Clinical Ophthalmology MSc Course
Oct 2018

AUTOFLUORESCENCE IMAGING

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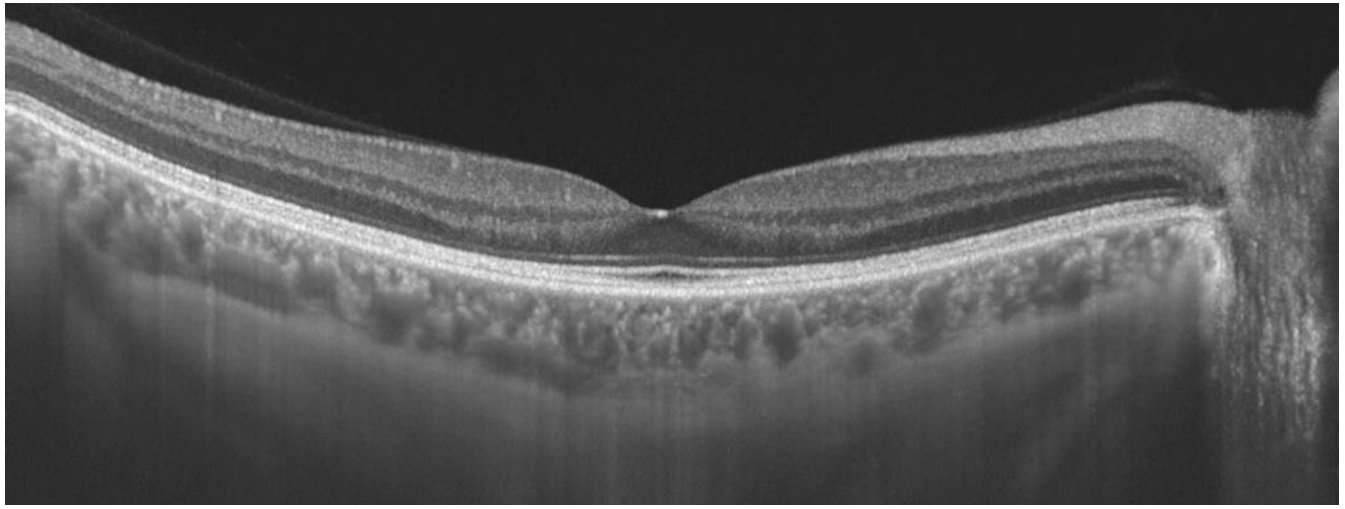
Traditional model

- Hello, I'm Dr X…
- What's wrong?
- Let me have a look
- I think we need to get some investigations
- Let me inspect these images

Current model



- Review imaging
- Inspect integrity of retinal layers
- Formulate provisional diagnosis and management plan
- Hello, I’m Dr X…

Importance of imaging…

- Why image? What's wrong with clinical examination?
  - **Document** findings (for monitoring or further opinions)
    - *vs* scribbles on paper or blobs on electronic patient records
  - Can be ***quicker*** for the patient
  - Detect abnormalities **not discernible** on clinical examination
  - Refine diagnosis and improve our understanding of disease
  - Monitor changes including efficacy of treatment

Non-invasive imaging modalities

- *En face*
  - Colour fundus photography, contact (e.g. retcam), non-contact
  - Ultra-widefield imaging (pseudocolour; white light)
  - Red-free imaging
  - Infra red reflectance
  - Blue light reflectance (also red, green)
  - **Short wavelength autofluorescence**
  - **Near infra red autofluorescence**

- Cross-sectional
  - Ultrasound
  - Optical coherence tomography: time domain, spectral domain, swept source

  - OCT angiography (*en face* and cross-sectional)

Outline

- Definition
- Historical perspective
- Some current devices
- Clinical applications: examples
  - AMD; CSCR; hydroxychloroquine
  - Inflammatory disease
  - Inherited retinal disease
  - New characterisations
- Further developments
  - Two wavelength autofluorescence
  - Photopigment bleaching and regeneration
  - Quantitative autofluorescence

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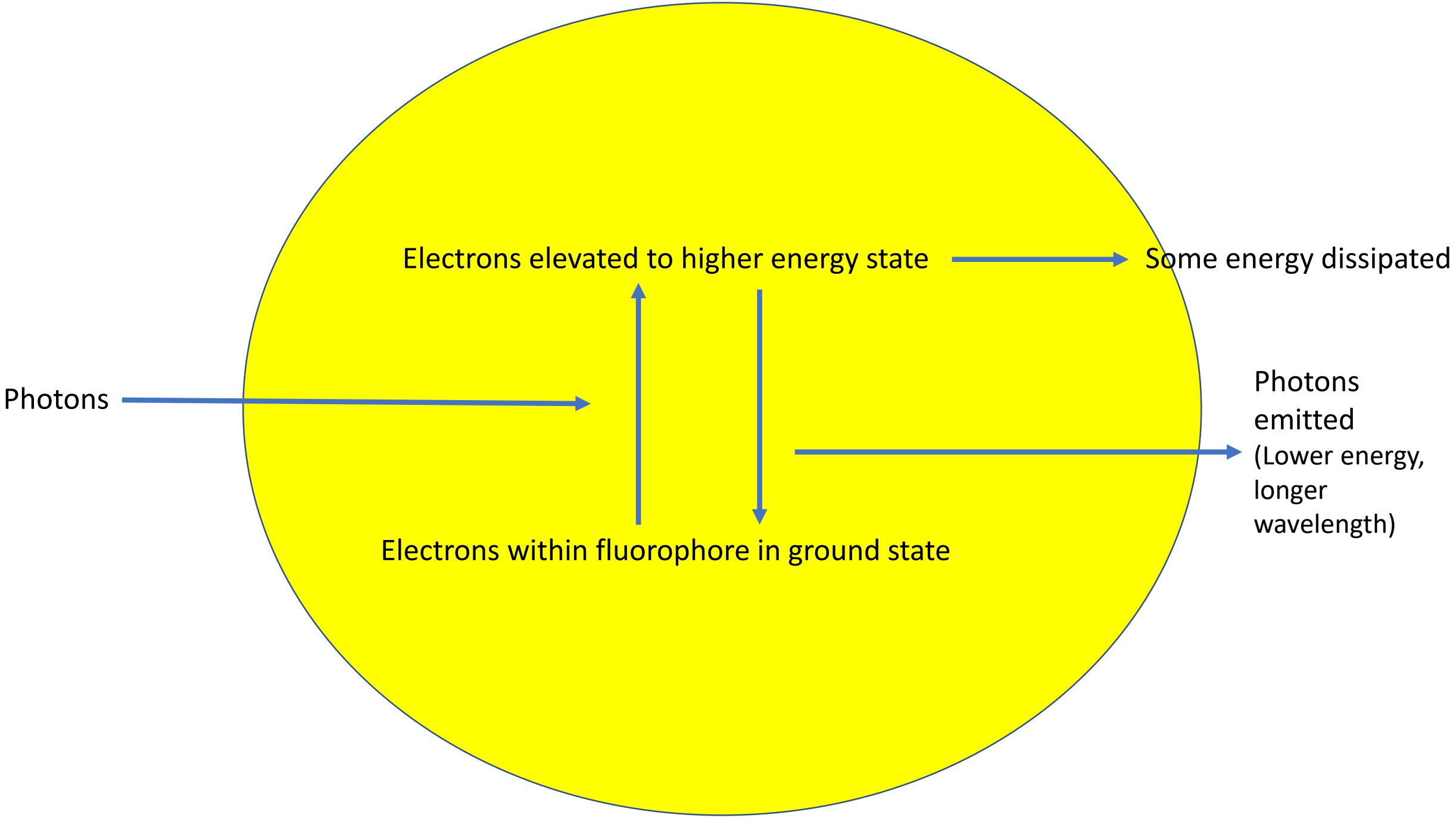
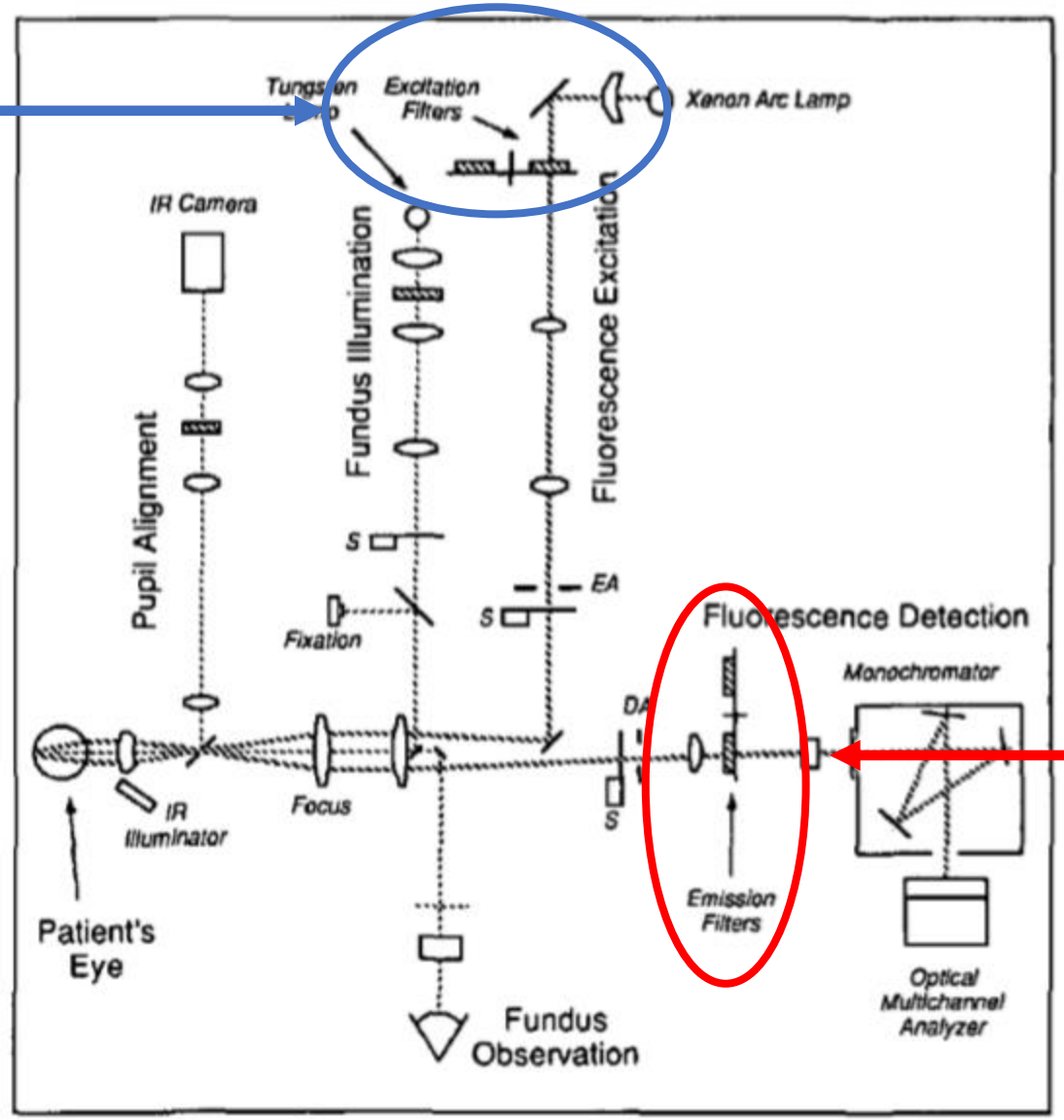
Definition

