Developing Treatments for Dry AMD: A Workshop Focus on Geographic Atrophy (GA)

Phenotype and Genotype of GA

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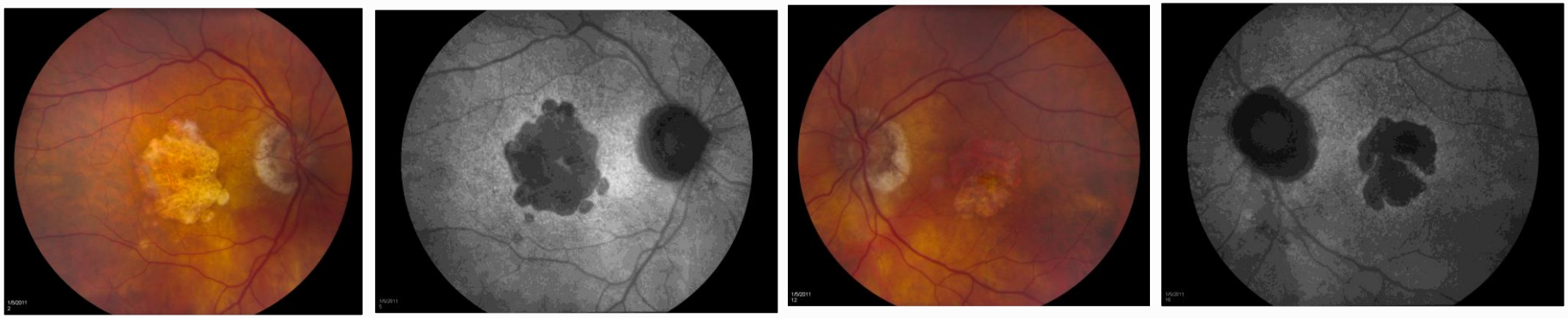
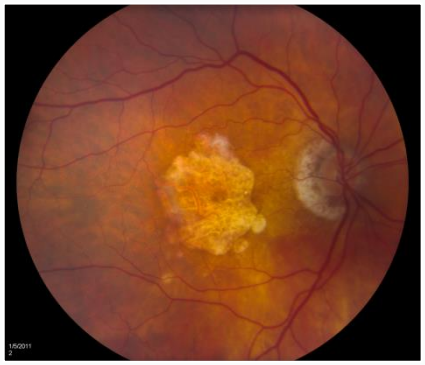
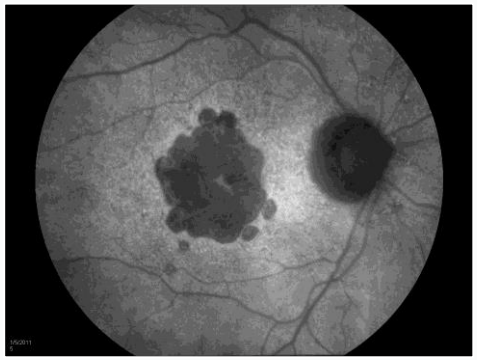
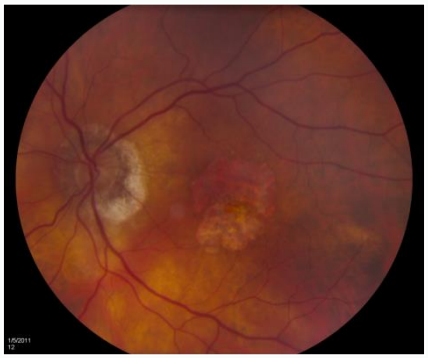
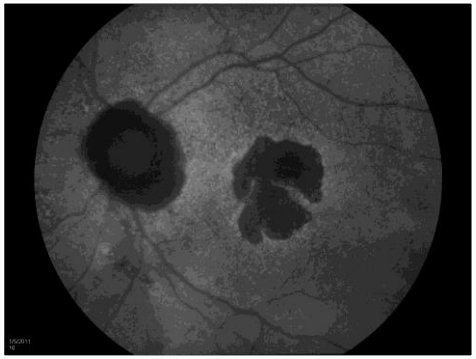


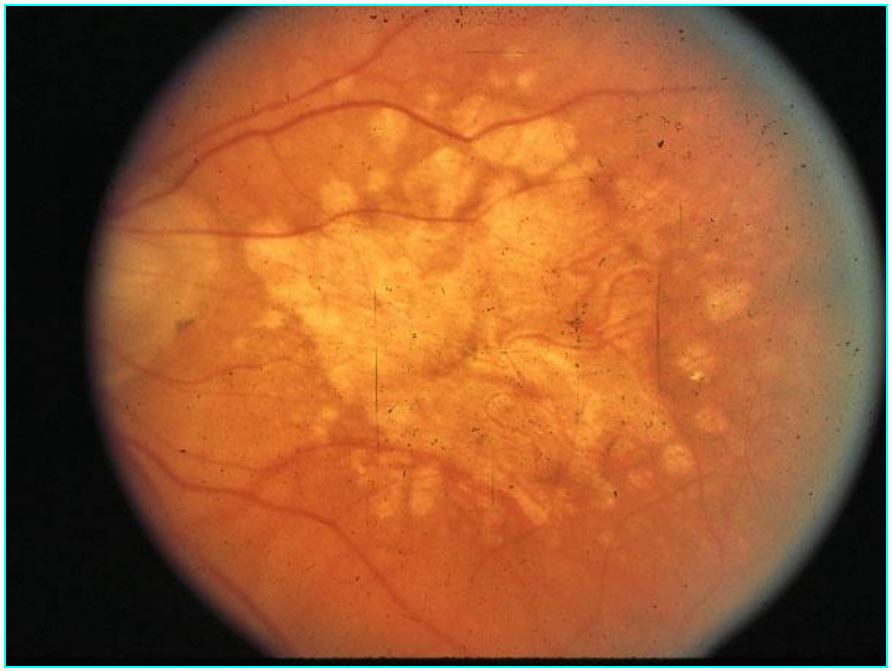
Phenotype of Geographic Atrophy (GA)

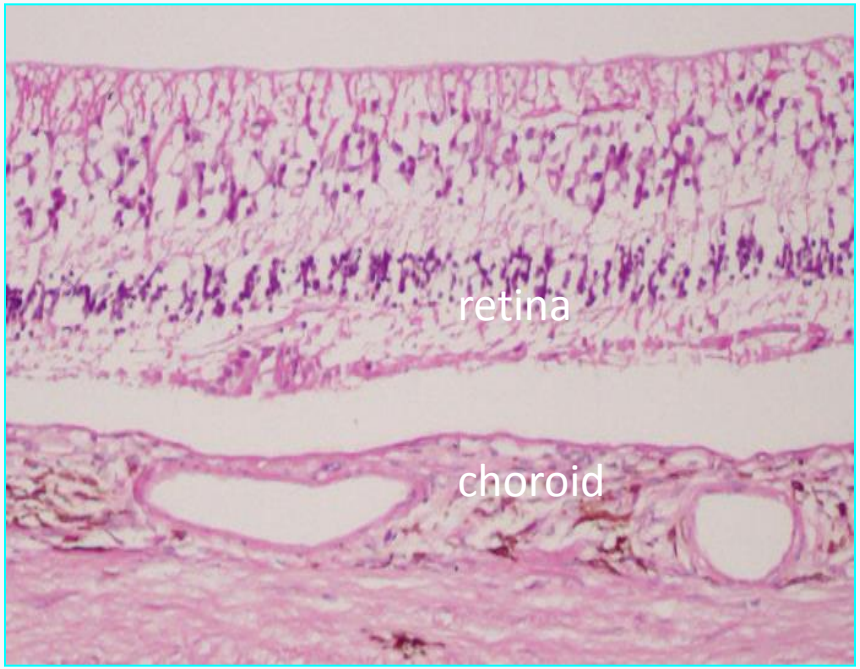
No Financial Disclosures

Clinical Definition of Geographic Atrophy

- **Depigmented Area (175 µ to 433 µ in AREDS2)**
- **Sharply Demarcated**
- **Choroidal Vessels Visible**





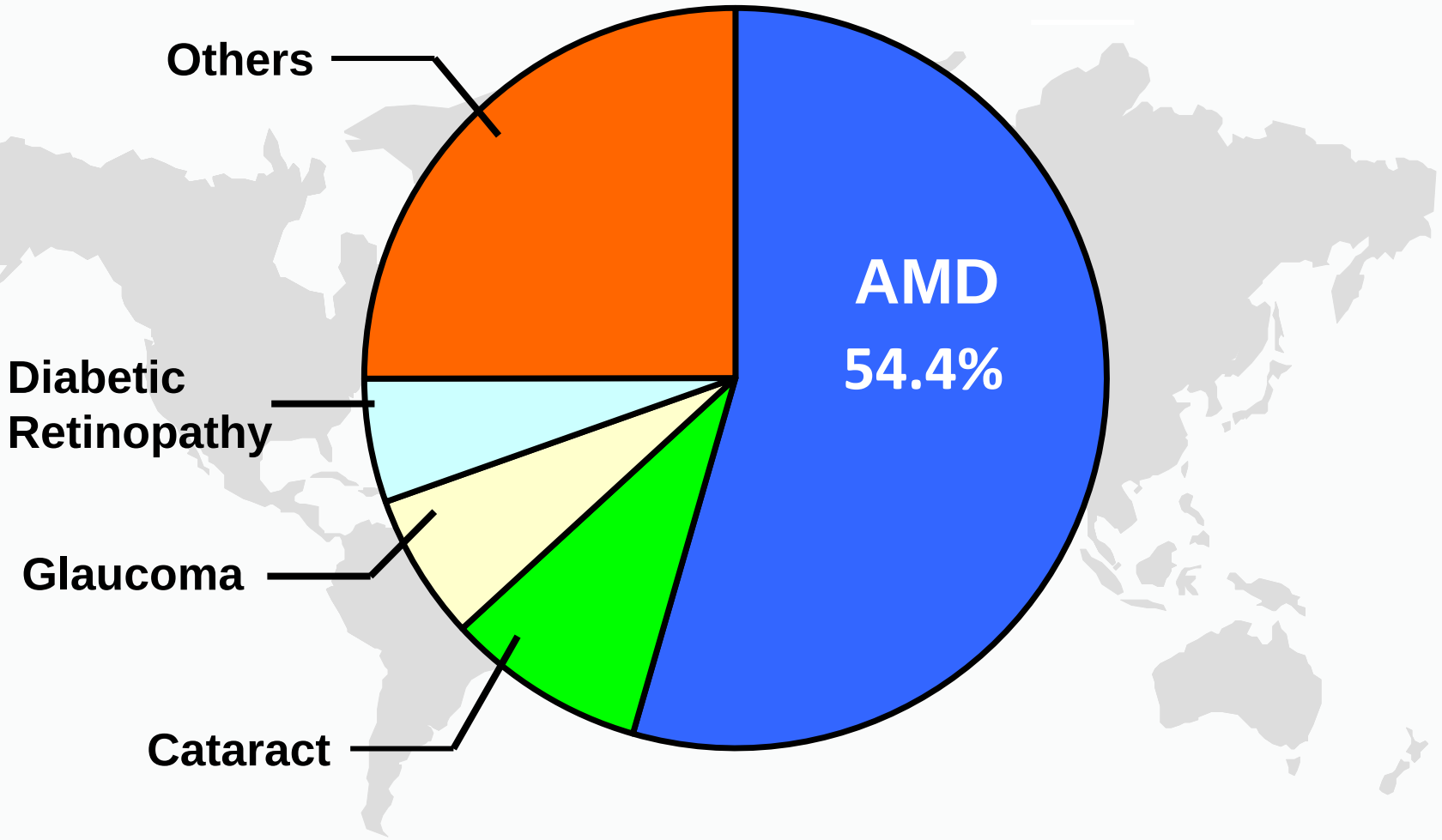
Phenotype of GA: Goals

- **Burden of Disease (Functional Challenges)**
- **Defining the phenotypic characteristics of GA**
  - **Drusen**
  - **Reticular Pseudodrusen**
  - **Geographic Atrophy**
- **Impact of Phenotypic Heterogeneity**

AMD: Disease Background

- **AMD is ranked 3rd in the World Health Organization's review of the leading causes of blindness worldwide**
- **In developed countries, AMD is the leading cause of blindness due to the growing number of people over 70 years of age**
- **As populations grow and demographic shifts move towards an increase in the predominance of older age groups, the incidence of AMD will increase**

Eye Diseases Prevalence Research Group
Causes of Blindness in Whites



The Eye Diseases Prevalence Research Group. Arch Ophthalmology 2004; 122: 564-572

Eye Diseases Prevalence Research Group

- Meta-analysis of population-based studies in US, Australia and Europe
- Estimated prevalence and distribution of AMD in US by age, race/ethnicity and gender using data from the 2000 US Census
- Prevalence of neovascular AMD and/or GA among individuals aged ≥40 years
  - 1.47% overall (1.75 million)
  - 1.02% neovascular AMD (1.22 million)
  - 0.81% GA (970,000)
- Incidence of AMD in 2020
  - Increase by >50% from 1.75 million to 2.95 million

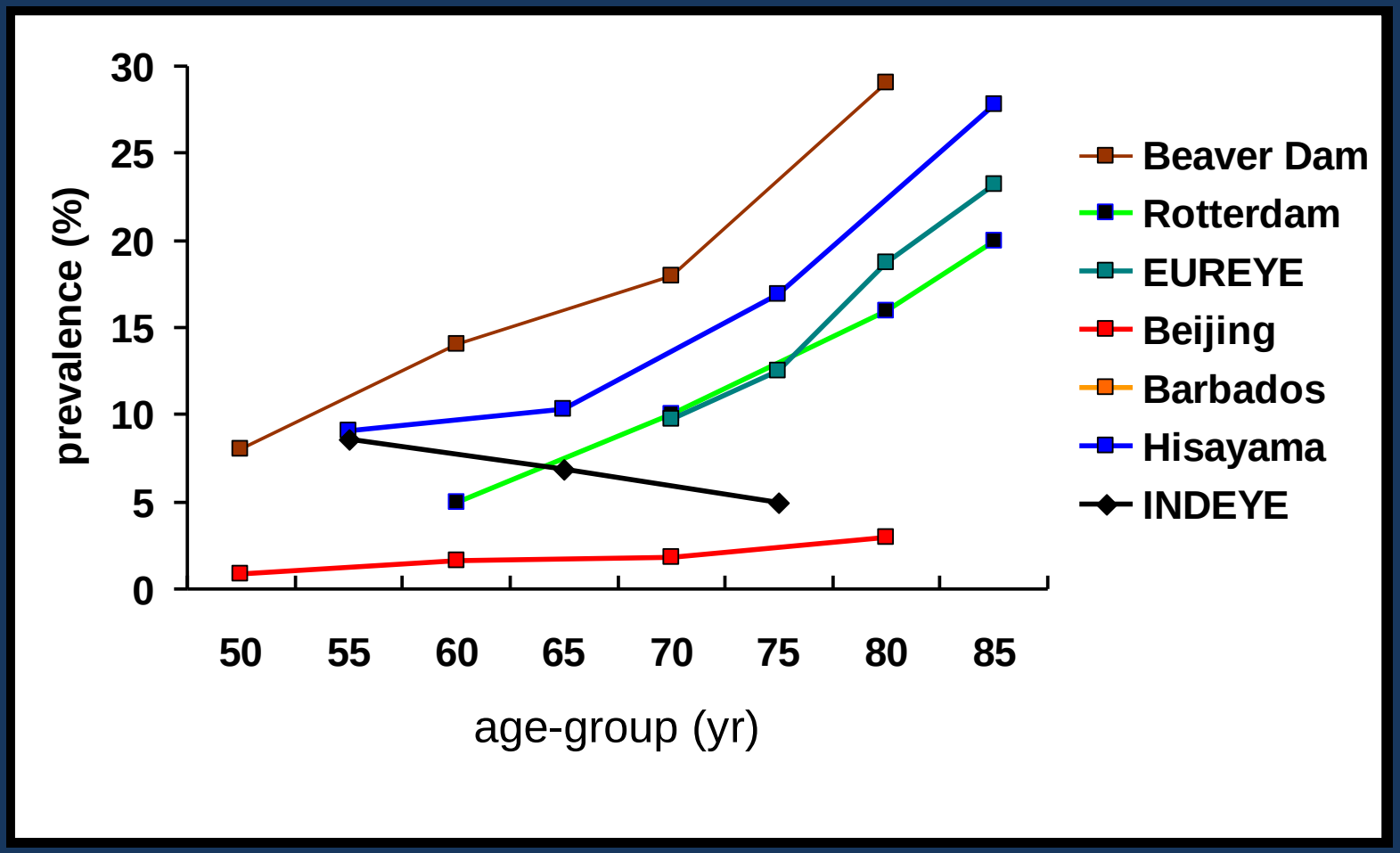
The Eye Diseases Prevalence Research Group. Arch Ophthalmology 2004; 122: 564-572

