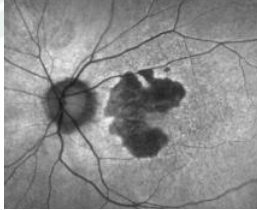


### Advances in Understanding Geographic Atrophy

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### Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board
  - Carl Zeiss
  - Allergan
  - Regeneron
  - Genentech
  - Tarsus
  - Orasis
  - Iveric
  - Apellis

2

**Release Details**      2/17/2023

FDA Approves SYFOVRE™ (pegcetacoplan injection) as the First and Only Treatment for Geographic Atrophy (GA), a Leading Cause of Blindness

February 17, 2023


- SYFOVRE slowed GA progression with increasing effects over time
- Approved for all patients with GA, with dosing flexibility every 25 to 60 days
- Well-demonstrated safety profile following ~12,000 injections over 24 months



3

August 4, 2023

Iveric Bio Receives U.S. FDA Approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a New Treatment for Geographic Atrophy



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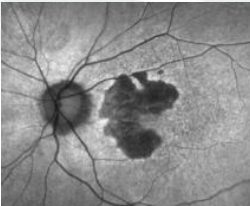


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Geographic Atrophy (GA) is a very hot topic!

6

### Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2<sup>o</sup> to CNV




- Patients Affected
  - 90% dry or nonexudative
  - 10% wet or exudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry

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### Neovascular AMD: Risk Factors

- Emerging risk factors
  - Age<sup>1</sup>
  - Race<sup>2</sup>
  - Smoking<sup>2</sup>
  - Family history<sup>3</sup>
  - Variation in the complement factor H gene<sup>4,6</sup> and other genes<sup>7</sup>



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### Late AMD = GA OR Neovascular AMD

**Globally, late AMD affects<sup>1</sup>**

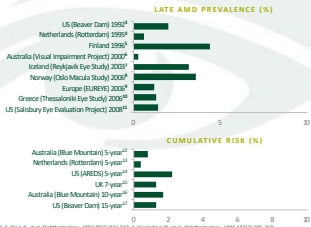
- 2020: >11 million
- 2040: >18 million

**Prevalence increases with age**

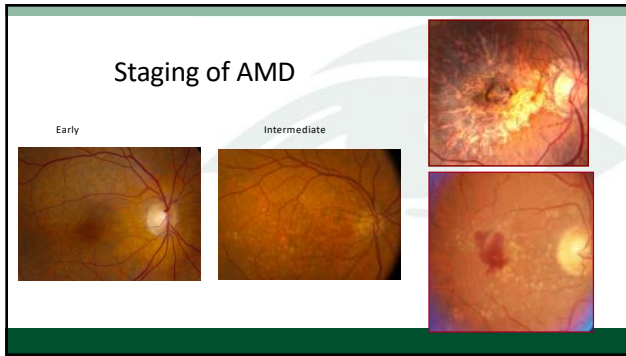
- From age 50: prevalence quadruples every 10 years of age<sup>2</sup>

**Geographic atrophy**

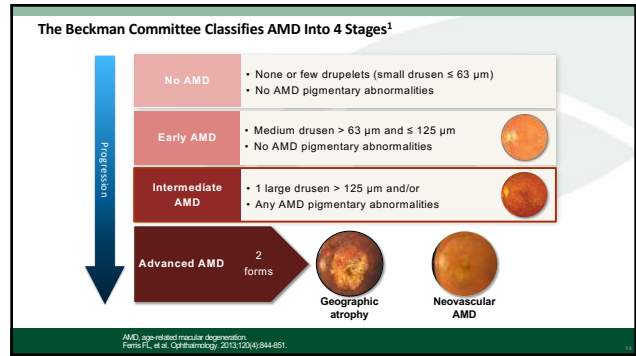
- Accounts for ~35% of late AMD and 20% of legal blindness attributed to AMD<sup>3,9</sup>



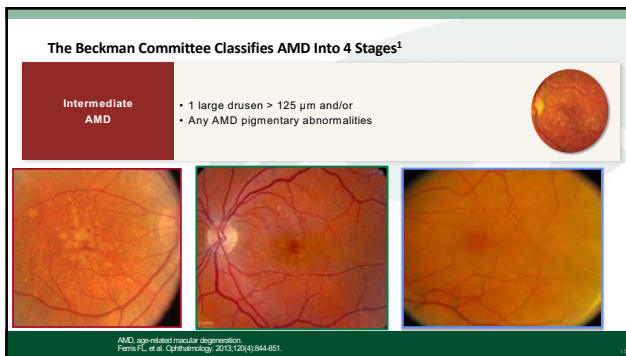
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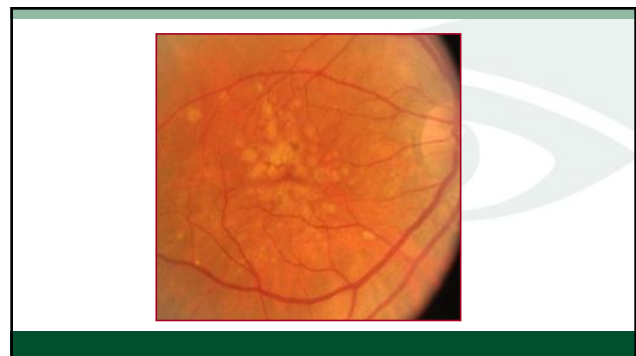
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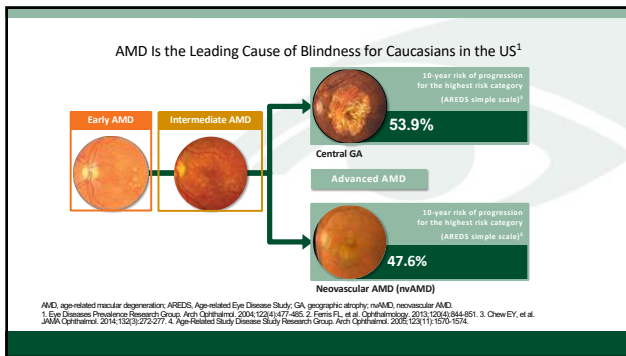
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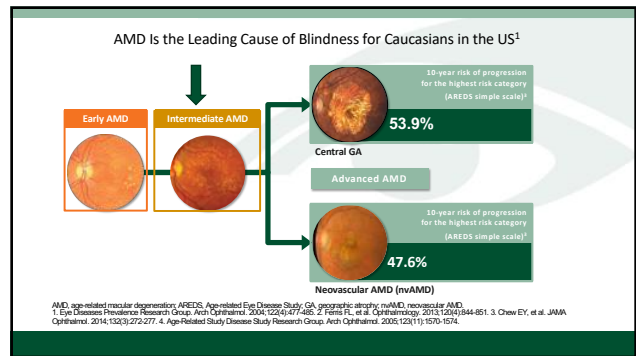
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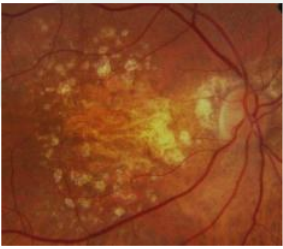
17



