SUNY DMC
Department of Ophthalmology
Grand Rounds 11-20-2014

Frank Cao, MD PL-2
Clinical Assistant Instructor

History

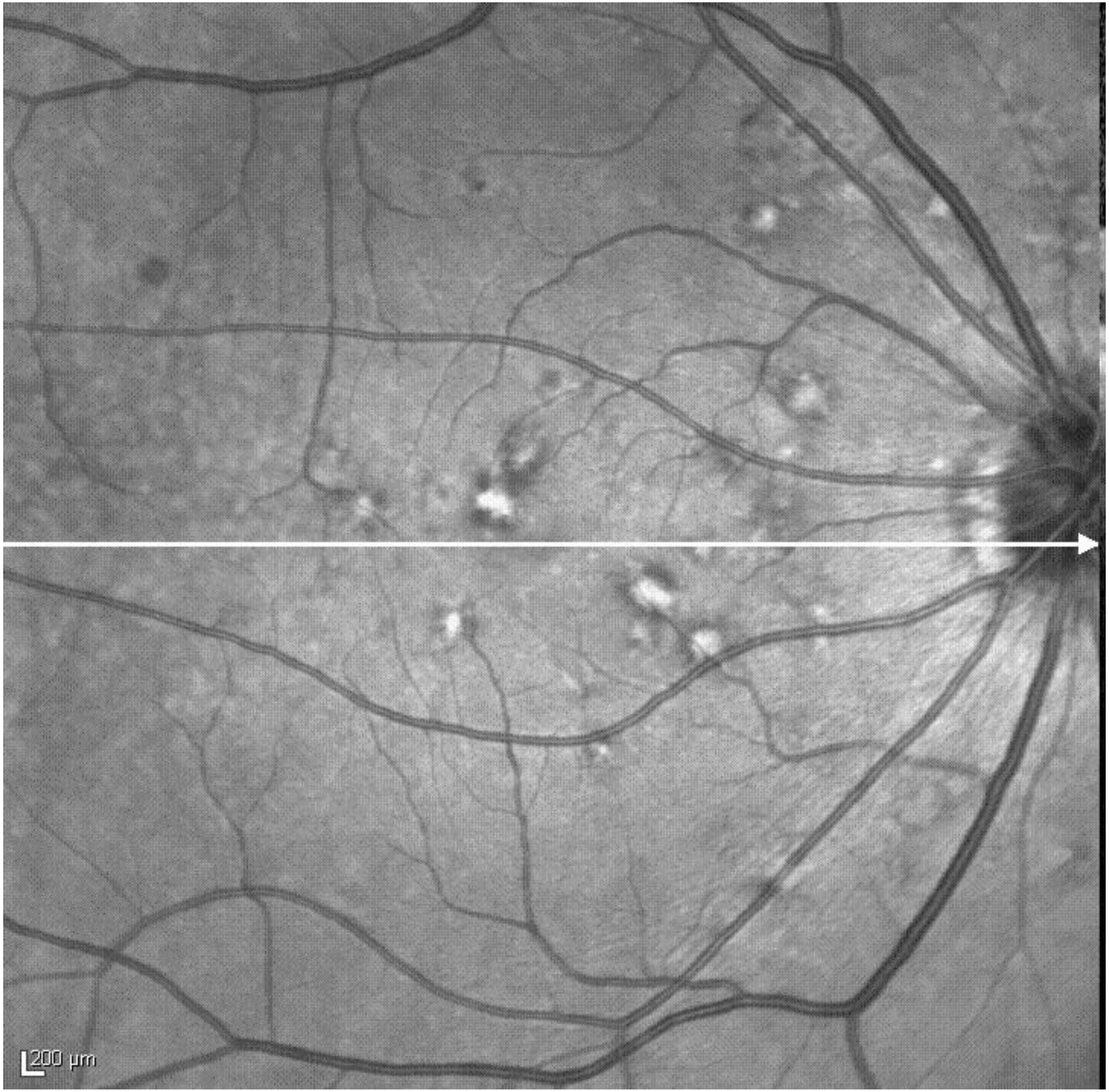
- HPI: 44 YO Greek male referred from general ophthalmologist for retina evaluation of fundus lesions.
- PMH: denies
- PSH: denies
- POH: s/p LASIK OU, episcleritis OS
- SH: social EtOH
- FH: no early blindness
- Meds: none
- Gtt: none
- All: NKDA

Exam

- DVasc: OD 20/20-2; OS: 20/20-2
- NVasc: OD 20/30; OS 20/25
- Pupils: 5-2, no APD
- EOM: Full OU
- CVF: ftcf OU
- Tapp: 15/15