Summary of prevalence of AMD worldwide

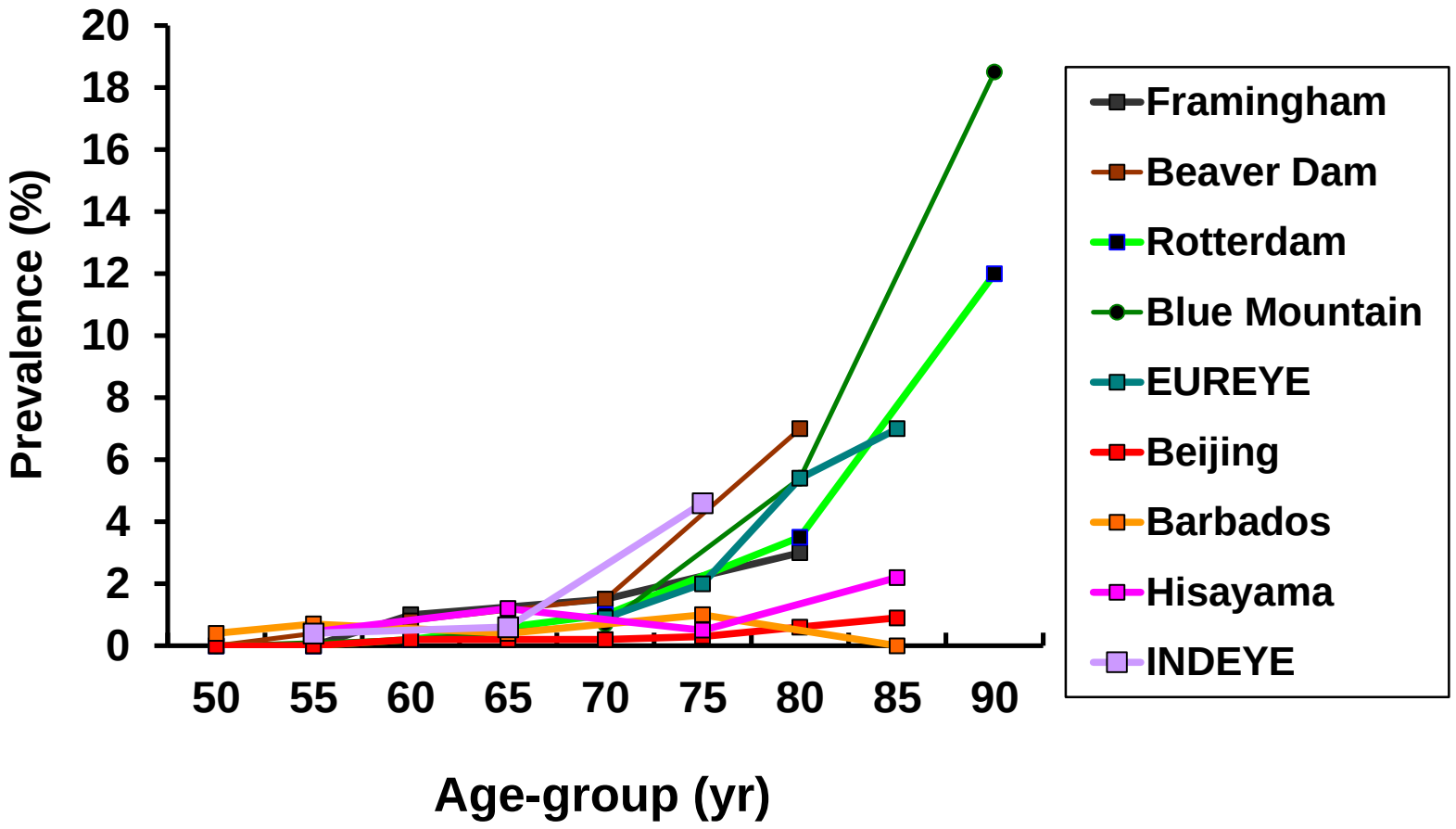
	AMD			
	Any	Early	Late	Neovascular
Framingham Eye Study	8.8%			
Beaver Dam Eye Study			1.6%	1.2%
EUREYE	3.32%			2.3%
Rotterdam Eye Study	1.7%			1.1%
Blue Mountains Eye Study	1.9%			
Reykjavik Eye Study			GA 3.5%	0.7%
Fungata Study		4.3%*	0.6%*	
Hisayama Study				0.67%
Singapore Malay Eye Study		3.5%	0.34%	
Beijing Eye Study		1.4%	0.2%	0.1%
INDEYE Study		0.3%	1.2%	

**in participants over 50 years old*

Prevalence of Early AMD



Prevalence of Advanced AMD



BMIR AMD Classification Committee

Ophthalmol 2013;120(4):844-51.

Clinical Classification of Age-Related Macular Degeneration

*Frederick L. Ferris III, MD,[1] C. P. Wilkinson, MD,[2] Alan Bird, MD,[3] Usha Chakravarthy, MD,[4] Emily Chew, MD,[1] Karl Csaky, MD,[5] SriniVas R. Sadda, MD,[6] on behalf of the Beckman Initiative for Macular Research Classification Committee**

Objective: To develop a clinical classification system for age-related macular degeneration (AMD).

Design: Evidence-based investigation, using a modified Delphi process.

Participants: Twenty-six AMD experts, 1 neuro-ophthalmologist, 2 committee chairmen, and 1 methodologist.

Methods: Each committee member completed an online assessment of statements summarizing current AMD classification criteria, indicating agreement or disagreement with each statement on a 9-step scale. The group met, reviewed the survey results, discussed the important components of a clinical classification system, and defined new data analyses needed to refine a classification system. After the meeting, additional data analyses from large studies were provided to the committee to provide risk estimates related to the presence of various AMD lesions.

Main Outcome Measures: Delphi review of the 9-item set of statements resulting from the meeting.

Results: Consensus was achieved in generating a basic clinical classification system based on fundus lesions assessed within 2 disc diameters of the fovea in persons older than 55 years. The committee agreed that a single term, *age-related macular degeneration*, should be used for the disease. Persons with no visible drusen or pigmentary abnormalities should be considered to have no signs of AMD. Persons with small drusen (<63 μm), also termed *drupelets*, should be considered to have normal aging changes with no clinically relevant increased risk of late AMD developing. Persons with medium drusen (≥63–<125 μm), but without pigmentary abnormalities thought to be related to AMD, should be considered to have early AMD. Persons with large drusen or with pigmentary abnormalities associated with at least medium drusen should be considered to have intermediate AMD. Persons with lesions associated with neovascular AMD or geographic atrophy should be considered to have late AMD. Five-year risks of progressing to late AMD are estimated to increase approximately 100 fold, ranging from a 0.5% 5-year risk for normal aging changes to a 50% risk for the highest intermediate AMD risk group.

Conclusions: The proposed basic clinical classification scale seems to be of value in predicting the risk of late AMD. Incorporating consistent nomenclature into the practice patterns of all eye care providers may improve communication and patient care.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2013;xx:xxx © 2013 by the American Academy of Ophthalmology.*

**Group members listed after the references in Appendix 1.*

AMD Classification

“No Apparent Aging Changes”

- No Drusen Within 2 DD of the Fovea
- No Pigmentary Abnormalities

AMD Classification

"Normal Aging Changes"

Only Small Drusen
Within 2 DD of Fovea

and

No Pigmentary Abnormalities
(Thought to be Related to AMD)

AMD Classification

"Early AMD"

- Any Medium Drusen (62µ – 125µ) Within 2 DD of Fovea

and

- No Pigmentary Abnormalities (Thought to be Related to AMD)

AMD Classification

"Intermediate AMD"

- Any Large Drusen (>125µ) Within 2 DD of Fovea (Includes Drusenoid RPE Detachment)

and/or

- Pigmentary Abnormalities Associated with at Least Medium Drusen

Beckman AMD Classification Committee

"Late AMD"

- Apparent Signs of Macular Neovascularization Within 2DD of Fovea &/or Associated Signs (Fluid, RPE Elevation, Hemorrhage, Lipid, Fibrosis)

and/or

- Geographic Atrophy Within 2DD of Fovea
  Punched-out Retinal Lesions with
  Sharp Edges and Visible Choroidal Vessels

Classification of AMD	Definition Lesions within 2DD of Fovea
No Apparent Aging Changes	No Drusen No RPE Abnormalities*
Normal Aging Changes	Drusen < 63µ (Drupelets) No AMD-RPE Abnormalities*
Early AMD	Medium Drusen (63-125µ) No AMD-RPE Abnormalities*
Intermediate AMD	Any Large Drusen (> 125µ) Any AMD-RPE Abnormalities*
Late AMD	Neovascular AMD, Any Geographic Atrophy or Both

*Thought to be Related to AMD (at Least Medium Drusen)

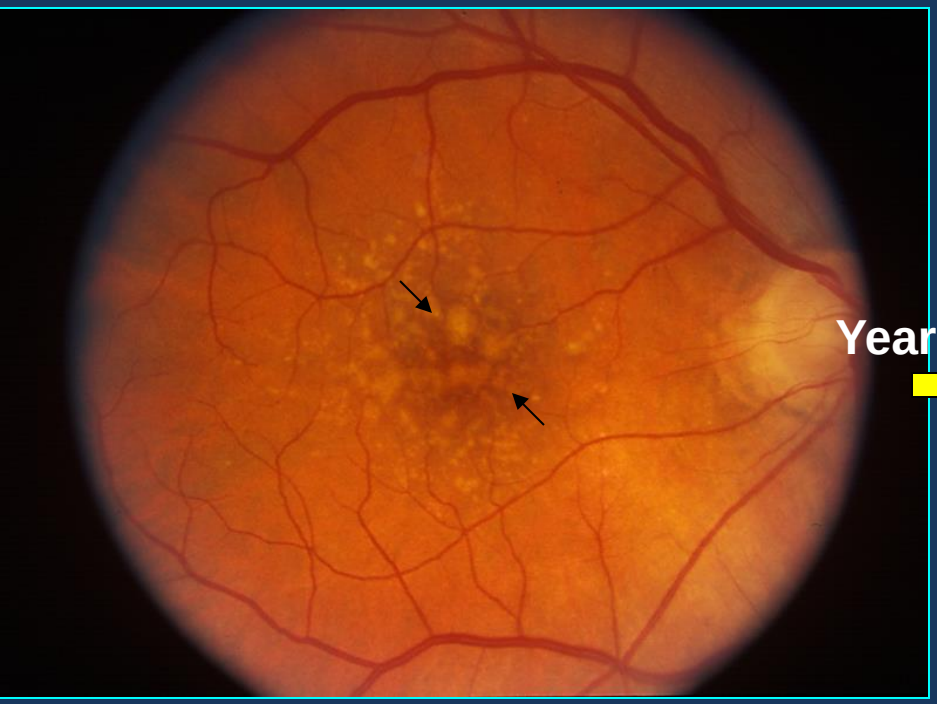
How Does GA Develop?

Study Design

- Two AREDS Clinical Centers
- Identify Eyes Developing GA after 4th Yr
- 95 Eyes Identified
- Grade all Photos Prior to GA Development

Ophthalmology 2008;115:1026-1031

Clinical Example



Yearly photos

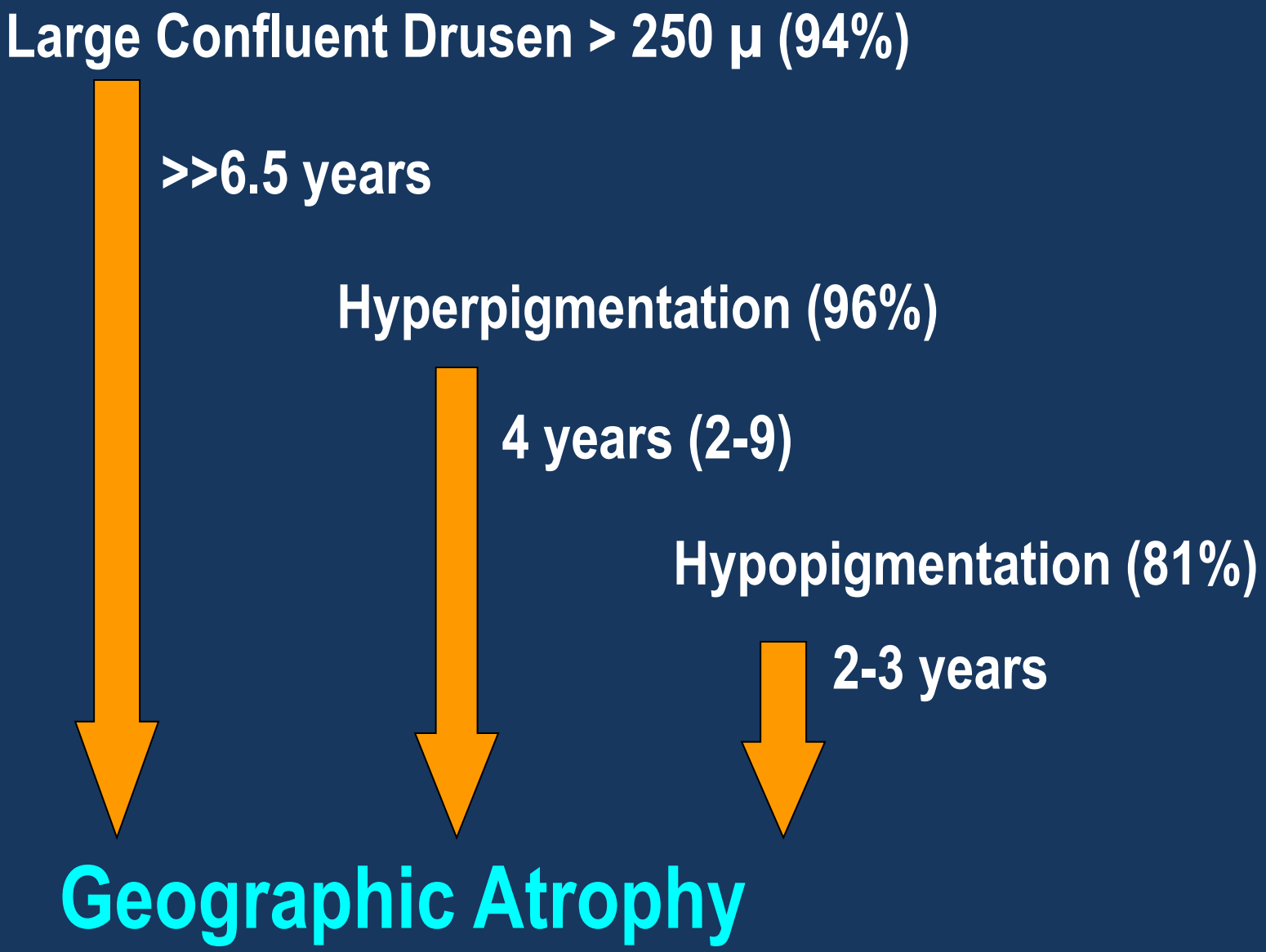
1993- Baseline

1999 - Onset of GA

Eyes Graded for Potential Risk Factors

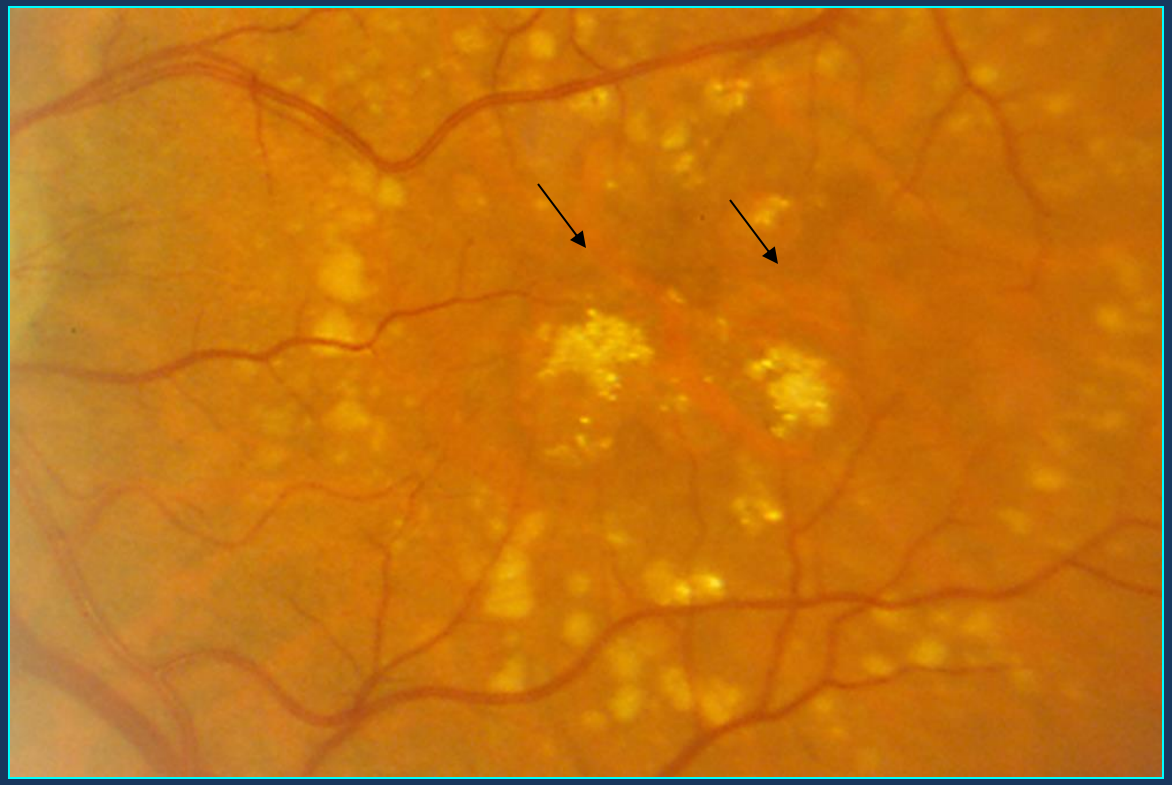
- Drusen Characteristics
- Pigmentary Changes
- Other Features (e.g. Calcification, etc)

