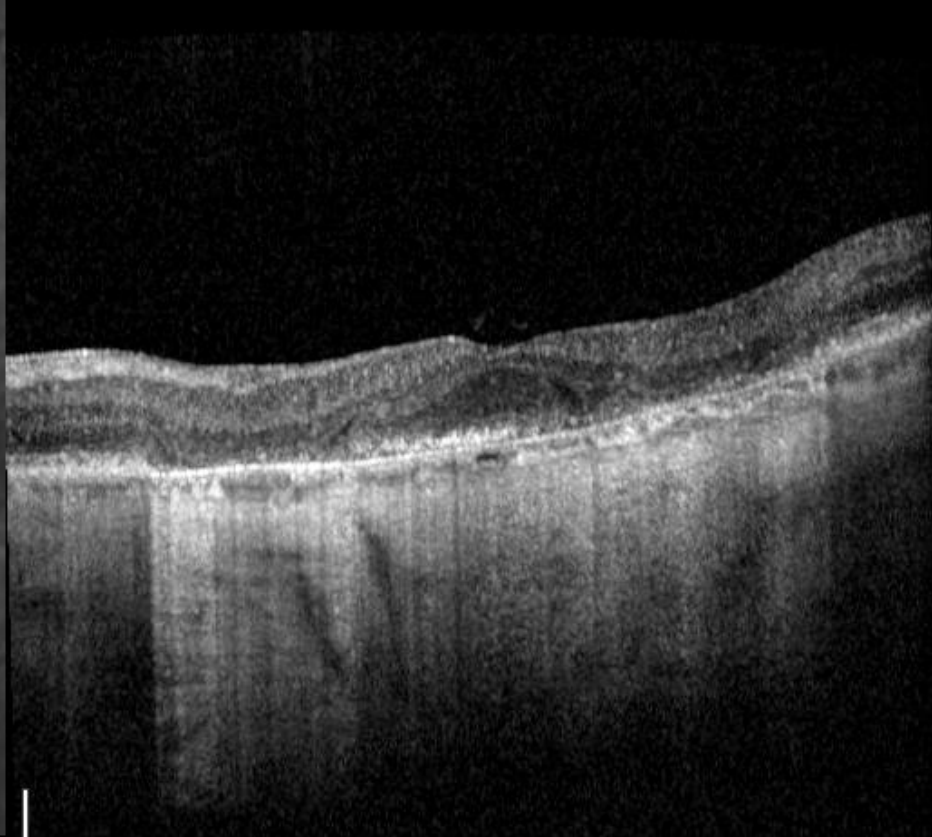


11/11/2022, OS

IR&OCT 30° ART [HS] ART(6) Q: 34



200 μ m



200 μ m

2/22/2023, OS

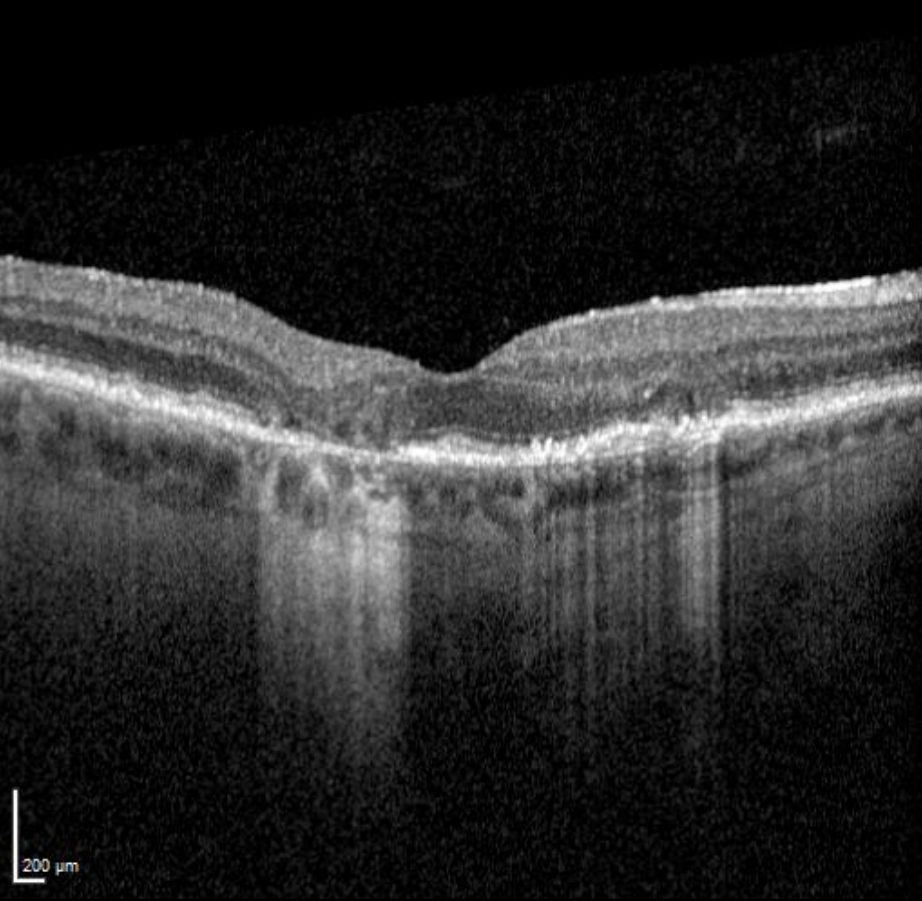
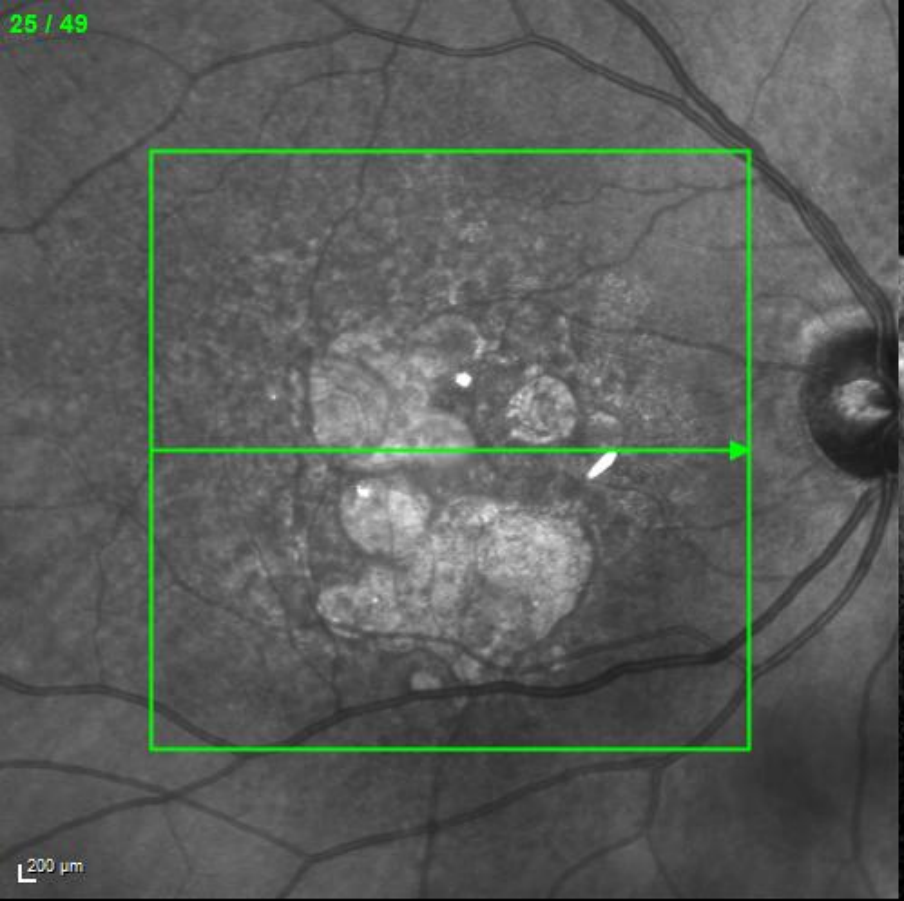
IR&OCT 30° ART [HS] ART(6) Q: 36

Case 2 - 75 YO WM

In 02/2020:

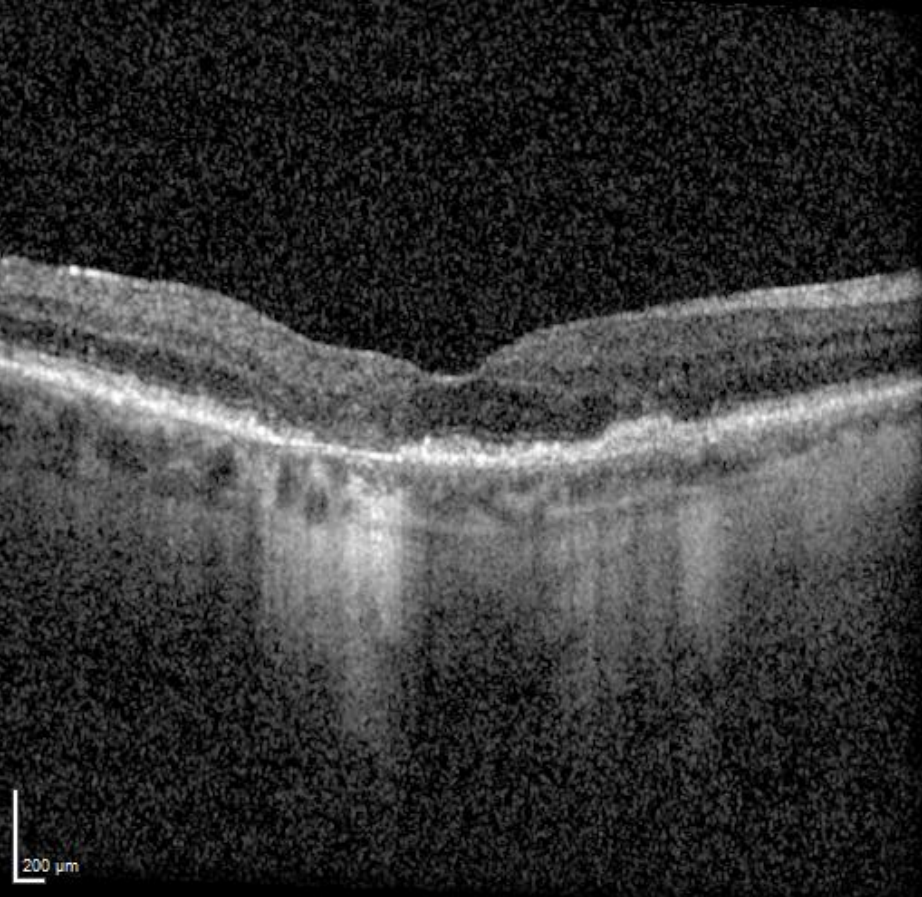
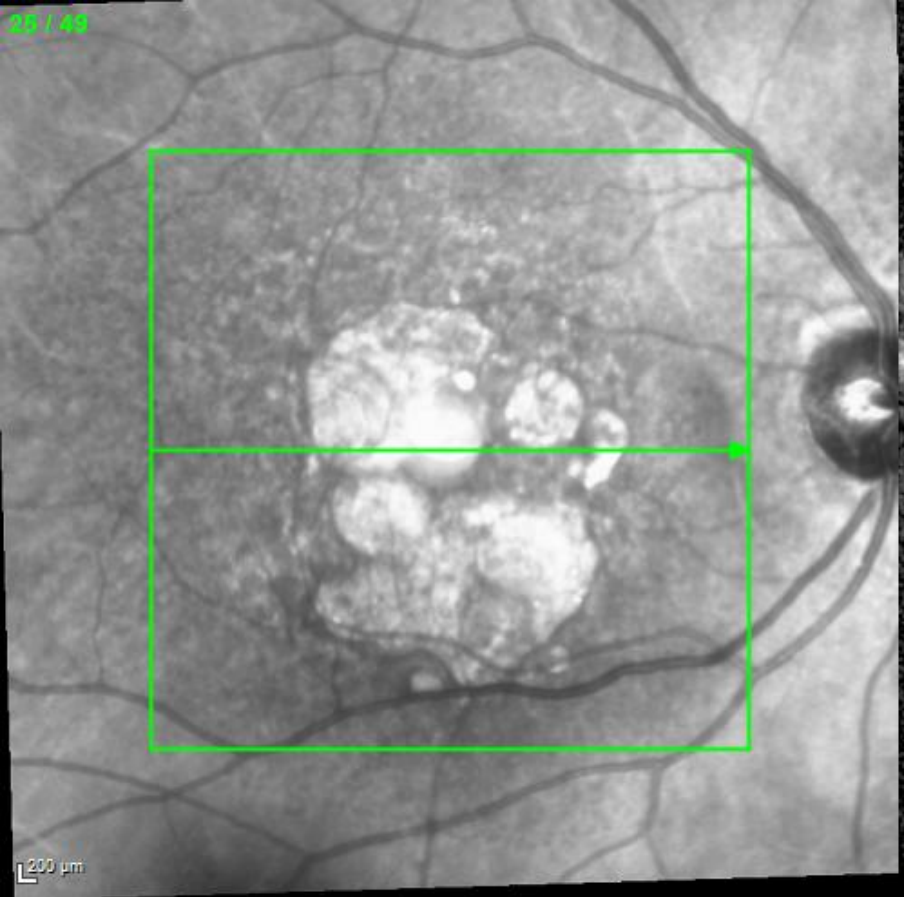
- ▶ Initially referred for dry AMD eval OU
- ▶ (+) Former smoker, (+) FHx of AMD - brother
- ▶ Med Hx: DM, HTN, Multiple Myeloma, s/p Cardiac Pacemaker

