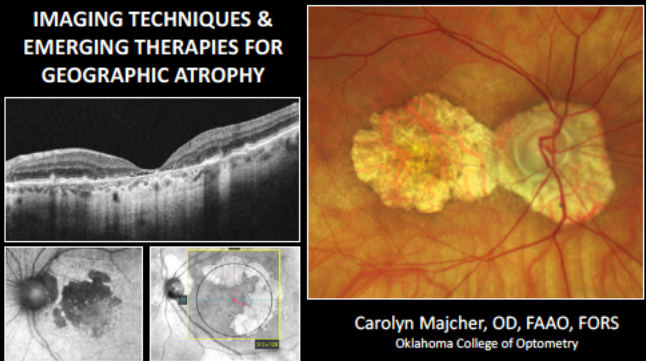


IMAGING TECHNIQUES & EMERGING THERAPIES FOR GEOGRAPHIC ATROPHY



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1

DISCLOSURES

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Disclosures:

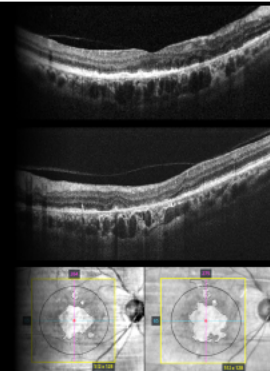
- Paid consultant/speaker for:
 - Carl Zeiss Meditec
 - Regeneron Pharmaceuticals
 - Iveric Bio
 - Optomed
 - Apellis Pharmaceuticals
- Paid advisory board member for LENZ Therapeutics, Notal Vision, Ocuterra
- Non-financial support (writing assistance) from Roche

All financial relationships have been mitigated

2

ROAD MAP

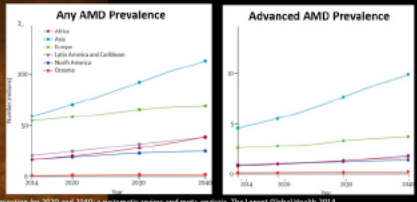
- Intro to AMD
- AMD staging/classification
- Geographic atrophy (GA)
- Imaging technologies for GA detection & monitoring
- New complement inhibition therapies for GA
- Referral considerations
- Patient education



3

AGE RELATED MACULAR DEGENERATION

- Leading cause of blindness in the developed world in persons >50yo
 - Characterized by drusen, RPE abnormalities, geographic atrophy (GA), choroidal neovascularization (CNV)
- Prevalence of AMD is expected to ↑ to 22 million by the year 2050
 - # of cases of advanced AMD is expected to ↑ from 1.7 million in 2010 to 3.8 million in 2050

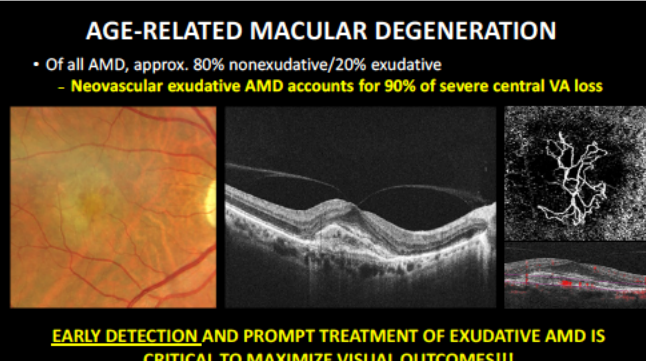


Global prevalence of AMD and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet Global Health 2014.

4

AGE-RELATED MACULAR DEGENERATION

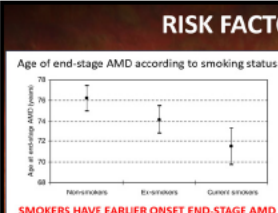
- Of all AMD, approx. 80% nonexudative/20% exudative
 - Neovascular exudative AMD accounts for 90% of severe central VA loss



EARLY DETECTION AND PROMPT TREATMENT OF EXUDATIVE AMD IS CRITICAL TO MAXIMIZE VISUAL OUTCOMES!!!

5

RISK FACTORS FOR AMD & GA



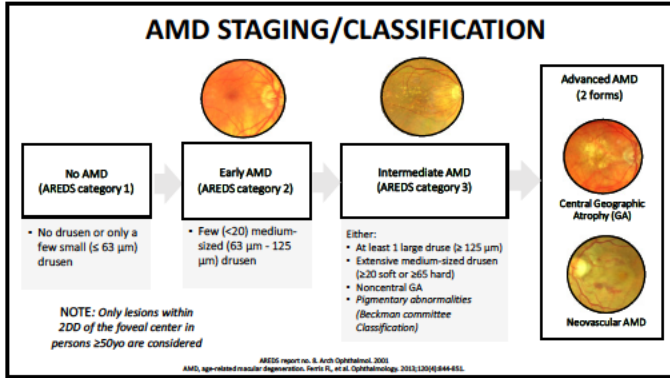
Age of end-stage AMD according to smoking status

SMOKERS HAVE EARLIER ONSET END-STAGE AMD

- Older age - (↑ risk of GA development)
 - No assoc with GA expansion
- Caucasian
- Genotype/family HX of AMD
 - ARMS2/HTRA1 (↑ risk of GA development & expansion)
 - CFH
- Smoking (↑ risk of GA development & expansion)
 - Most sig modifiable risk factor for AMD (odds ratios = 2.35-3.12 current vs never)
- Hypertension - (mild assoc)
- Heart disease - (mild assoc)
- High BMI/Obesity - (mild assoc)
- Hypercholesterolemia (high dietary cholesterol intake esp saturated fats and cholesterol)
- Diet low in omega 3, vitamins/minerals, carotenoids, antioxidants

American Academy of Ophthalmology. Preferred Practice Patterns. Age-related macular degeneration. Preferred Practice Patterns 2018. Retinal 15, 645-650. doi:10.1016/j.ppp.2018.03.003

6



7

INTERMEDIATE NON-EXUDATIVE AMD

AREDS category 3 Either:

- At least one large drusen ($\geq 125 \mu\text{m}$, \sim width of retinal vein at disc margin)
- Extensive medium-sized drusen (≥ 20 soft; ≥ 65 hard)
- Pigmentary abnormalities (Beckman Committee Classification)
- Noncentral GA

Risk for conversion to advanced AMD is $\sim 18\%$ within 5 years
★ **Image!!! & intentionally look for neo AND GA**
Monitor more frequently (~ 3 to 6 months), home self-screening (amsler/Foresee home), OTC AREDS 2 supplements, edu on diet & behavior modifications

8

AMD STAGING/CLASSIFICATION

Advanced AMD (AREDS category 4): 2 forms

- 1) Central GA
- 2) Neovascularization
 - Non-exudative
 - Exudative
 - Active
 - Inactive

Among pts that already have neovascular AMD in one eye, the risk for neo in the fellow non-exudative eye is $\sim 42\%$ at 5 yrs!!!