18

### Geographic Atrophy

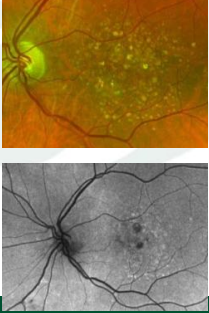
- Advanced/late form of dry AMD
- Atrophy of the RPE and photoreceptors



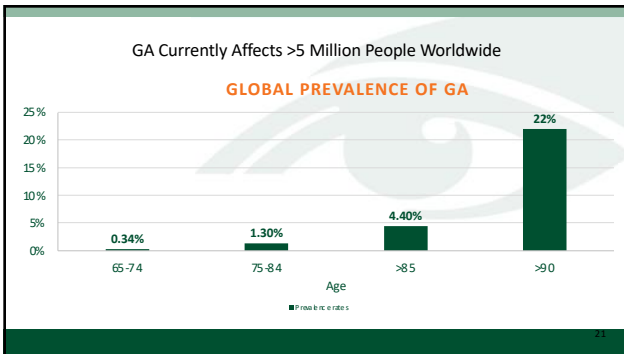
19

### GA Is More Common Than We Realize?

- We haven't been looking for it
  - In part because there was no treatment
- The focus has been detecting the conversion from dry to wet
- Often starts extrafoveal and small
  - Unless you are looking for it – you may not realize that it is present

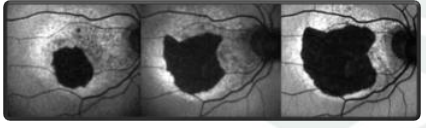


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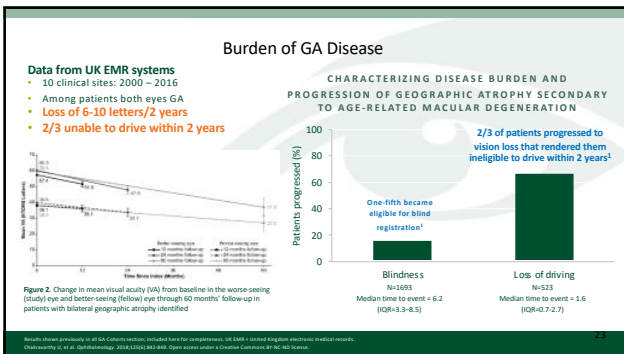
### Progression of GA is Slow – BUT not that Slow!



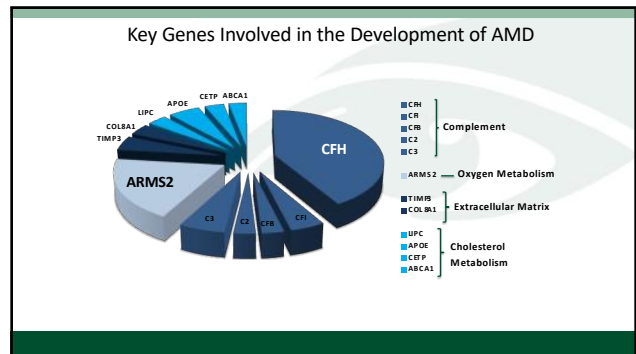
- On average, GA lesions enlarge by 1.5 to 2.1 mm<sup>2</sup>/year (0.6 to 0.8 MPS disc areas)<sup>1,2</sup>
- Median time to evolution of GA:<sup>3</sup>
  - 2.5 years:** median time to develop central GA (after GA diagnosis)
  - 7 years:** median time to develop bilateral GA (i.e. GA in both eyes) after development of GA in the first eye
- Previous lesion involvement predicts subsequent enlargement<sup>2</sup>

1. Holz FG, et al. Am J Ophthalmol 2007;143:469-72; 2. Sunness RS, et al. Ophthalmology 2007;114:271-7; 3. Lindblad AS, et al. Arch Ophthalmol 2009;127:1168-74.

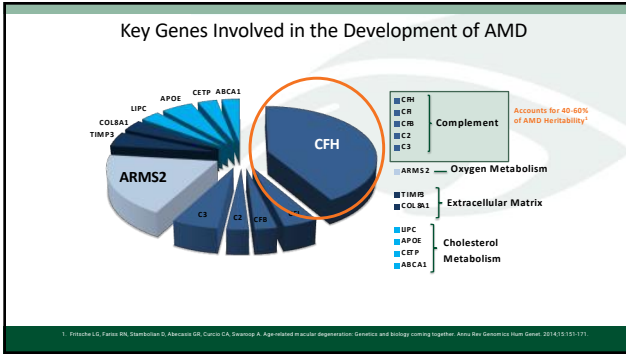
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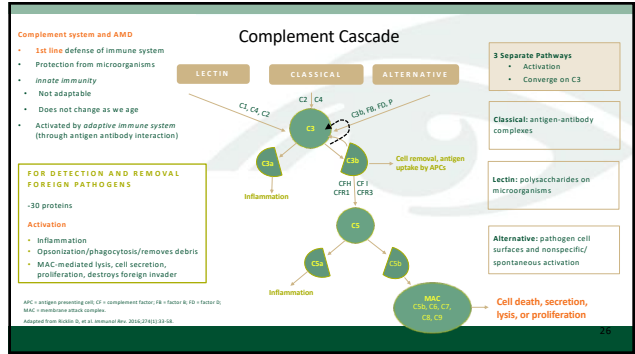
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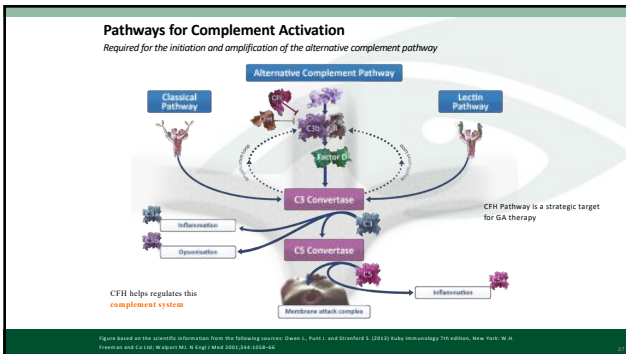
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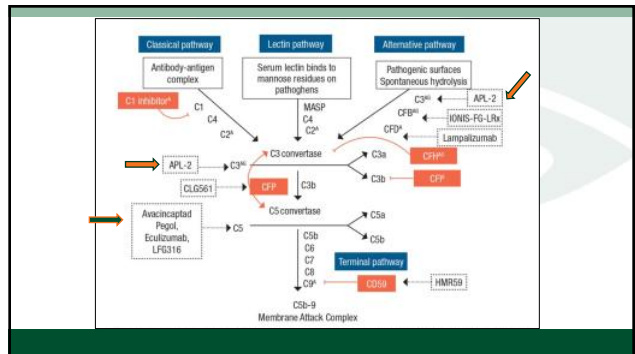
25