Lesions Preceding GA

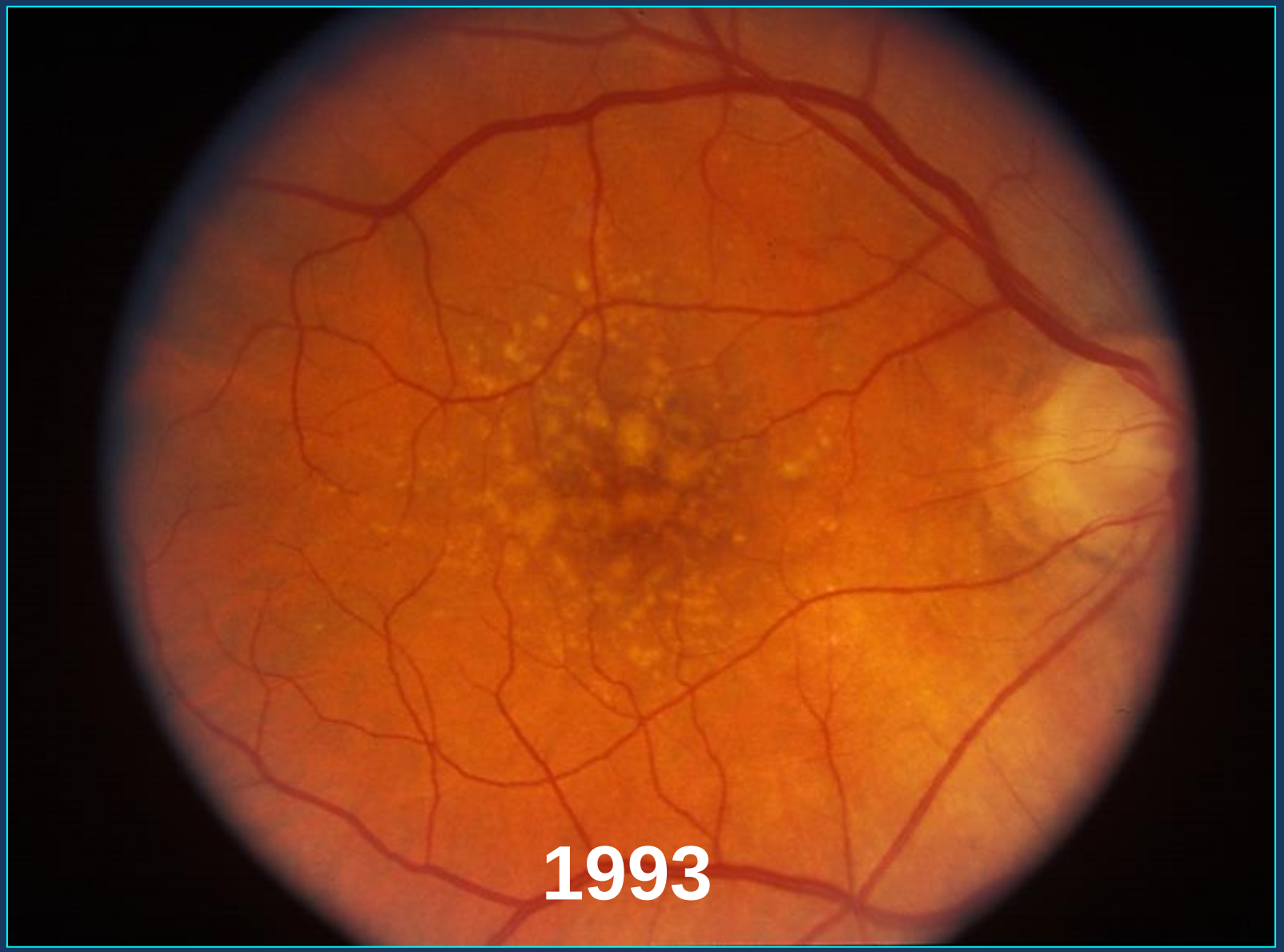


Crystalline Deposits

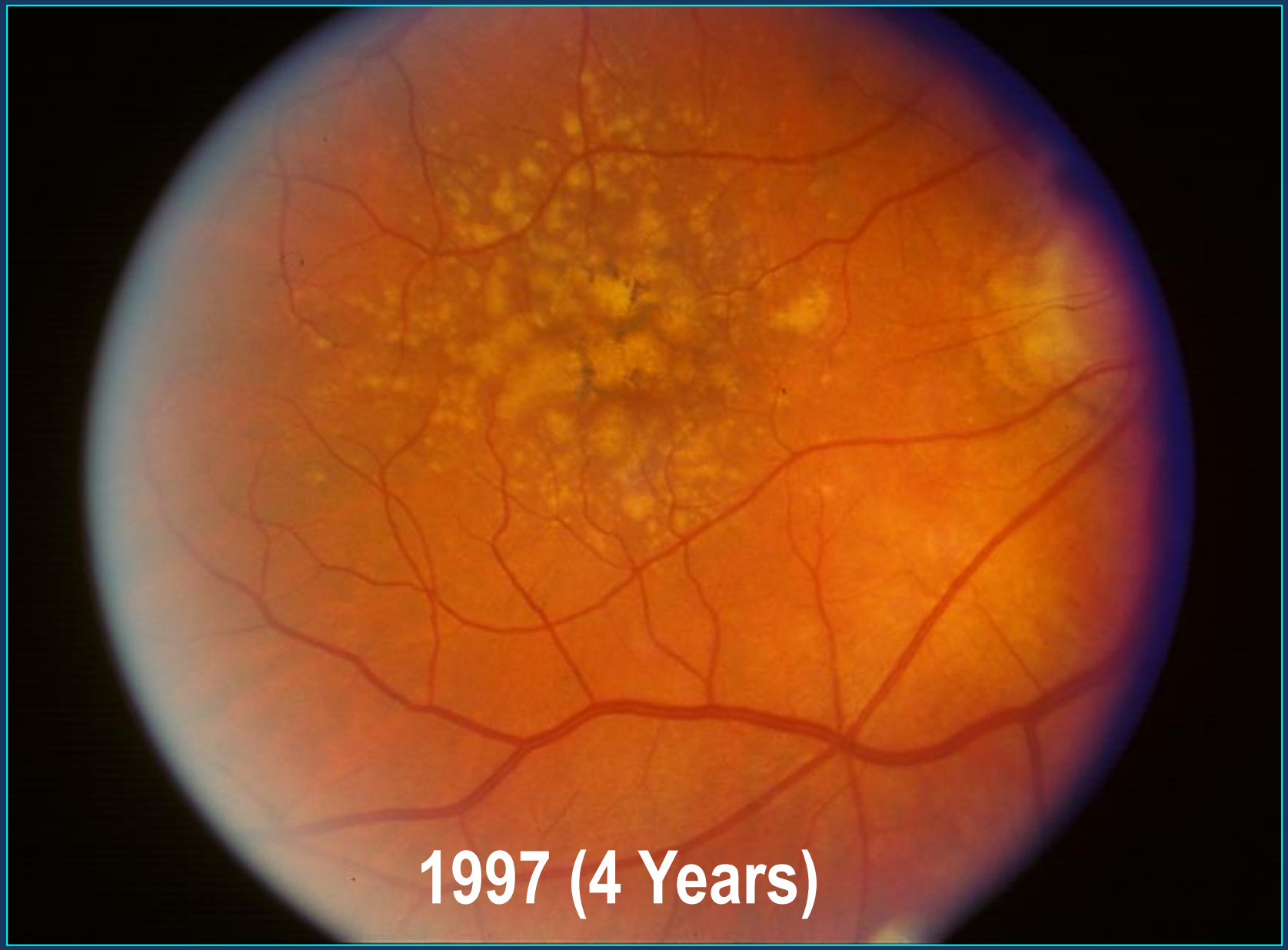
- Often Present Near Drusen Just Prior to GA (23%)
- May be Unphagocytized Material