- Fluorescence – Light absorbing substance (“fluorophore”) re-emits photons of a longer wavelength (e.g. fluorescein, indocyanine green)
- “Autofluorescence” – intrinsic fluorescence property of the tissue, without requiring injection of extrinsic dye
- In retinal imaging, excitation is usually with short wavelengths (“short wavelength autofluorescence” or “blue light autofluorescence”)
- Main fluorophore appears to be a component of lipofuscin (A2E or other molecule(s))

- *Another modality is **near infrared** autofluorescence (fluorophore here is melanin)*


Electrons elevated to higher energy state
Some energy dissipated
Photons
Photons emitted
(Lower energy, longer wavelength)
Electrons within fluorophore in ground state

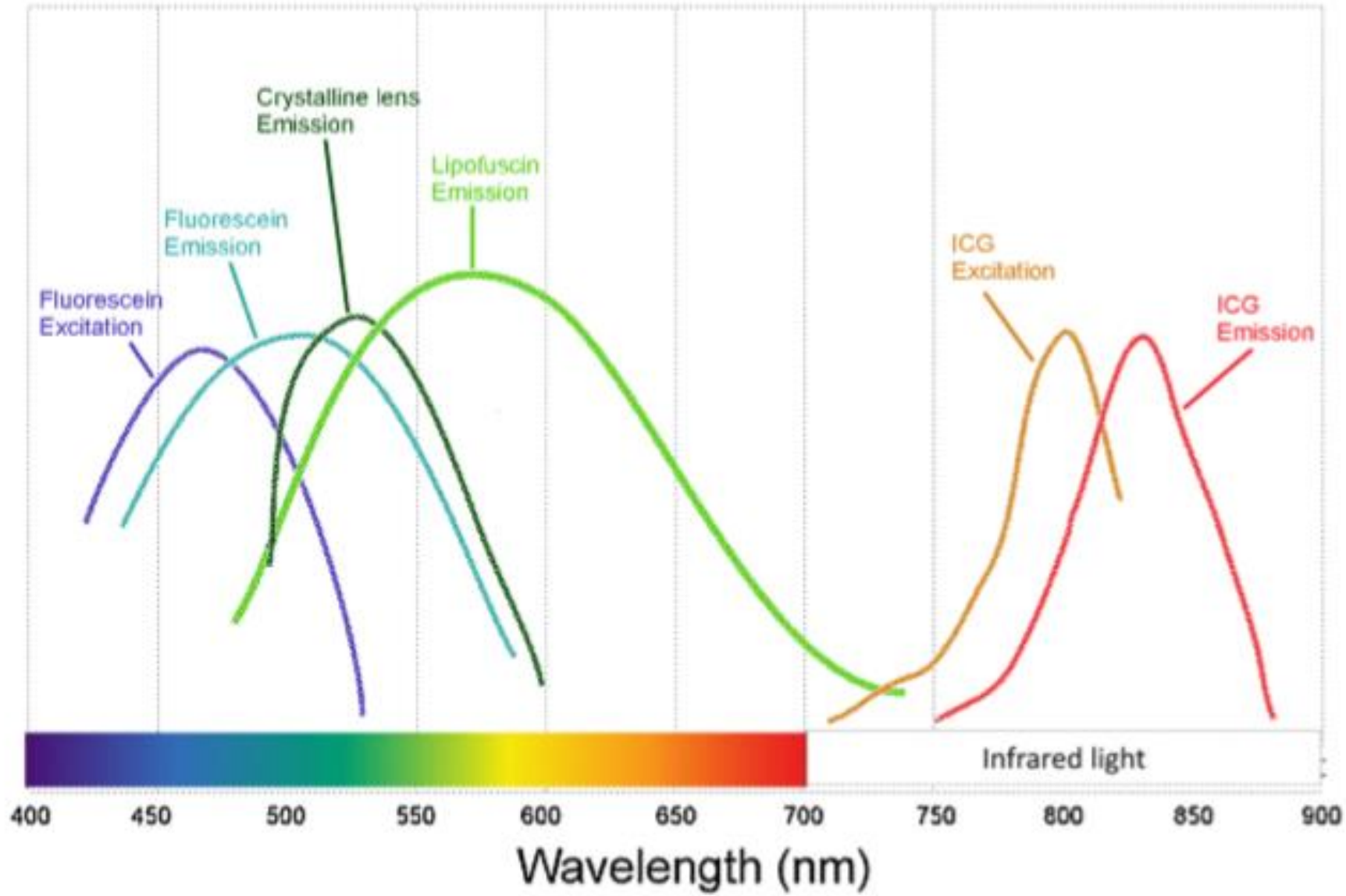
Excitation filters



Emission filters

Delori et al., 1995

FIGURE 1. Optical diagram of the fundus spectrophotometer. EA = confocal excitation; DA = detection apertures; S = shutters; IR = infrared.