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### Graveyard of Failed CFH Inhibitors – 1<sup>st</sup> Generation

- ✘ Eculizumab**
  - C5 inhibition
- ✘ LFG-316**
  - C5 inhibition
- ✘ Lampalizumab**
  - Factor D inhibition

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### Current FDA Approved Complement Inhibitors – 2<sup>nd</sup> Generation

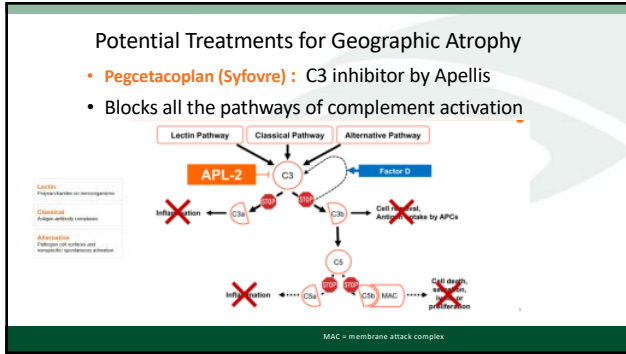
**NOVEL THERAPIES FOR GA THAT TARGET THE COMPLEMENT PATHWAY**

Study drug (Company)	Complement Target	Delivery Method	Current Trial Phase	Most Recent Trials	Study Status
Avacincaptad pegol (Iveric Bio)	C5	IVI	3	GATHER2 GATHER1	Complete
Pegcetacoplan (Apellis)	C3	IVI	3	OAKS, DERBY	Complete

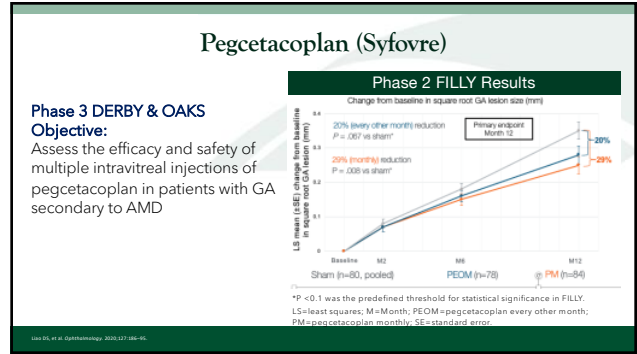
GA, geographic atrophy; IM, intravitreal injection

Lee Y, Patel D. Geographic Atrophy: Targeting the Complement Pathway. Retina Today. November/December 2021. <https://www.retinatoday.com/retina/2021/11/04/geographic-atrophy-targeting-the-complement-pathway/> (accessed March 15, 2022).

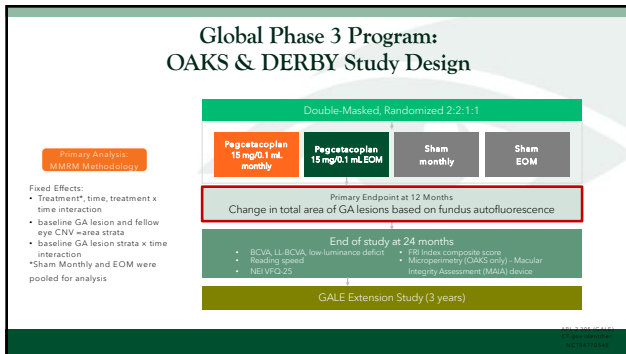
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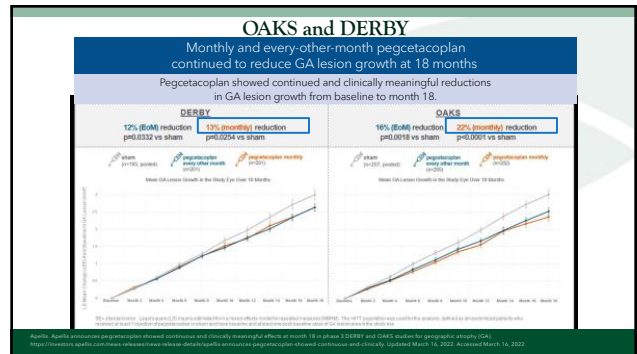
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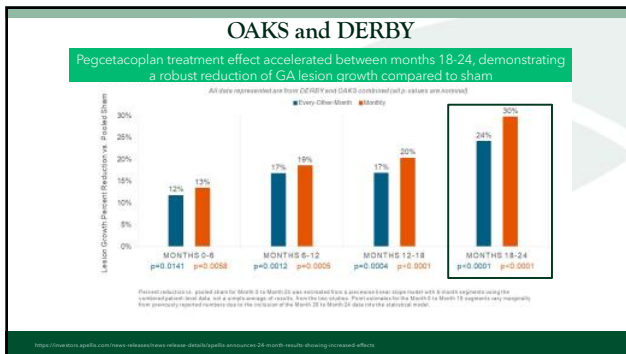
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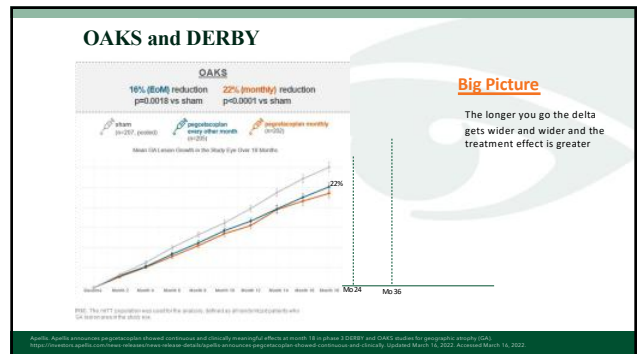
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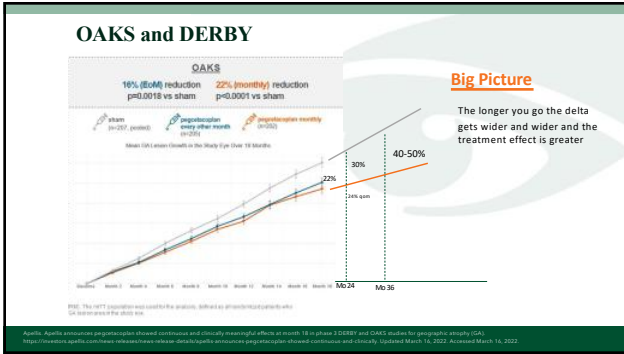