Exam

- SLE: s/p lasik changes OU, otherwise unremarkable
- DFE: see photos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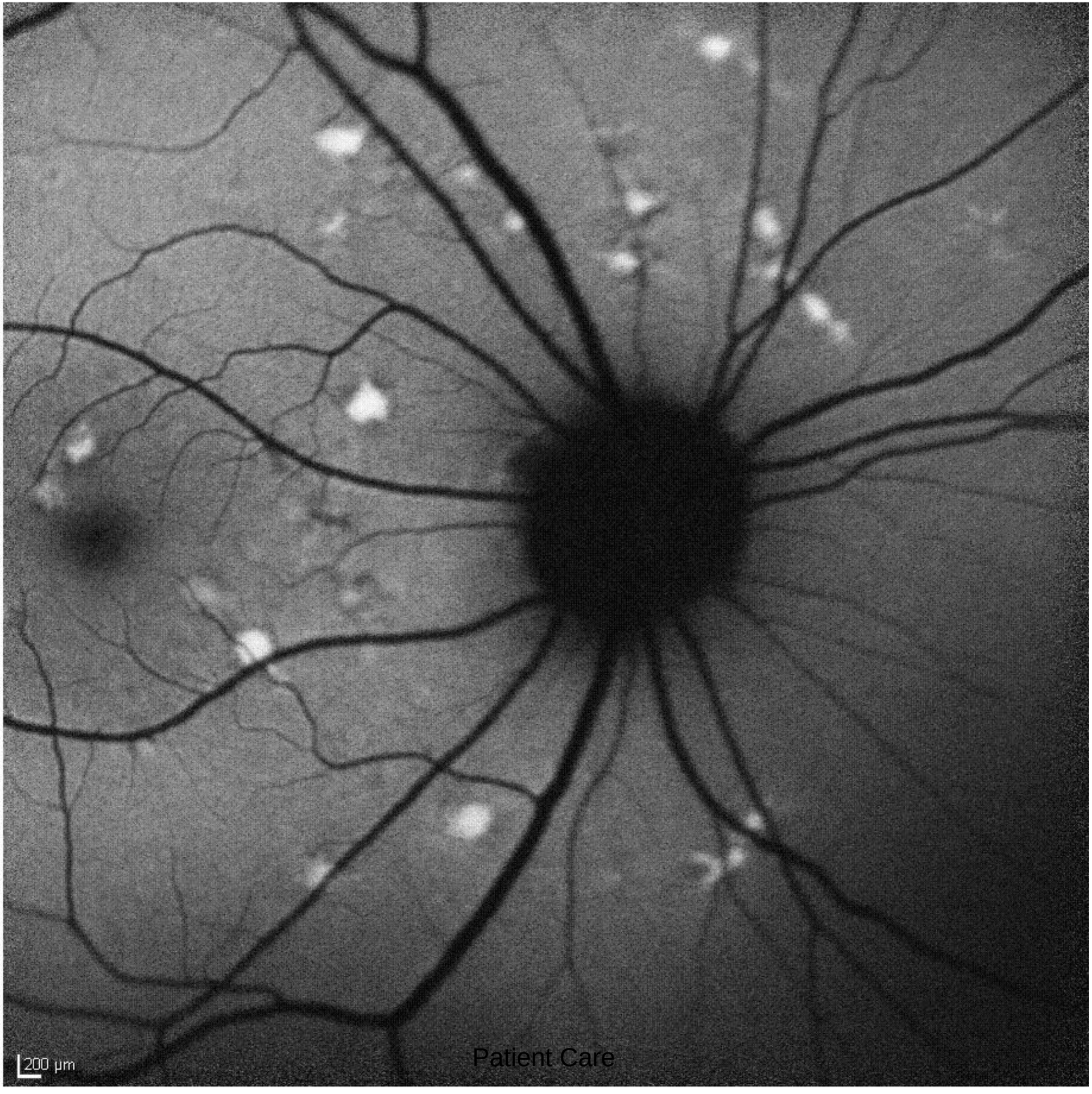
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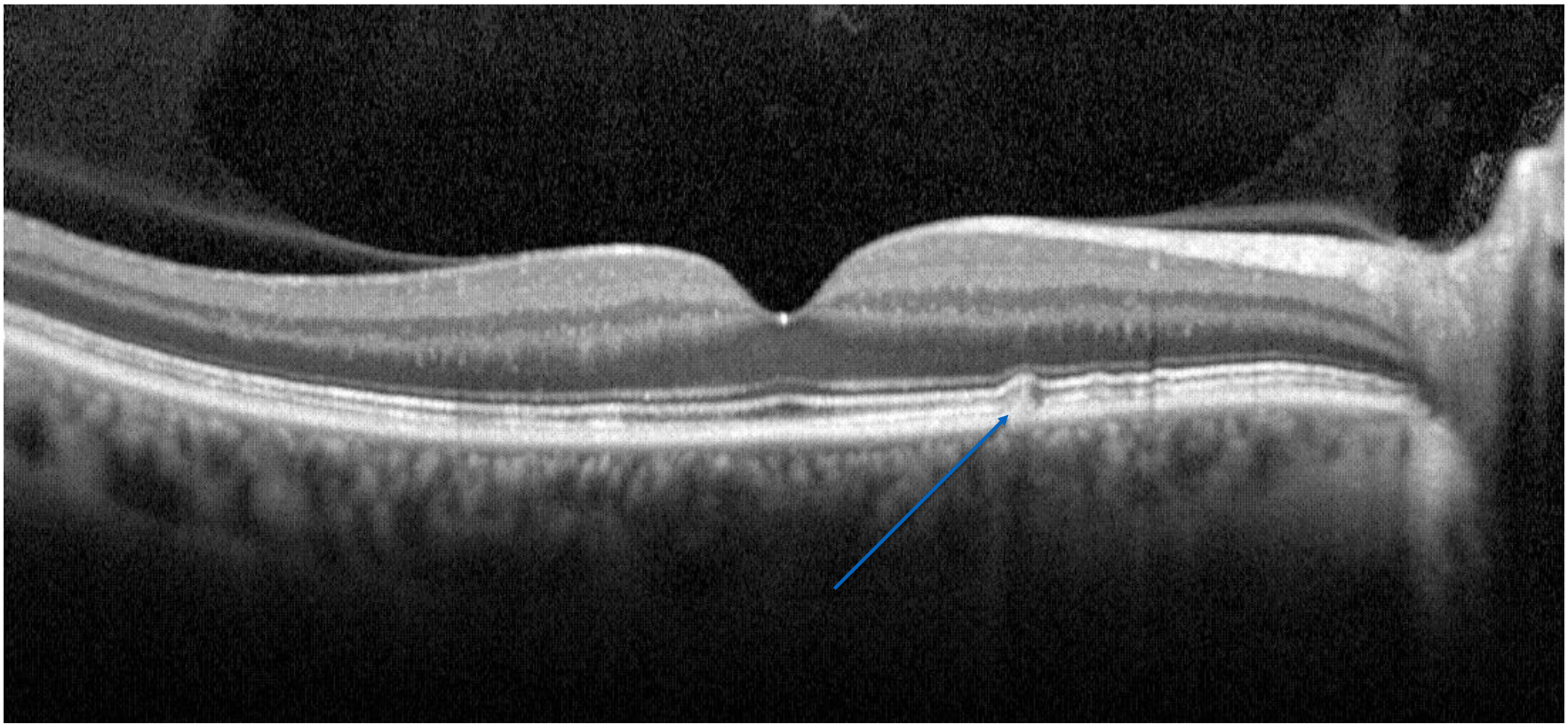