Crystalline lens
Emission
Lipofuscin
Emission
Fluorescein
Emission
Fluorescein
Excitation
ICG
Excitation
ICG
Emission
Infrared light
400
450
500
550
600
650
700
750
800
850
900
Wavelength (nm)

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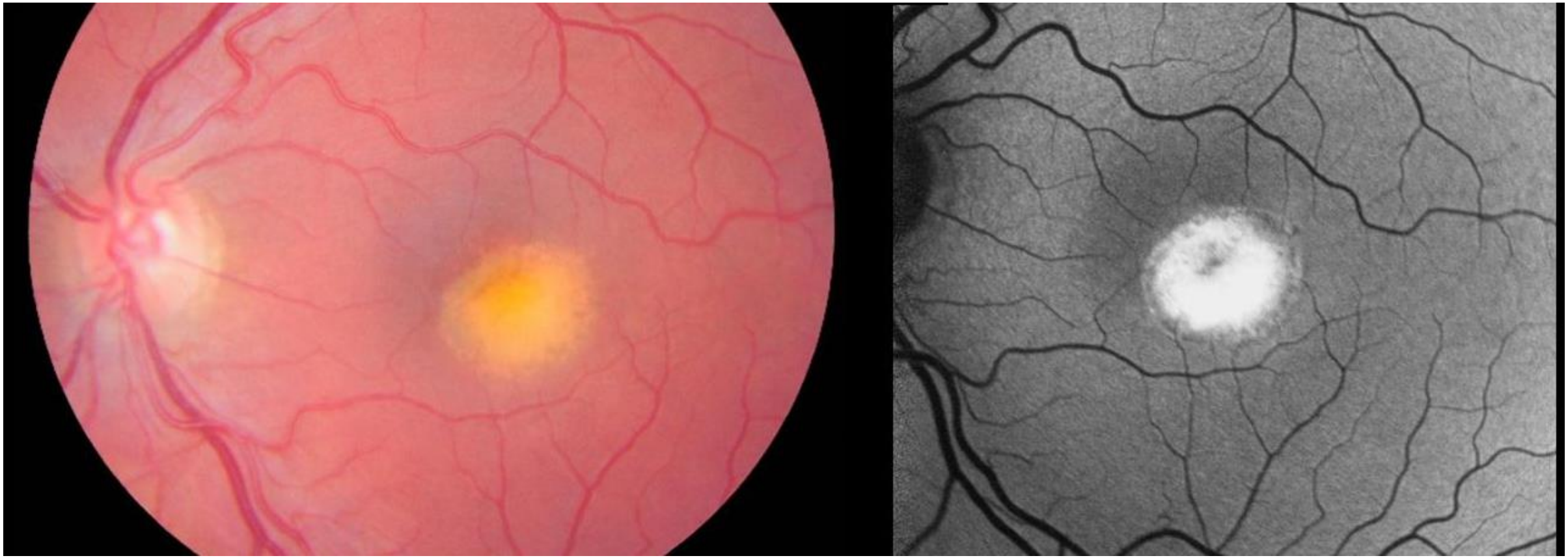
British Journal of Ophthalmology, 1978, **62**, 256–260

Fluorescence in Best's vitelliform dystrophy, lipofuscin, and fundus flavimaculatus

STEVEN ABBOTT MILLER

From the Retina Service, Department of Ophthalmology, University of Wisconsin, Madison, Wisconsin

SUMMARY Control photographs, with the Baird Atomic B4 and B5 filters in place prior to fluorescein injection, show exposure of the film corresponding to (1) the small yellow vitelliform lesions at the edge of a disrupted disc, (2) the pseudohypopyon in a vitelliform cyst, (3) orange lipofuscin overlying a malignant melanoma, and (4) some of the flecks in a case of fundus flavimaculatus. Because of transmission overlap between the filters, the relative contribution of reflected light and true autofluorescence is difficult to quantitate. Reflectile structures such as the optic nerve or a white scar were essentially unexposed, but minimal fundus detail was seen. Some parallels exist between lipofuscin and the content of a disrupted vitelliform lesion.



Appl Opt. 1994 Nov 1;33(31):7439-52. doi: 10.1364/AO.33.007439.

Spectrophotometer for noninvasive measurement of intrinsic fluorescence and reflectance of the ocular fundus.

Delori FC.

British Journal of Ophthalmology 1995; **79:** 407–412

Distribution of fundus autofluorescence with a scanning laser ophthalmoscope

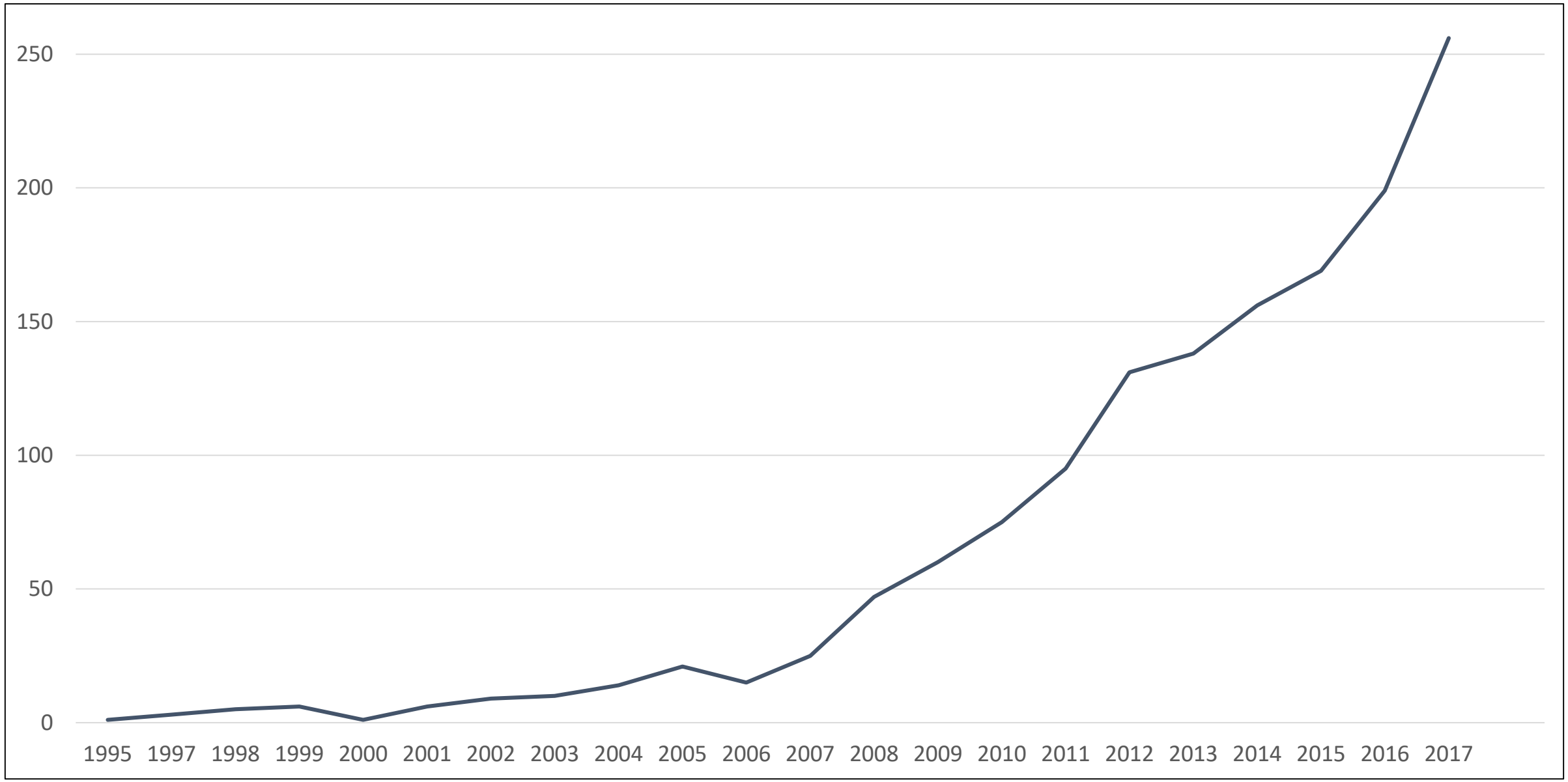
A von Rückmann, F W Fitzke, A C Bird

Invest Ophthalmol Vis Sci. 1995 Mar;36(3):718-29.

In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics.

Delori FC[1], Dorey CK, Staurenghi G, Arend O, Goger DG, Weiter JJ.