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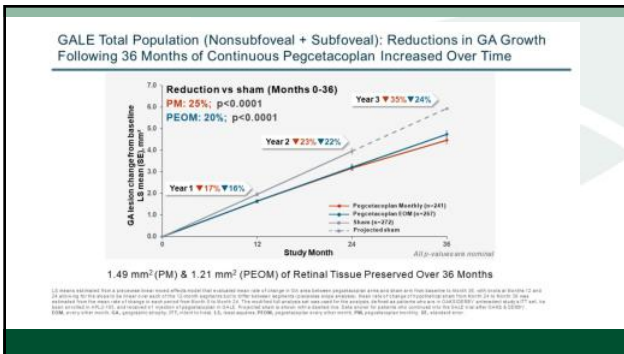
37

### BREAKING NEWS

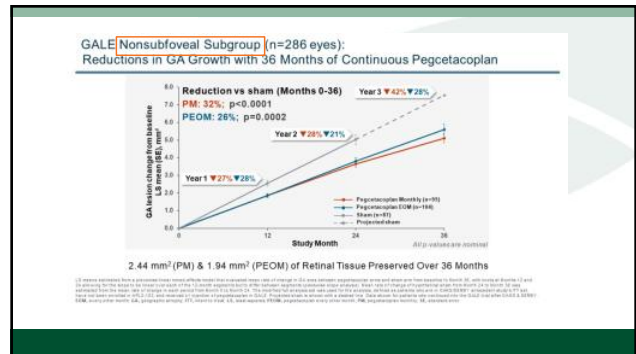
#### Latest News from AAO Nov 2023

- Gale Study: 3 Year Extension Study of 792 patients
- Pegcetapoplan (Mo and EOM) showed increasing effects over time
  - Reductions in GA growth of 35% and 24%, respectively, between months 24 and 36
  - **Non Subfoveal GA: reduced growth rate by up to 45% between treatment months 24 to 30**

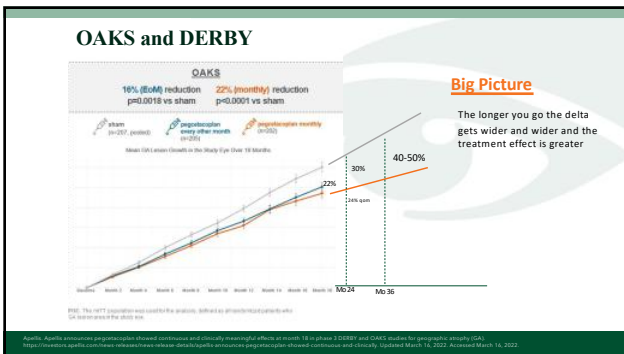
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### Pegcetapoplan: Take-Away Points

- The primary endpoint was a change in GA lesion size from baseline
- There was no prevention of vision loss
  - 60% of patients randomized had subfoveal lesions
- GA not getting better – just getting worse more slowly
- Seems to be more effective the longer patients received the medication or does it just take longer to see the benefit?
  - In a disease that is slow growing?

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Apellis: Pegcetacoplan

Is that a significant treatment effect for GA?

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ASRS American Society of Retina Specialists

July 19, 2023

ASRS reports six cases of occlusive retinal vasculitis linked to pegcetacoplan injection

Jul 19, 2023  
David Hutton

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Pegcetacoplan (Syfovre) – Serious Adverse Events (SAE’s)  
Here is what we know

- July 15 initial email from ASRS describing 6 cases of occlusive retinal vasculitis
- Developed between 7-13 days after initial injection
- To date: 83,000 total injections
  - 1 in 10,000 risk
  - Lower than endophthalmitis
  - Is that an acceptable risk?
- Retinal specialists are “spooked”
- AAO: IOI = 0.26% per injection among all patients treated

45

Avacincaptad Pegol (Izervay): Iveric

August 4 Iveric Bio Receives U.S. FDA Approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a New Treatment for Geographic Atrophy

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving Izervay in the U.S. was 25.5 - 35.0%

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Avacincaptad Pegol: Iveric

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving AP in the U.S. was 25.5 - 32.0%

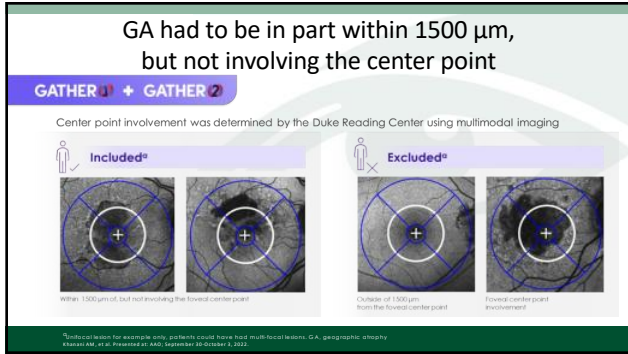
47

C5 Activation

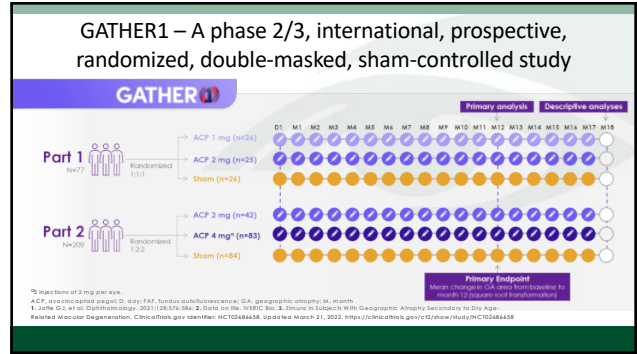
- C5a is a priming agent for inflammasome activation in RPE cells
- C5a upregulates inflammasome-related genes
- Inflammasome activation increases levels of IL-1β and IL-18 (both induce RPE degeneration)
- NLRP3 inflammasome, IL-1β, and IL-18 are present in postmortem eyes with geographic atrophy secondary to dry AMD
- C5b causes MAC formation
- Lipofuscin component bisretinoid A2E prevents clearance of MAC in RPE cells, leading to accumulation and inducing mitochondrial damage and cell death