Needs anti-VEGF!

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AREDS AMD Staging/Categories

AMD Category	Drusen Size ¹	Drusen Area ²	Pigment Abnormalities ³	Neov. Eye
1	None or small ($< 63 \mu\text{m}$)	$< 125 \mu\text{m}$ diameter circle ($< 1 - 15$ drusen) total	None	None or Best eye
2	Small ($63 - 125 \mu\text{m}$)	$125 \mu\text{m}$ diameter circle (total 1-24 drusen)	Absent or present, but GA absent	None or Best eye or Category 1
3a	Intermediate ($125 - 175 \mu\text{m}$)	All small drusen OR medium-sized (total $> 125 \mu\text{m}$) pigment abnormalities present	Absent or present, but central GA absent	None or Best eye or Category 1 or 2
3b	Large ($\geq 175 \mu\text{m}$)	OR large ($\geq 175 \mu\text{m}$) OR none required, if intermediate GA is present	Absent or present, but central GA absent	None or Best eye or Category 1 or 2
4a	First eye worse or Category 3a, 3b, or 3c			GA $\geq 20\%$ in the fellow eye or AMD ⁴ or associated degenerating choroid in presence ⁵ of advanced AMD ⁶
4b	First eye worse or Category 3a, 3b, or 3c			GA $\geq 20\%$ due to AMD, but advanced AMD ⁷ not present ⁸

AREDS report no. 8 Arch Ophthalmol. 2001

10

GEOGRAPHIC ATROPHY (GA)

- Advanced/late form of dry AMD
- Irreversible atrophy of the RPE, photoreceptors & choriocapillaris (in the absence of neovascularization)
 - Atrophy = tissue loss/attenuation
- Affects > 8 million worldwide & 1.5 mil in US ($\sim 20\%$ w/ AMD)
- Accounts for 10-20% of legal blindness from AMD

AREDS Research Group. Change in Area of GA in the AREDS. AREDS report number 26. Arch Ophthalmol. 2008
Kwanen TJ, et al. AREDS2 Research Group. Progression of GA in AREDS2. AREDS2 Report #16. Ophthalmology 2018

11

RISK FACTORS FOR AMD & GA

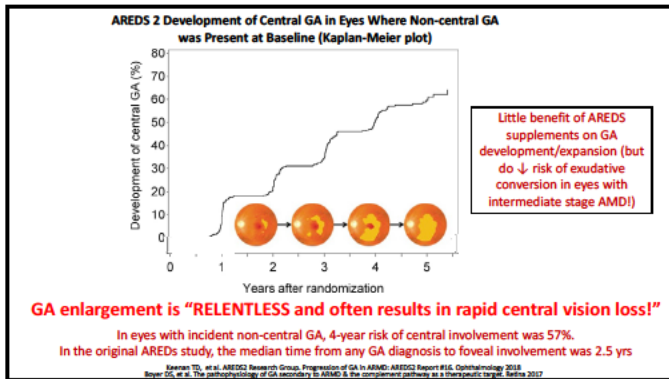
FASTER PROGRESSION!!!

- Central Monofocal
- Extrafoveal Multifocal
- Smaller lesions
- Larger lesions
- Bilateral GA

A. Growth rate of GA area according to baseline GA area

Kwanen TJ, et al. AREDS2 Research Group. Progression of GA in AREDS2. AREDS2 Report #16. Ophthalmology 2018
Kwanen TJ, et al. AREDS2 Research Group. Progression of GA in AREDS2. AREDS2 Report #16. Ophthalmology 2018

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THE FUNCTIONAL & MENTAL HEALTH IMPACTS OF AMD

- Areas of GA correspond to dense scotomas (areas of missing vision)
 - Even non-central GA can cause sig **difficulties with reading, facial recognition, mobility, driving, & independence**
 - Leads to **social isolation, ↑ risk of falls**
- **↑ risk for mental health problems in individuals with visual impairment from AMD (depression, anxiety)**
- Older adults with visual impairment are **2x more likely to have depression**
- **↑ rates of mortality & suicide among the visually impaired**

Burrows D, et al. Emotional and social consequences of age-related low vision. Vis Impair Res 2002
McCarty CA, et al. Vision impairment predicts 5 year mortality. Br J Ophthalmol 2001
Pietro L, et al. FAF and microperimetry in measuring GA secondary to AMD. British Journal of Ophthalmol 2012

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UTILITY OF IMAGING IN GA

- Color Fundus Photography (CFP)**
 - GA detection and monitoring (couple with other imaging modalities if available)
- Optical Coherence Tomography (OCT)**
 - Identify high risk biomarkers for progression to GA & advanced AMD
 - Identify and monitor GA enlargement
 - Predicting GA expansion
 - Detect conversion to exudative/neovascular AMD
- Scanning Laser Ophthalmoscopy (SLO)**
 - Similar to CFP & FAF (higher res FAF)
- Fundus Autofluorescence (FAF)**
 - Detection of early GA
 - Monitoring GA area
 - Predicting GA expansion
 - Visualization of reticular pseudodrusen/subretinal drusenoid deposits (SDDs)
- OCT Angiography (OCTA)**
 - Detect nonexudative neovascularization
 - Detect conversion to neovascular AMD

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GA IMAGING MODALITIES

- Color fundus photography (CFP)
- **Fundus autofluorescence (FAF)**
- Near-infrared reflectance (NIR)
- **OCT**
 - Cross sectional B-scan (AKA raster)
 - Enface OCT

Classification of Atrophy Meetings (CAM) Group

"It seems reasonable (and rather jolly marvelous) to incorporate information from multiple imaging sources to confirm the presence of GA"

A MULTIMODAL IMAGING APPROACH IS OPTIMAL for detection and measurement of GA and its associated features.

Holt, PG, et al. Imaging Protocols In Clinical Studies In Advanced AMD: Recommendations from Classification of Atrophy Consensus Meetings. Ophthalmology 2017

16

GA IMAGING- COLOR FUNDUS PHOTOGRAPHY (CFP)

- A **sharply demarcated, usually circular zone of partial or complete RPE depigmentation**, typically with **exposure of underlying large choroidal vessels**
- **Less sensitive in detecting early GA** and NOT an ideal way track enlargement over time

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FUNDUS AUTOFLUORESCENCE (FAF)

- Hyperfluorescence**
 - **Impending RPE damage/GA EXPANSION!**
 - Advancing zones of degeneration
 - Lipofuscin deposition
- Hypofluorescence**
 - **Disruption/loss of the RPE and/or photoreceptors**
 - Blockage

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GA IMAGING - FUNDUS AUTOFLUORESCENCE (FAF)

ONE OF THE PRIMARY METHODS USED TO DETECT & MONITOR GA LESIONS (SUPERIOR FOR EARLY GA DETECTION COMPARED TO CFP)!!!