- ▶ VA (cc): OD: 20/20
 OS: 20/20



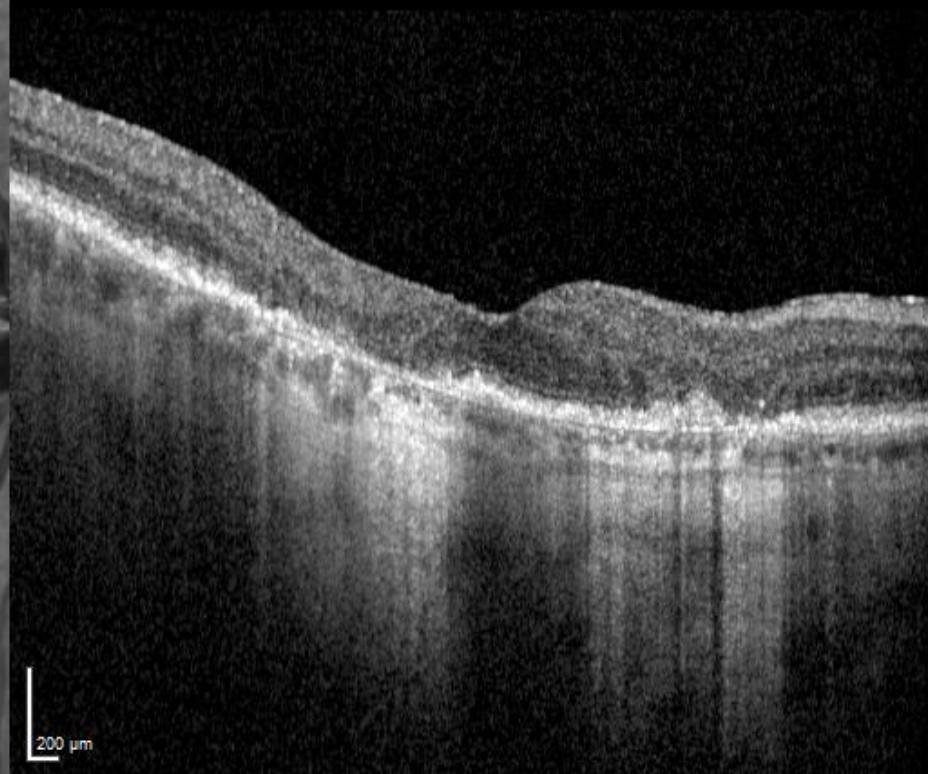
2/5/2020, OD

IR&OCT 30° ART [HS] ART(6) Q: 34



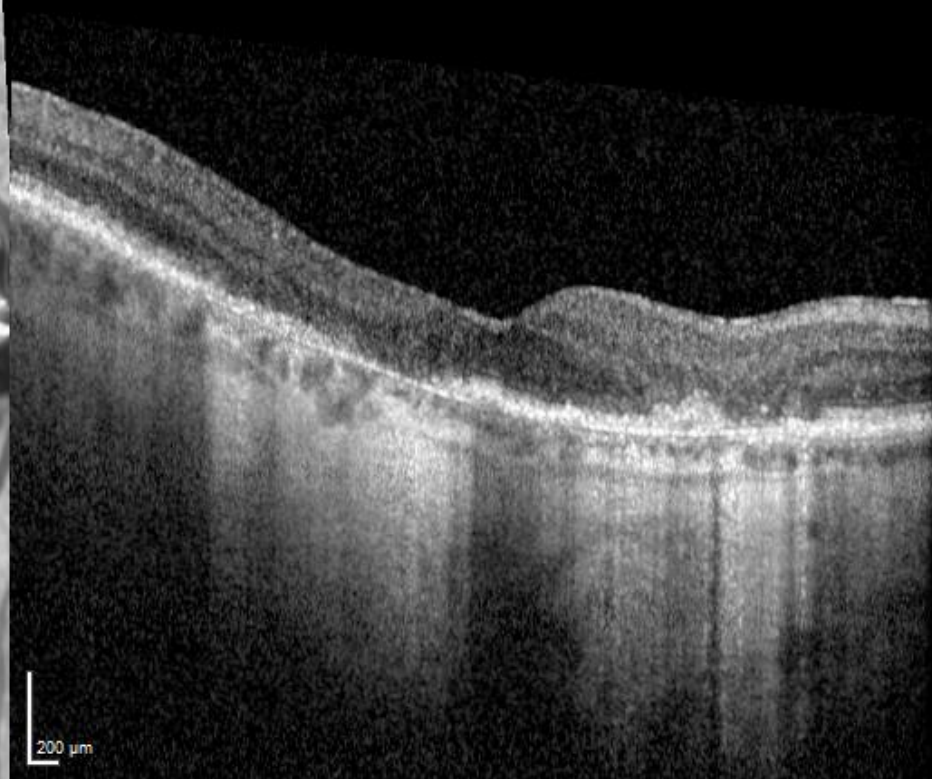
6/10/2020, OD

IR&OCT 30° ART [HS] ART(5) Q: 25



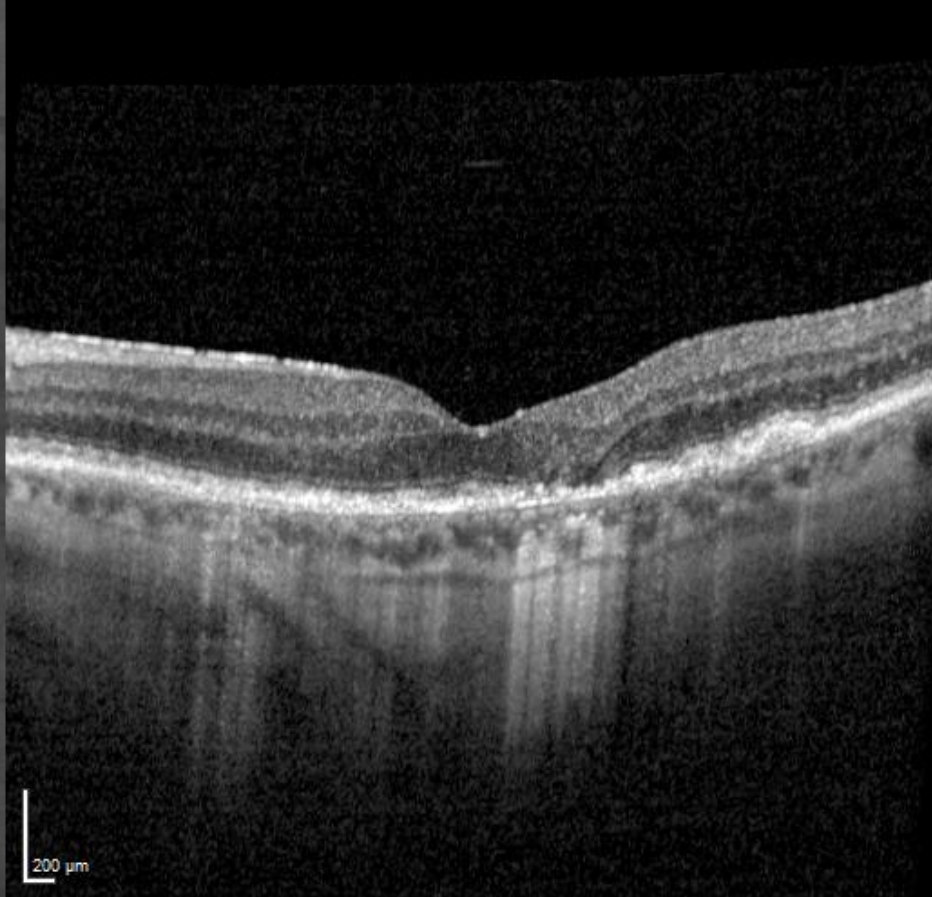
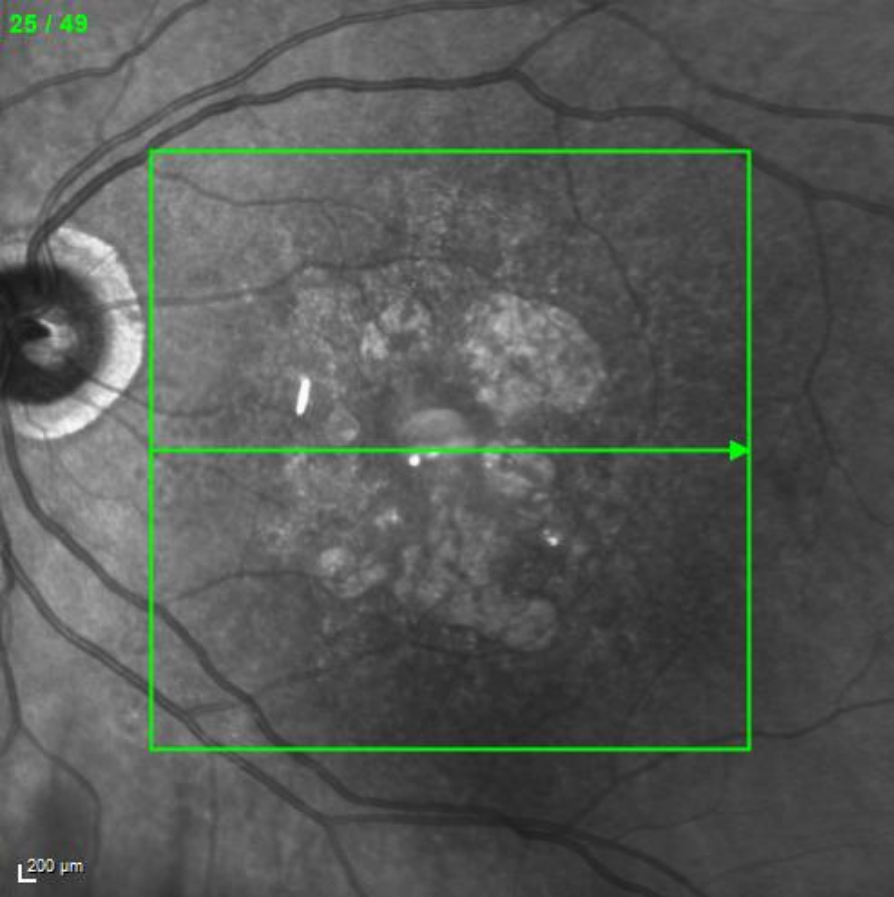
9/21/2022, OD