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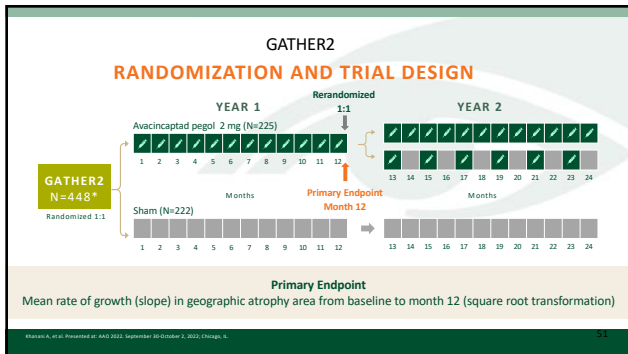




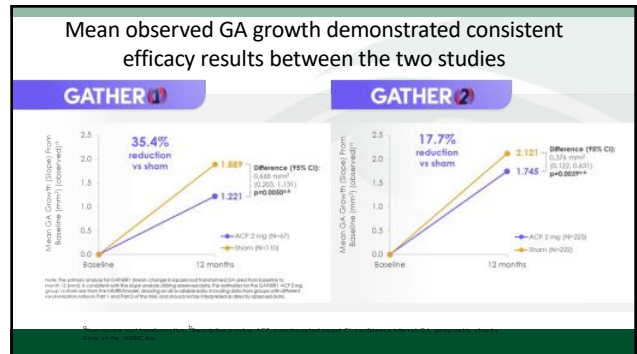
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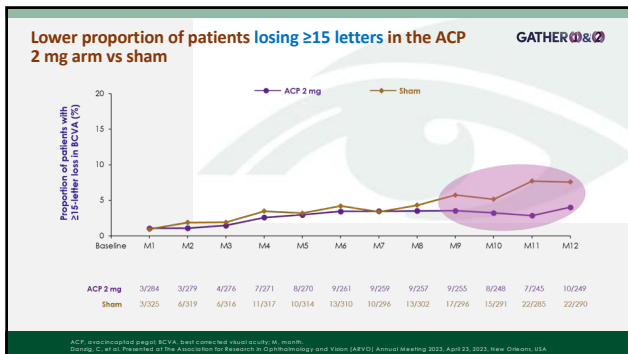
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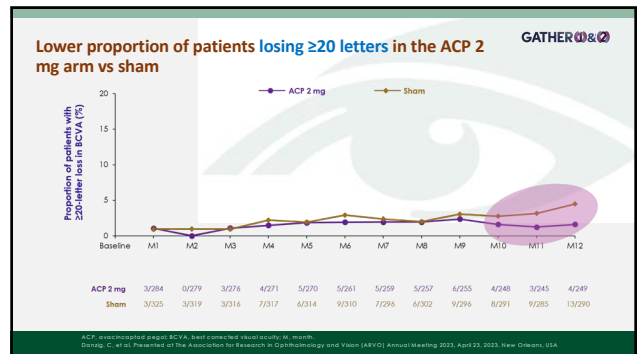
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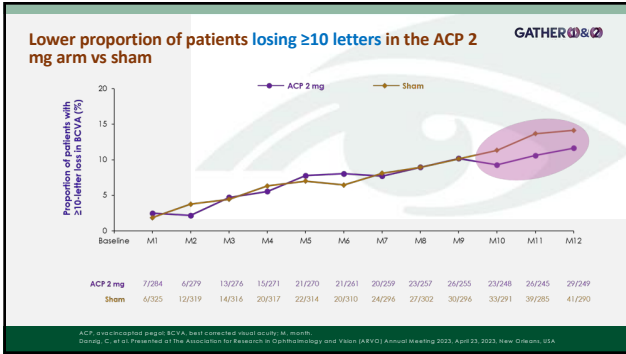
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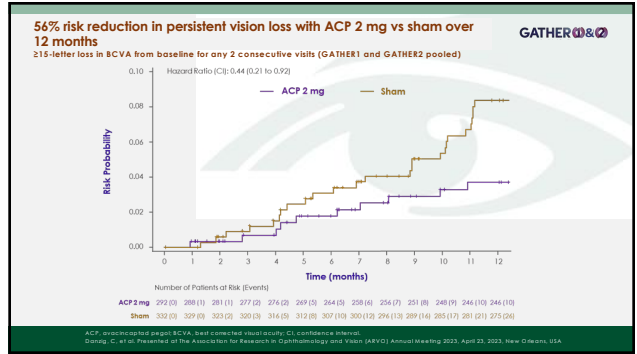
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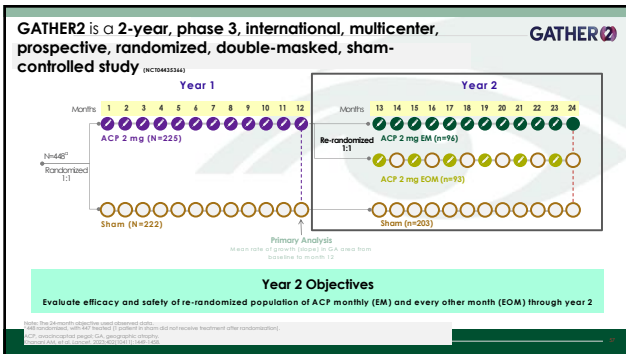
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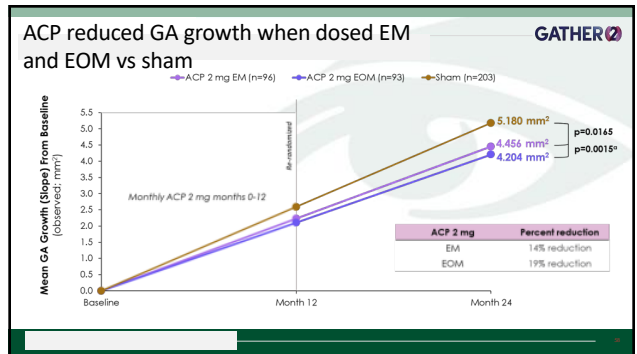
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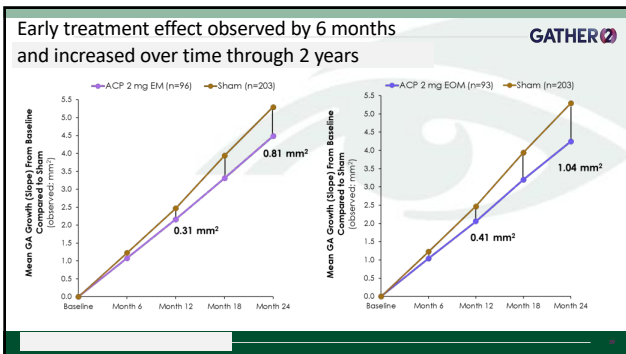
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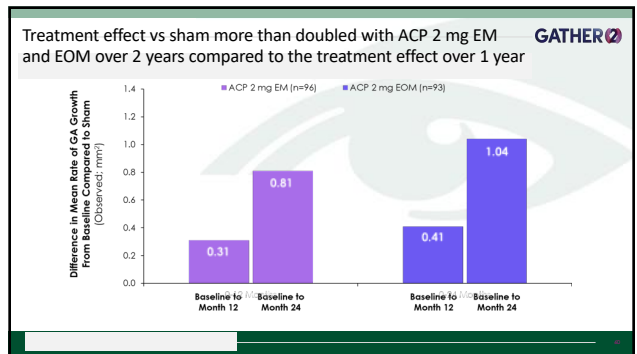
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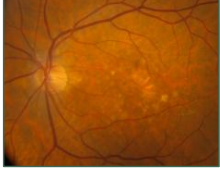
**Cross-trial comparison of Zimura and intravitreal pegcetacoplan in geographic atrophy**