GA = well-demarcated hypofluorescent or dark areas

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PROGNOSTIC VALUE OF GA PHENOTYPIC FAF PATTERNS

Slow Progression

No abnormality (0.38 mm²/yr)

Focal (0.81 mm²/yr)
Single or individual small spots of ↑ FAF adjacent directly to margin of GA

GA progression per year for the pooled data groups

Rapid Progression

Banded (1.81 mm²/yr)
↑ FAF adjacent directly to margin of GA in an almost continuous ring shape

Diffuse (1.77 mm²/yr)
↑ FAF at the margin and elsewhere

The GAIN Study. Am J Ophthalmol. 2015;160: 345-353.e5.
Holz FG, et al (FAM-Study Group). Progression of GA and impact of FAF patterns in ARMD. Am J Ophthalmol. 2007 Mar;143(3):463-72.

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PROGNOSTIC VALUE OF GA PHENOTYPIC FAF PATTERNS

Fastest Rate of Progression!!

Diffuse Trickling (3.02 mm²/yr)
Diffuse pattern + high intensity at margin that seeping towards the periphery

The GAIN Study. Am J Ophthalmol. 2015;160: 345-353.e5.
Holz FG, et al (FAM-Study Group). Progression of GA and impact of FAF patterns in ARMD. Am J Ophthalmol. 2007 Mar;143(3):463-72.

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GA IMAGING: NEAR-INFRARED (NIR) REFLECTANCE

Near-Infrared Reflectance

- On NIR GA is bright (hyperreflective)
- On FAF GA is dark (hypo-autofluorescent)

Fundus Autofluorescence

M. Pfau et al. Green-Light Autofluorescence Versus Combined Blue-Light Autofluorescence and NIR Imaging in GA Secondary to AMD. IOVS 2017

22

GA IMAGING - OCT ANGIOGRAPHY (OCTA) IMAGING OF GA

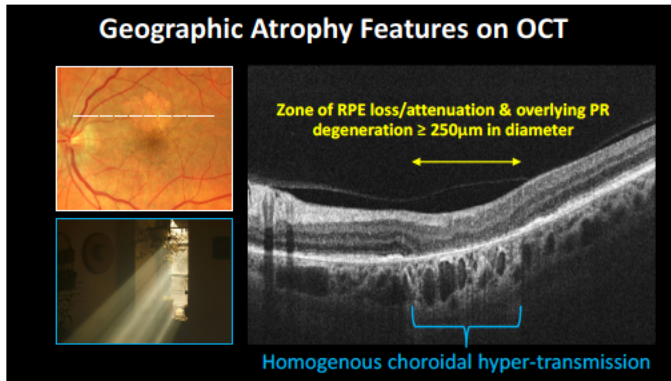
Highlights loss of the choriocapillaris (allows for visualization of the deep/larger choroidal vessels)

GA can easily be MISTAKEN for CNV!

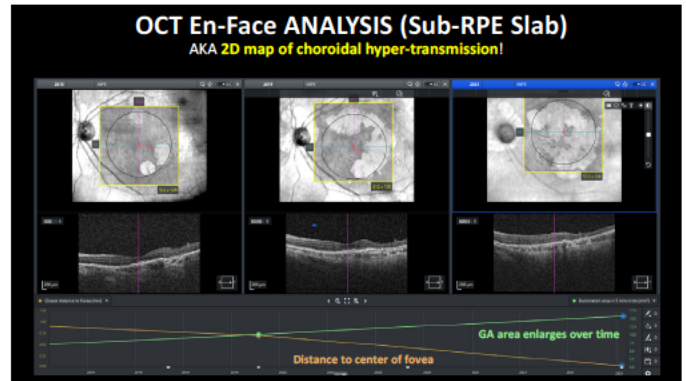
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OPTICAL COHERENCE TOMOGRAPHY (OCT)