IR&OCT 30° ART [HS] ART(6) Q: 30



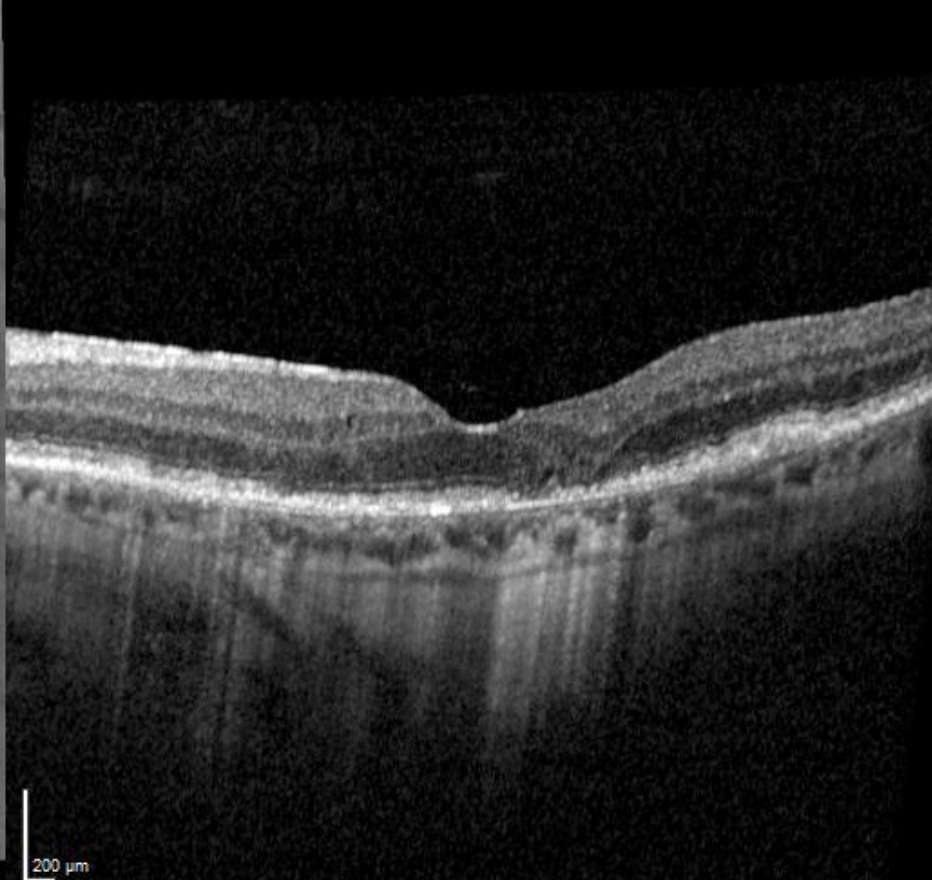
3/22/2023, OD

IR&OCT 30° ART [HS] ART(6) Q: 30



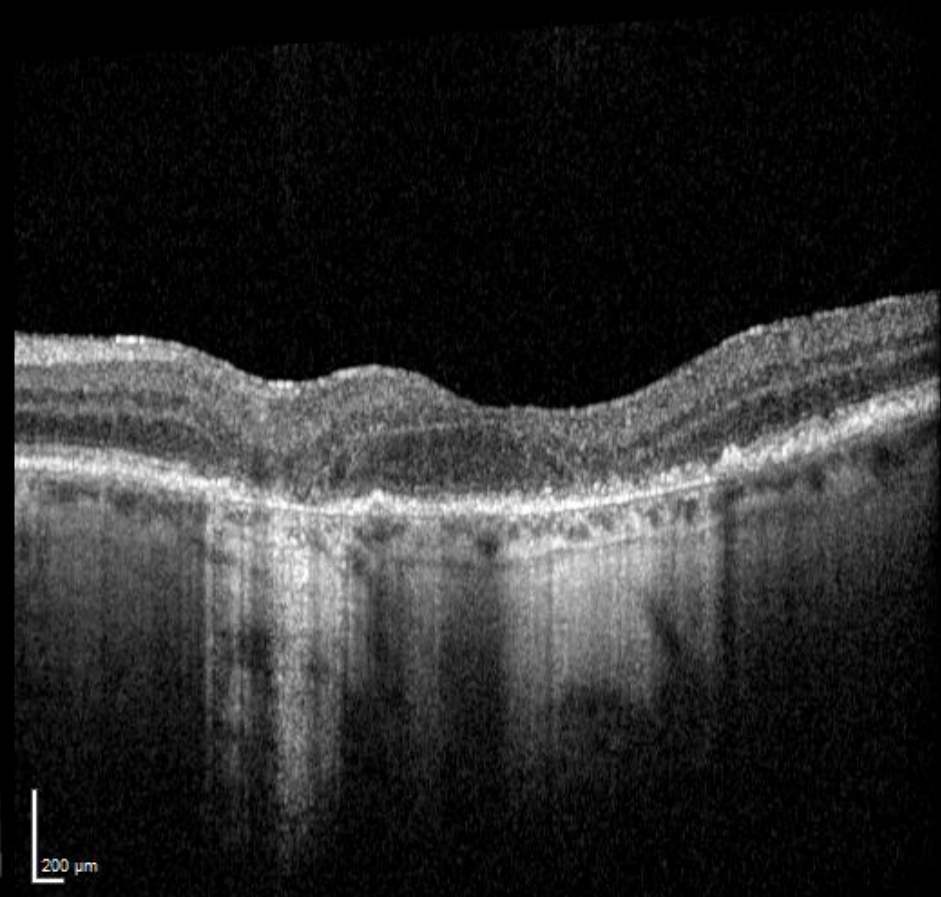
2/5/2020, OS

IR&OCT 30° ART [HS] ART(15) Q: 32



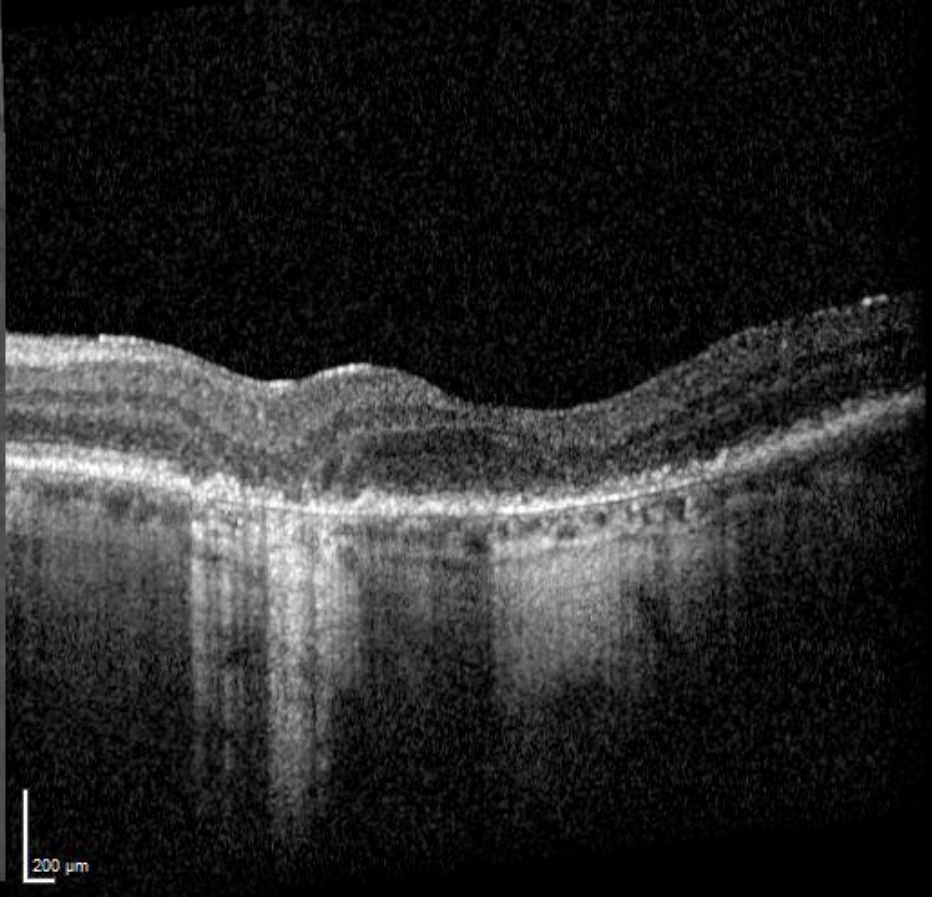
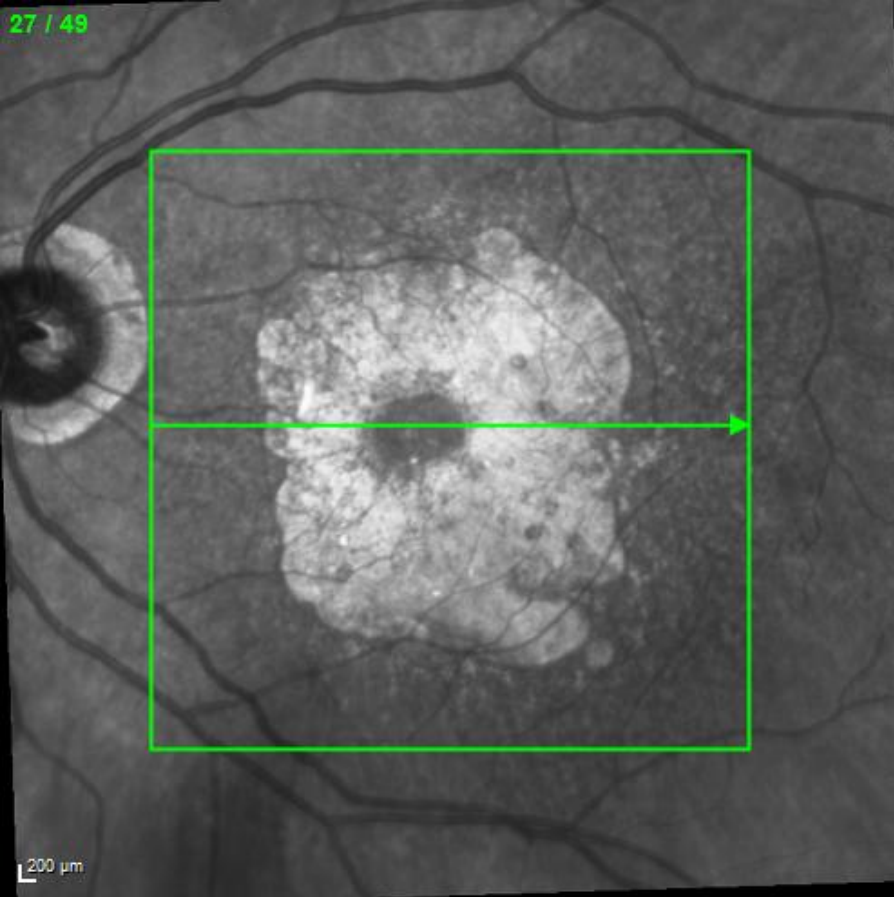
6/10/2020, OS

IR&OCT 30° ART [HS] ART(17) Q: 36



9/21/2022, OS

IR&OCT 30° ART [HS] ART(6) Q: 36



3/22/2023, OS

IR&OCT 30° ART [HS] ART(4) Q: 31

Case 2 - 75 YOM

Diagnosis:

- ▶ Advanced AMD OU
 - ▶ GA without subfoveal involvement OU

Treatment:

- ▶ AREDS2 recommended
- ▶ Monitored q4-6 mos

Syfovre?



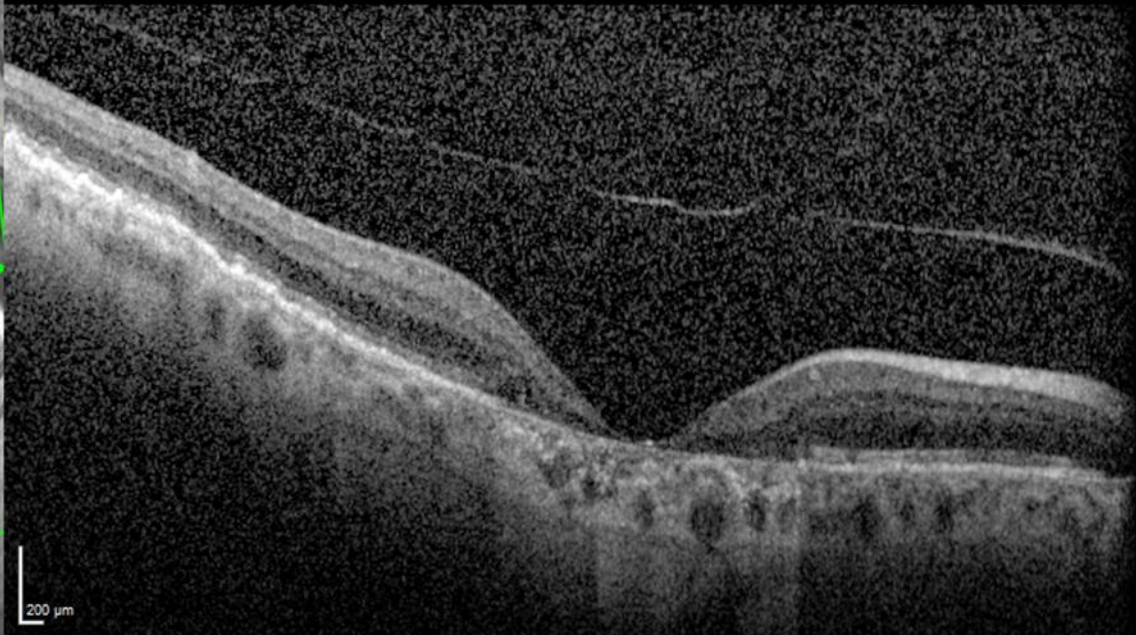
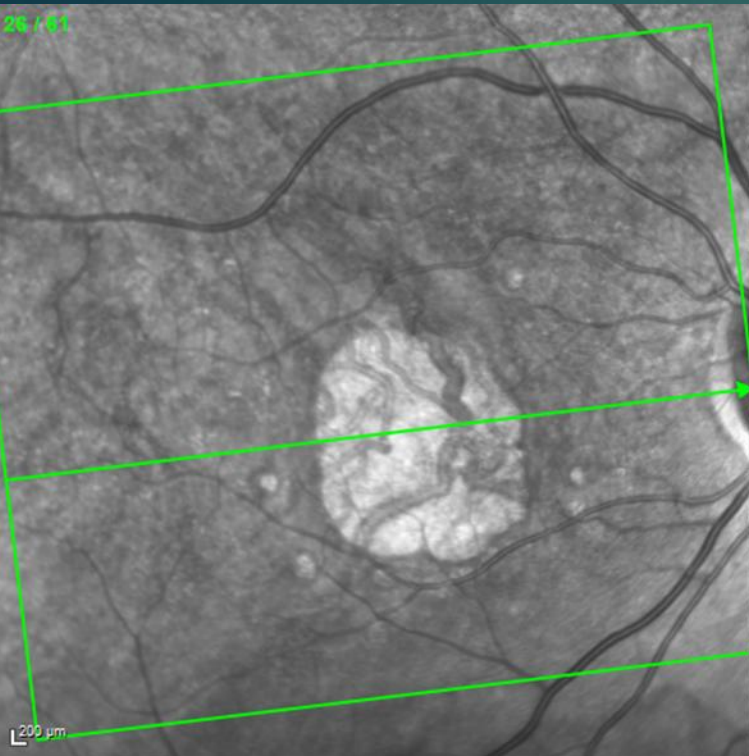
Case 3 - 69 YO WF

In 02/2020:

- ▶ 2nd opinion for wet AMD OU
- ▶ History of 3 injection OD, 1 injection OS; last injection 3 years ago
- ▶ Currently taking AREDS2 daily
- ▶ (-) Never smoker, (-) FHx of AMD
- ▶ Med Hx: none!