Project (company)	Zimura (Iveric Bio)		Intravitreal pegcetacoplan (Apellis)			
	Gather2	Gather1	Derby		Oaks	
Trial			Monthly	Every other month	Monthly	Every other month
Change in GA area vs sham at 12mo	14%*	27%*	12%	11%	22%	16%
p value	0.0064	0.0072**	0.0528 (N/S)	0.0750 (N/S)	0.0003	0.0052
Choroidal neovascularisations	7%***	9%***	7%^	3%^	5%^	5%^

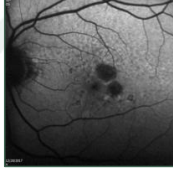
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### Imaging Modalities in Diagnosing and Monitoring AMD


Color Fundus Photography (CFP)



Autofluorescence



OCT



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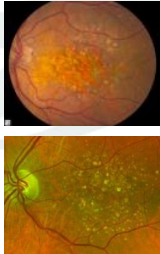
### Limitation of Color Fundus Photos for GA Detection

**Definition of GA by color imaging:**

- Sharply demarcated borders
- Depigmentation
- Increased visibility of choroidal vessels

**CONS**

- Often insufficient contrast
- Smaller lesion can easily be missed

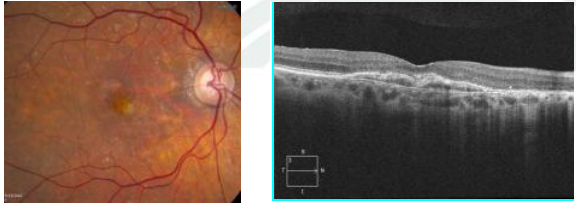


16016, 41 et al. Ophthalmology. 2017;124(6):1464-1476. Images courtesy of Christine K. Boudreau, MD, FRCPC.

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### OCT for AMD Detection

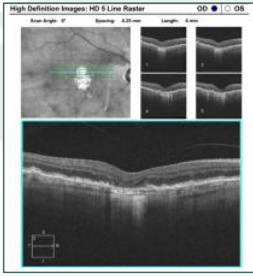
Focus has been on conversion from dry to wet



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### OCT for GA Detection

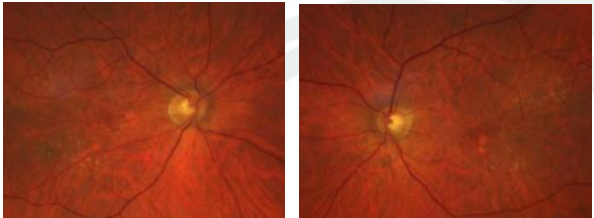
- Recognition of GA features on b-scan
  - Hypertransmission defect
- Important to look at en face image
  - Or the IR image
- Recognition of biomarkers for progression



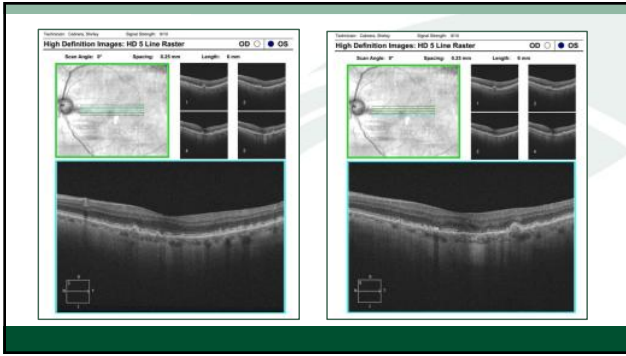
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### 79-year-old White Male with Intermediate Dry AMD

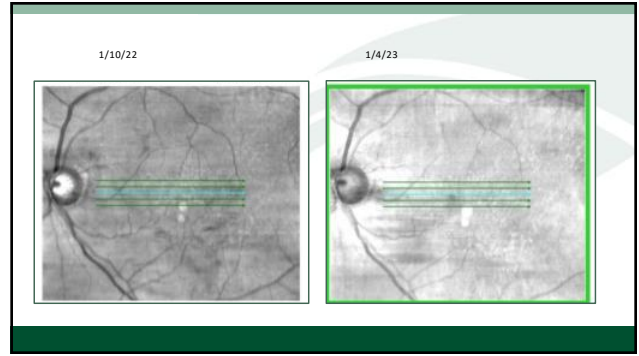
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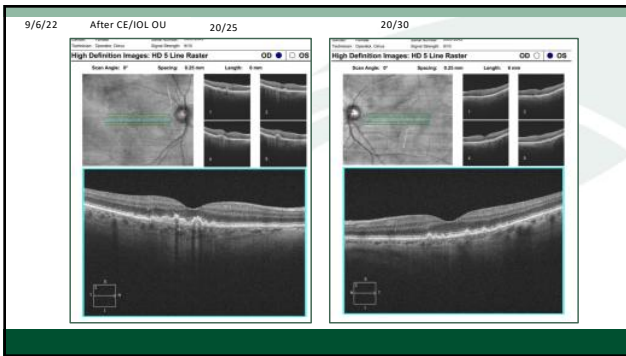
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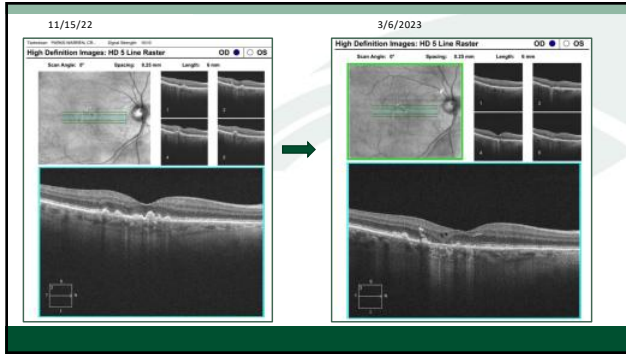
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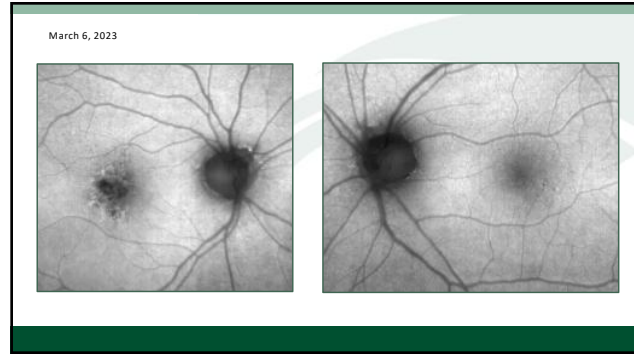
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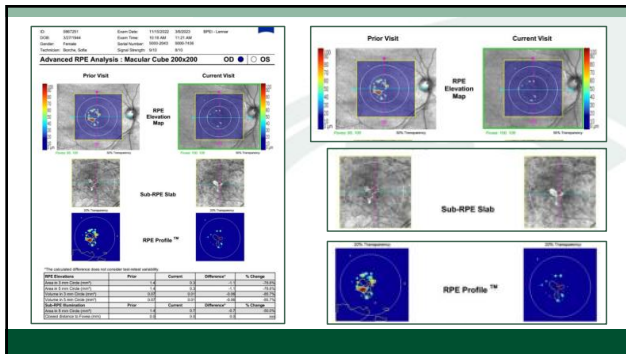
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### Blue Light Fundus Autofluorescence (FAF)