PubMed hits per year for “fundus autofluorescence”



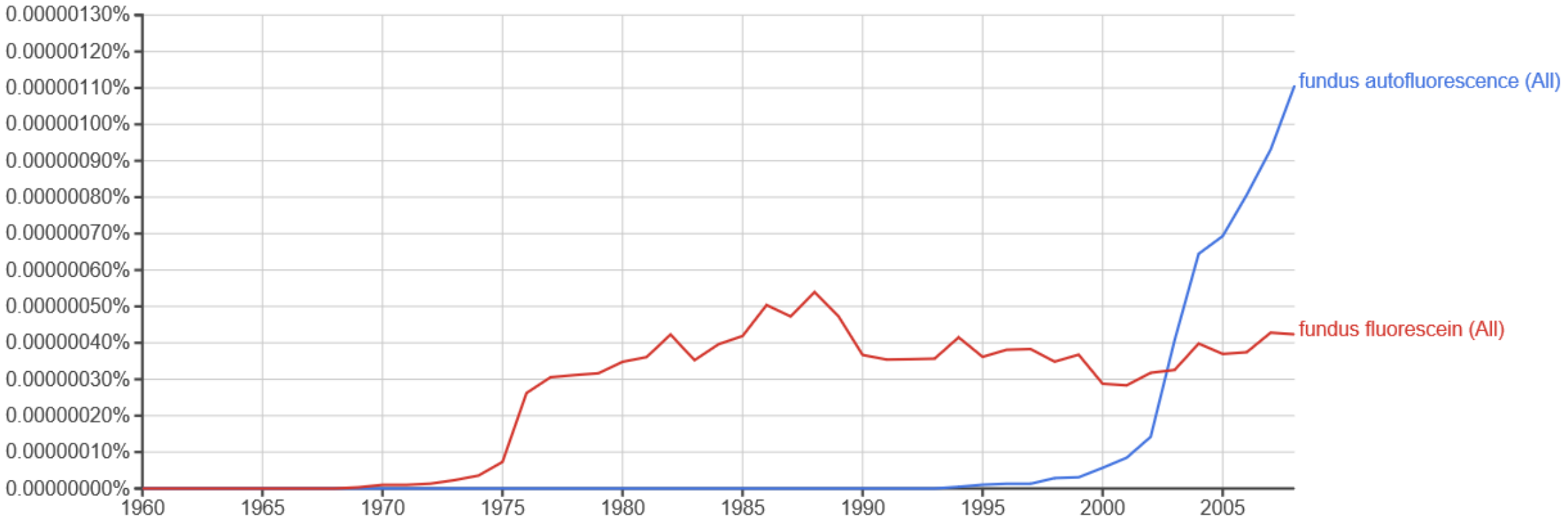
Google Books Ngram Viewer

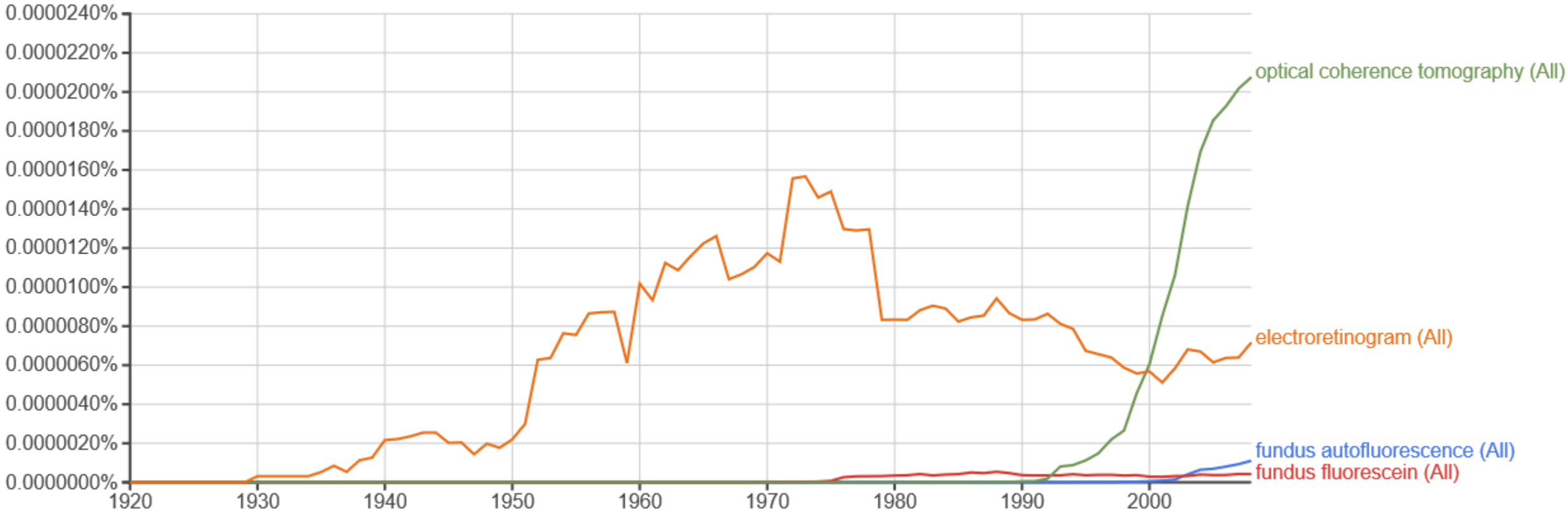
Graph these comma-separated phrases: fundus autofluorescence,fundus fluorescein ✕ ☑ case-insensitive

between 1960 and 2008 from the corpus English with smoothing of 3 . Search lots of books

Share Tweet

Embed Chart

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optical coherence tomography (All)
electroretinogram (All)
fundus autofluorescence (All)
fundus fluorescein (All)

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Yung *et al. Int J Retin Vitr (2016) 2:12*
DOI 10.1186/s40942-016-0035-x

International Journal of Retina and Vitreous

REVIEW Open Access

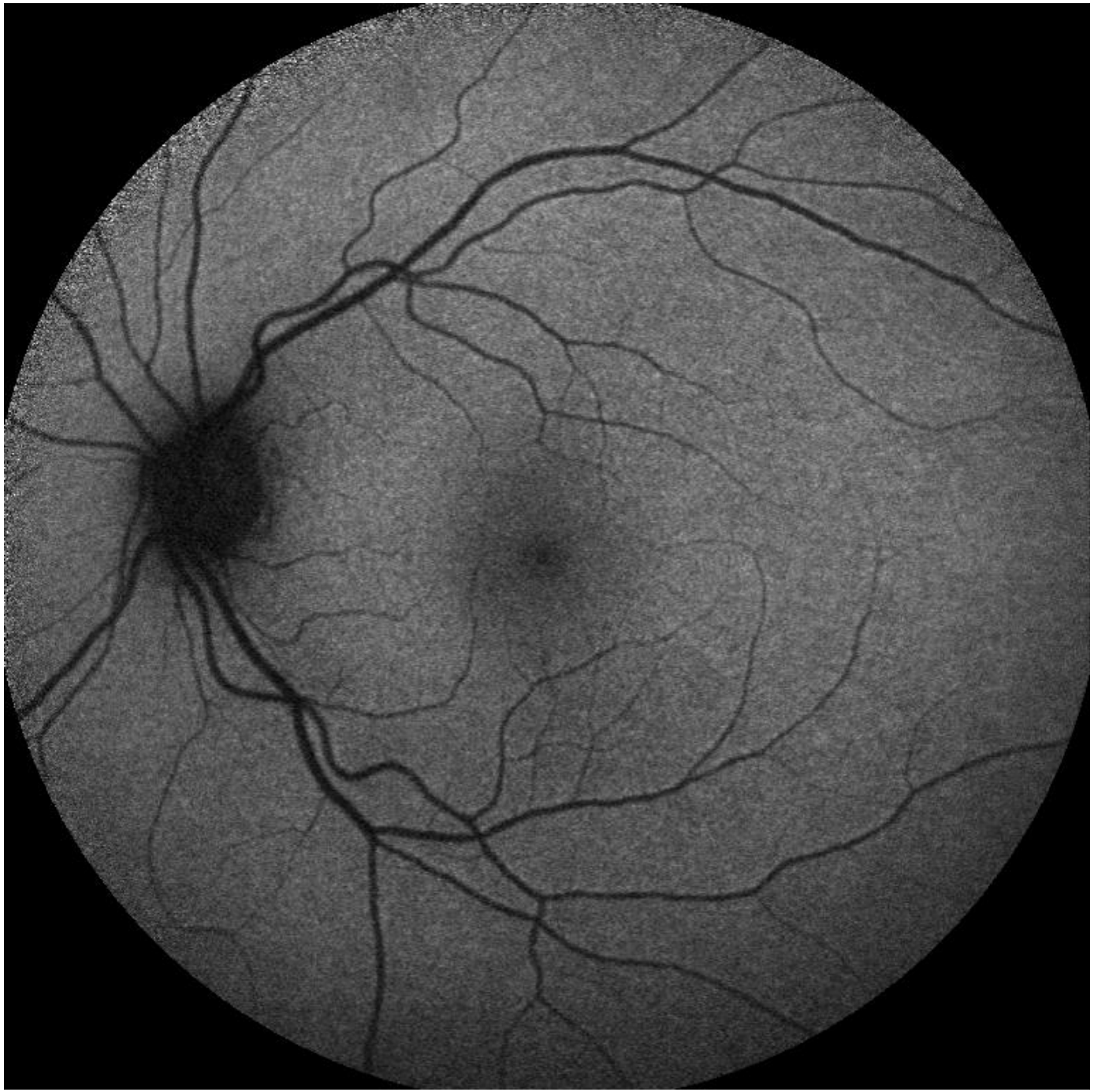
Clinical applications of fundus autofluorescence in retinal disease