- ▶ VA (cc): OD: CF @ 5ft
 OS: 20/30

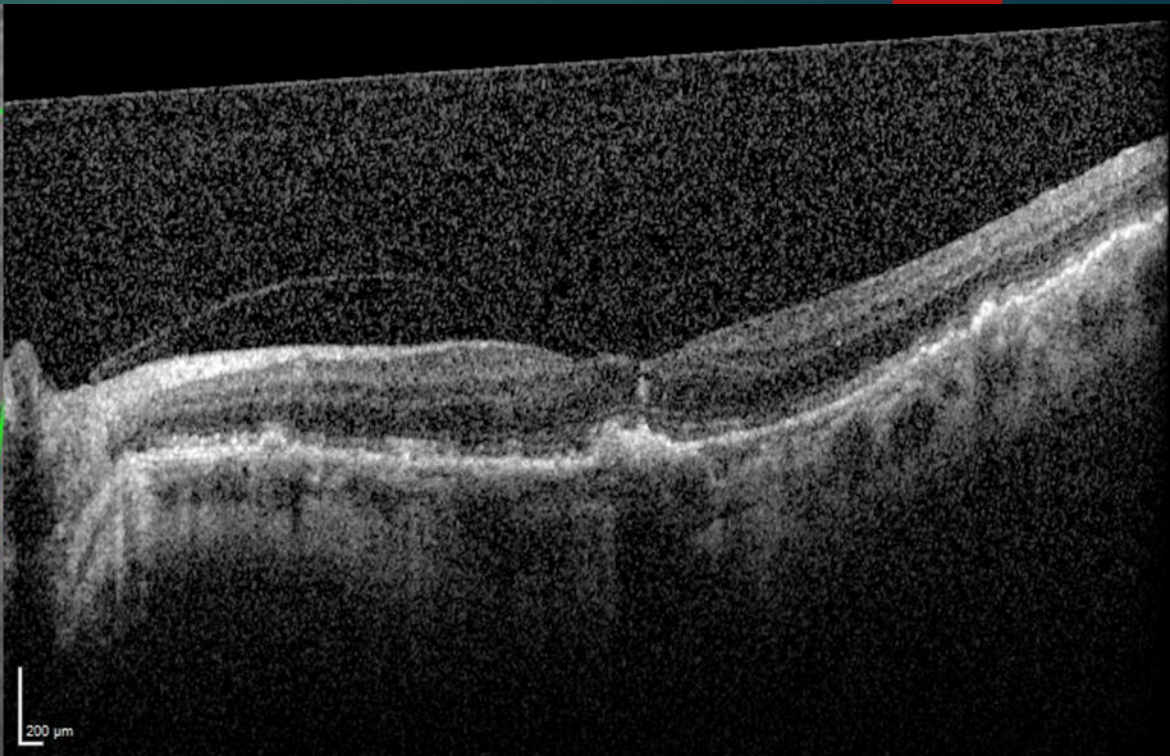
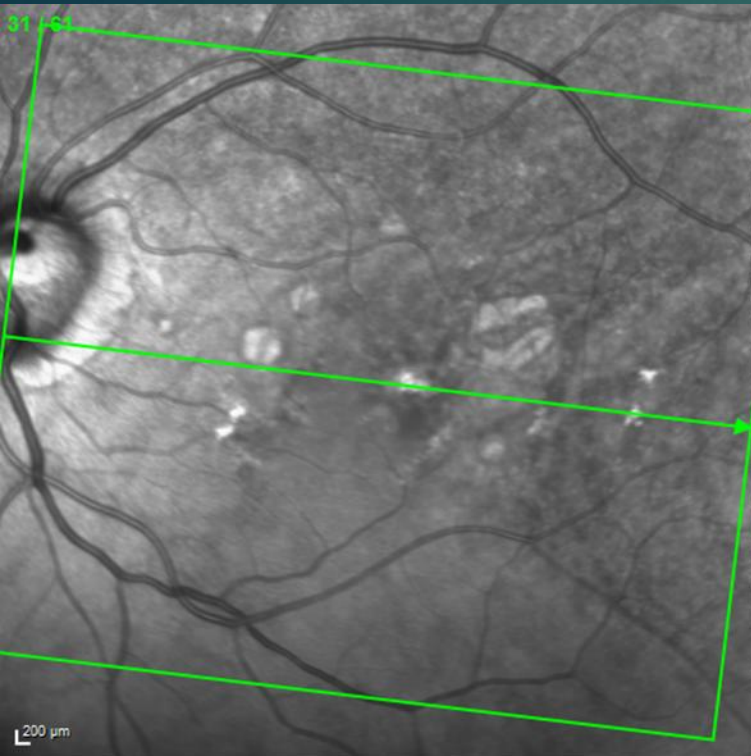
Case 3 - 69 YO WF



12/14/2018, OD

IR&OCT 30° ART [HS] ART(4) Q: 25

Case 3 - 69 YO WF



12/14/2018, OS

IR&OCT 30° ART [HS] ART(2) Q: 23

Case 3 - 69 YO WF

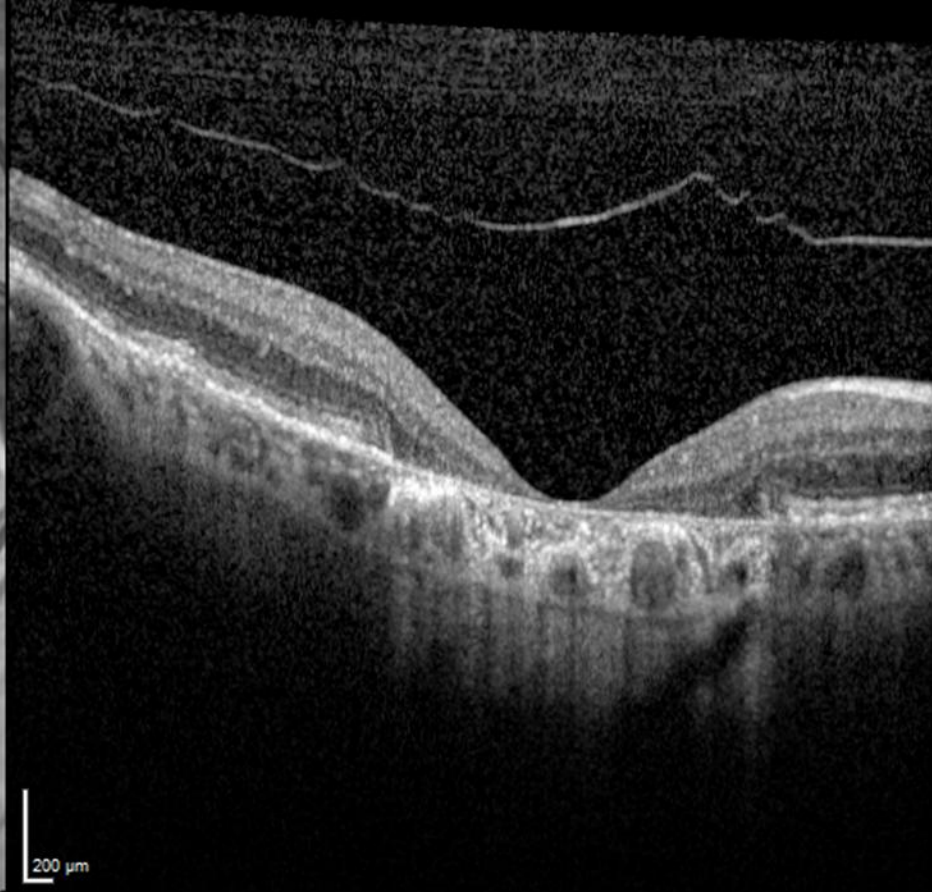
Diagnosis:

- ▶ Inactive Wet AMD OU

Treatment:

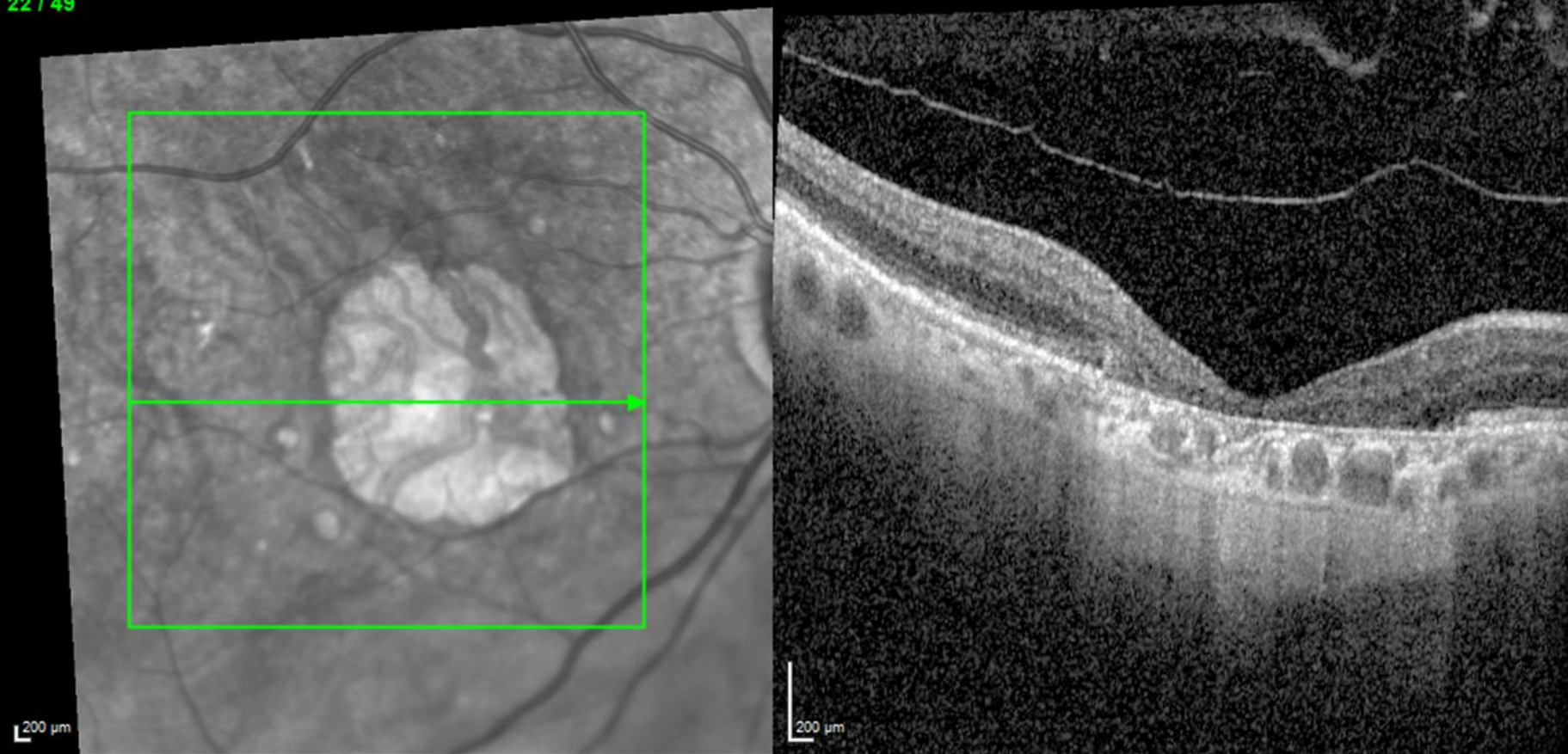
- ▶ Observe, no further injections recommended
- ▶ Followed q4-6 mos

- ▶ On subsequent follow-up patient has now developed progressive GA OS in the better seeing eye