- GA is one of the most important applications of FAF
- GA is identified as large patches of decreased autofluorescence
- Good for documenting progression
- Enlargement of GA on FAF was a key outcome measure in clinical trials

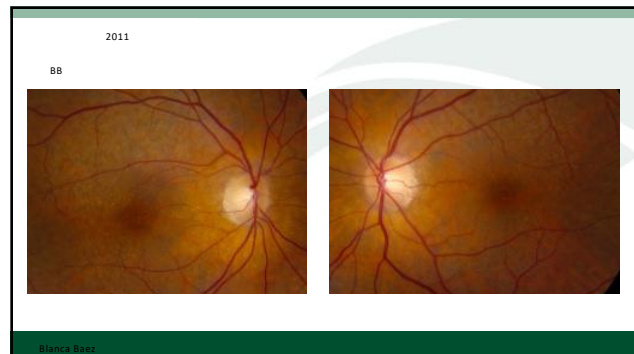
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### Progression of GA

- On average, GA lesions enlarge by 1.5 to 2.1 mm<sup>2</sup>/year (0.6 to 0.8 MPS disc areas)<sup>1,2</sup>
- Median time to evolution of GA:<sup>3</sup>
  - 2.5 years: median time to develop central GA (after GA diagnosis)
  - 7 years: median time to develop bilateral GA (i.e. GA in both eyes) after development of GA in the first eye
- Previous lesion involvement predicts subsequent enlargement<sup>3</sup>

1. Hole FG, et al. Am J Ophthalmol 2007;143:663-72; 2. Sunness FS, et al. Ophthalmology 2007;114:271-7; 3. Lindblad AS, et al. Arch Ophthalmol 2009;127:1168-74.

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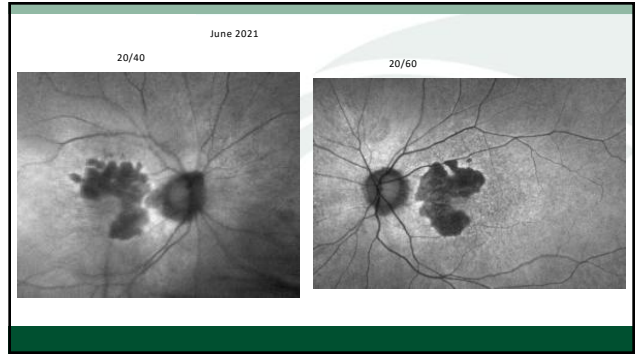


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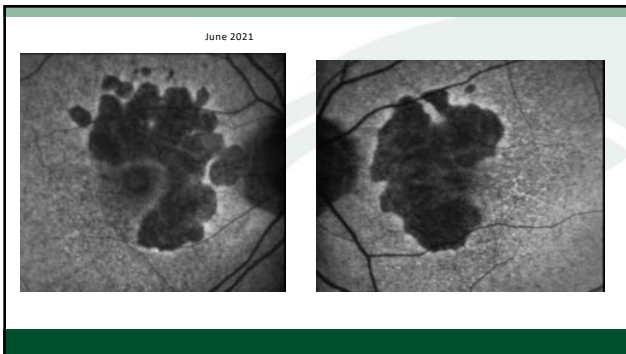




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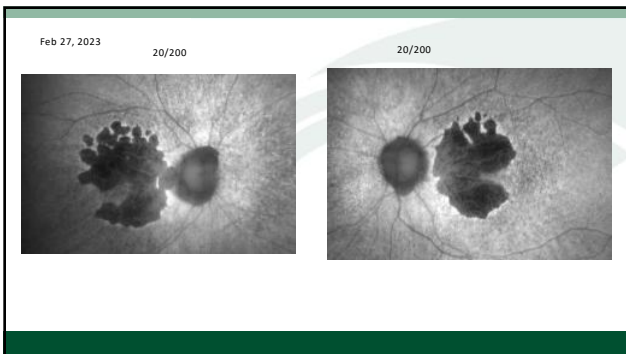
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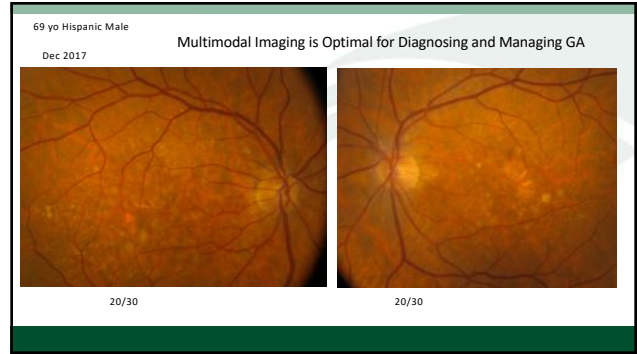