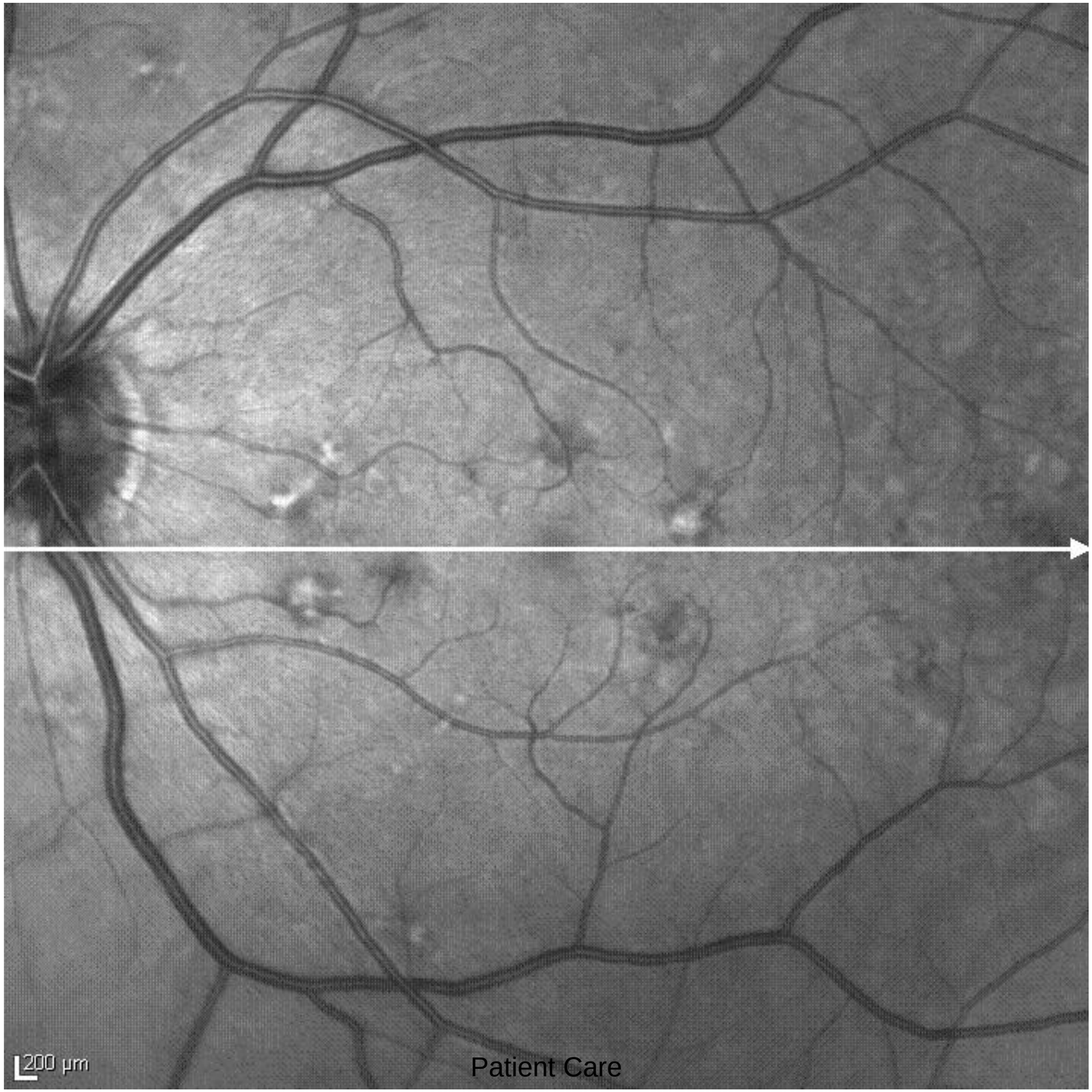
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