Madeline Yung[1], Michael A. Klufas[1] and David Sarraf[1,2*]

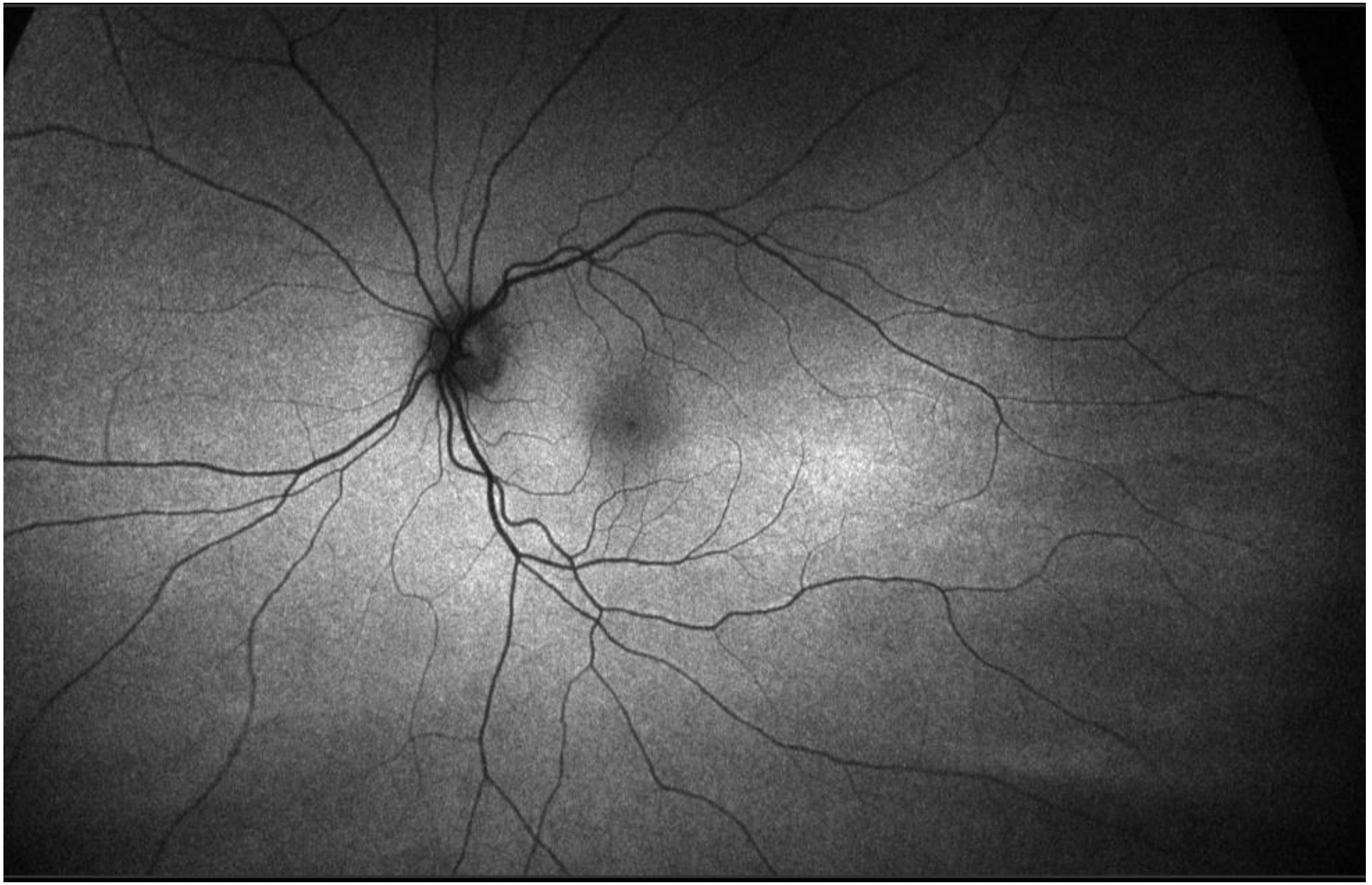
Table 1 Fundus autofluorescence imaging modalities. Excitation wavelengths, barrier filters, fields of view, advantages, and disadvantages of commercially available FAF systems. Although some systems use multiple wavelengths, only the FAF excitation wavelength is provided