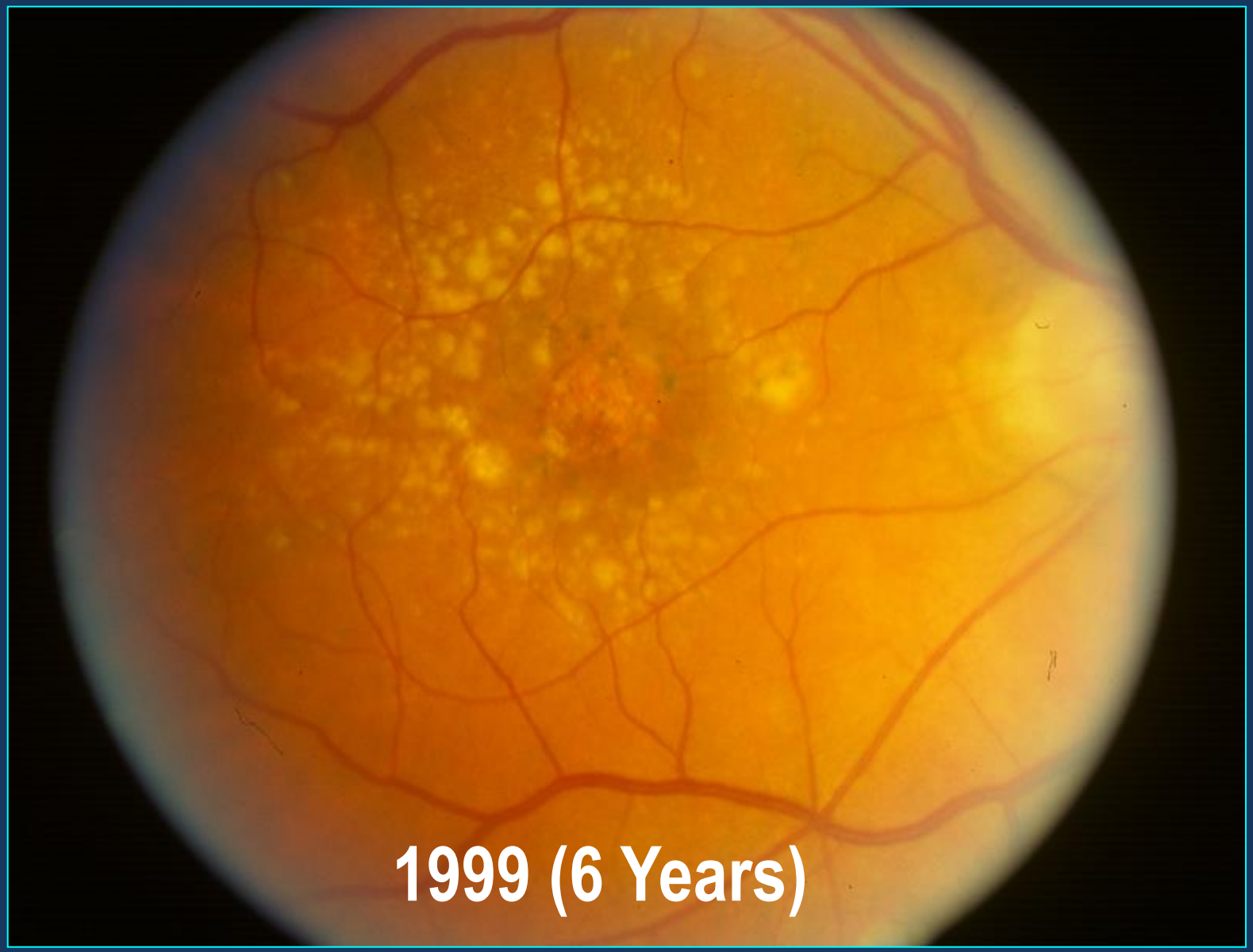
Example – Unifocal GA



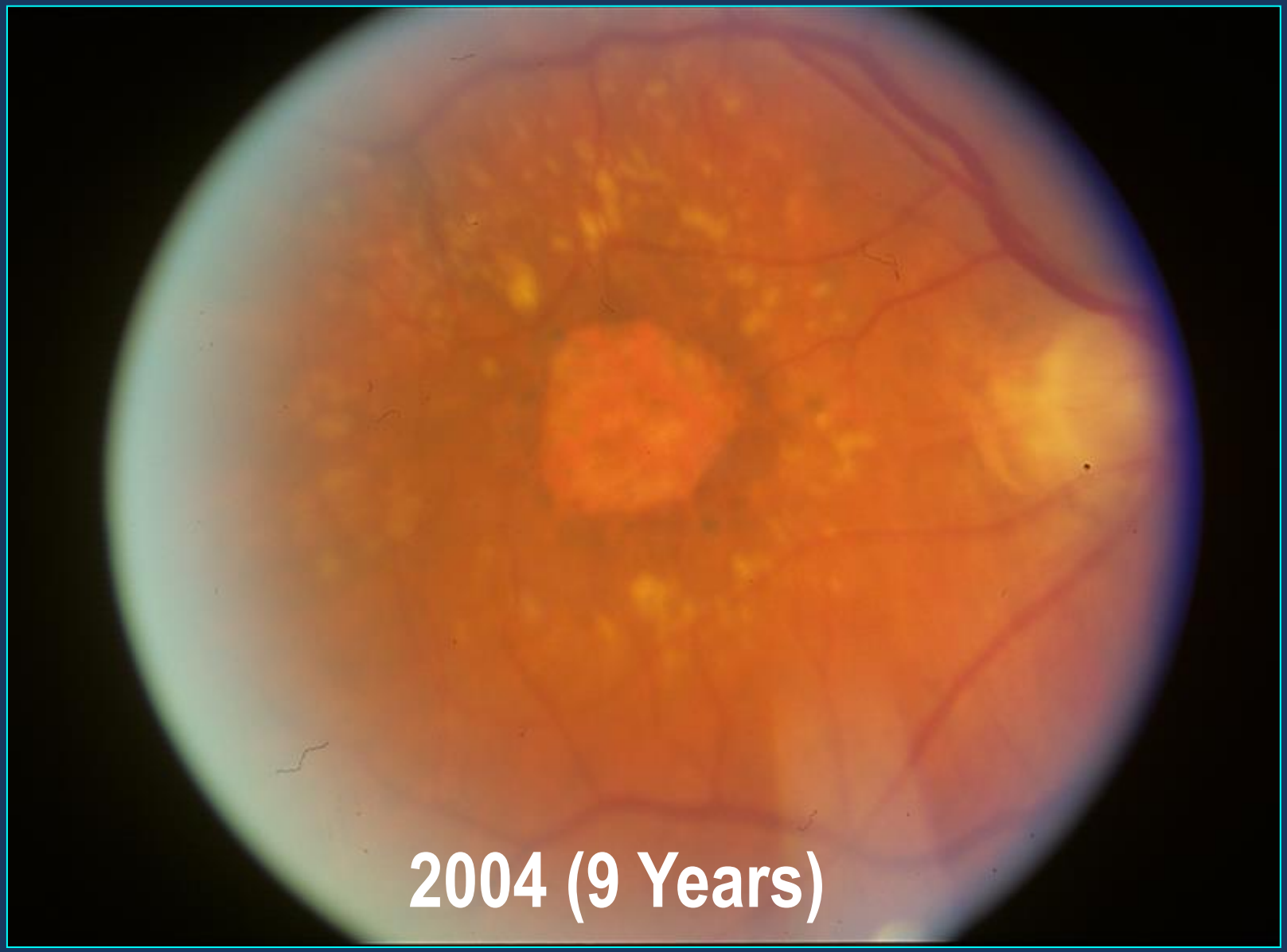
Example – Unifocal GA



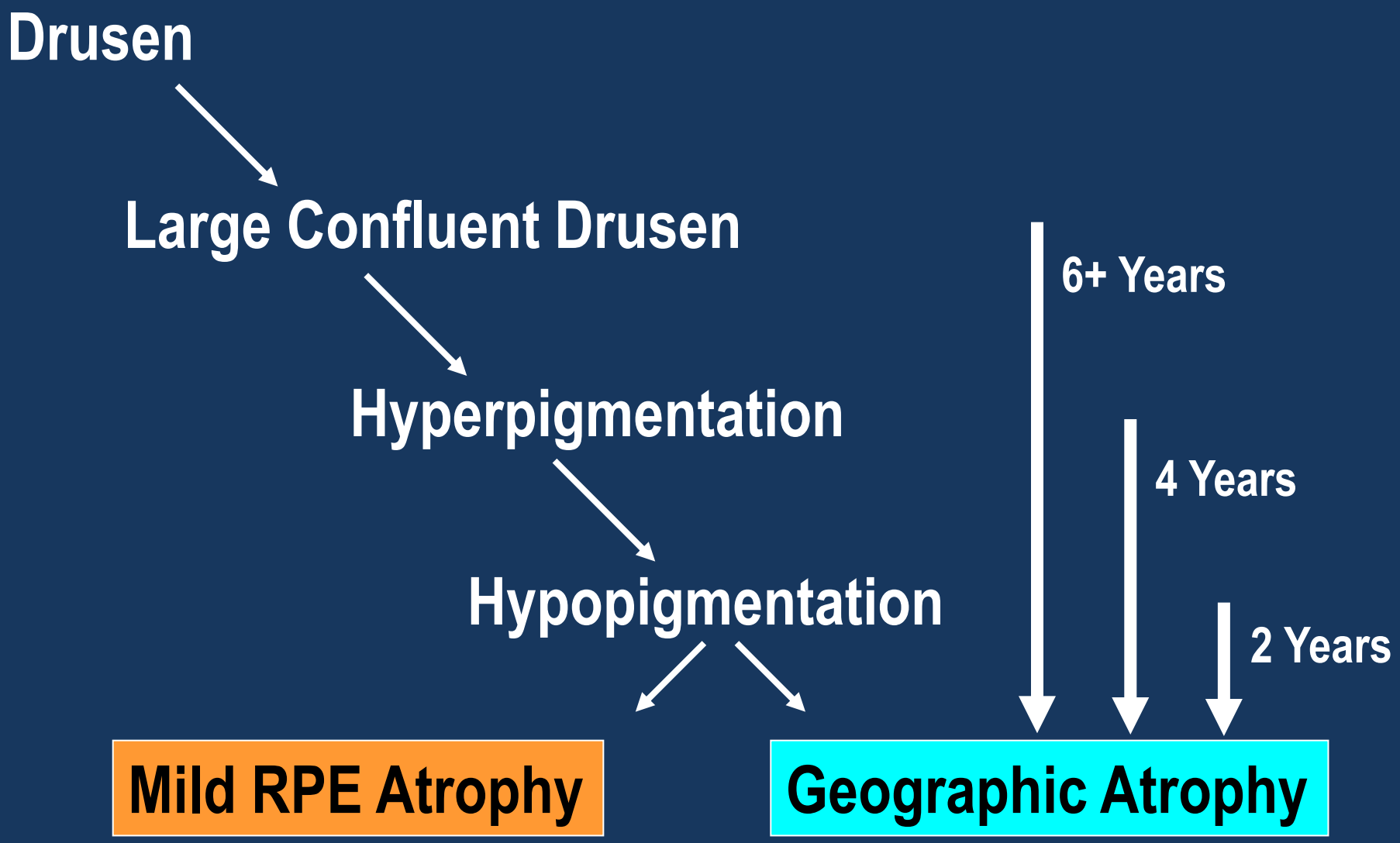
Example – Unifocal GA



Example – Unifocal GA



Progression to Geographic Atrophy



Progression to Geographic Atrophy

Drusen

Large Confluent Drusen

Hyperpigmentation

Hypopigmentation

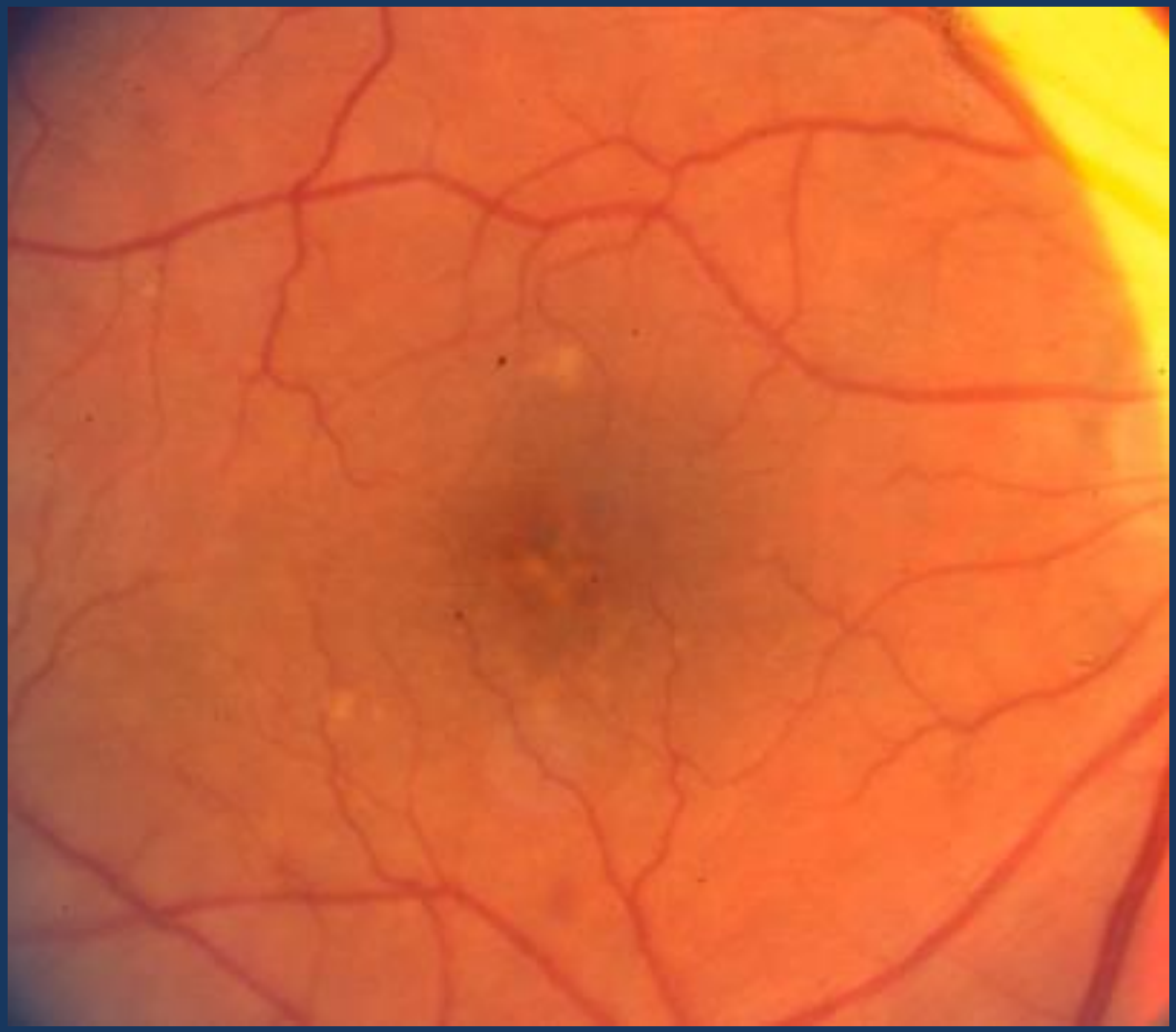
Angiogenesis

Neovascularization

Mild RPE Atrophy

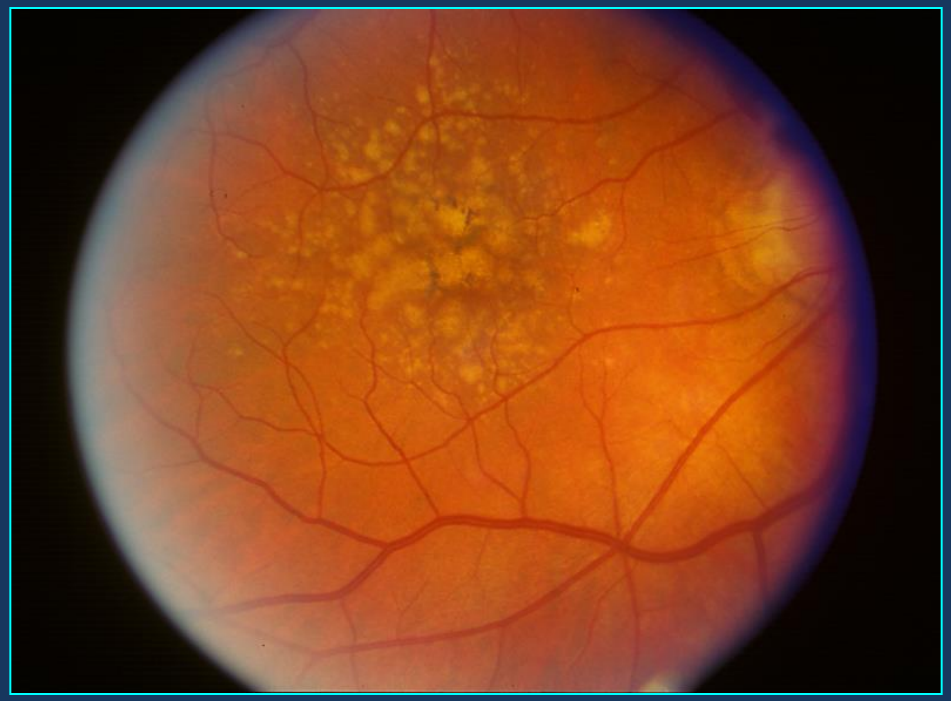
Geographic Atrophy

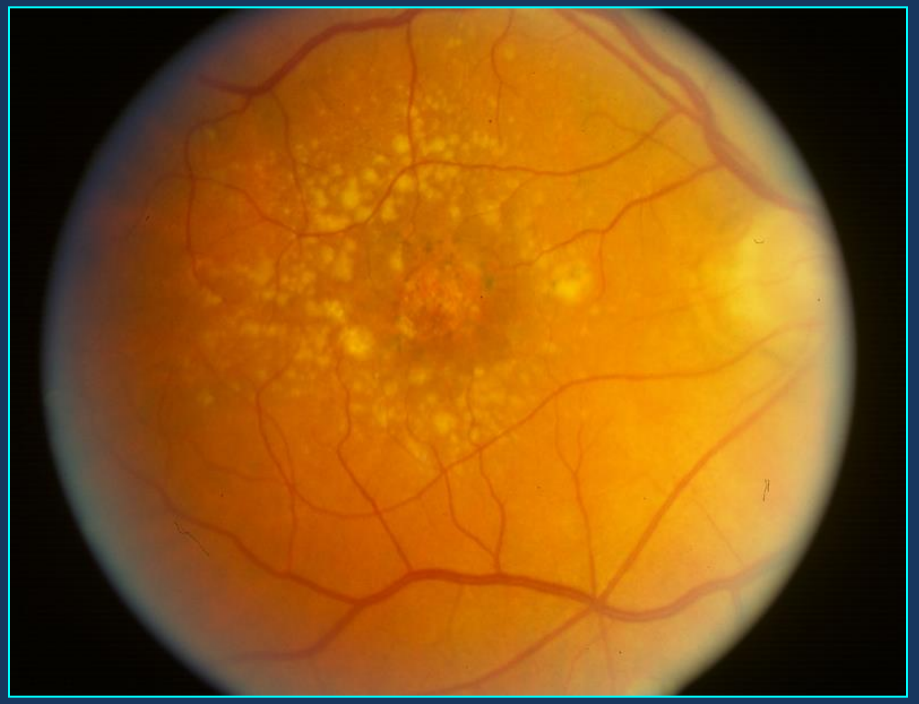
20 year history of GA development



Initial Appearance of GA

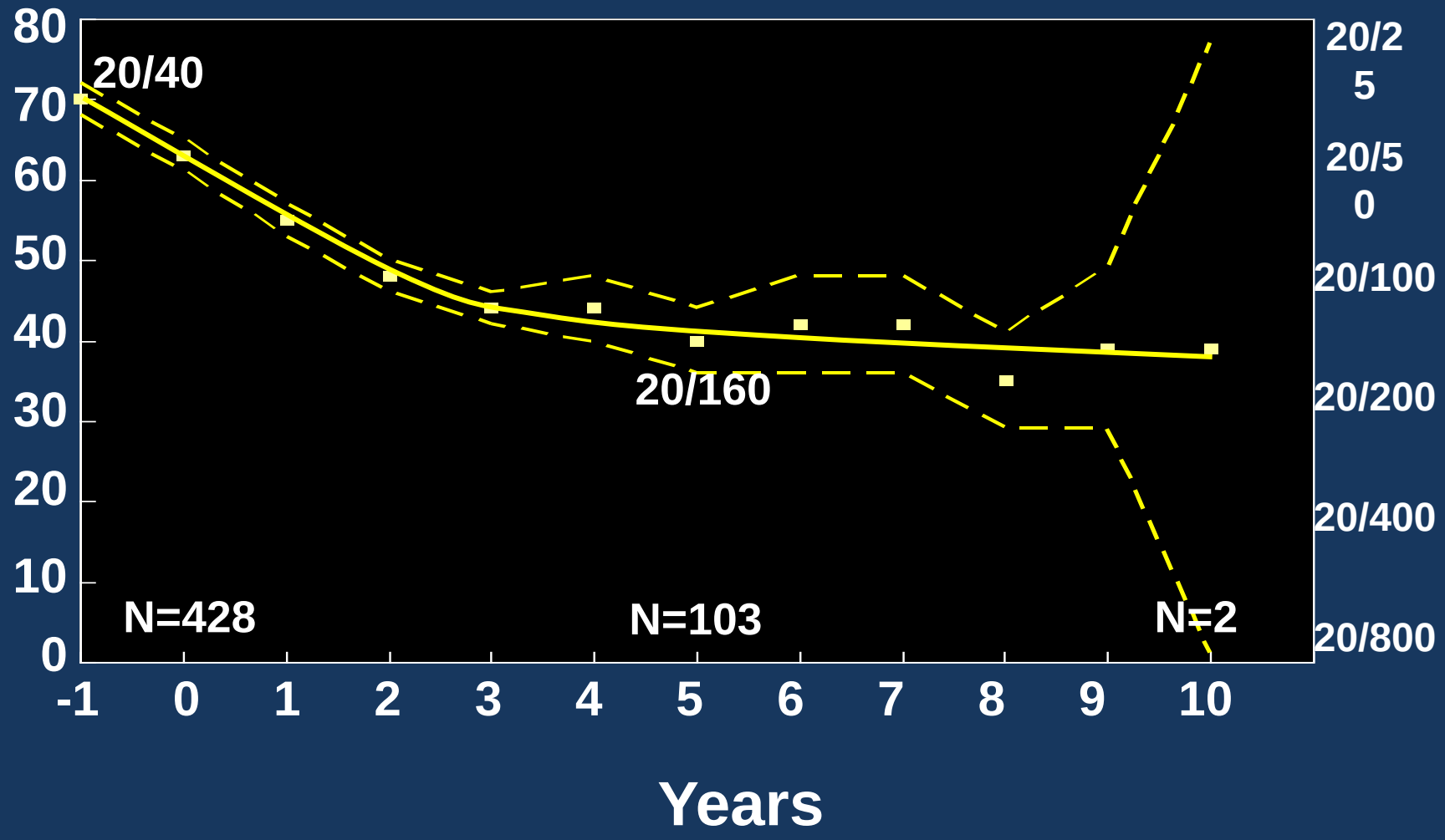
- 24% (23/95) had Center Involvement
- 32% (30/95) had Multiple Areas of GA