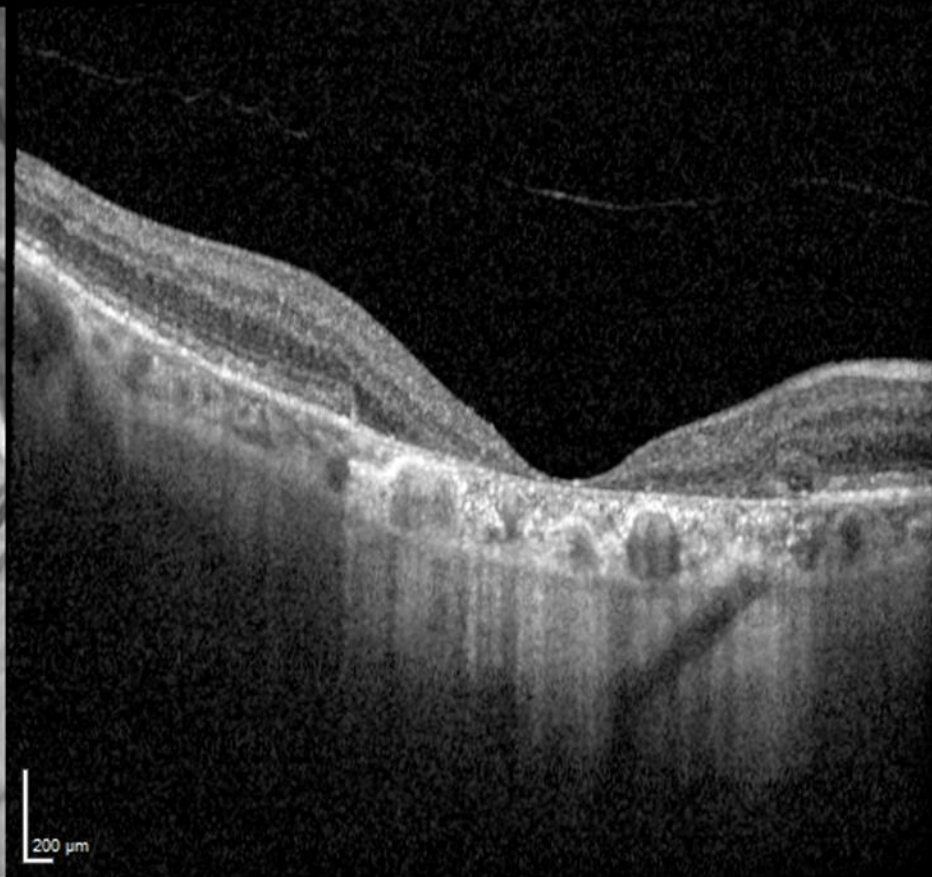
5/22/2019, OD

IR&OCT 30° [HS] ART(7) Q: 28



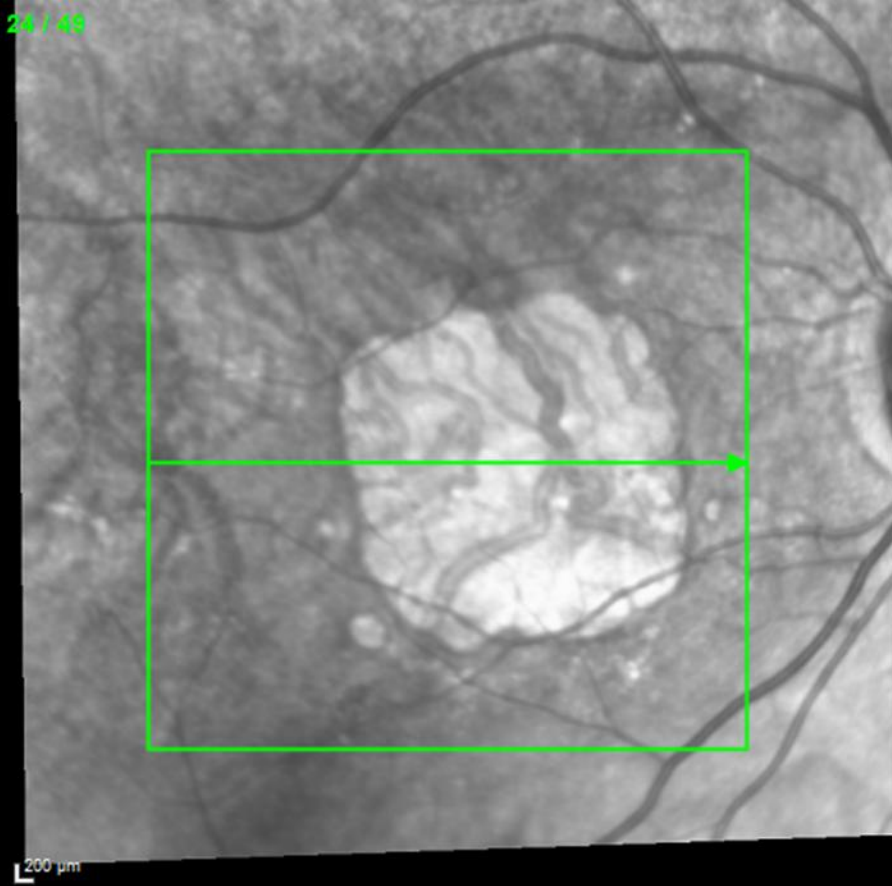
9/14/2020, OD

IR&OCT 30° ART [HS] ART(6) Q: 23



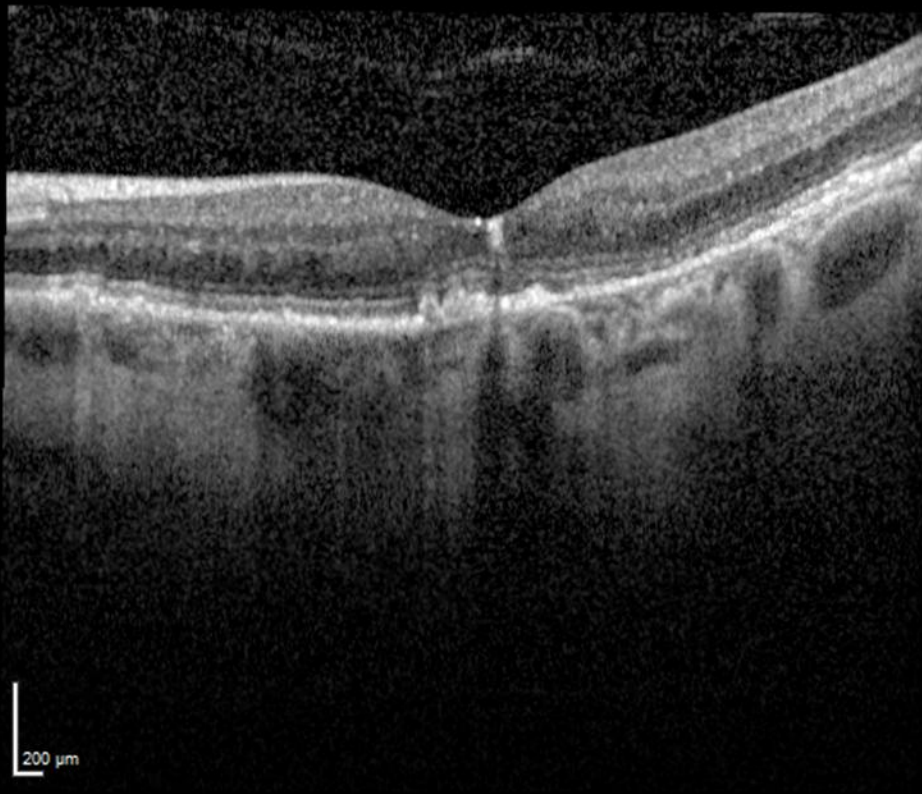
3/16/2022, OD

IR&OCT 30° ART [HS] ART(7) Q: 32



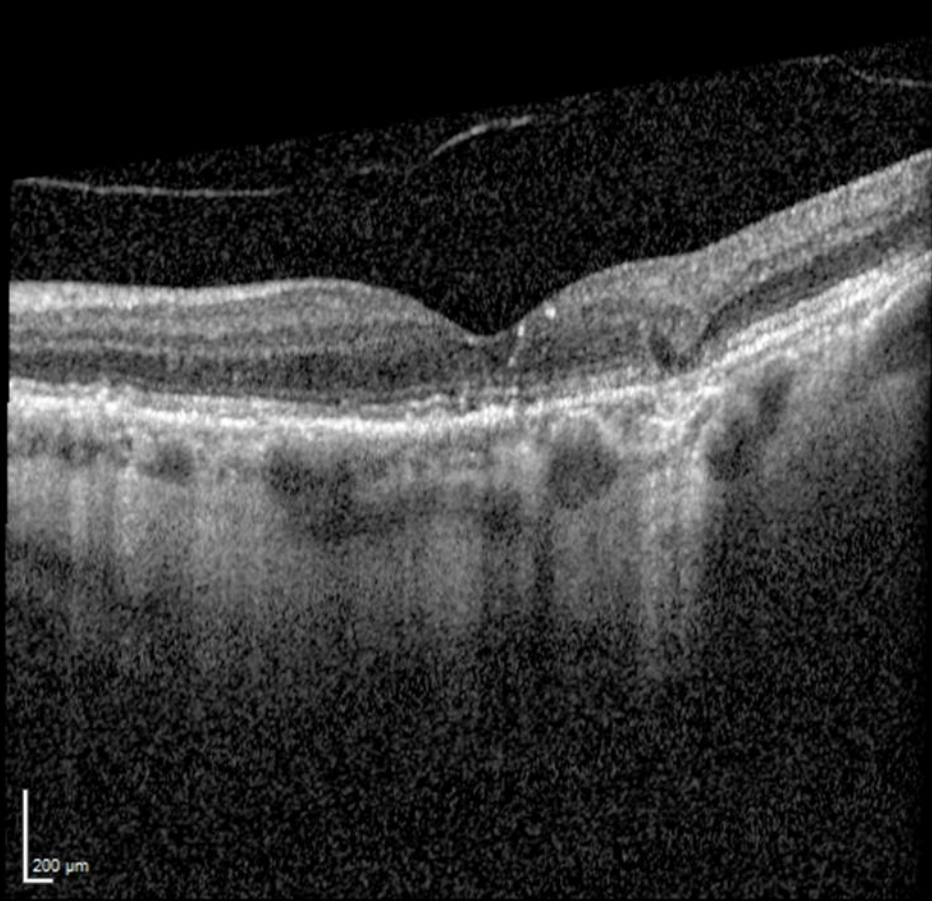
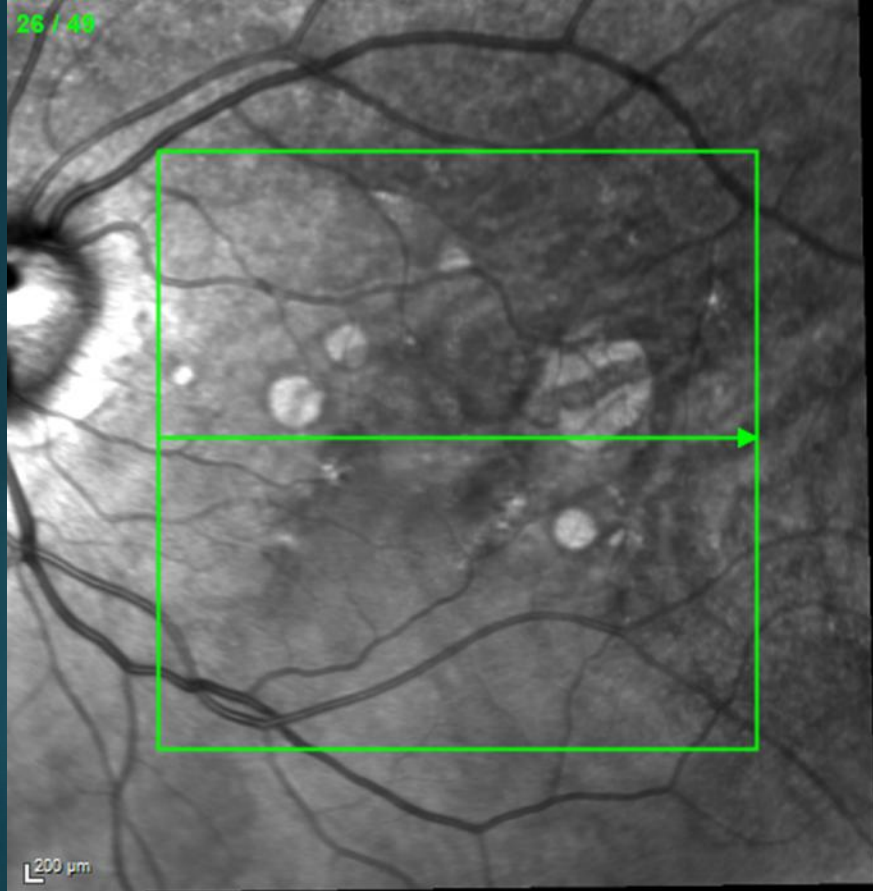
3/22/2023, OD

IR&OCT 30° ART [HS] ART(6) Q: 21



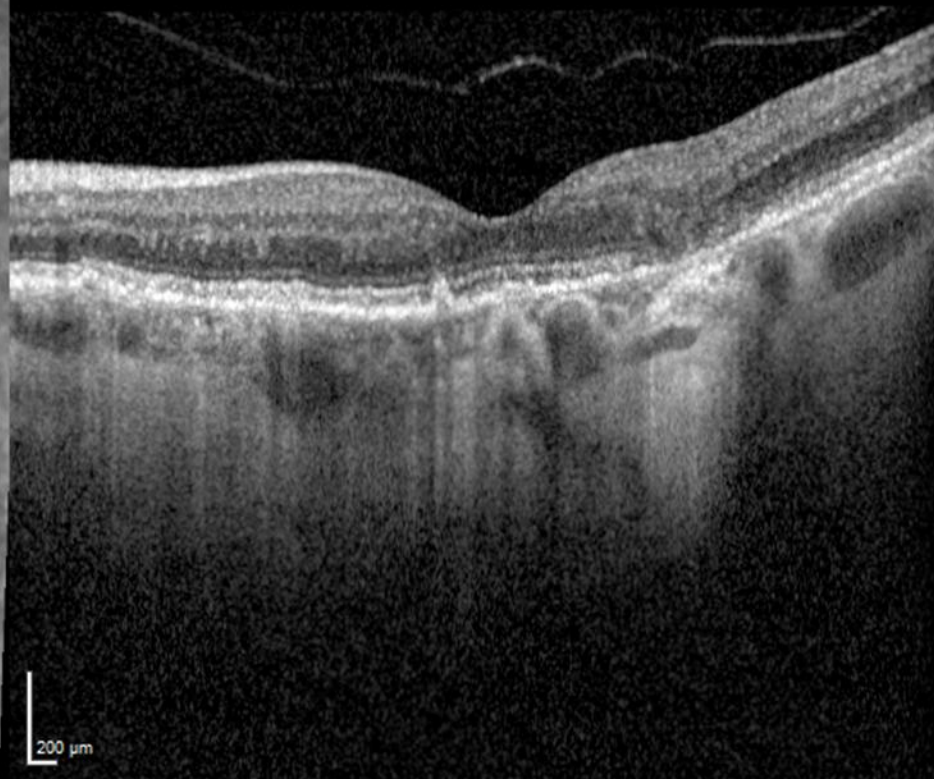
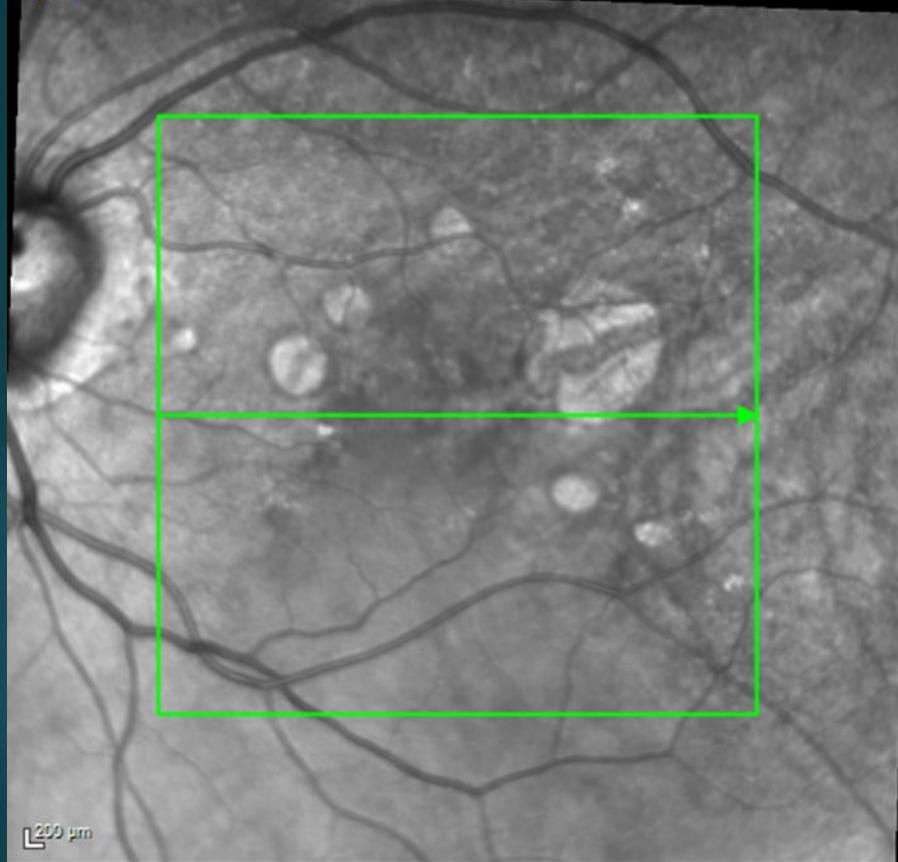
5/22/2019, OS