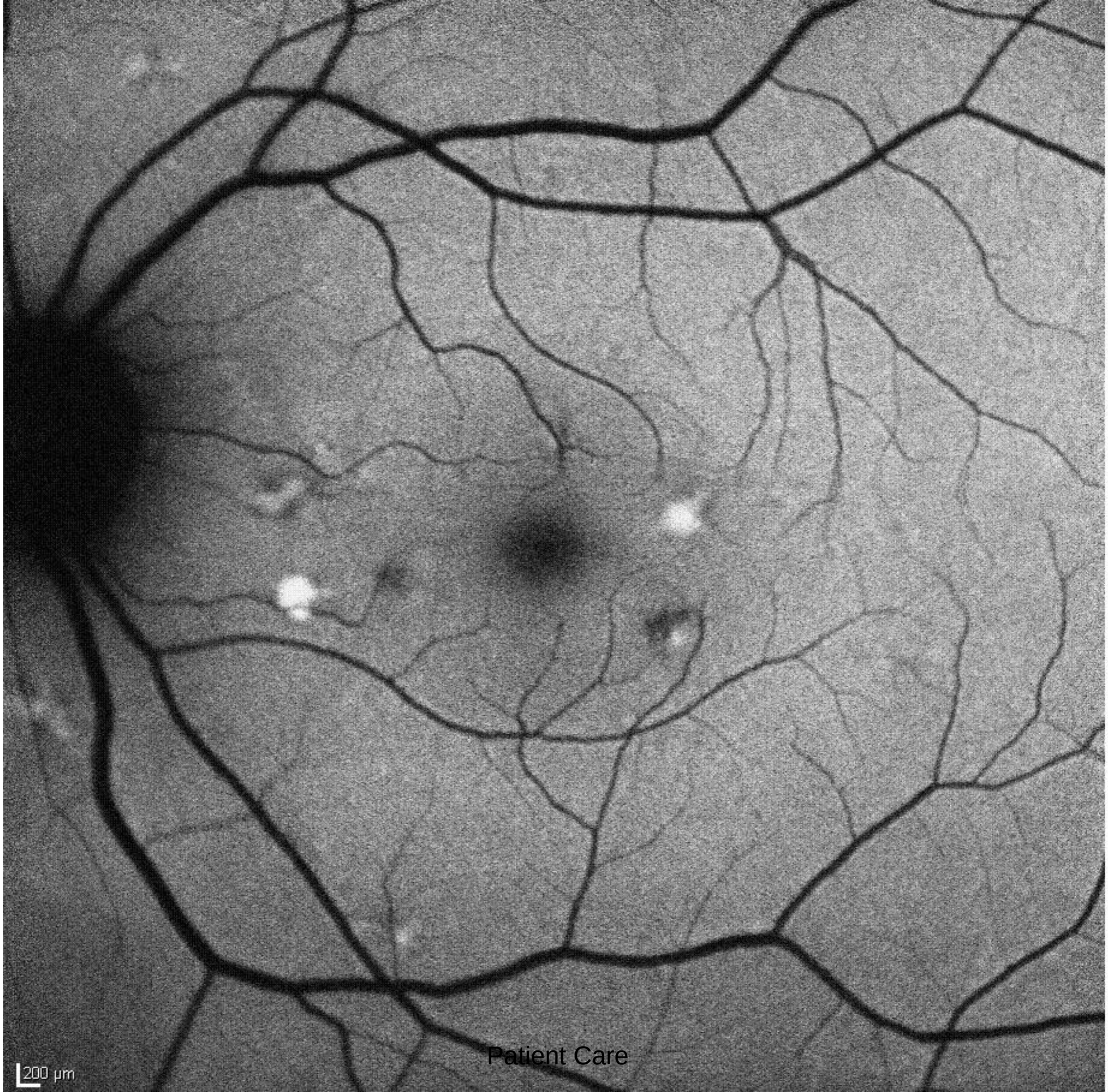
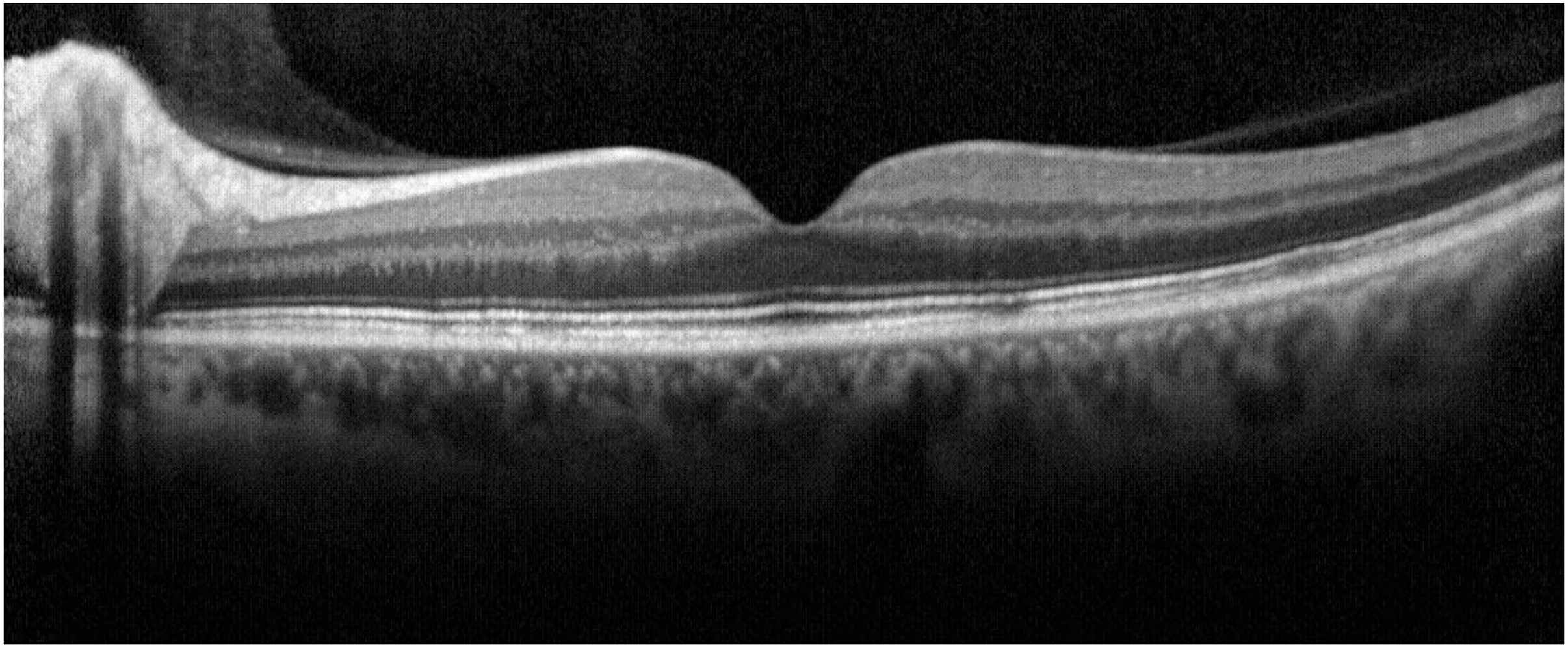
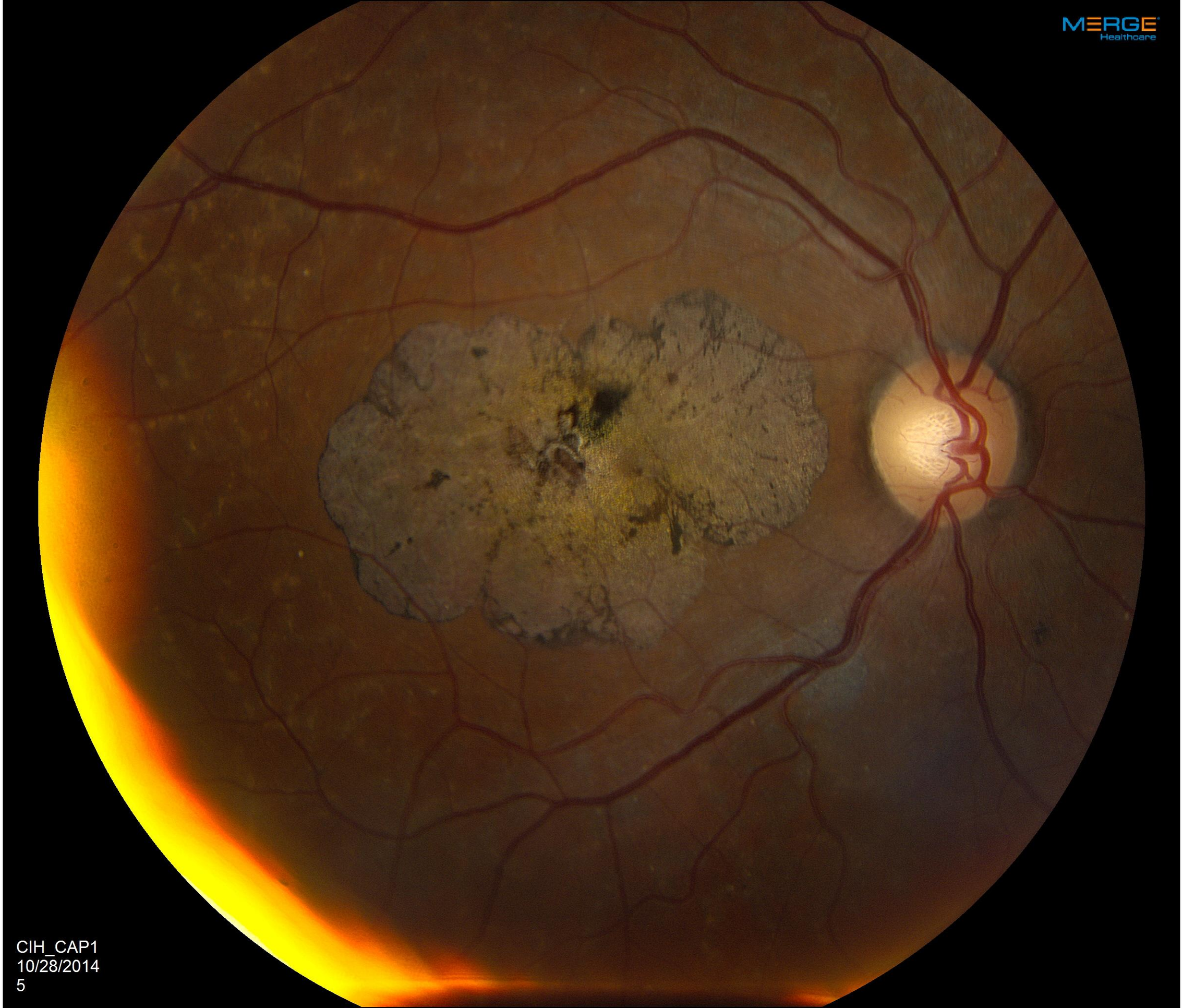