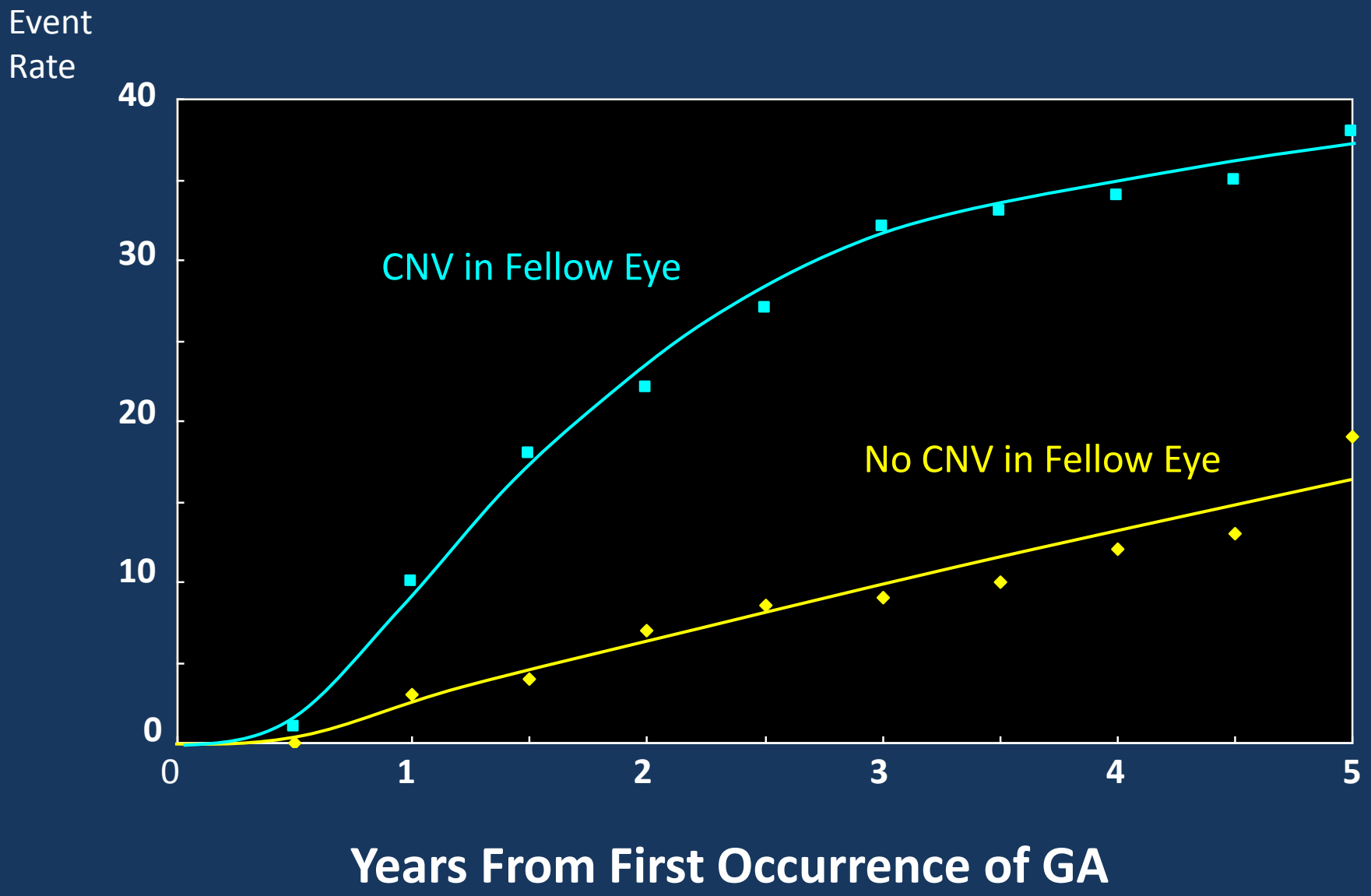


VA Score after Central GA

Median VA Score

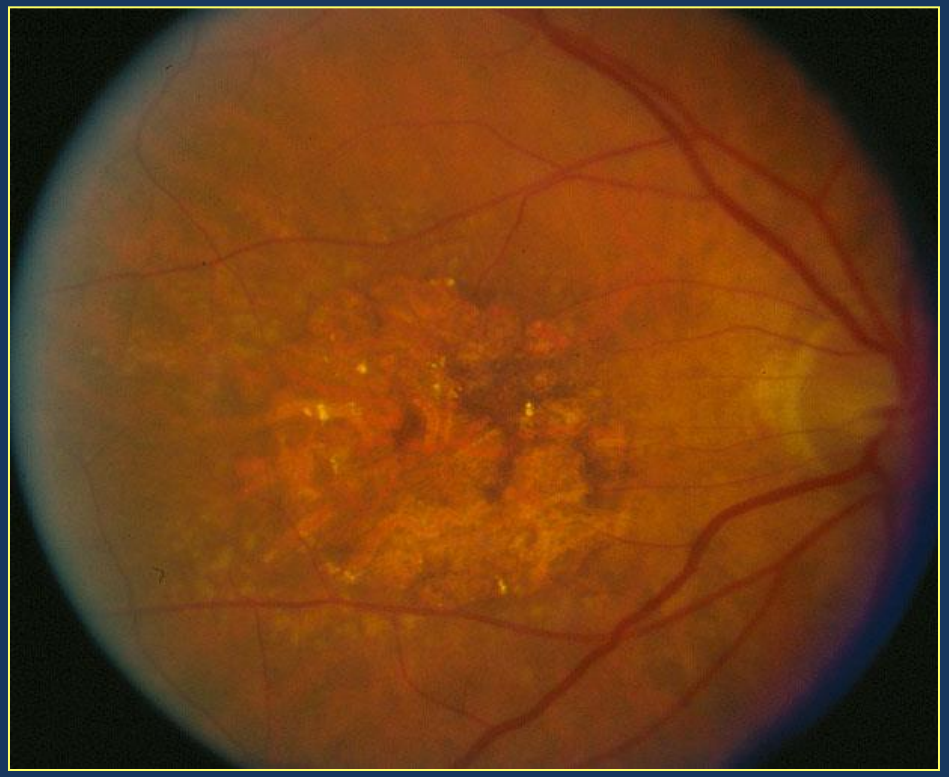


Development of CNV in Eyes with GA

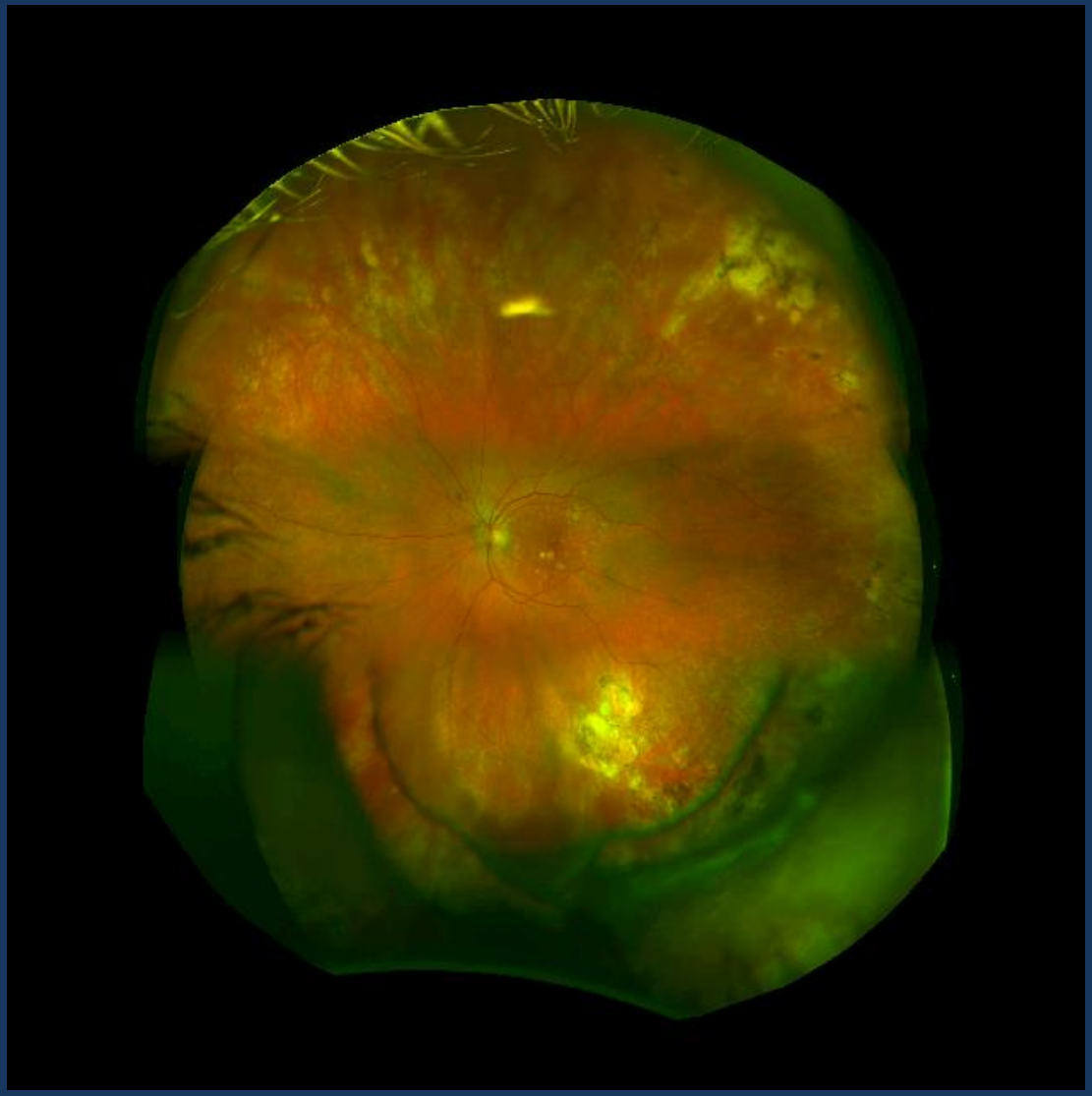


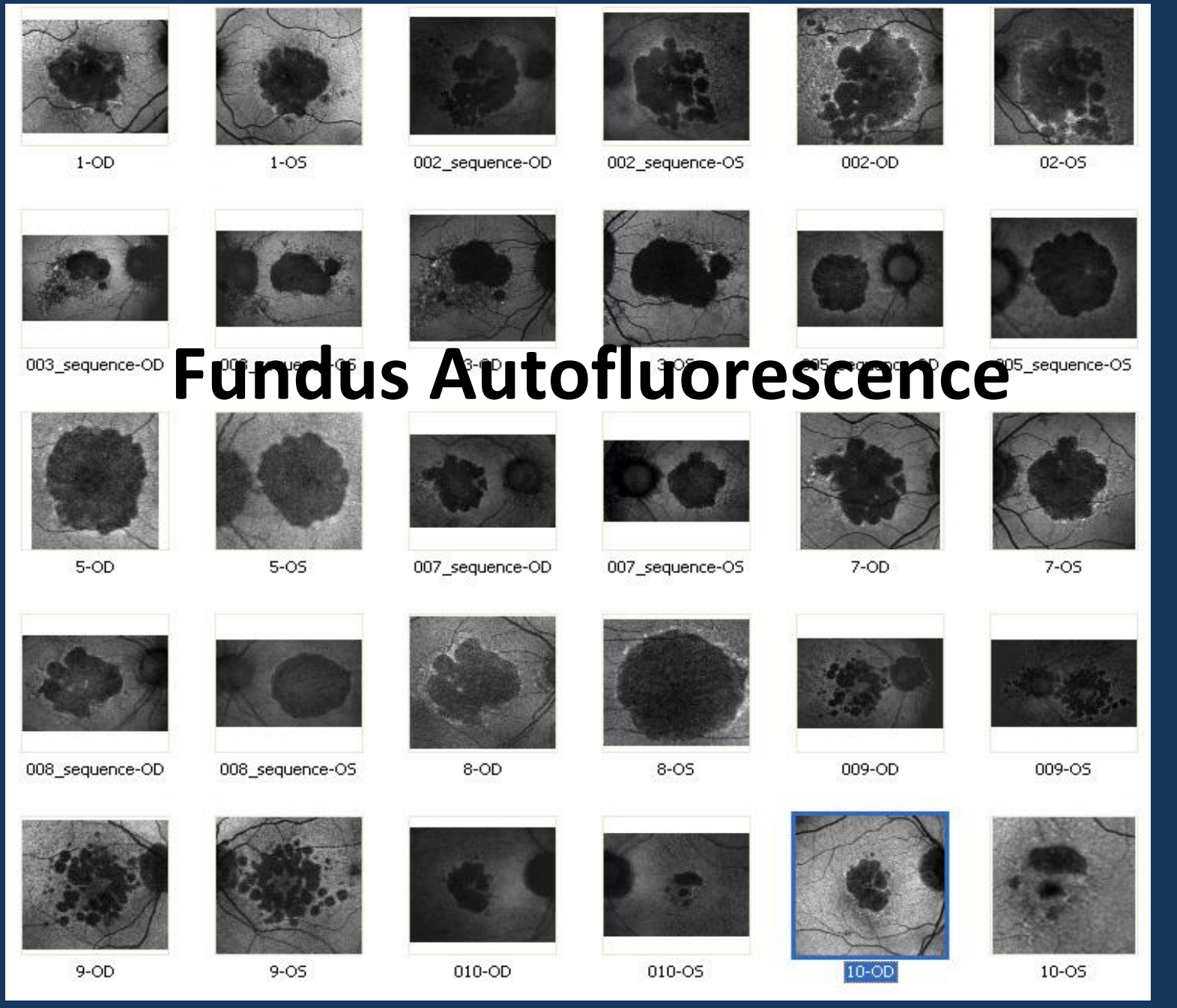
Fundus Lesions

Central Geographic Atrophy (CGA)