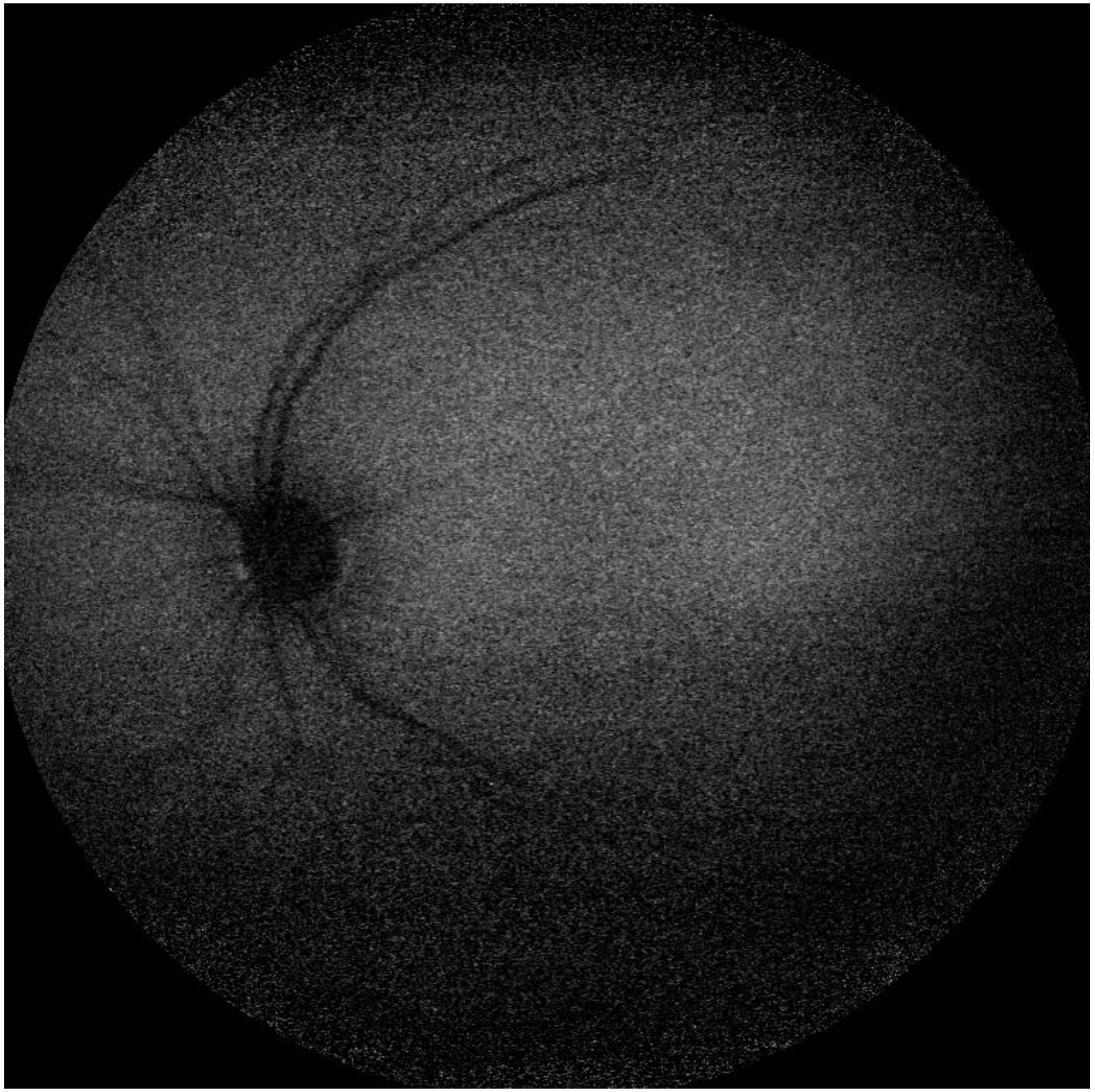
Imaging modality	Fundus autofluorescence imaging systems	Excitation wavelength	Barrier filter (nm)	Field of view	Advantages	Disadvantages
Fundus camera					Better for visualizing exudative retinal disease, red-shifted wavelengths decrease absorption by macular pigments and reduce lens interference, can be used with FA, color imaging, decreased motion artifact, more comfortable for patient	No real-time averaging, poor contrast, capture more reflected and scattered light, prone to pseudo-autofluorescence
	Topcon TRC-50DX	535–585 nm	615–715	20, 35, 50	Non-mydriatic, also offers FA, ICG	
	Zeiss Visucam 224/524	510–580 nm	650–735	30, 45	Non-mydriatic. Visucam 524 with FA and optional ICG	
	Canon CR-2 plus AF (non mydriatic)	530–580	640	35, 45	Non-mydriatic, also offers cobalt setting	
Confocal scanning laser ophthalmoscope (cSLO)					Confocal optics reduces interference from the lens, real-time averaging, high contrast, high resolution, decreased scattered light	Excitation beam is absorbed by macular pigments, cannot be preceded by fluorescein angiography, fixation loss, monochromatic, patient discomfort
	Heidelberg retinal angiograph (HRA 2)	488 nm	500	20, 30, 55	No longer commercially available	
	Heidelberg spectralis	488 nm	500	20, 30, 55	Also offers red-free, FA, ICG, simultaneous FA/ICG, infrared reflectance, multicolor imaging, dual wavelength technology can calculate macular pigment density, spectral domain OCT	
	Zeiss prototype SM 30 4024 (ZcSLO)	488 nm	521	20, 40	No longer commercially available	
	Rodenstock (RcSLO)	488 nm	515	20, 40	No longer commercially available	
	Nidek F-10	490 nm	510	40, 60	Also offers multicolor imaging, retro-mode, FA, ICG	
Widefield cSLOs					Detects peripheral findings, non-mydriatic, brief image acquisition time, can be used with FA	Disadvantages vary by system and lens
	Optos ultra-widefield	532 nm, 633 nm	540	200	Decreased absorption by macular pigments, also offers color fundus, red-free, FA, ICG	No real-time averaging, poor contrast, distortion of peripheral retina, view limited in superior and inferior quadrants, lid/lash artifact

Spectralis



Optos





Albinism

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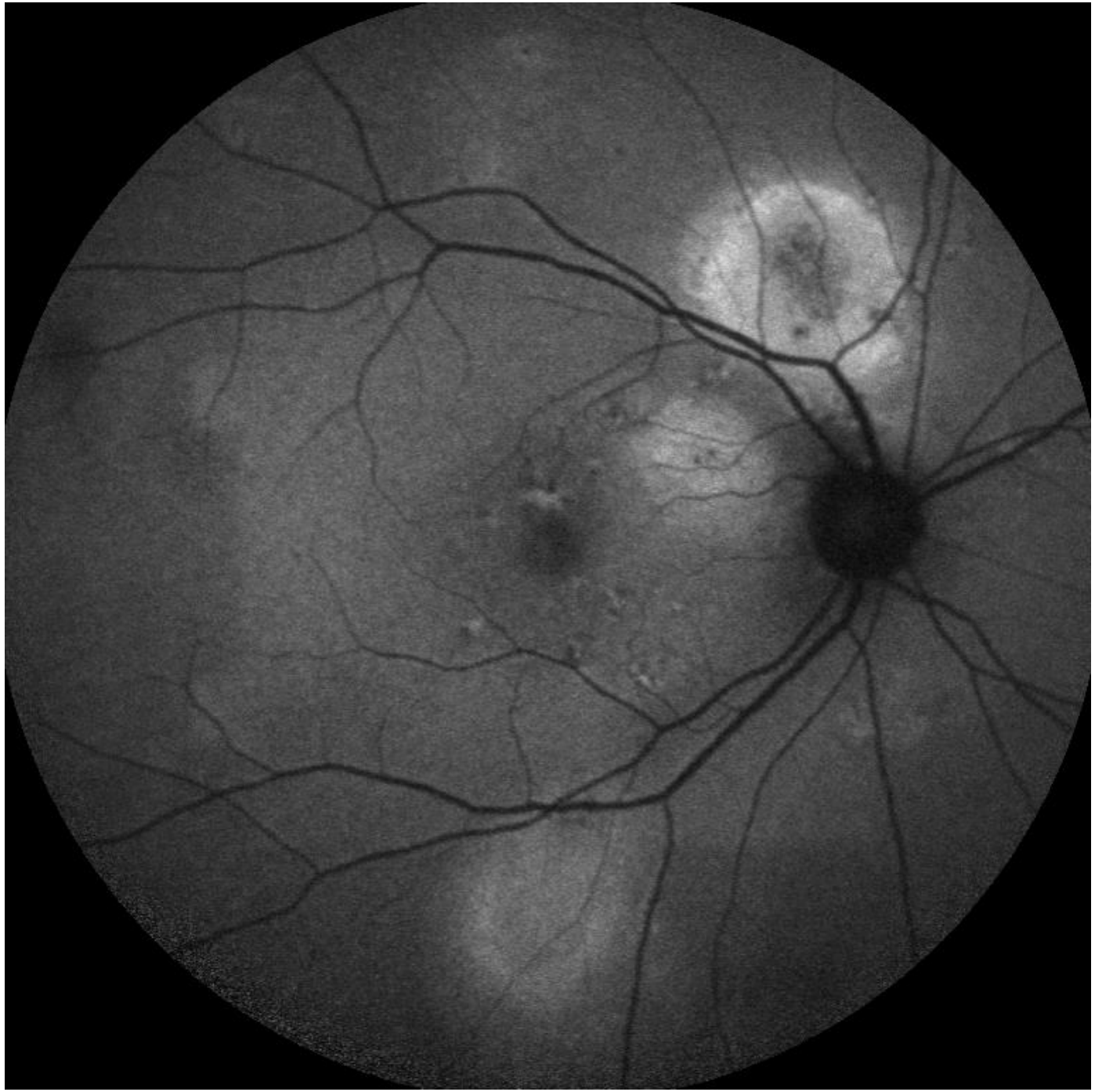
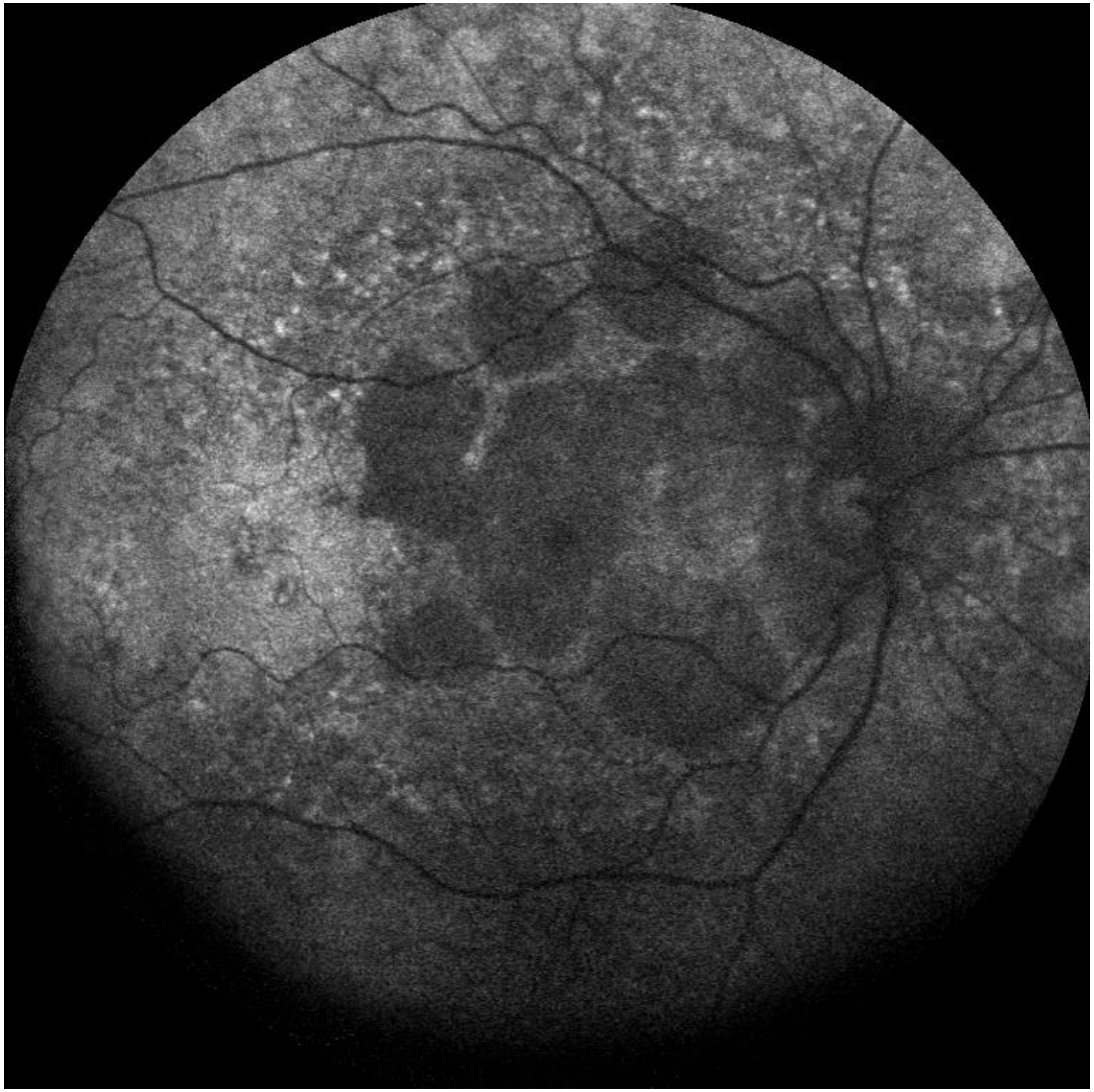
Increased AF	Reduced AF
Increased fluorophore Examples (lipofuscin-related) • Stargardt, Pattern dystrophy • Best disease and Vitelliform maculopathies (and CSCR subretinal material) Other fluorophores • Disc drusen • Astrocytic hamartomas	**Reduced fluorophore** Examples • RPE loss (AMD, inherited retinopathies) • Visual cycle disturbance (general reduction in AF, e.g. RPE65, RDH5, LRAT)
Window defect (loss of photopigment or macular pigment) • Outer segment loss (e.g. in white dot syndromes or photoreceptor pathology and CSCR) • Mactel	**Masking** • Haemorrhage • Fibrosis