Patient Care



Differential diagnosis

- Age related Macular Degeneration (Drusen)
- Bulls eye maculopathy
- Pattern dystrophy
- Stargardt disease or Fundus Flavimaculatus
- Cone rod dystrophy
- Retinitis Pigmentosa
- White Dot syndromes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Basics

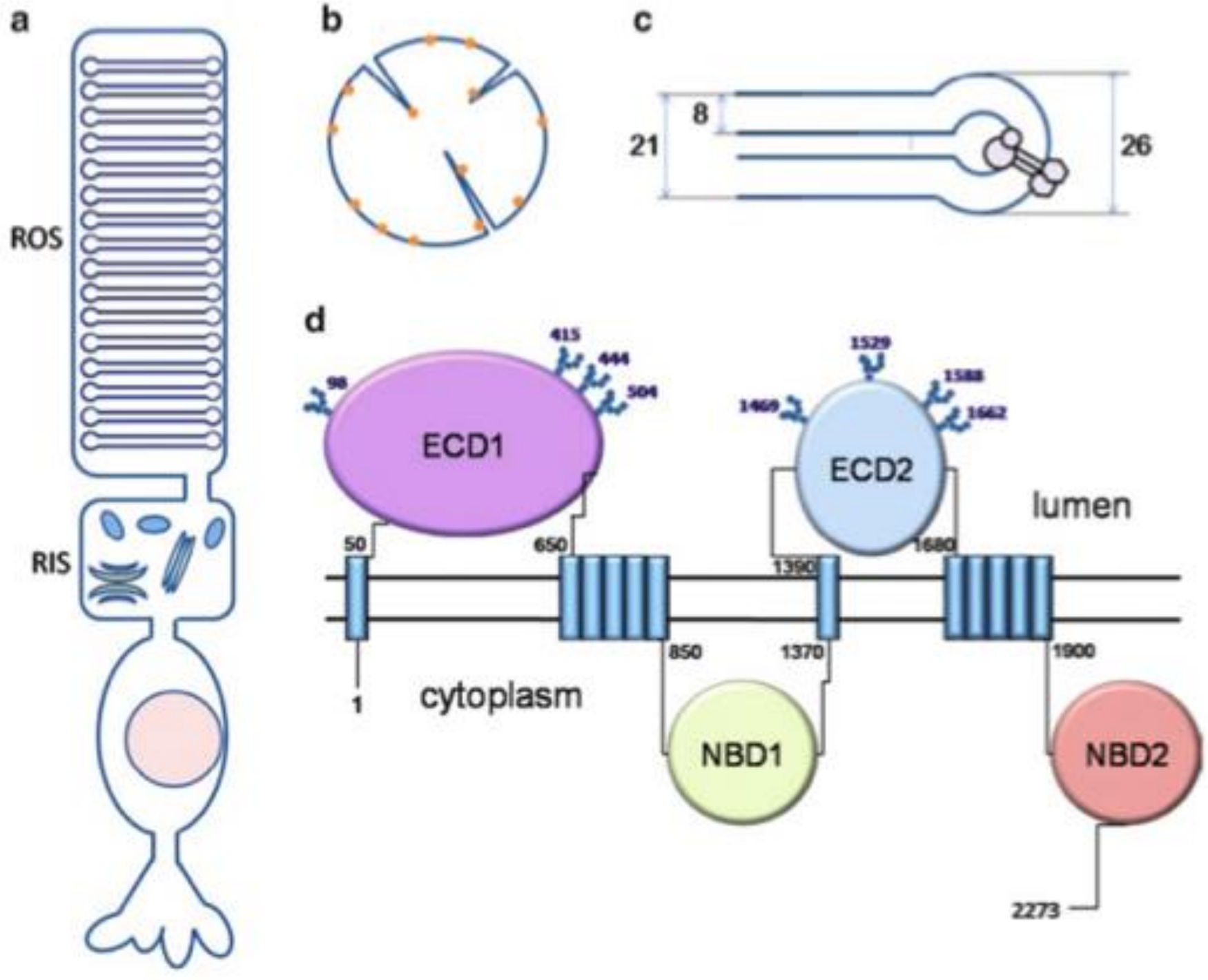
- Early 1900s Karl Stargardt describes disease in 7 patients in 2 families
- Prevalence estimated 1 per 8-10,000
- Fundus flavimaculatus (FFM) is a genetically linked clinically milder form of Stargardt
- Gene defect found in 1997 to encode for ABCA4

Genetics

- Autosomal recessive disease
- ABCA4 gene on chromosome 1, 6.8 kB
- > 600 disease associated variants in the gene
- ABCA4 microarray detects all currently known disease associated genetic variants or ~70% of all disease associated alleles
- Estimated that >1/20 individuals carry ABCA4 disease associated allele
- 3 most common mutations account for <10% of disease
- ABCA4 associations: Bulls eye maculopathy, AR cone rod dystrophy, AR RP, AMD

ABC transport

- ATP Binding casette transporters (ABC transporters) use ATP hyrolysis to translocate substrates across cell membranes
- 4 domains required: 2 nucleotide binding and 2 transmembrane
- 49 ABC transporters identified in human genome so far
- Localizes to rim of rod outer segment discs (cones as well)


a
ROS
RIS
b
c
8
21
26
d
ECD1
415
444
504
98
ECD2
1529
1588
1662
1469
lumen
50
650
1390
1680
850
1370
1900
1
cytoplasm
NBD1
NBD2
2273

ABCA4

Pathophysiology

- ABCA4 removes N retinylidene-phosphatidylethanolamine (NRPE) from disc space and transports to cytoplasm of rods and cones
- NRPE is formed by all trans retinal binding to phospholipid phosphatidylethanolamine
- Accumulation of NRPE in the disc space allows a second molecule of all trans retinal to bind to NRPE, forming A2E
- Diretinoid-pyridinium-ethanolamine (A2E), a component of lipofuscin, accumulates in disc space via disc shedding and phagocytosis and is toxic to RPE

Clinical characteristics

- Slowly progressive central vision loss, photophobia, color vision abnormality, central scotoma, slow dark adaptation
- Patients presenting over 20 years of age usually have better than 20/200 vision
- Age of onset highly variable, usually between childhood to early adulthood
- Color vision typically compromised (red-green)