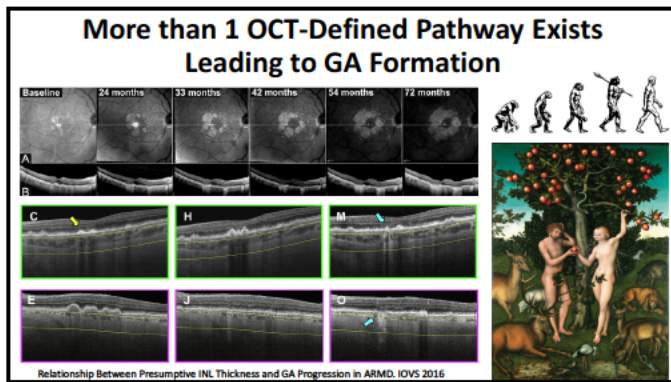
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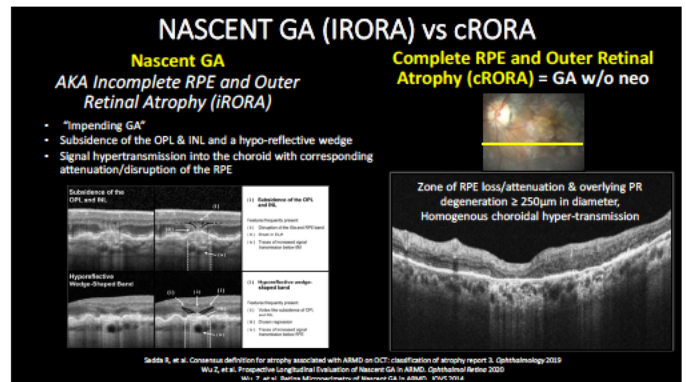
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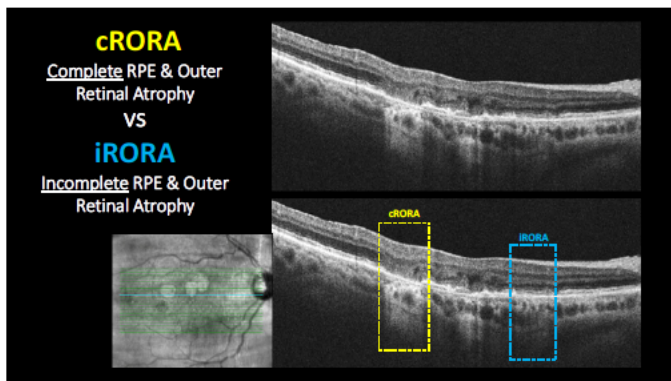
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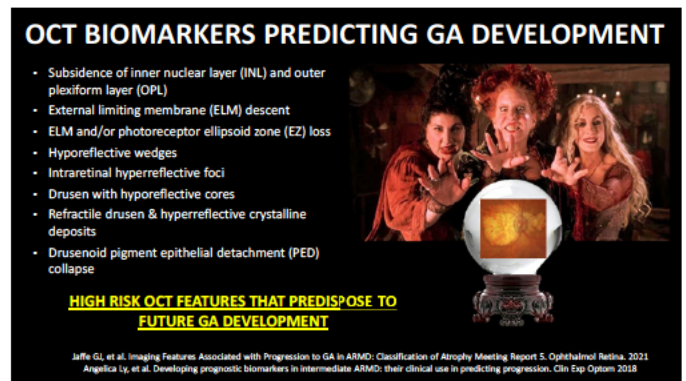
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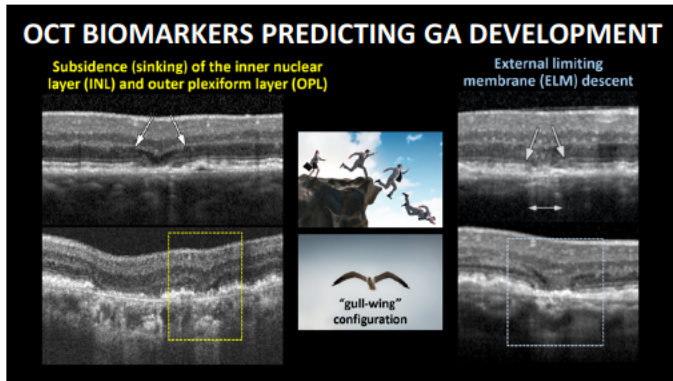
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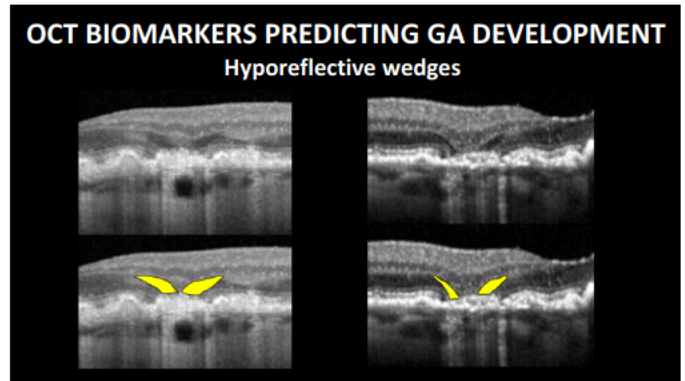
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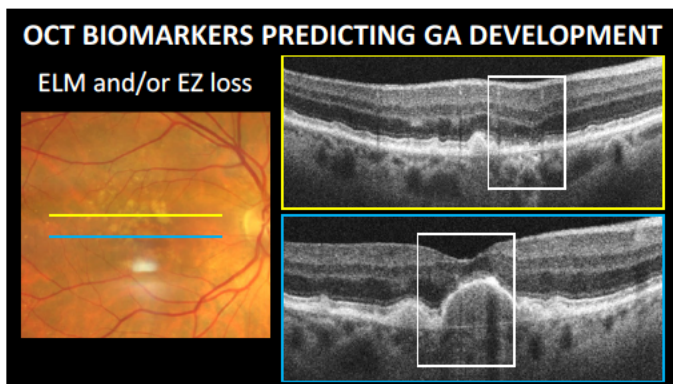
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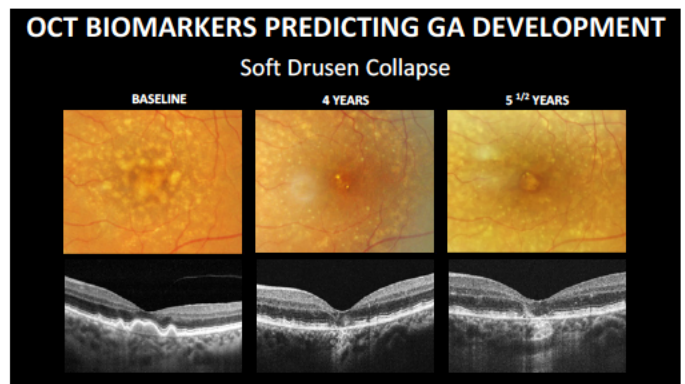
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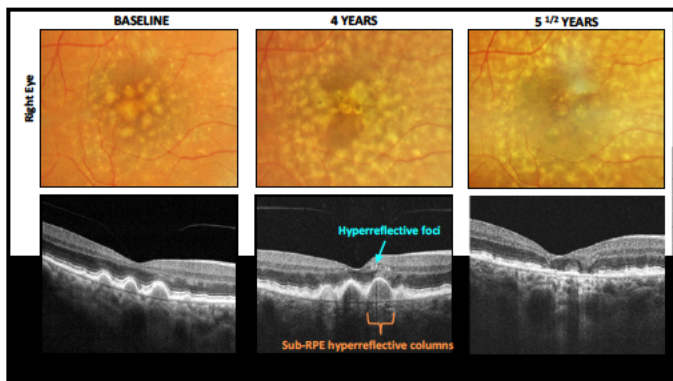
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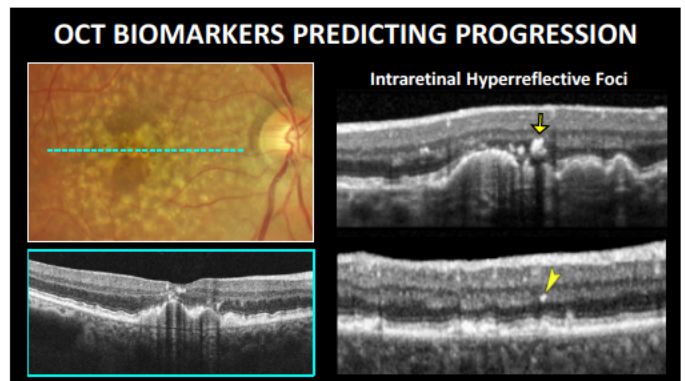
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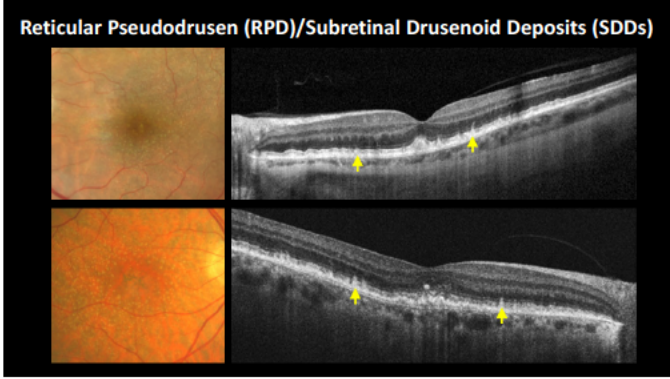
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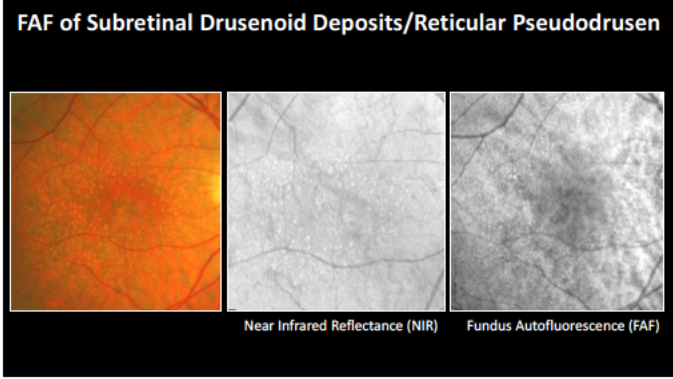
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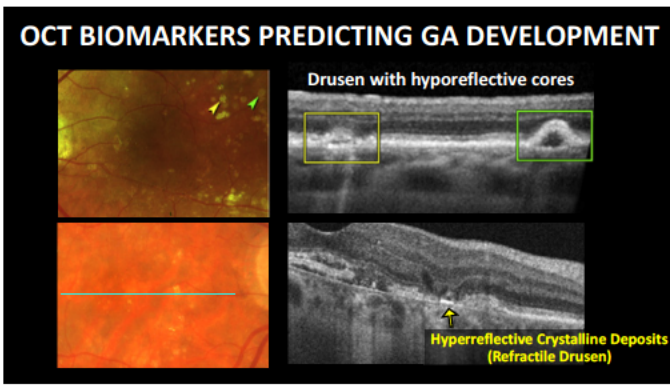
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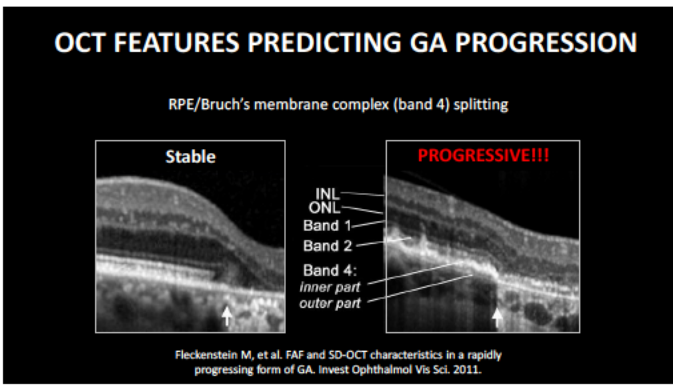
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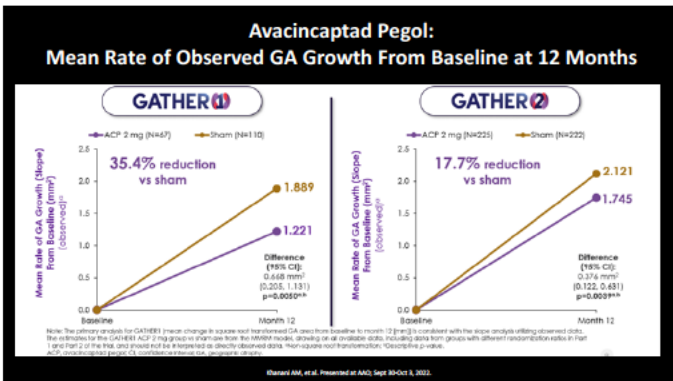
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Newly Approved Complement Inhibition Therapy for GA