Examples

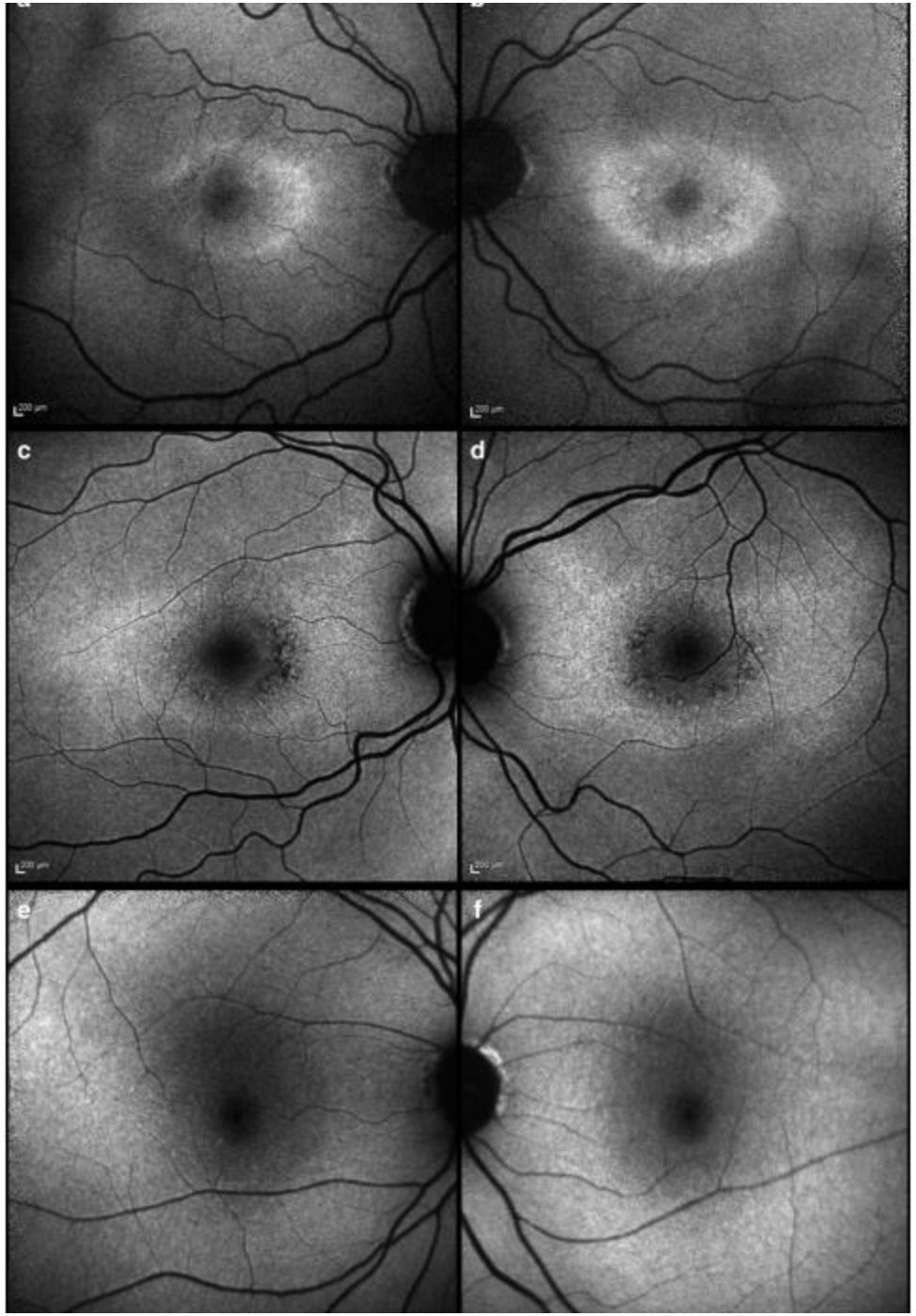
- AMD
- CSCR
- Mactel
- Drug toxicity
- Inflammatory disease: PIC, MEWDS, multifocal choroiditis, AZOOR
- Inherited retinal disease: ABCA4, Best, RP, pattern dystrophies, MIDD, carrier status in ocular albinism and choroideraemia