4 stages

- Gerald Fishman describes 4 stages of Stargardt's in 1976
- Stage I - pigmentary changes in fovea or parafovea (beaten metal), atrophic RPE, normal EOG/ERG, ring of flecks around fovea
- Stage II - flecks extending anterior to the arcades and/or nasal to optic disc, normal EOG/ERG but with delayed dark adaptation, normal peripheral field, possible central scotoma
- Stage III - resorption of flecks, widespread choriocapillaris atrophy, EOG abnormal, ERG may be abnormal
- Stage IV - further resorption of flecks, more widespread atrophy of choriocapillaris, greatly reduced ERG amplitudes

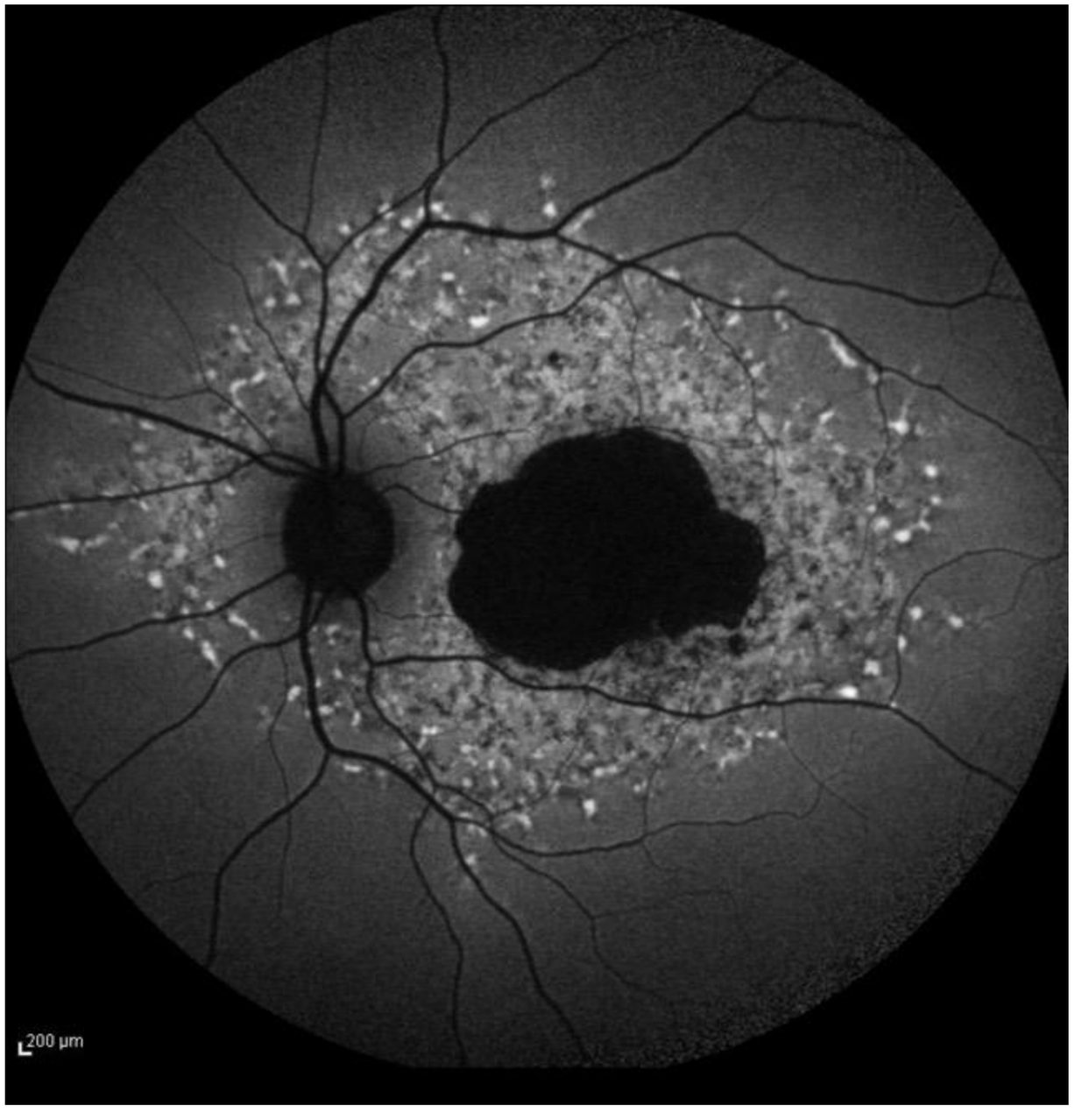
Fundus Autofluorescence

- Hyperfluorescence - areas of lipofuscin accumulation
- Hypofluorescence - areas of RPE atrophy
- Allows detection of RPE functional changes before clinically detectable
- Serves as a useful indicator of disease progression
- Sparing of peripapillary retina on FAF has been diagnostic criteria
    - Loss of sparing may correlate with widespread photoreceptor dysfunction and poorer visual prognosis