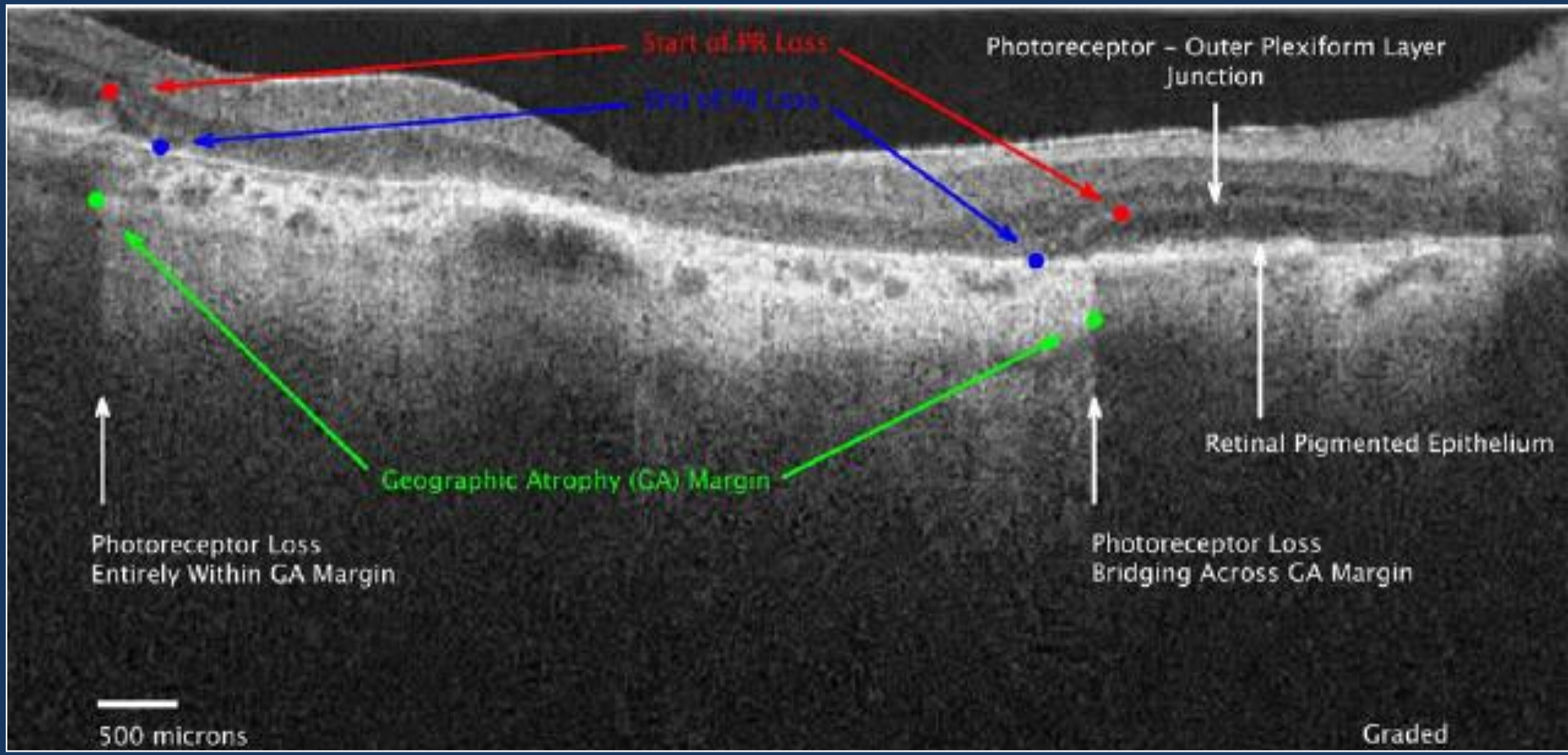
Peripheral drusen, reticular changes and GA





Fundus Autofluorescence

OCT in Phenotyping of Age-related Macular Degeneration



Ophthalmol 2009;116:1762-1769

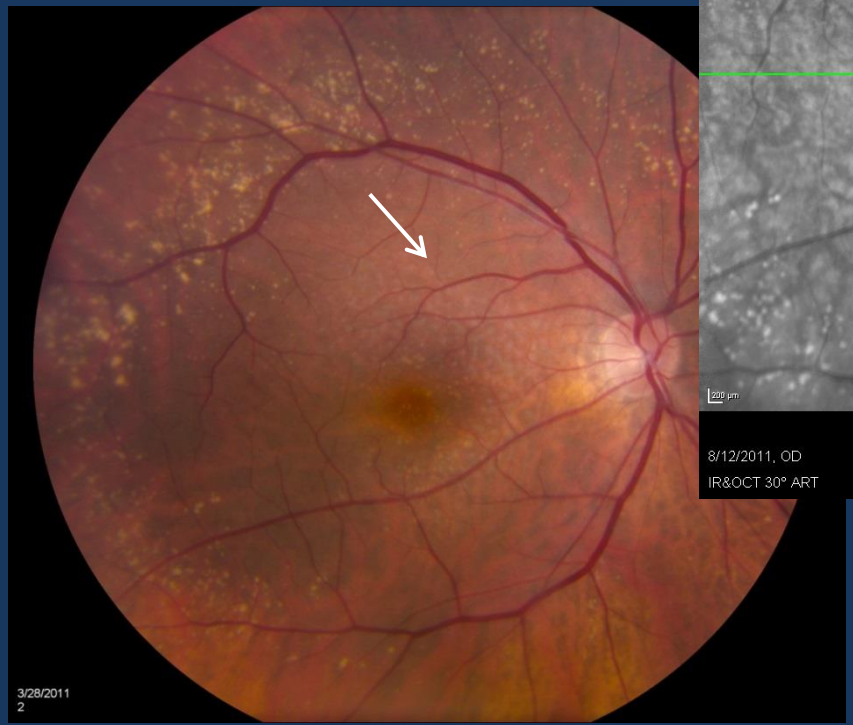
GA-Functional Changes

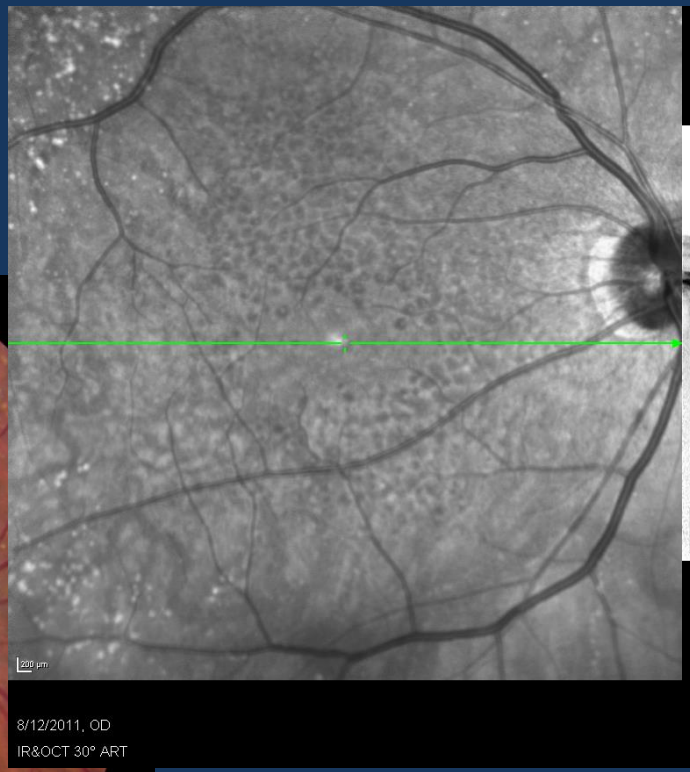
- Dark Adaptation Abnormalities
- Difficulties with Reading
- Problems recognizing faces
- Dense, irreversible scotomas

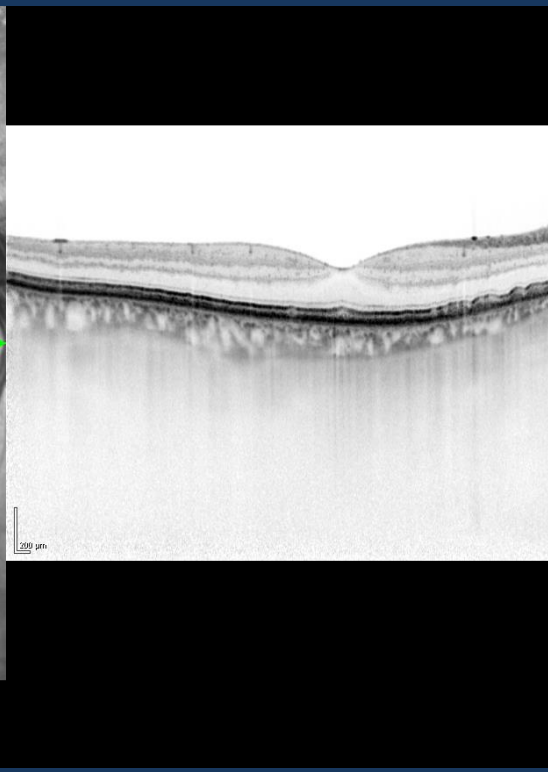
AMD Classification

Additional Issues

- Role of Pseudoreticular Drusen?







Reticular Pseudo-Drusen

- Mimoun G, Soubrane G, Coscas G. Macular drusen. J Fr Ophtalmol 1990;13:511-530

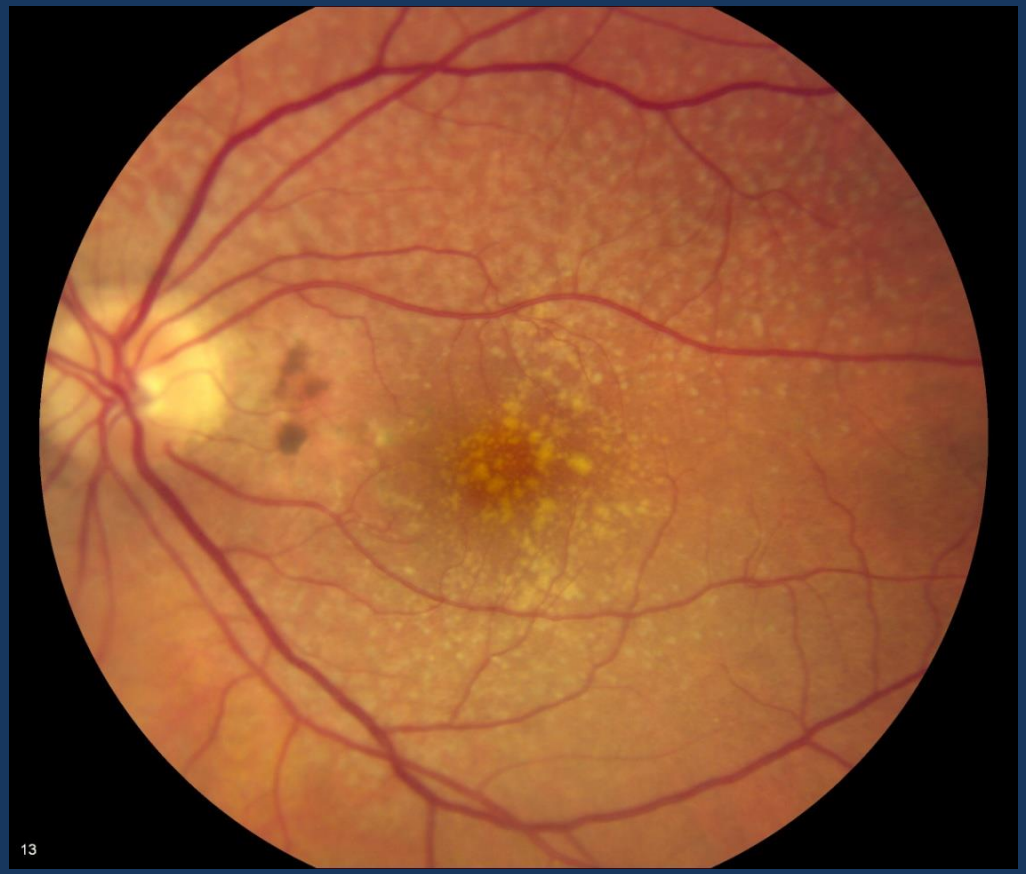
"In 1990 we described reticular pseudodrusen as a peculiar yellowish pattern in the macula of age-related macular degeneration AMD patients. In the original description we called this peculiar form of drusen "les pseudo-drusen bleus", because of their enhanced visibility using blue light."

Reticular Pseudo-Drusen

Reticular Pseudo-Drusen in Color Photographs

- Defined in AREDS Report 6

the term "reticular drusen" is applied to the yellowish material that looks like soft drusen arranged in ill-defined networks of broad interlacing ribbons

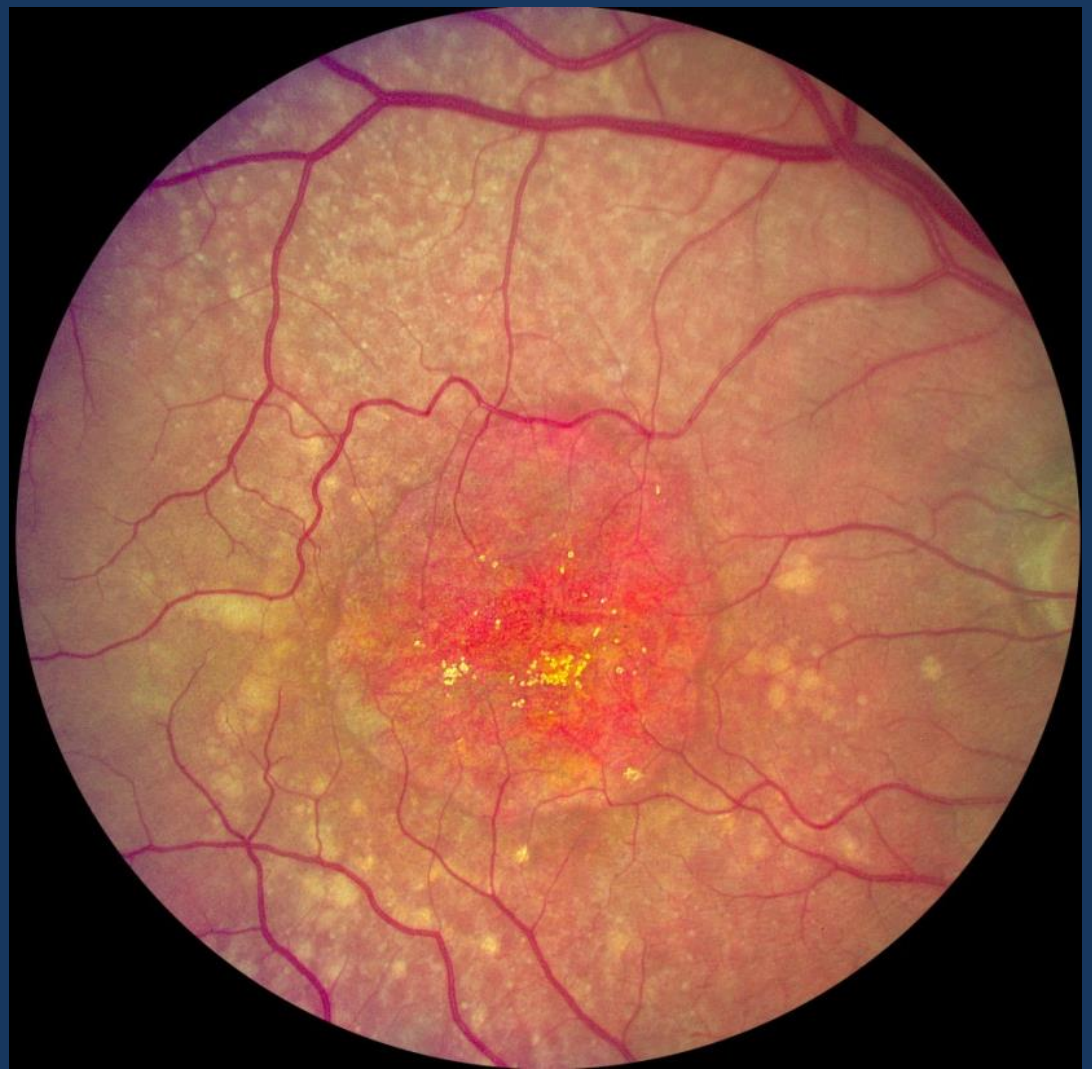


Reticular Pseudo-Drusen

Reticular Pseudo-Drusen in Color Photographs

- Reticular drusen associated with high risk of late AMD.