IR&OCT 30° ART [HS] ART(6) Q: 27



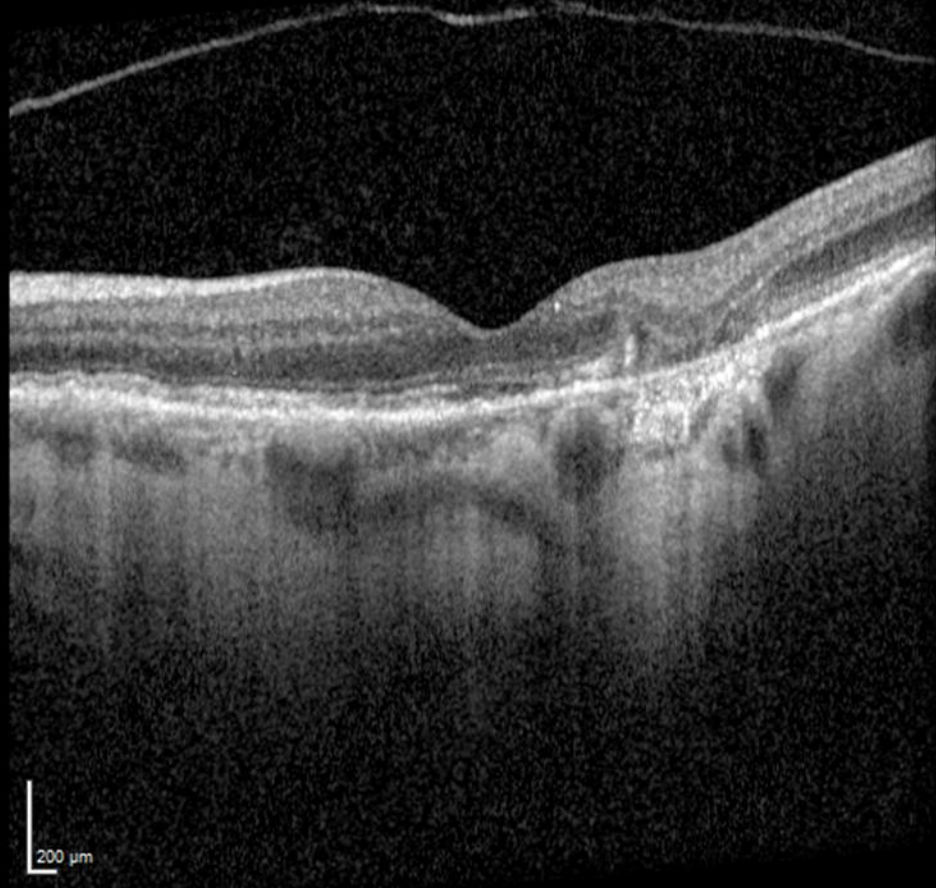
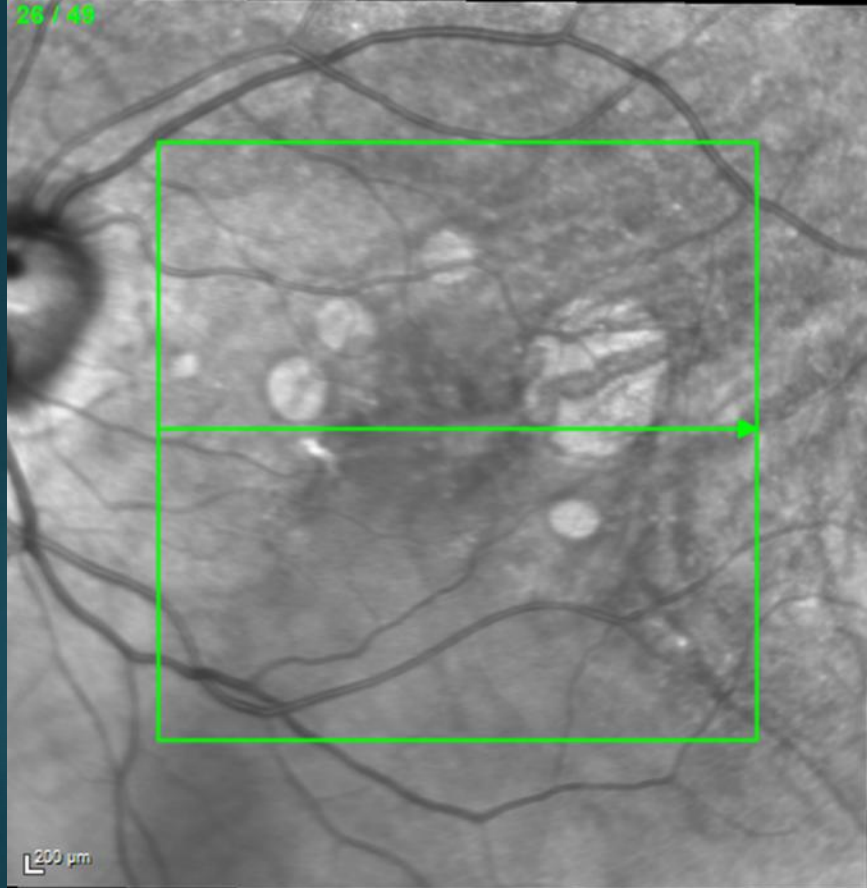
9/14/2020, OS

IR&OCT 30° ART [HS] ART(4) Q: 27



3/16/2022, OS

IR&OCT 30° ART [HS] ART(6) Q: 30



3/22/2023, OS

IR&OCT 30° ART [HS] ART(6) Q: 34

Syfovre?

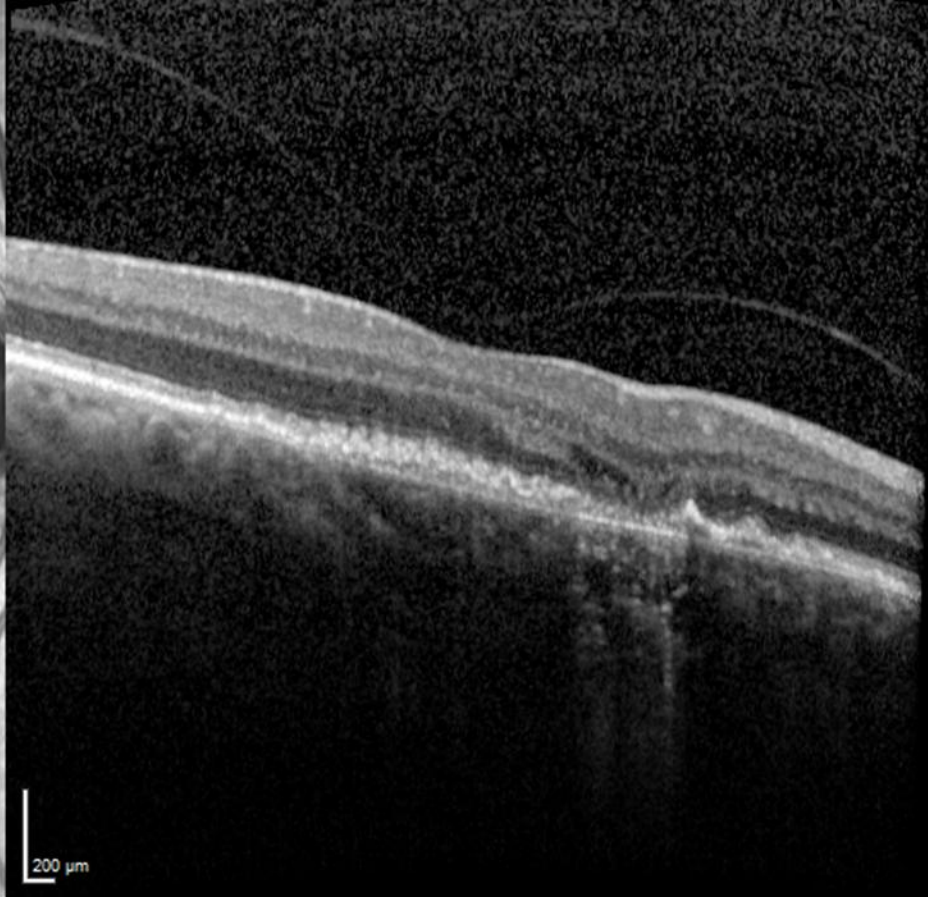


Case 4 - 71 YO WM

In 09/2018:

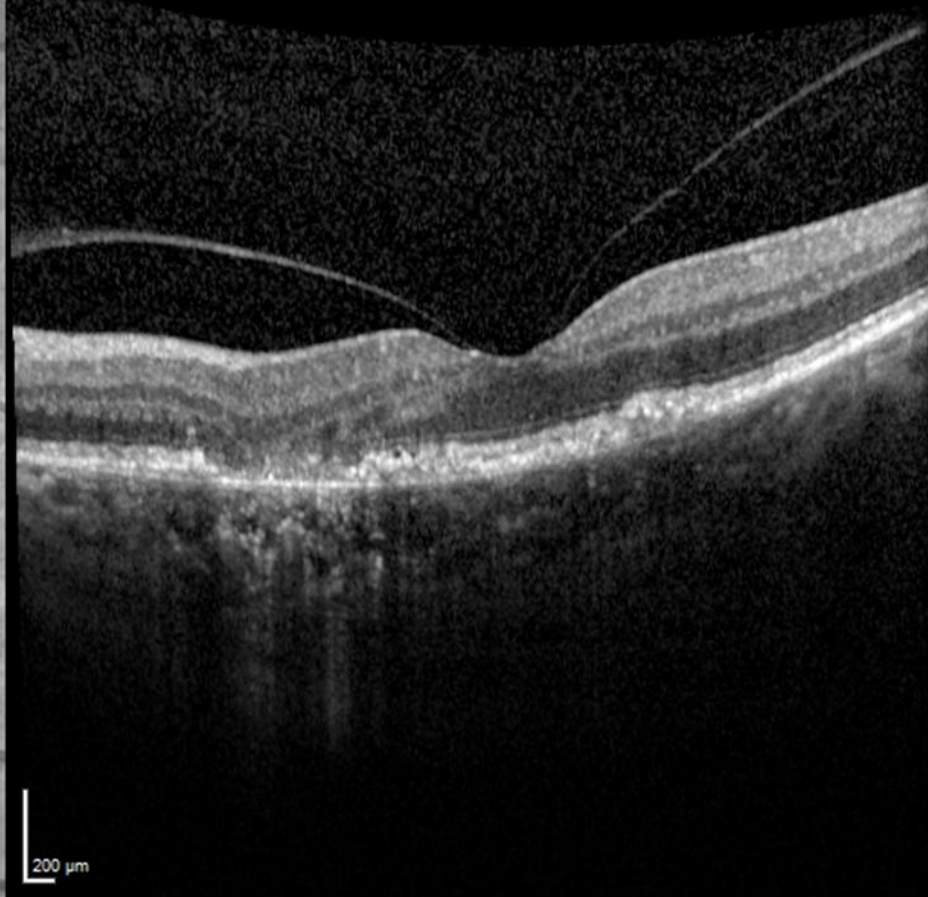
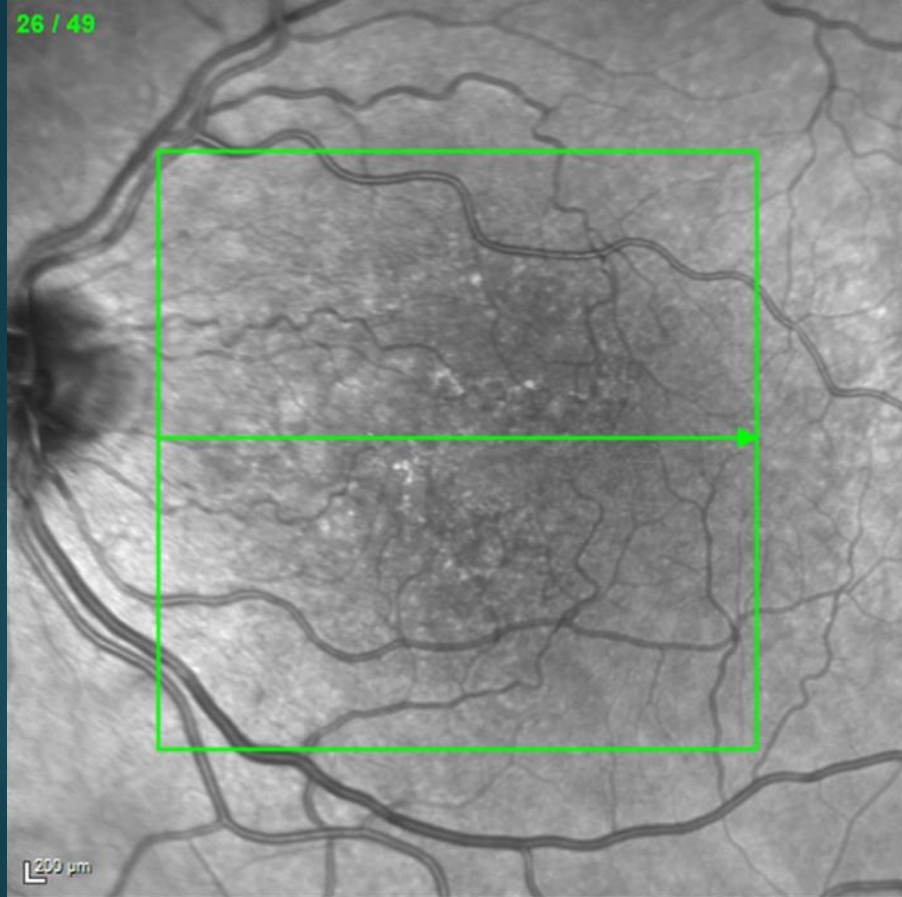
- ▶ Referral for dry AMD OU
- ▶ Currently taking AREDS2 daily
- ▶ (+) Former smoker, (+) FHx of AMD - mother
- ▶ Med Hx: HTN, Heart Disease s/p CABG, Arthritis