Fundus Autofluorescence

Red free and fundus autofluorescence

Fundus Autofluorescence

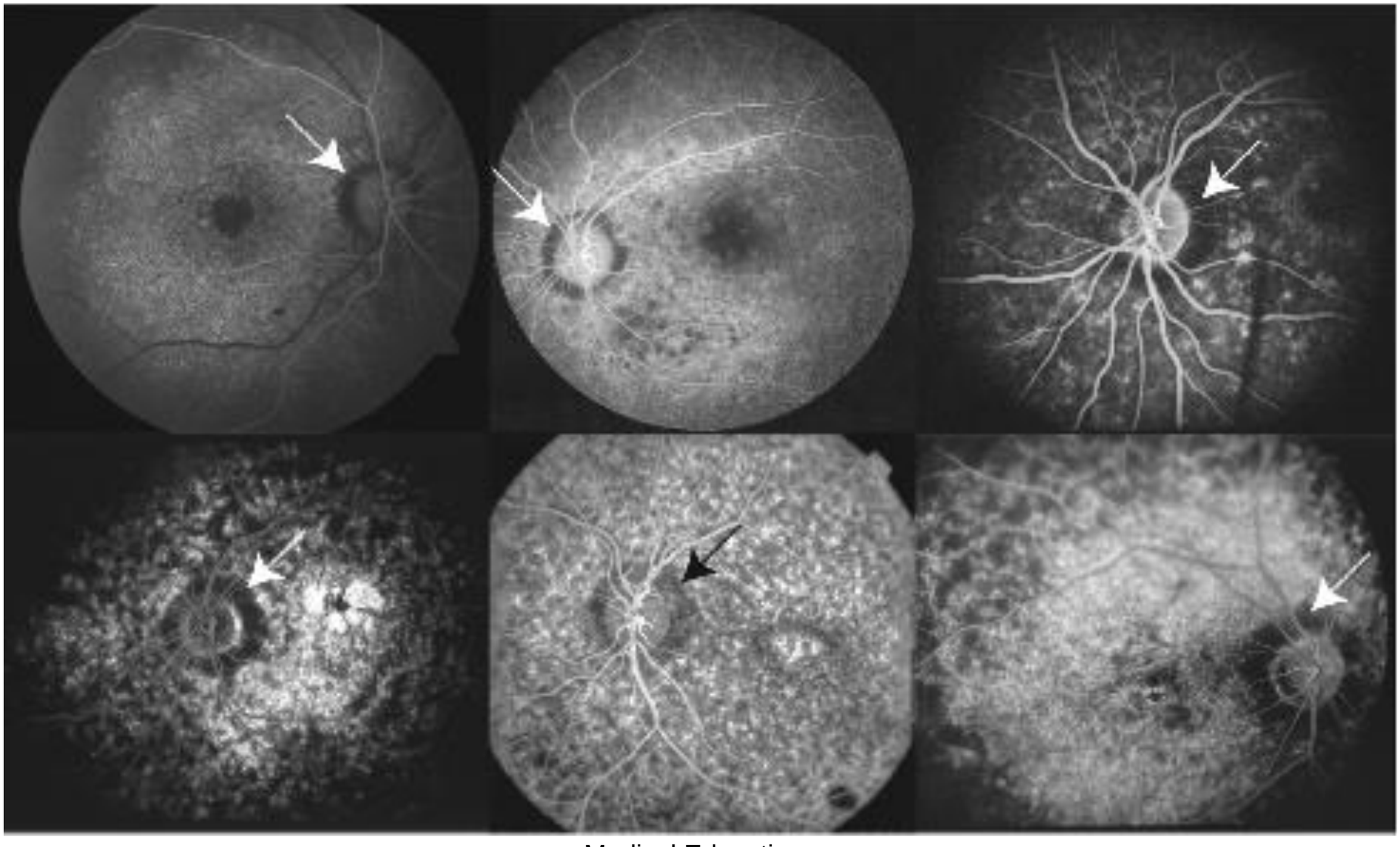


Medical Education

Fluorescein Angiography

- Dark choroid cited from 62 to 86% sensitive
- Background choroidal fluorescence blocked from lipofuscin accumulation in RPE
- Ring of hypofluorescence in the peripapillary region reported in 37% of 135 patients in a cohort study at Kellogg in 2009
- May be indicator of more severe disease

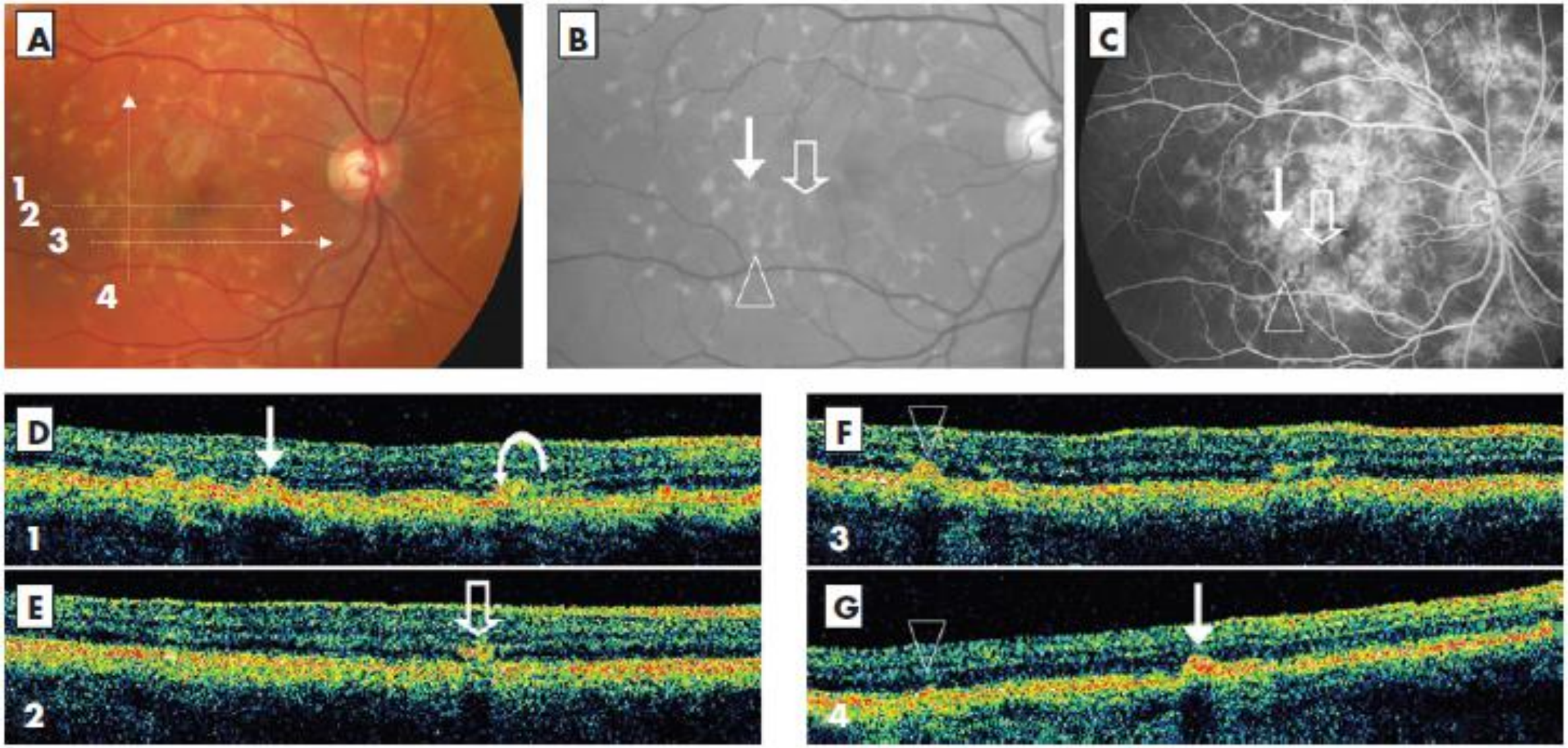
Fluorescein Angiography



Optical Coherence Tomography

- Voigt looked at 49 eyes of 26 patients with FFM using FAF, OCT, and FA
- Classified flecks based on location
- Hyper reflective deposits may be: in the inner RPE (type 1), or in the ONL clearly separated from the RPE (type 2)
  - Type 2 are rare in inherited maculopathies
  - Correlation between ellipsoid and BCVA