Klein et al.
Am J Ophthalmol.2008 February;145(2): 317-326

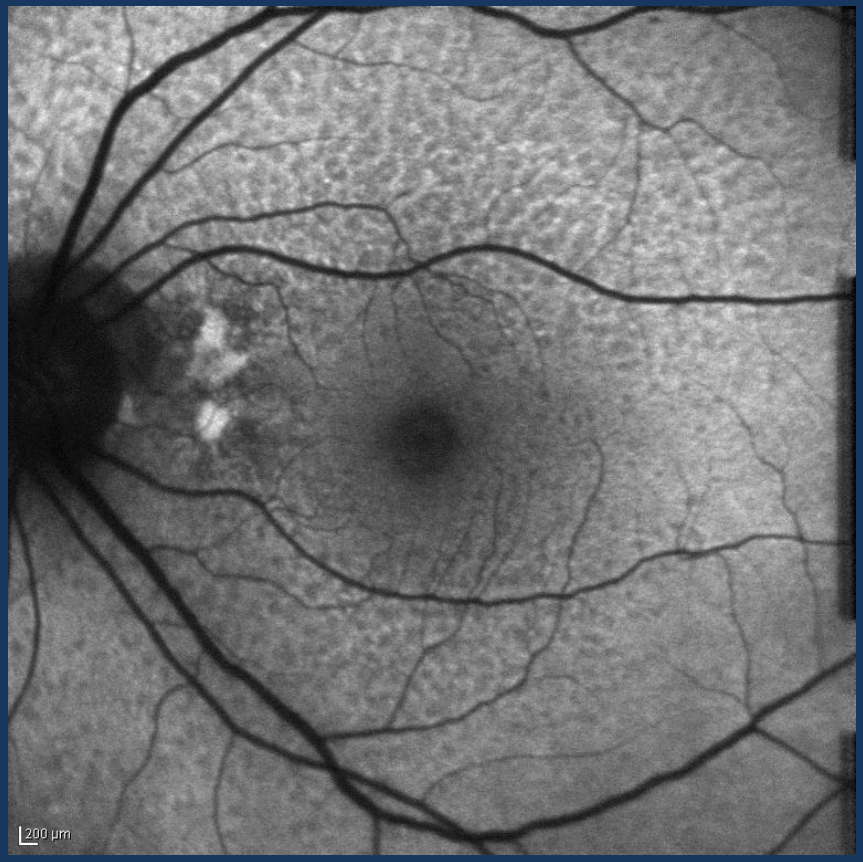


Reticular Pseudo-Drusen

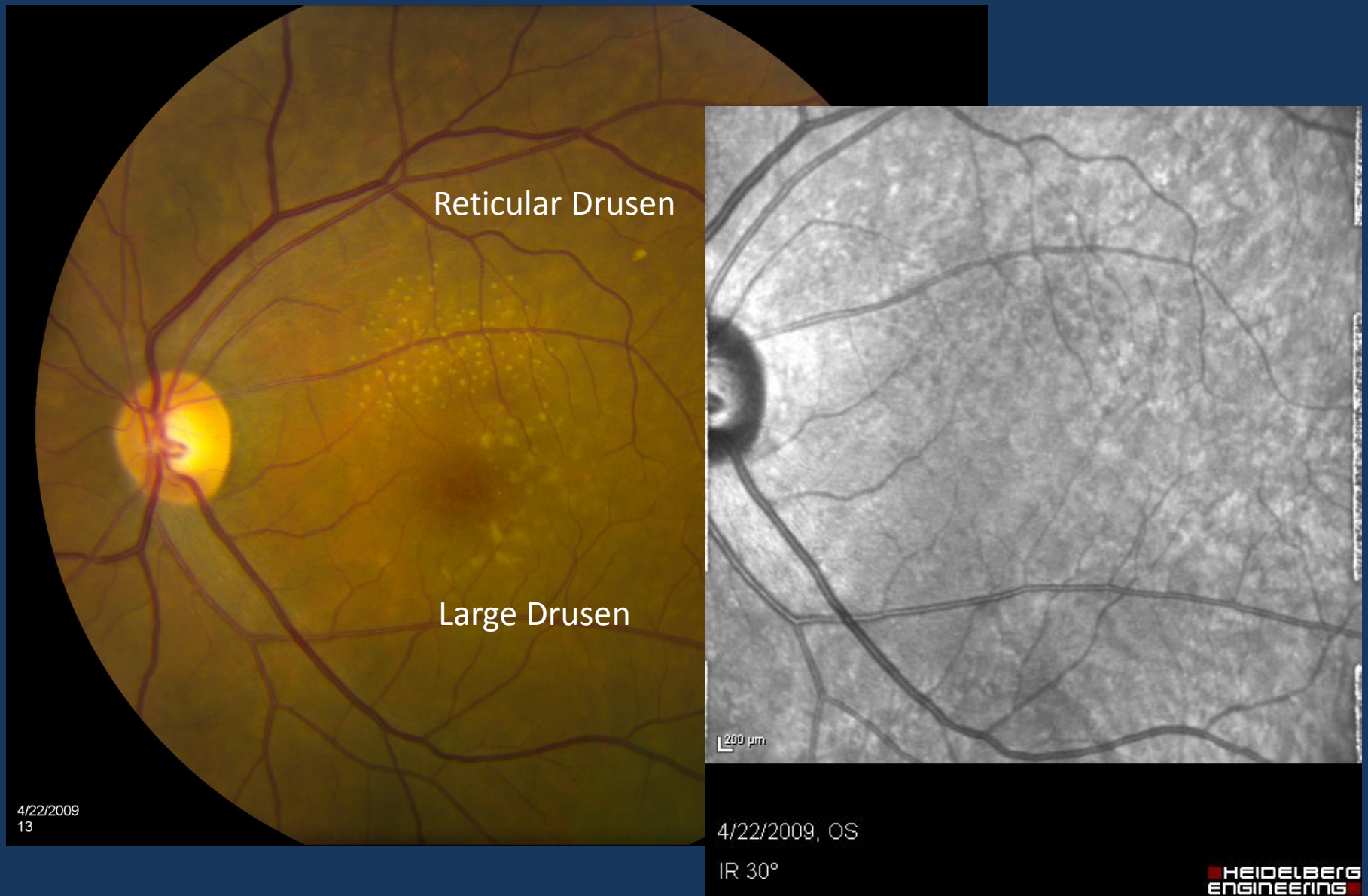
Reticular Autofluorescence

- Lois et al. :Definition of reticular AF " Ill-defined small areas of decreased AF surrounded by areas of increased AF" AJO 2002;133(3):341-9

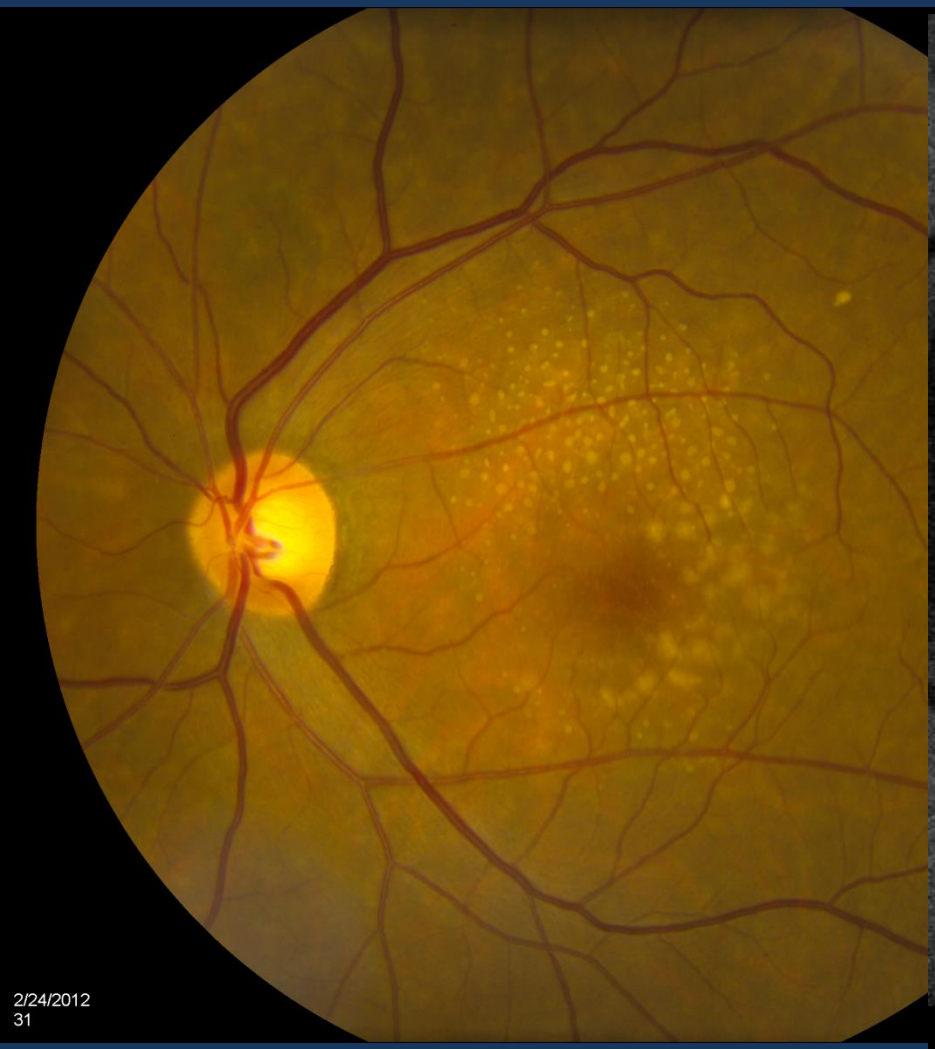
- Smith et al: correlation between reticular autofluorescence and reticular pseudo-drusen on multiple modalities ; "Reticular Macular Disease"