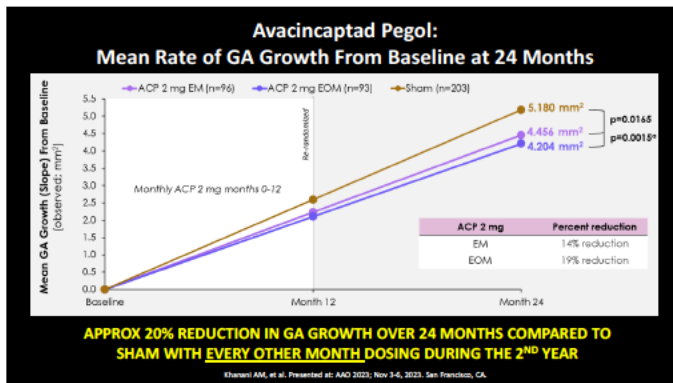
C5	Avacincaptad Pegol	Pegcetacoplan	C3
Approved Aug 2023	FDA Approval	Approved Feb 2023	
GA secondary to AMD/2mg intravitreal injection monthly for up to 12 months	FDA Indication/ Dosing	GA secondary to AMD/15mg intravitreal injection every 25-60 days (monthly or EOM)	
C5	MOA/Target	C3	
Gather 1 & Gather 2	Clinical Trials	OAKS & DERBY	
Only non-center point involving GA in part within 1500 µm from the foveal center included	Key differences in study design	GA secondary to AMD/15mg intravitreal injection every 25-60 days (monthly or EOM)	
Pts with CNV in fellow eye excluded		Only non-center point involving GA in part within 1500 µm from the foveal center included	
		CNV in the fellow eye was not exclusionary	

Inclusion criteria in all trials: - BCVA 20/320 or better, no neo or exudation in study eye
 - Total GA area between 2.5 - 17.5 mm² (1 - 7 disc areas) via FAF
Primary endpoint: Change in total GA lesion area on FAF