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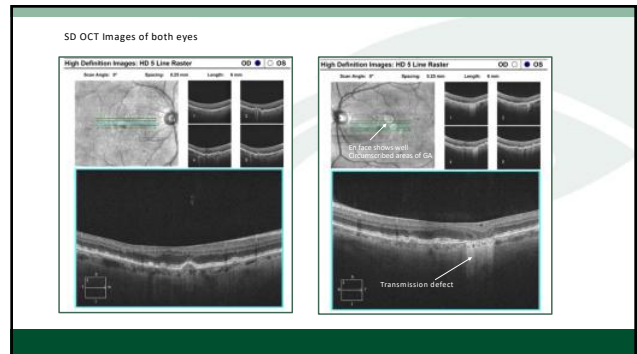
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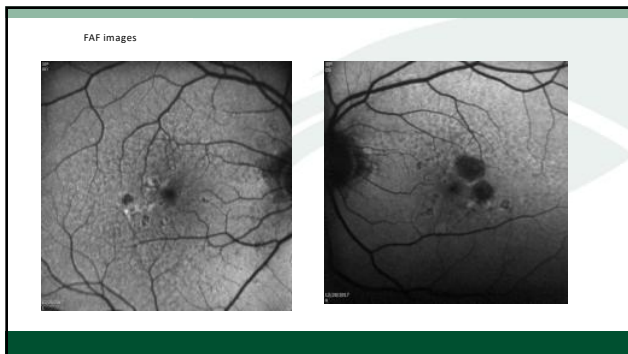
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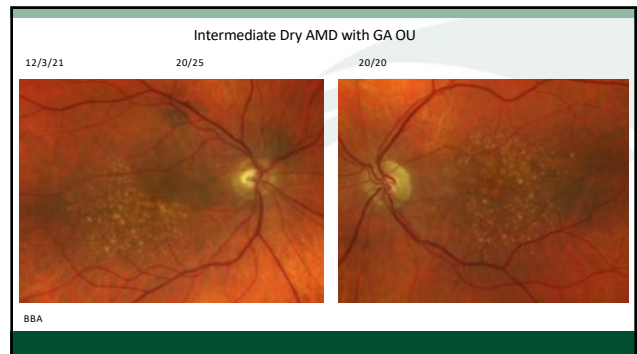
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88



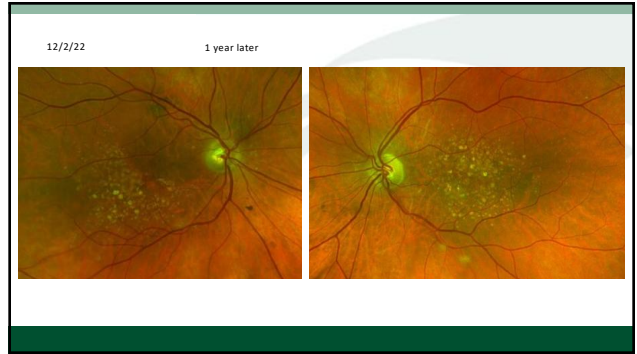
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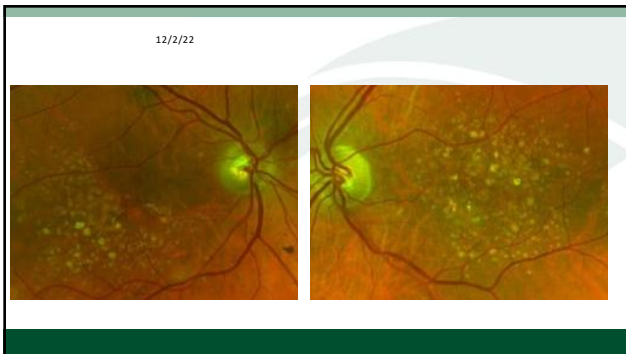
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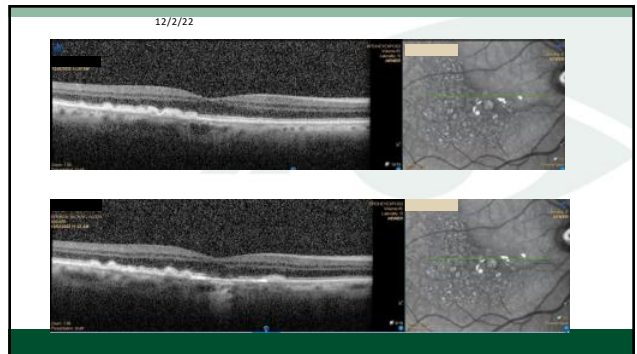
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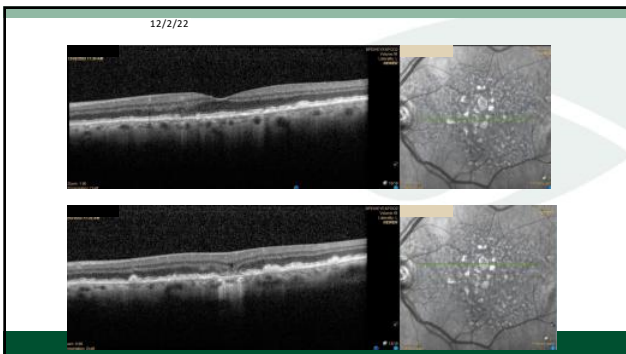
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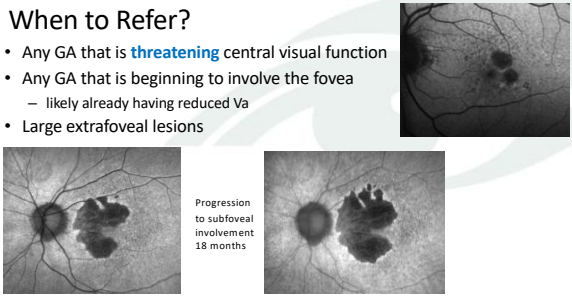
### Optimizing Referral Patterns

- Early diagnosis
  - Recognizing GA is much more prevalent than we think
- Using OCT/FAF imaging to confirm diagnosis
  - Establish a baseline
  - Rate of progression
- Determine proximity to the fovea -> risk of vision loss

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### When to Refer?

- Any GA that is **threatening** central visual function
- Any GA that is beginning to involve the fovea
  - likely already having reduced Va
- Large extrafoveal lesions




Progression to subfoveal involvement 18 months

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### When to Refer?

- Extrafoveal lesions that are not a threat to central Va?
- Central GA lesions that have already have sig loss of visual function?



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### Where we are today with GA?

- 2 FDA approved treatments
- Monthly ( or every other month) intravitreal injection
- IZERVAY may work more quickly
  - But slightly higher risk of CNV
- Syfovre – may have an increased risk of IOI

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