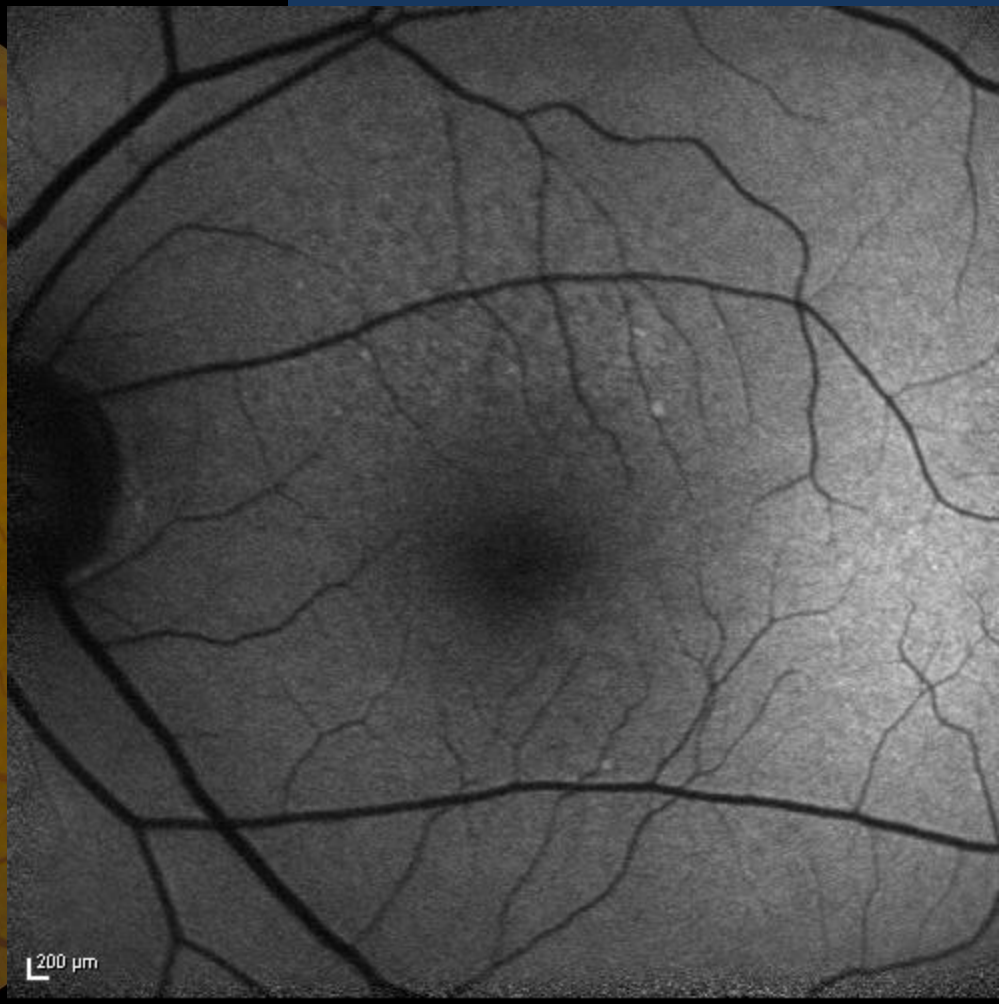


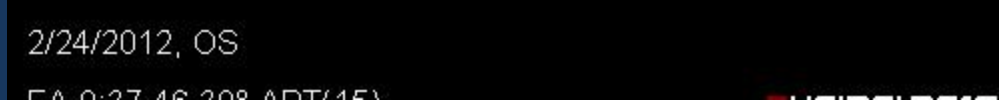
2009 60 yo Female, Neovascular AMD



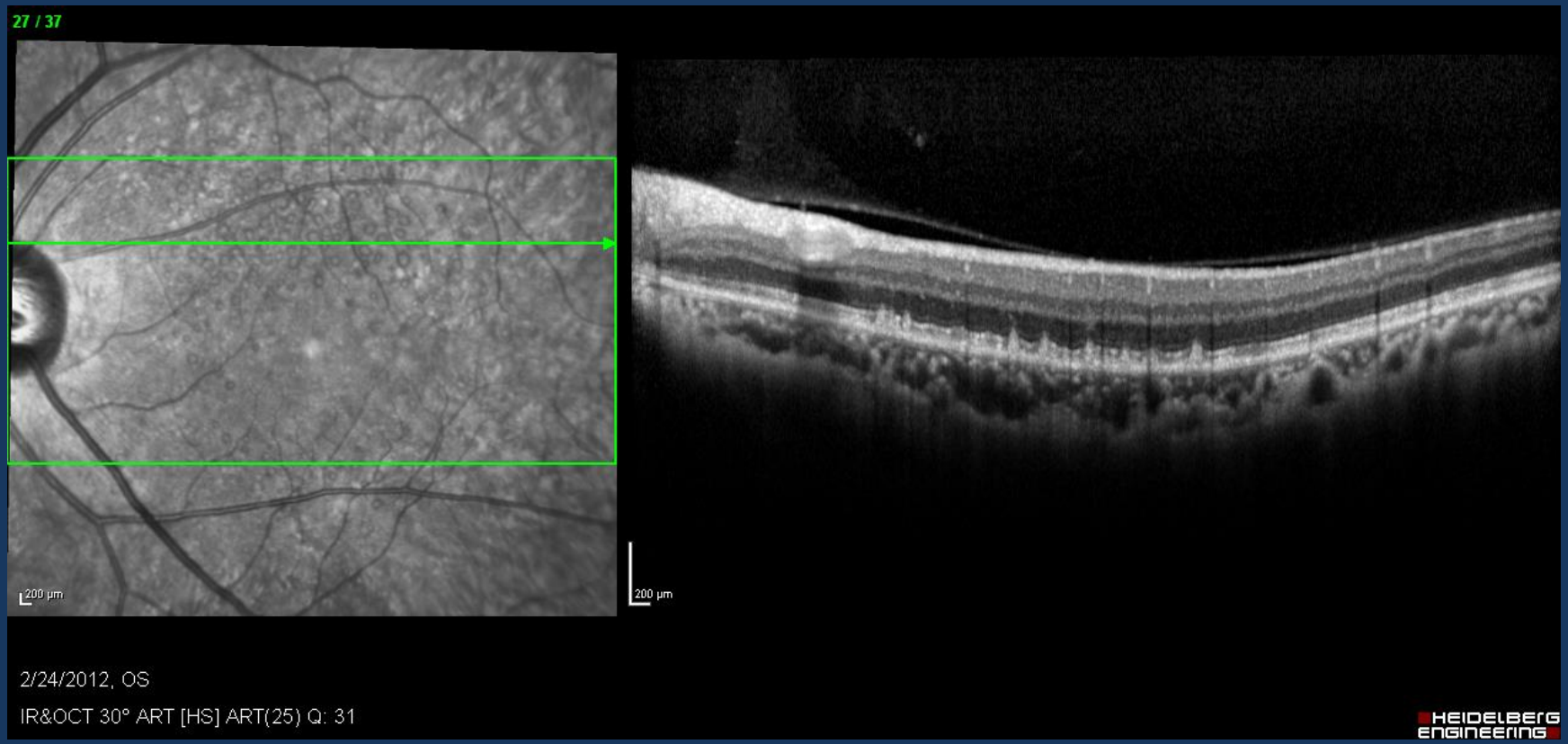
2012







2012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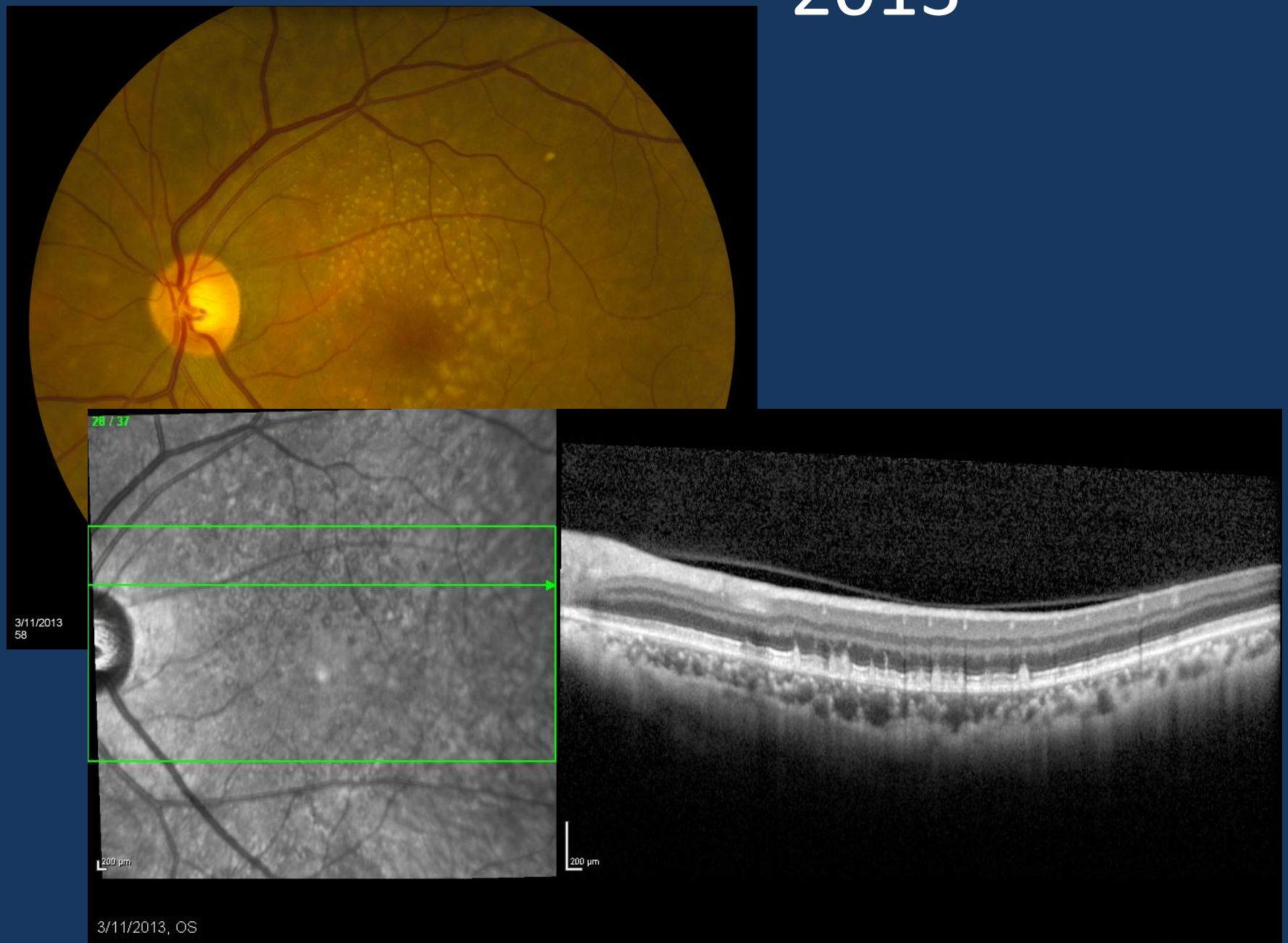
HEIDELBERG ENGINEERING

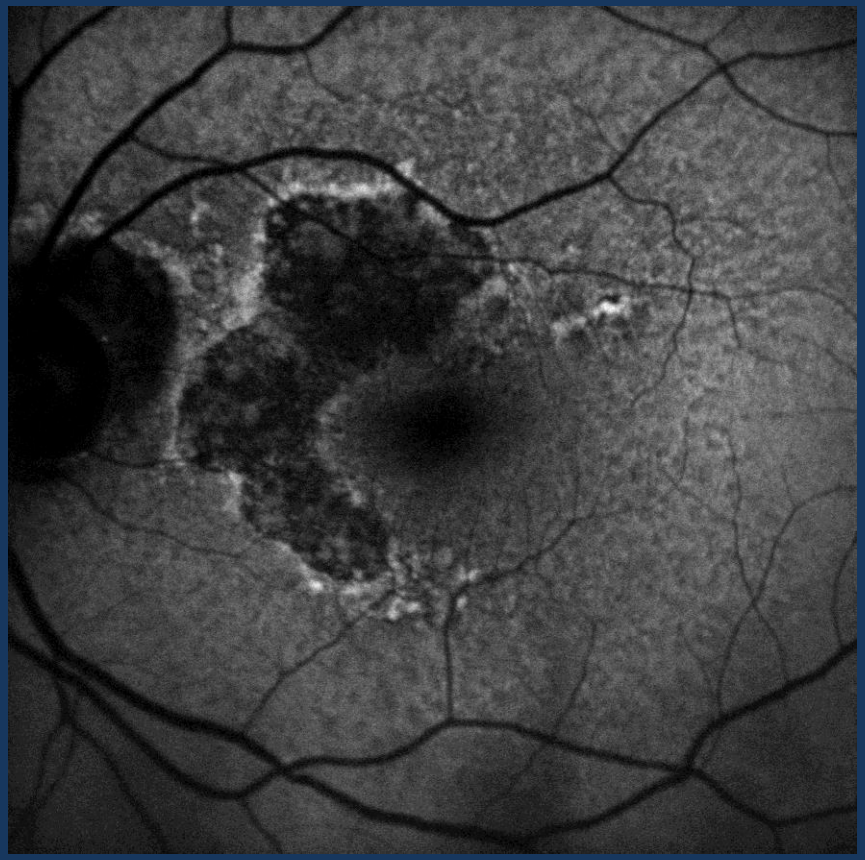
2013



Reticular Pseudo-Drusen

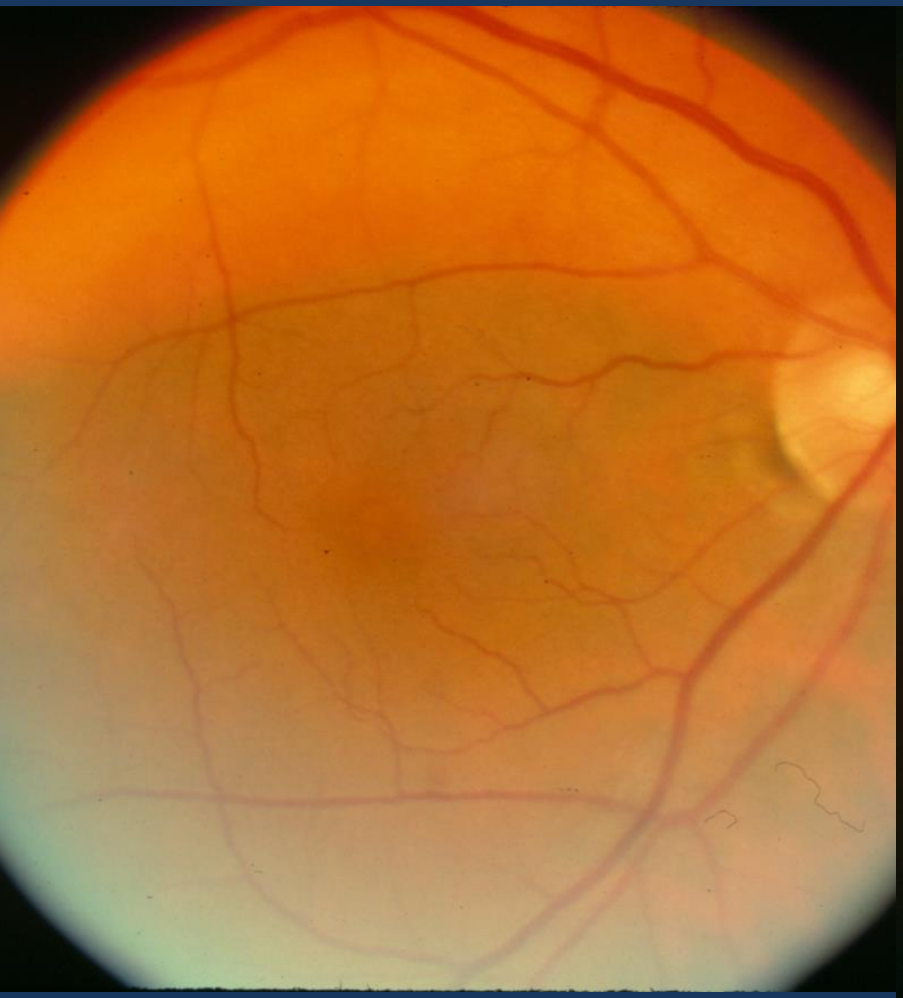
Reticular Autofluorescence

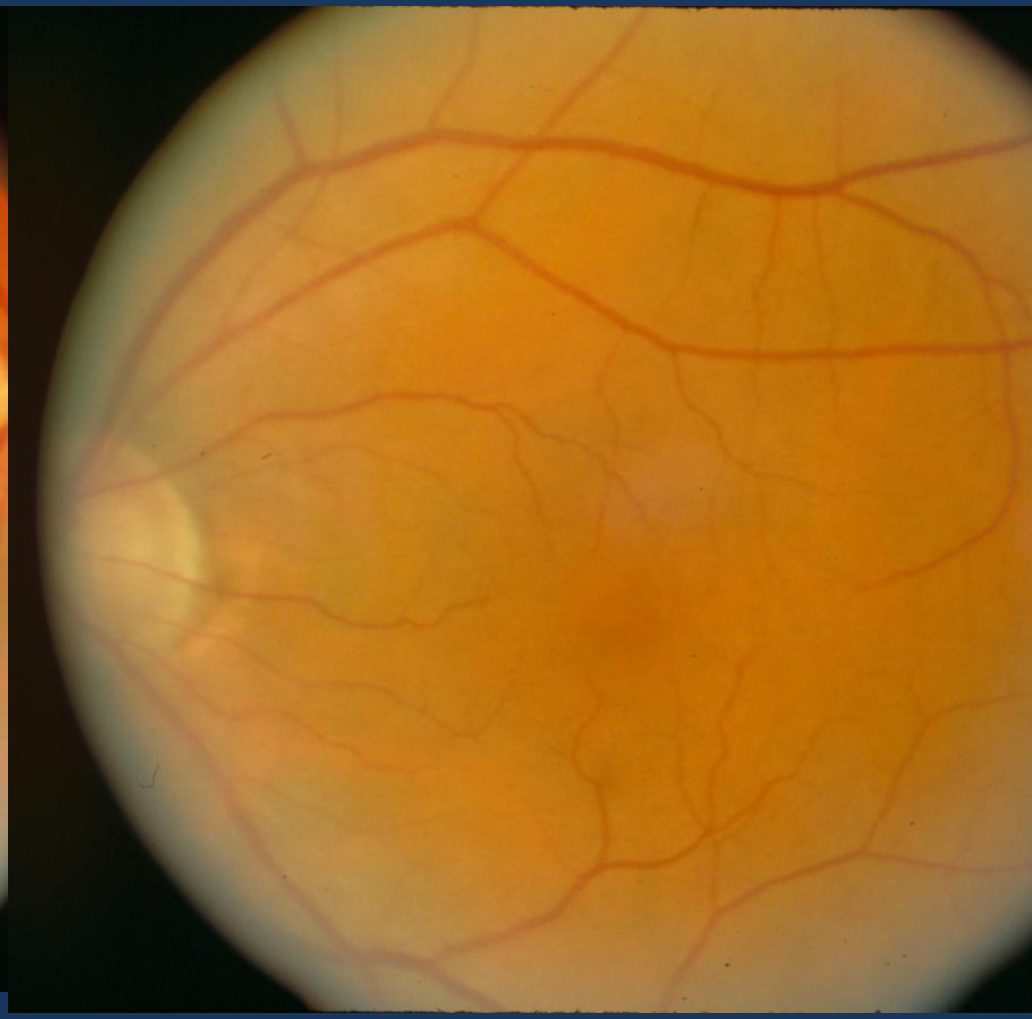
- Reticular drusen represent a common phenotypic hallmark in eyes with Geographic Atrophy.



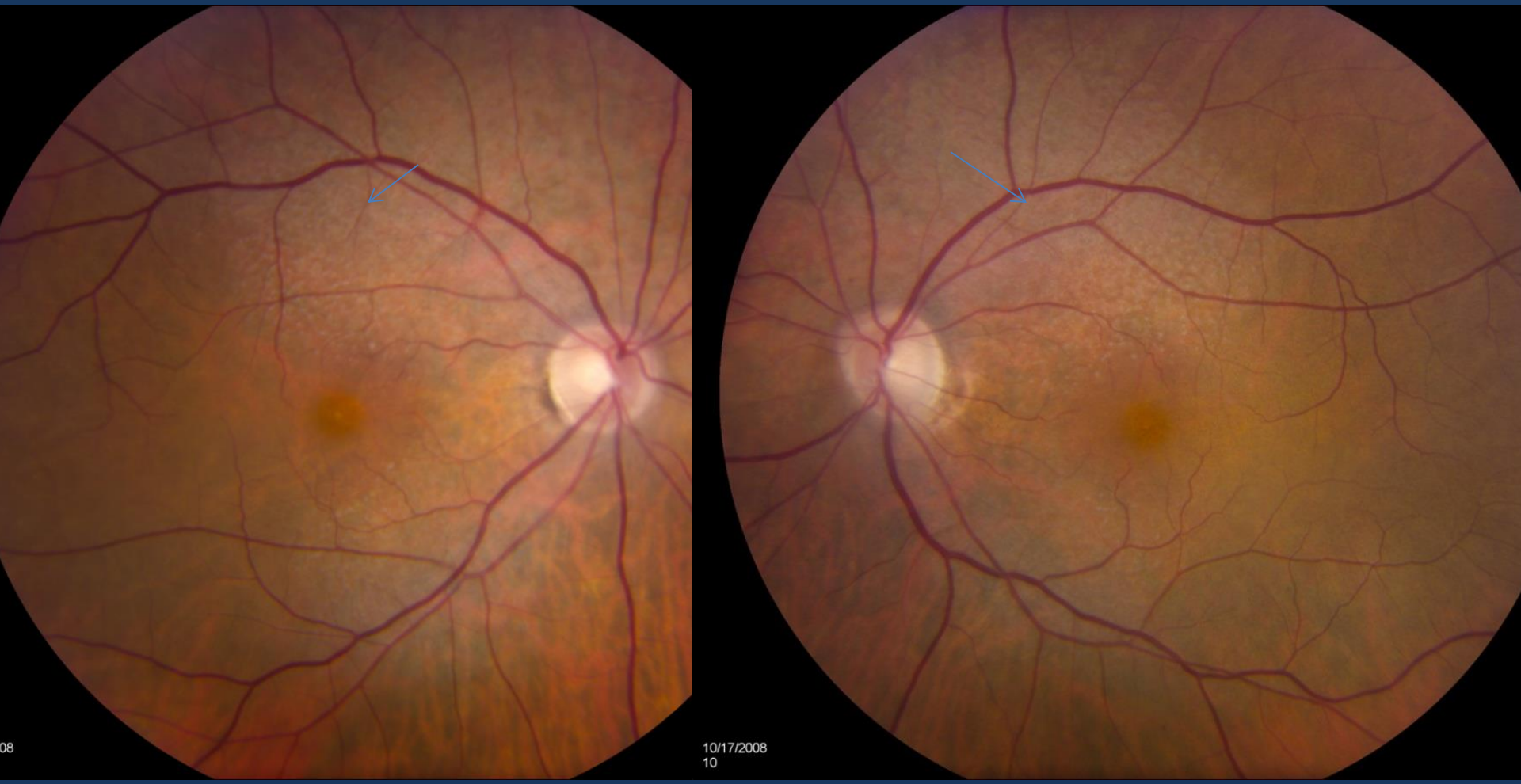
Holz et al., IOVS, August 2011,Vol 52,No. 9

1991 AREDS Participant-no AMD





2008 AREDS Participant-no AMD



Phenotype of Geographic Atrophy (GA)

Burden of disease-enormous and growing

Drusen and RPE pigmentary changes & Progression of GA

Reticular Drusen-Role? In AMD