Optical Coherence Tomography



Important Differentials

- Drusen
  - lesions show less hyperfluorescence
  - echolucent on OCT
- Pattern dystrophy
  - Better final VA, no dark choroid on FA
  - Hyperfluorescence tends to be more discrete, punctate and irregular
  - Autosomal dominant in many cases

Progstar

- Multi-center study will characterize disease progression and facilitate data collection on progression trends
- Primary outcome: lesion growth by FAF q6 month
- Secondary outcomes: retinal function by microperimetry, SD-OCT

Potential therapies

- Deuterated vitamin A: may block formation of A2E downstream the visual cycle

- KO ABCA4-/- mice raised on deuterated vitamin A generated less A2E and lipofuscin vs those fed vitamin A

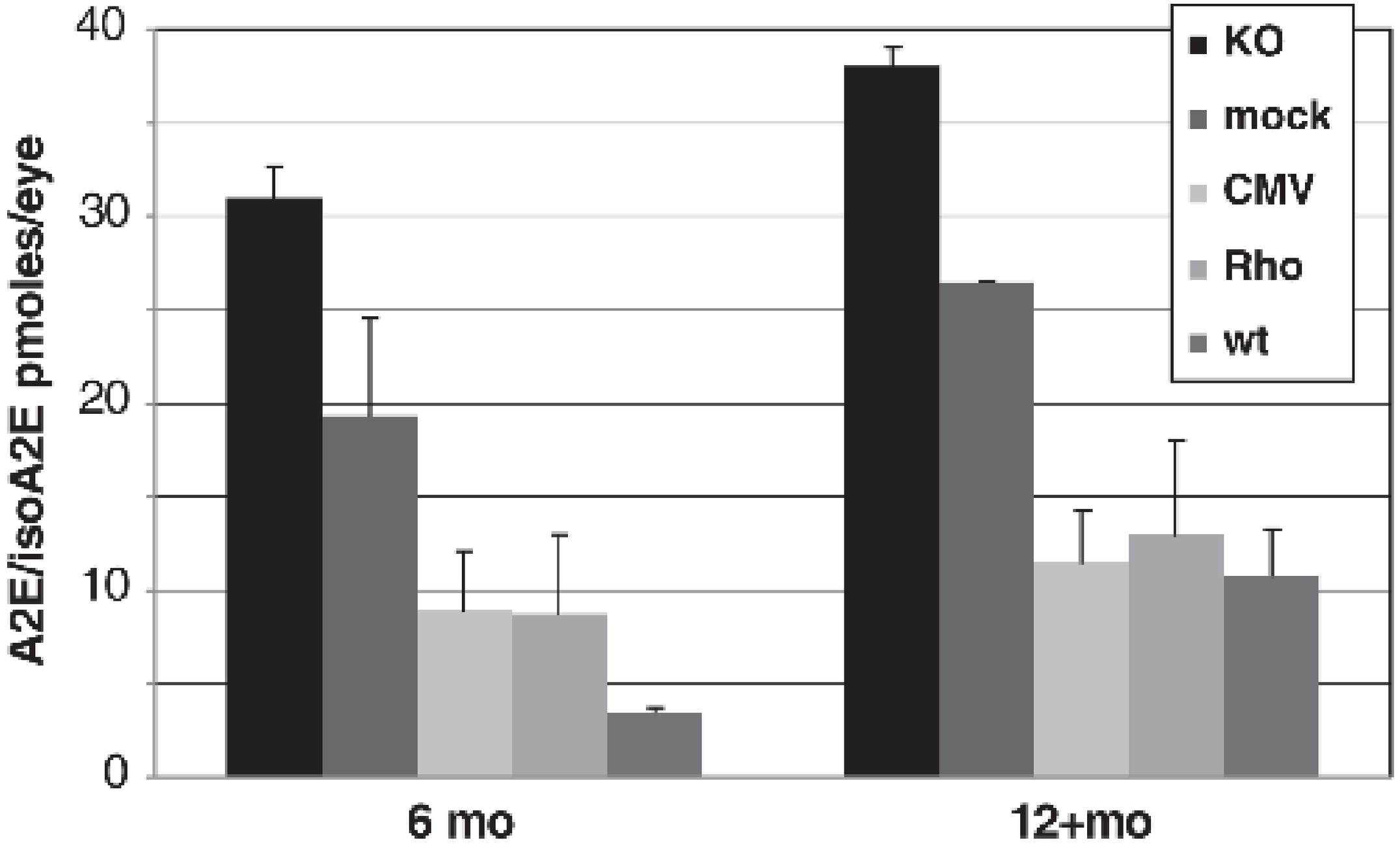
- In phase Ia trials

Ma L, Kaufman Y, Zhang J, Washington I. C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt disease. *J Biol Chem.* 2011;286:7966-7974.

Stargen

- Delivery of human ABCA4 gene to KO mice reduced accumulation of A2E in treated eyes
- Lentivirus vector used instead of adeno associated virus
- Requires subretinal injection
- Currently in phase I/IIa in US and Europe
- Studies in adult macaque and rabbit retinas indicate safety for subretinal delivery of stargen

Kong et al. Gene Therapy. “Correction of the disease phenotype in the mouse model of Stargardt disease by lentiviral gene therapy”(2008) 15, 1311–1320:



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Our Patient

- Patient advised of visual prognosis and treatment options and sent for second opinion with another retina specialist
- Encouraged UV blocking sunglasses and eye exams for all relatives

Reflective Practice

- Patient was examined and treated in a timely manner with respect and updated practice guidelines
- Case demonstrates presentation of a rare disease process
- After considering a wide differential diagnosis and examining the literature, the appropriate diagnostic modalities were chosen to narrow our differential, formulate a diagnosis, and monitor the patient and disease progression.
- Family and patient were educated about the disease process, natural course, and treatment options.
- Literature review was performed to ensure up to date guidelines regarding management were followed.

Core Competences

- **Patient Care**: The patient and family were treated compassionately and with respect and patient and family were included in medical decision making calculus.
- **Medical Knowledge**: Extensive literature review of corneal stingers was performed, and current practice guidelines were reviewed.
- **Practice-Based Learning and Improvement**: Close examination of patient was performed at each visit and treatment plan was altered accordingly.
- **Interpersonal and Communication Skills:** We communicated extensively with the patient and family at each clinical encounter.
- **Professionalism**: Patient and family were treated with respect during all clinical encounters.
- **Systems-Based Practice**: Appropriate and cost effective services were offered to patient.

Thank you

- Patient
- Dr Fletcher

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