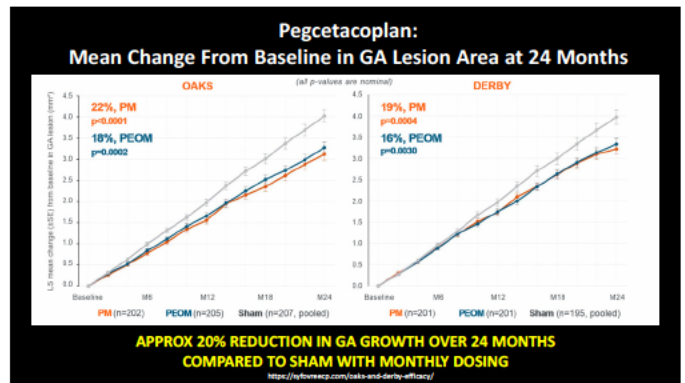
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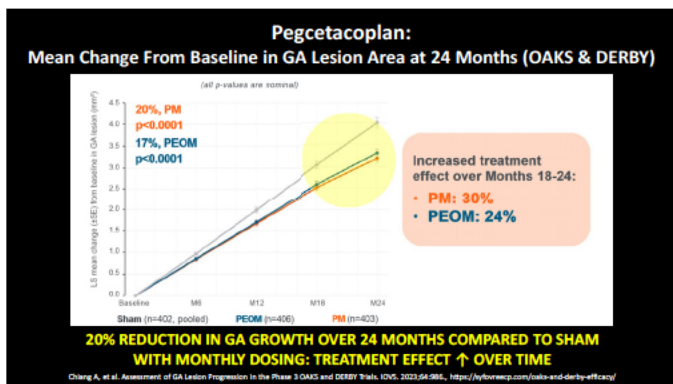
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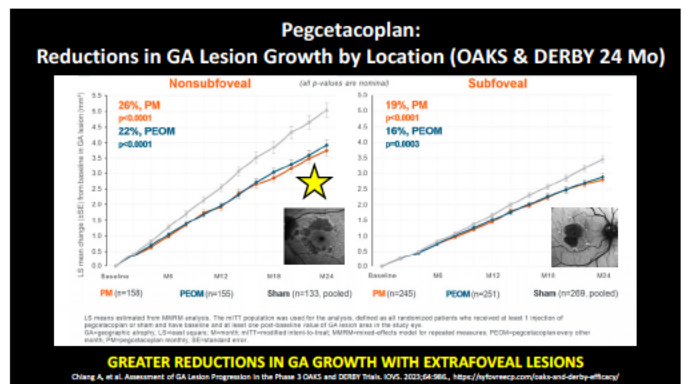
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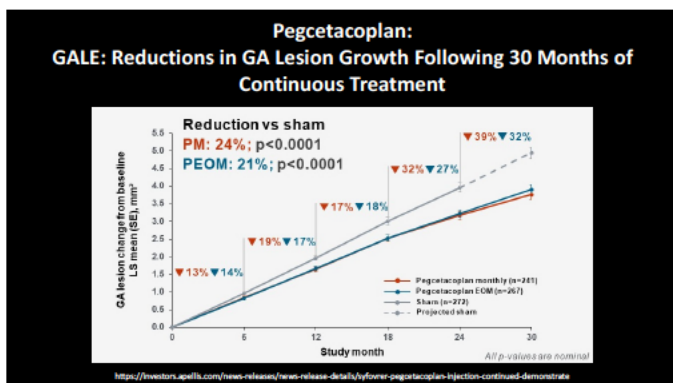
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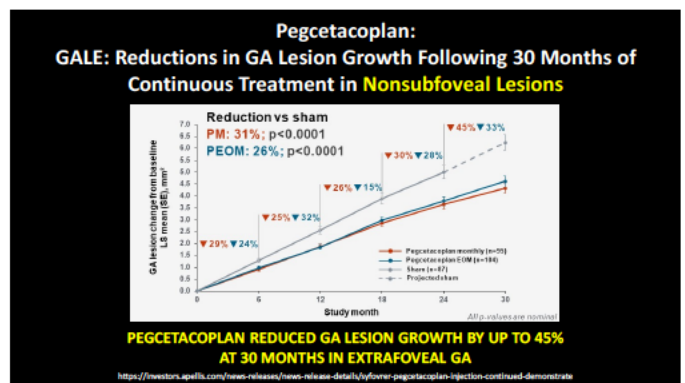
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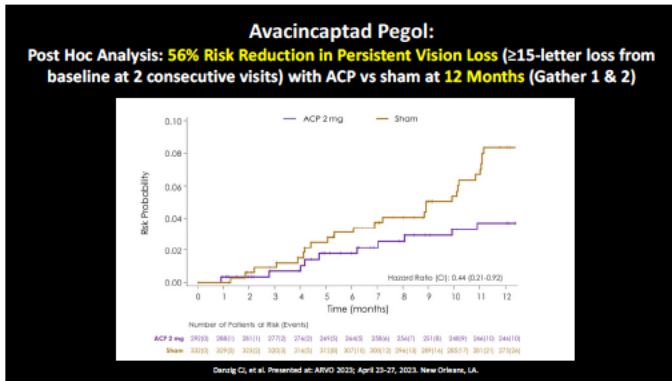
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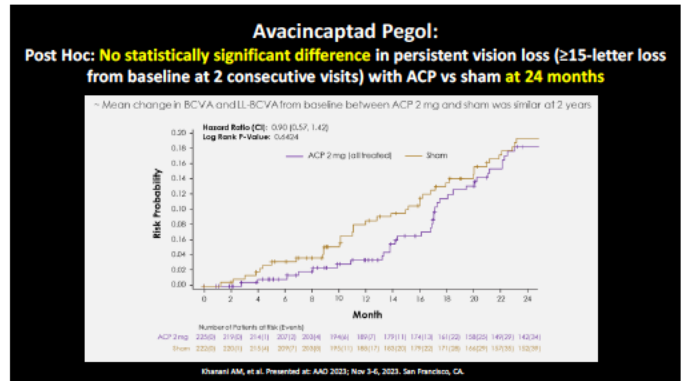
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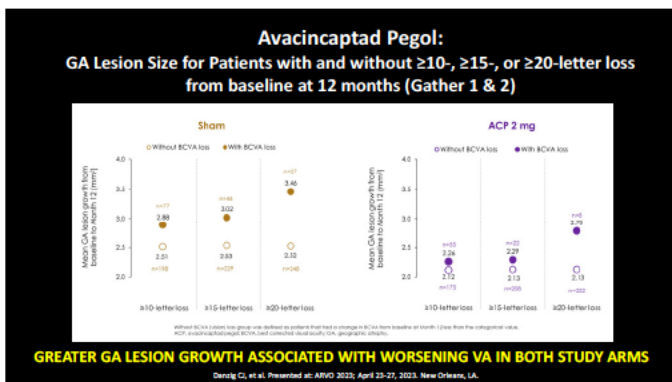
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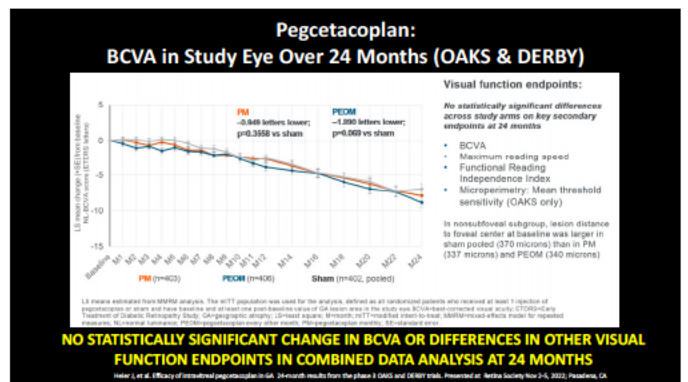
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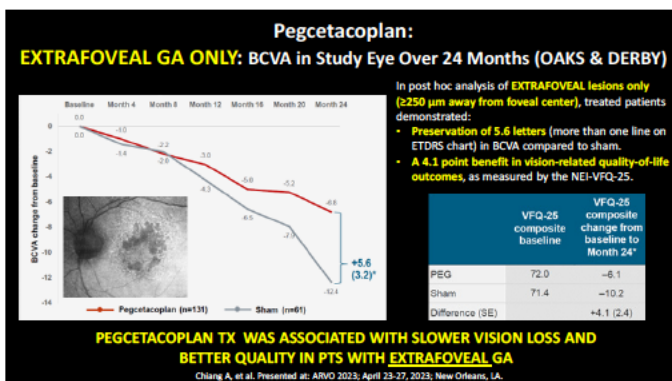
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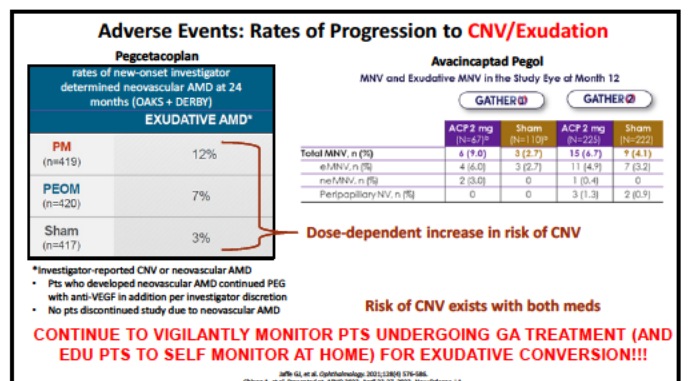