- ▶ VA (cc): OD: 20/25
 OS: 20/40 PH 20/20-



9/18/2018, OD

IR&OCT 30° [HS] ART(15) Q: 23



9/18/2018, OS

IR&OCT 30° ART [HS] ART(16) Q: 26

Case 4 - 71 YO WM

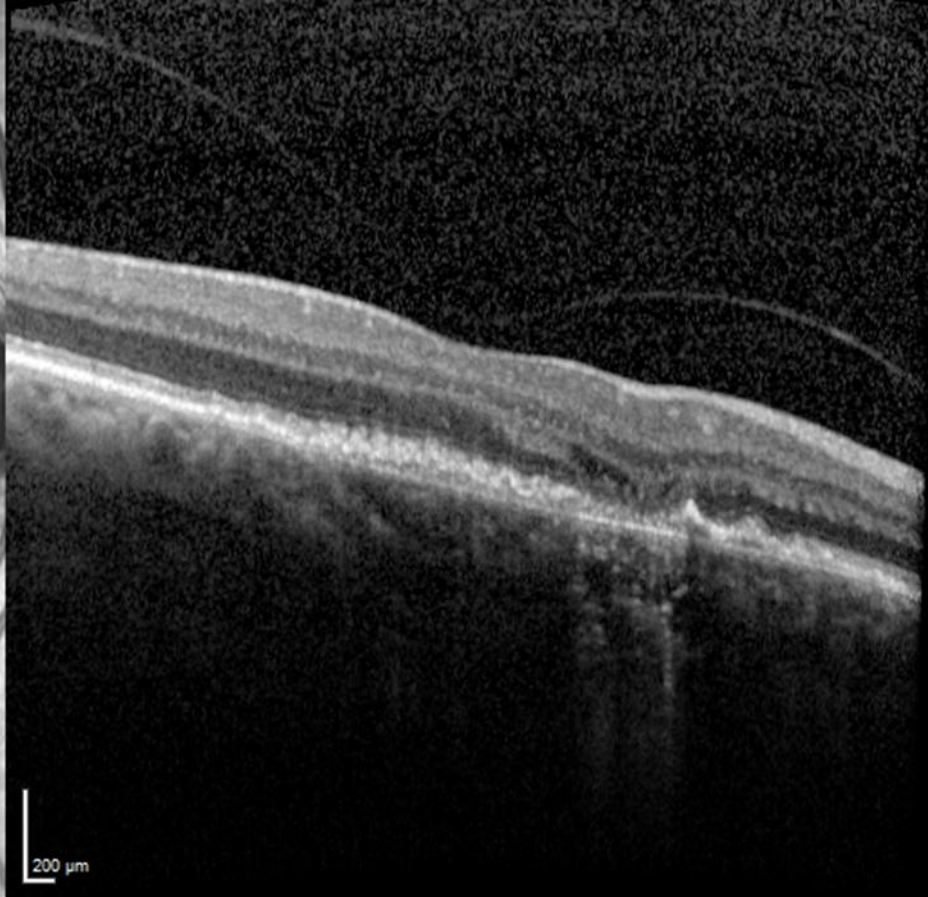
Diagnosis:

- ▶ Dry AMD OU

Treatment:

- ▶ Continue AREDS2
- ▶ Followed q4-6 mos

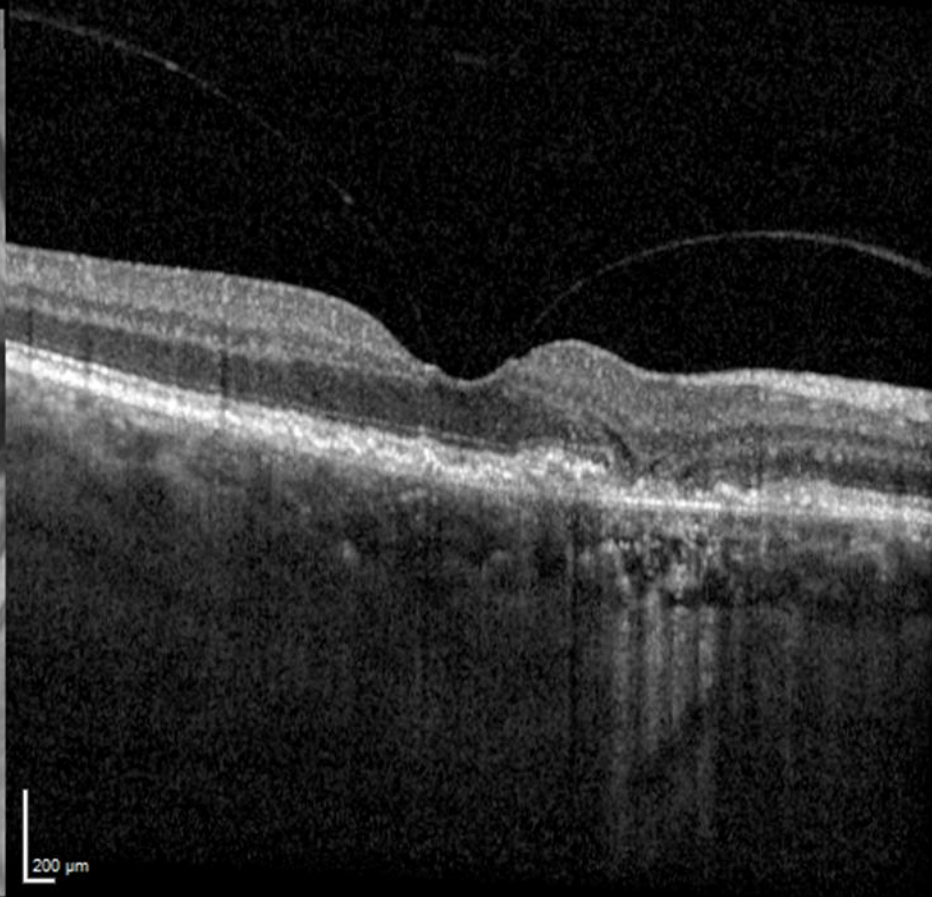
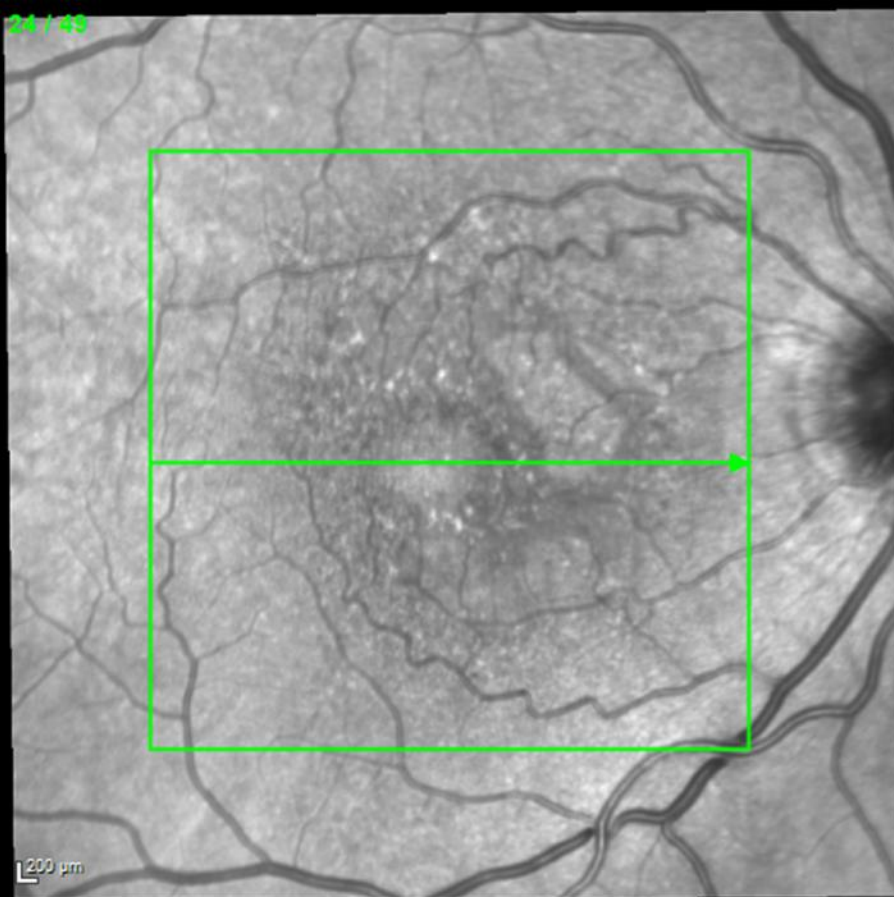
- ▶ Patient later developed wet AMD OS and underwent Avastin and Eyelea injections