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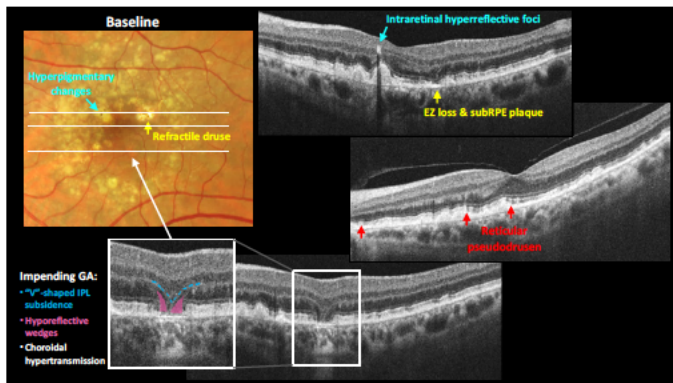
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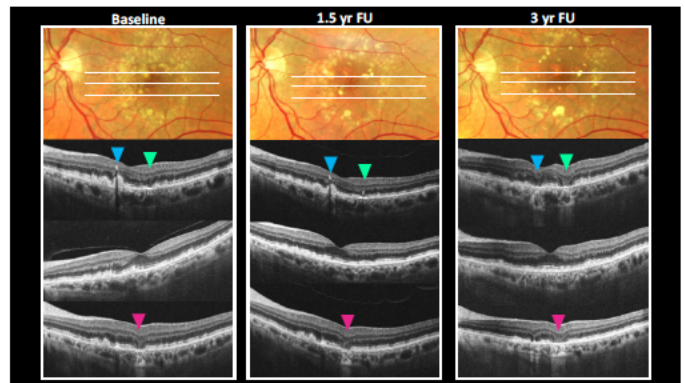
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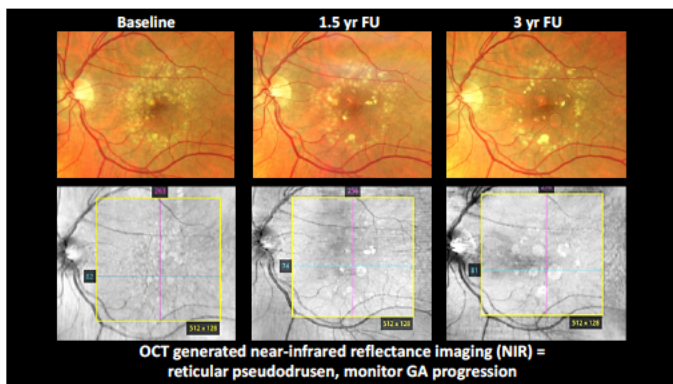
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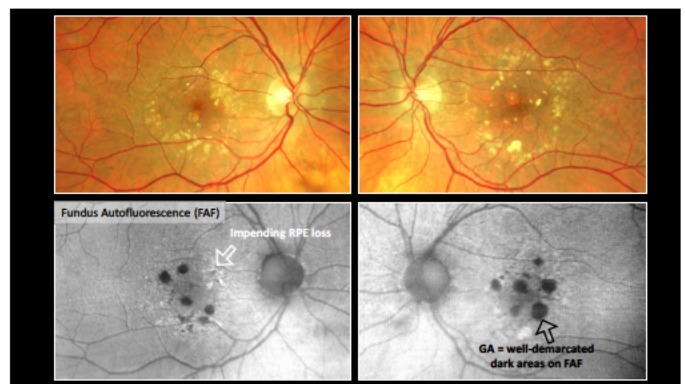
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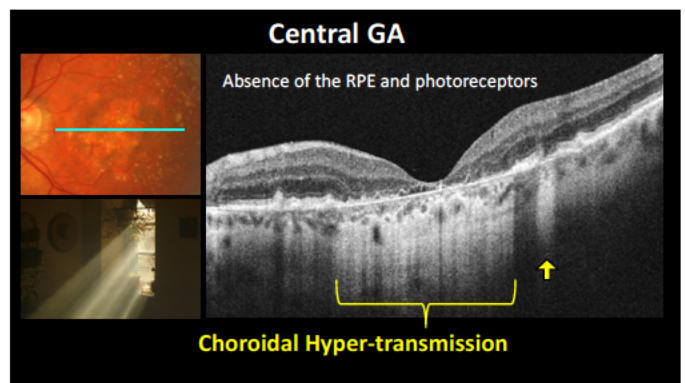
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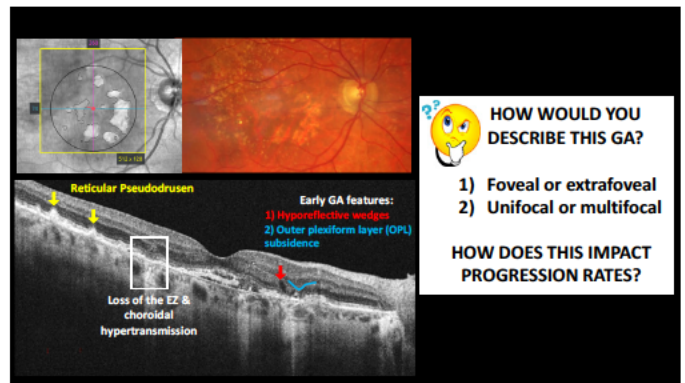
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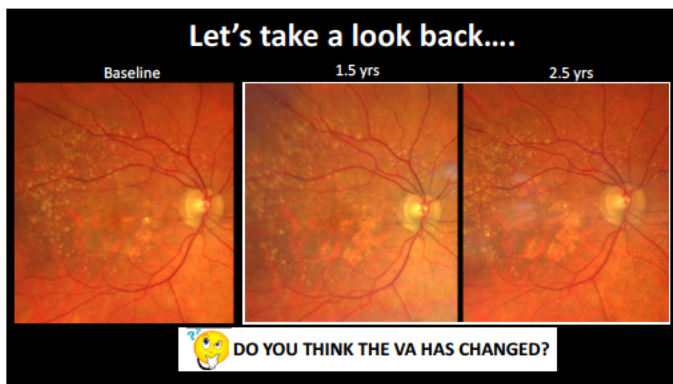
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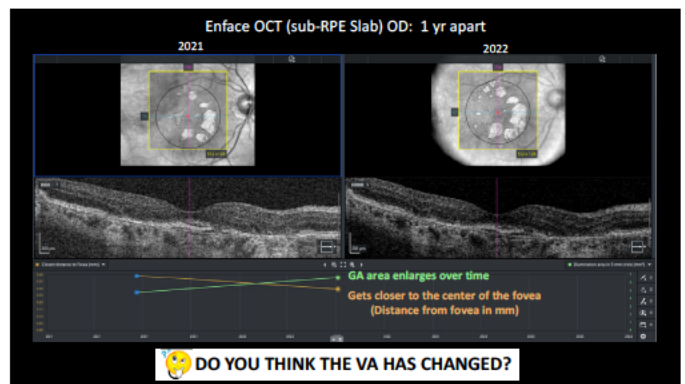
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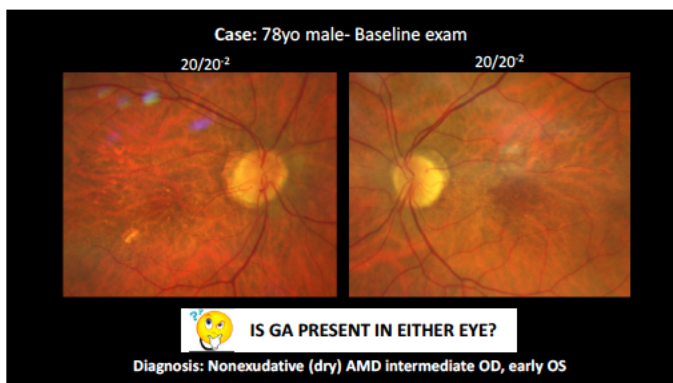
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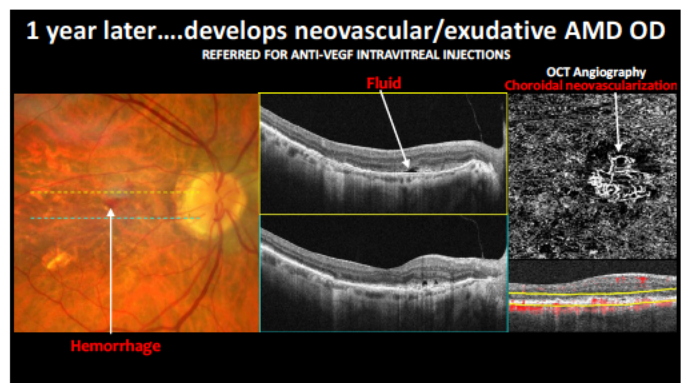
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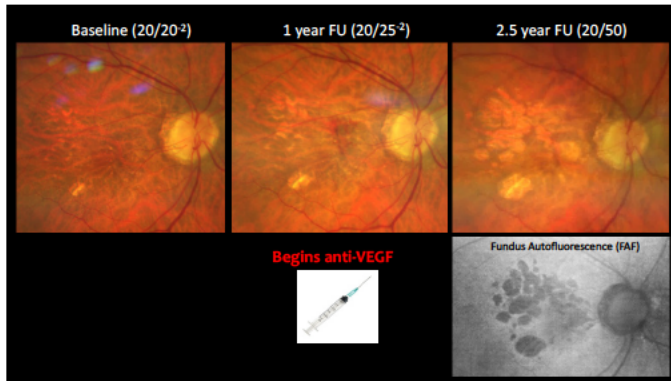
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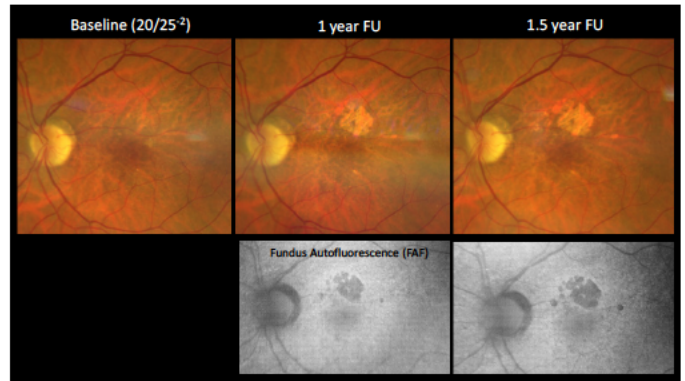
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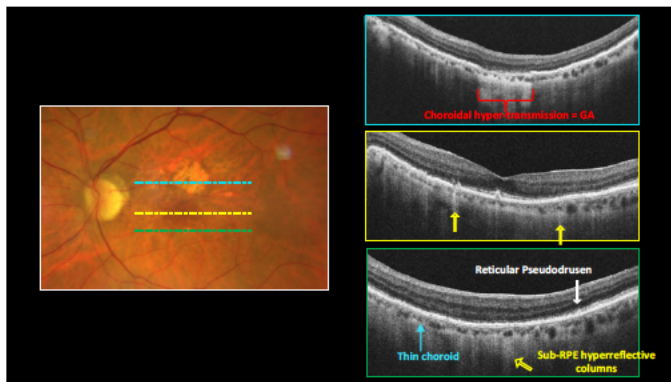
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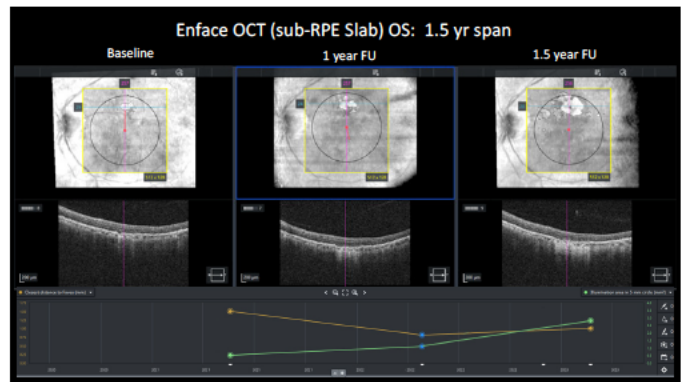
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GA Take Home Message

- OCT & FAF are the primary GA imaging modalities
- Be familiar with OCT features of GA & high-risk biomarkers
- Visual acuity (VA) often remains stable while extra foveal GA expands & comes closer to the center of the fovea (VA is a poor indicator of GA expansion)
- Once GA is central VA is severely and irreversibly affected
- OCT enface imaging allows for monitoring GA progression (also get quantitative data/trend analysis)
- Set realistic expectations when referring

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Thank You!

Majcher@nsuok.edu

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