9/18/2018, OD

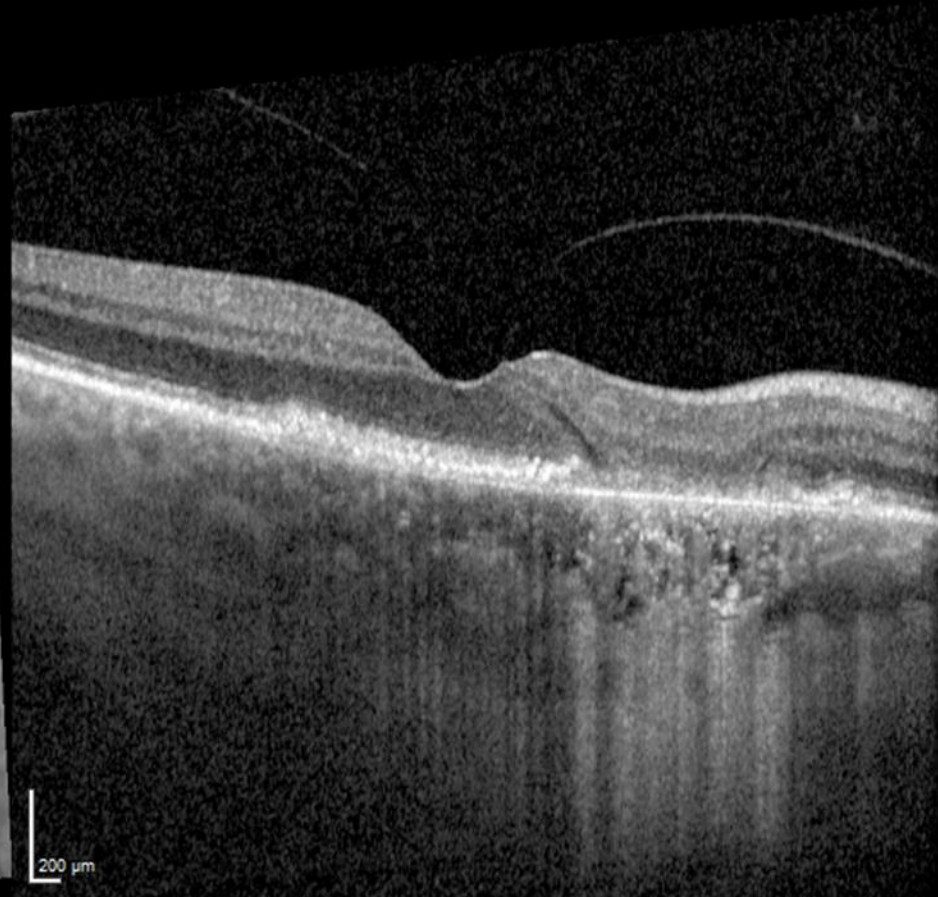
IR&OCT 30° [HS] ART(15) Q: 23

24 / 49



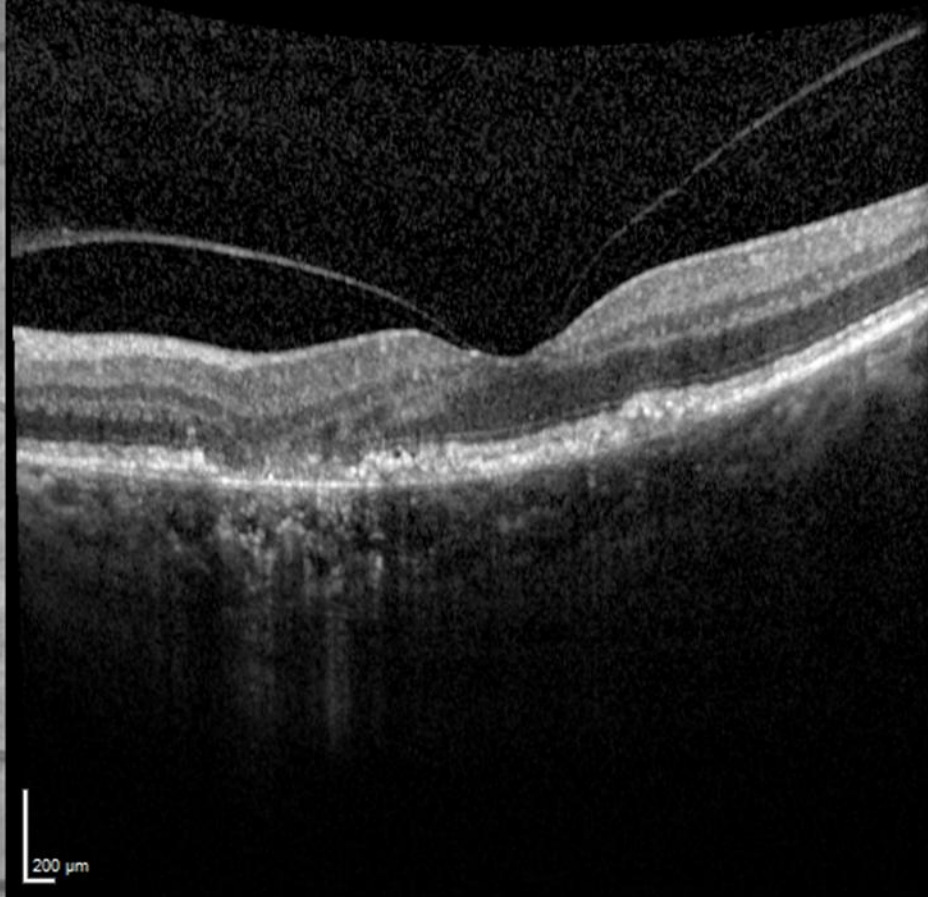
10/7/2020, OD

IR&OCT 30° ART [HS] ART(10) Q: 33



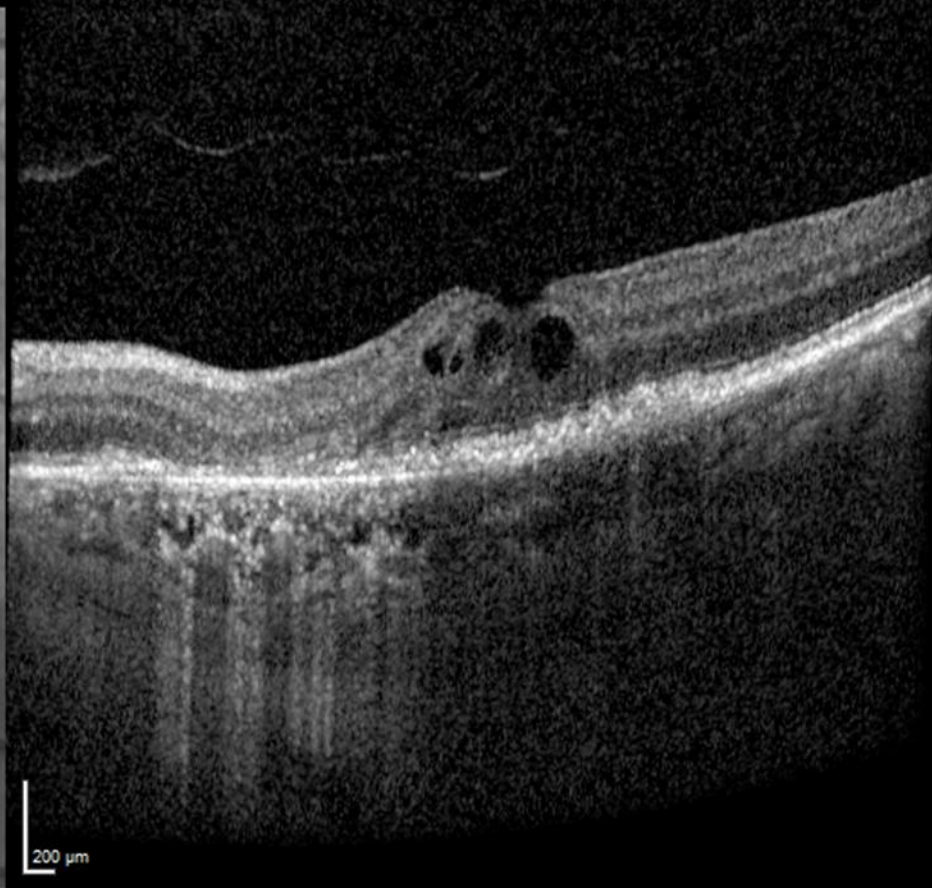
10/12/2022, OD

IR&OCT 30° ART [HS] ART(12) Q: 28



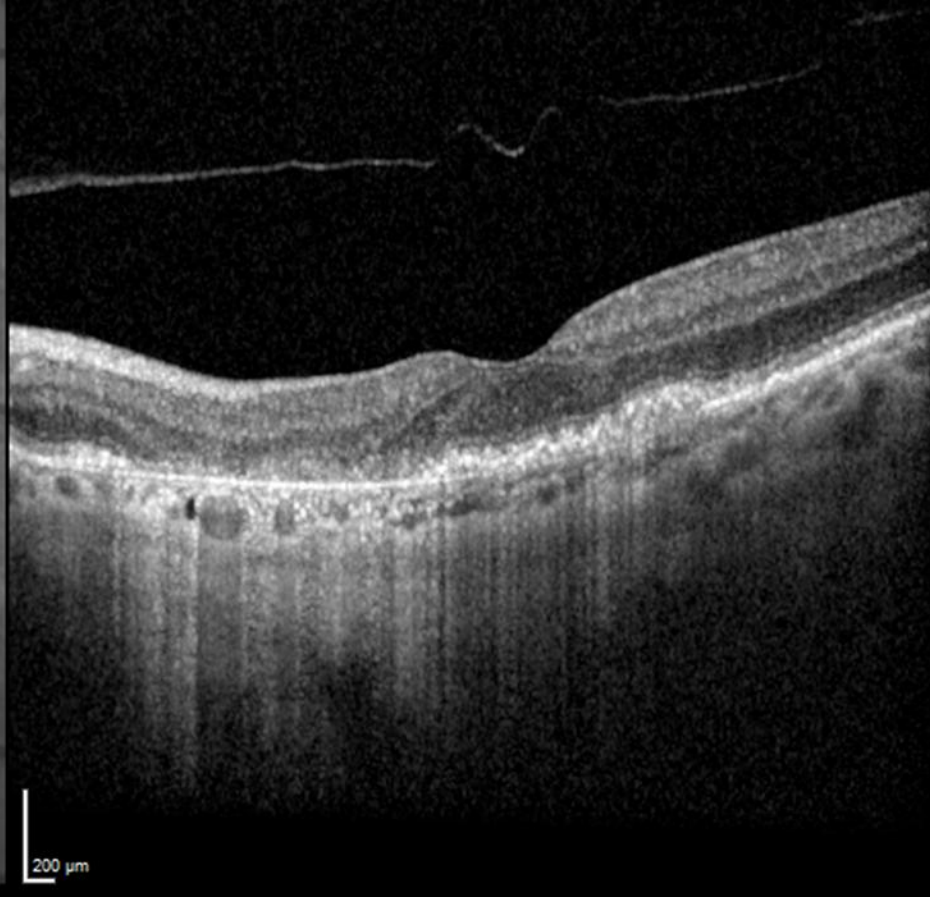
9/18/2018, OS

IR&OCT 30° ART [HS] ART(16) Q: 26



10/7/2020, OS

IR&OCT 30° ART [HS] ART(6) Q: 28



10/12/2022, OS

IR&OCT 30° ART [HS] ART(6) Q: 36

Syfovre?



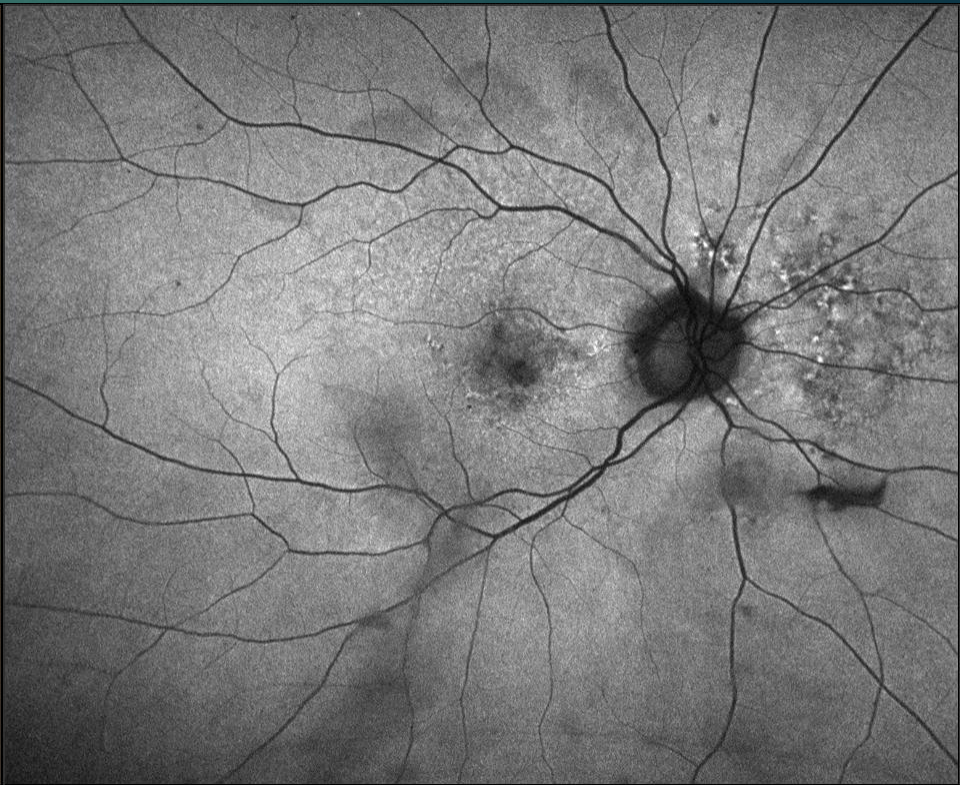
Case 5 - 77 YO WF

In 02/2023:

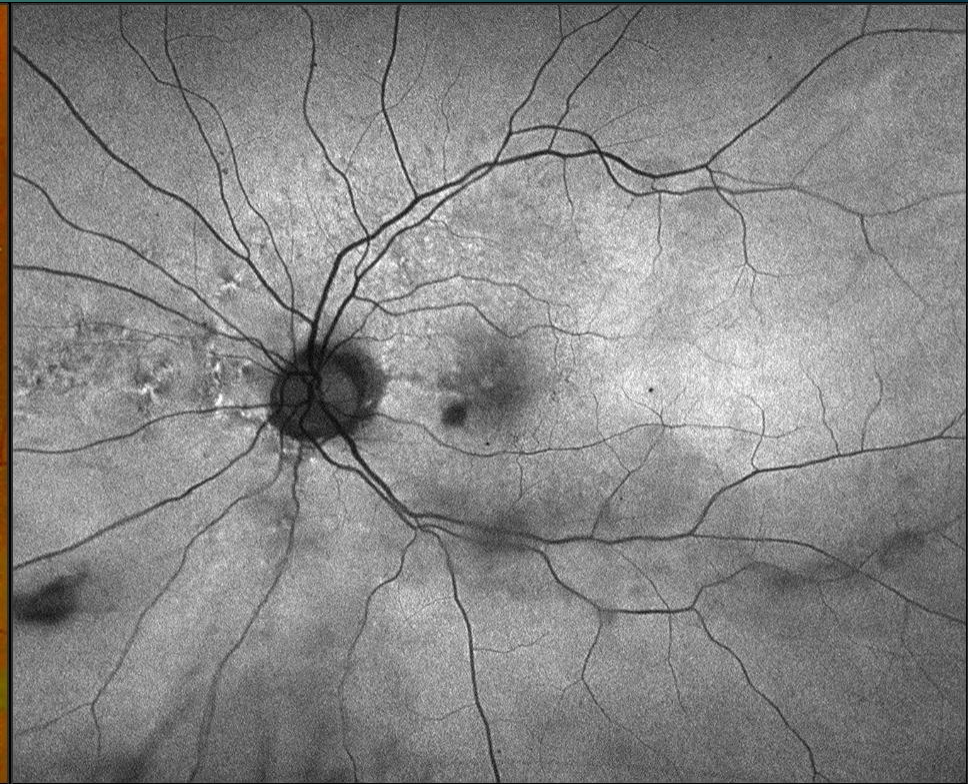
- ▶ Referral for dry AMD OU
- ▶ Currently taking AREDS2 daily
- ▶ (-) Former smoker, (-) FHx of AMD
- ▶ Med Hx: HTN, DM, Hyperlipidemia, Colon Cancer s/p Colectomy with Ileostomy

- ▶ VA (cc): OD: 20/70 PHNI
 OS: 20/40 PHNI

Case 5 - 77 YO WF



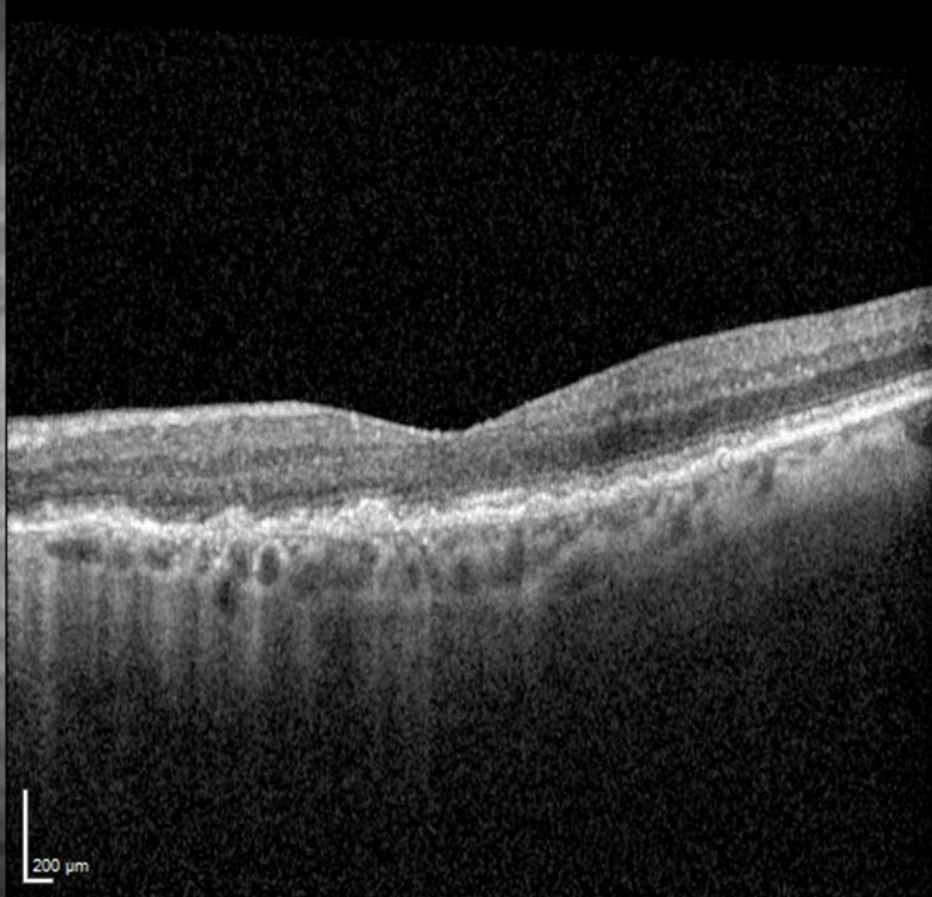
Case 5 - 77 YO WF





2/15/2023, OD

IR&OCT 30° ART [HS] ART(6) Q: 31



2/15/2023, OS

IR&OCT 30° ART [HS] ART(5) Q: 31

Case 4 - 71 YO WM

Diagnosis:

- ▶ Advanced Dry AMD
 - ▶ GA without subfoveal involvement OU

Treatment:

- ▶ Continue AREDS2
- ▶ Syfovre?

Questions?