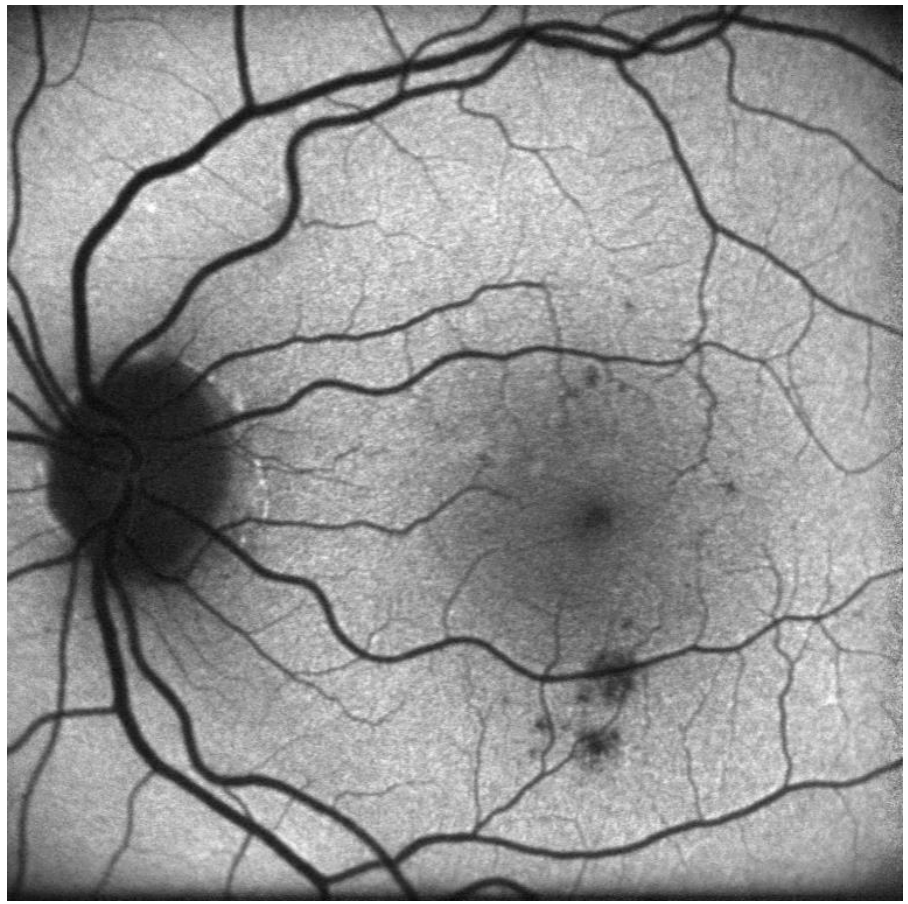
CSCR

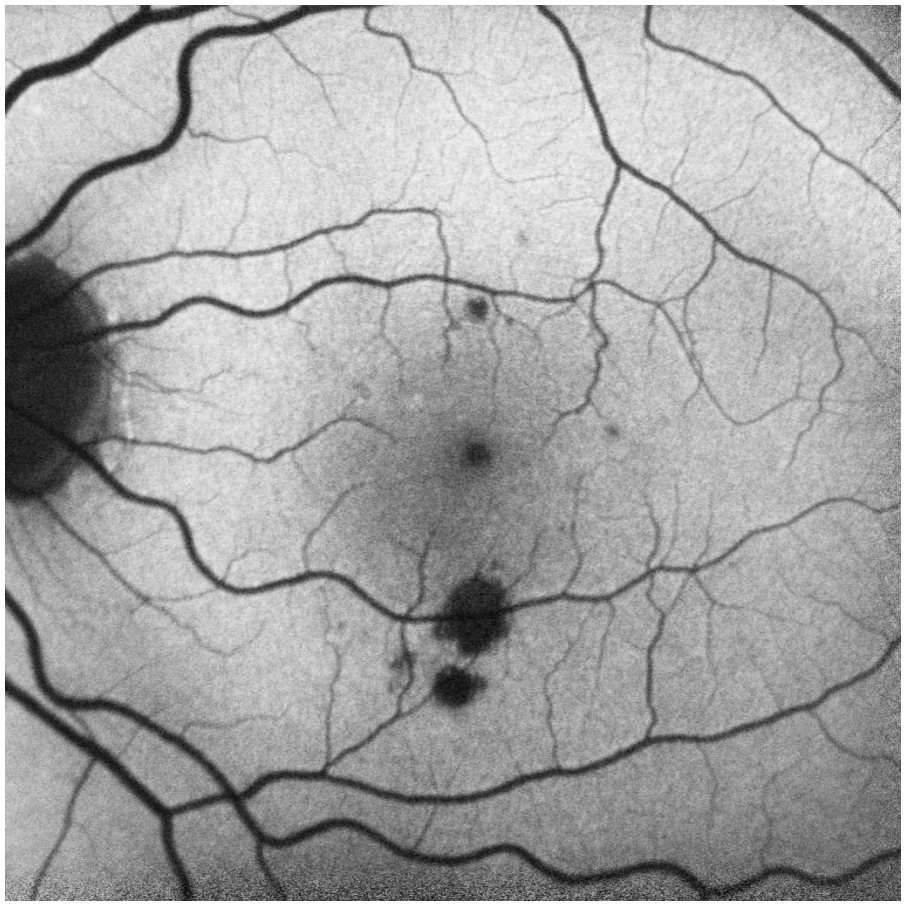


AMD?
MIDD?

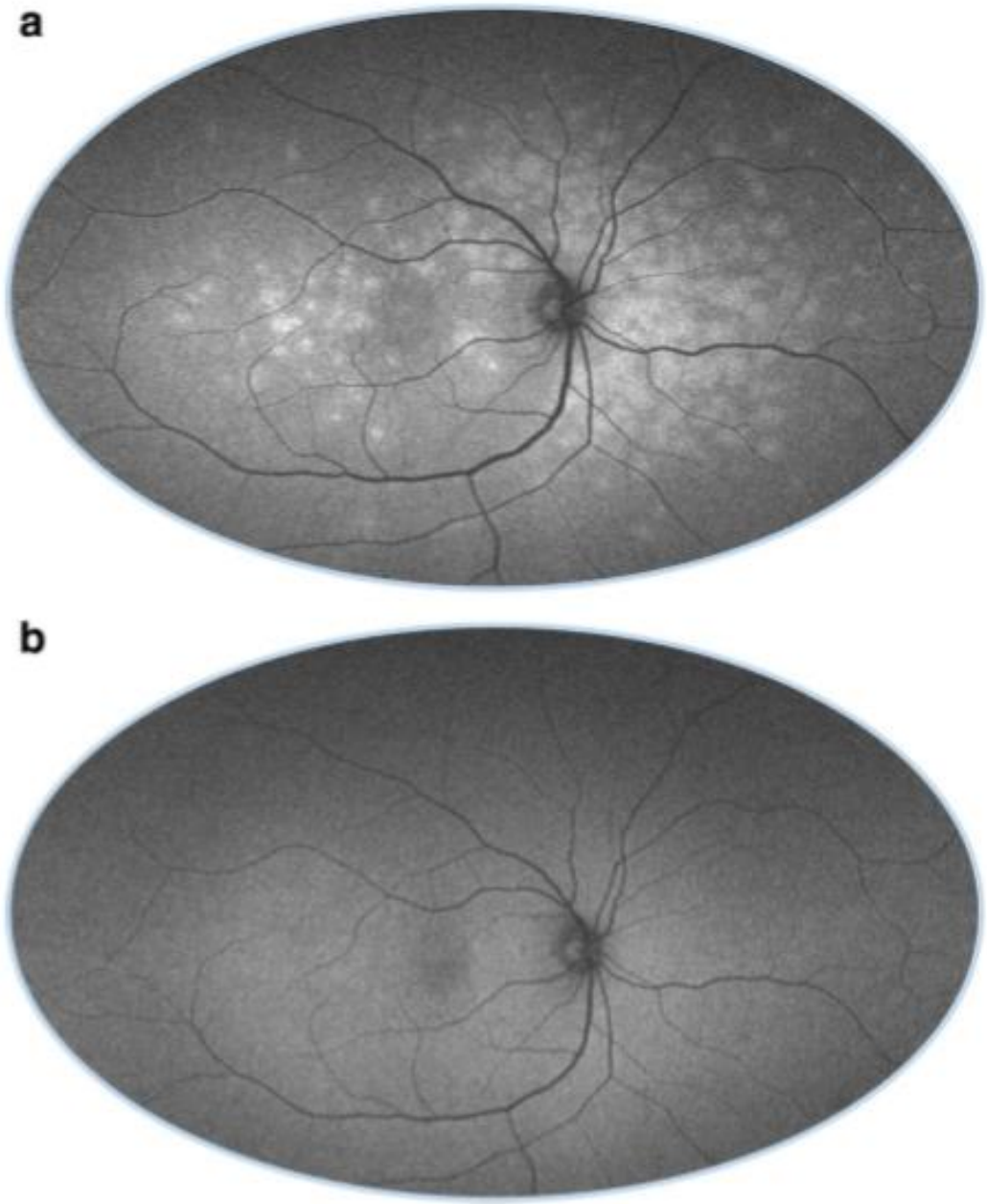


HCQ retinopathy
Yusuf *et al*. *Eye* 2017



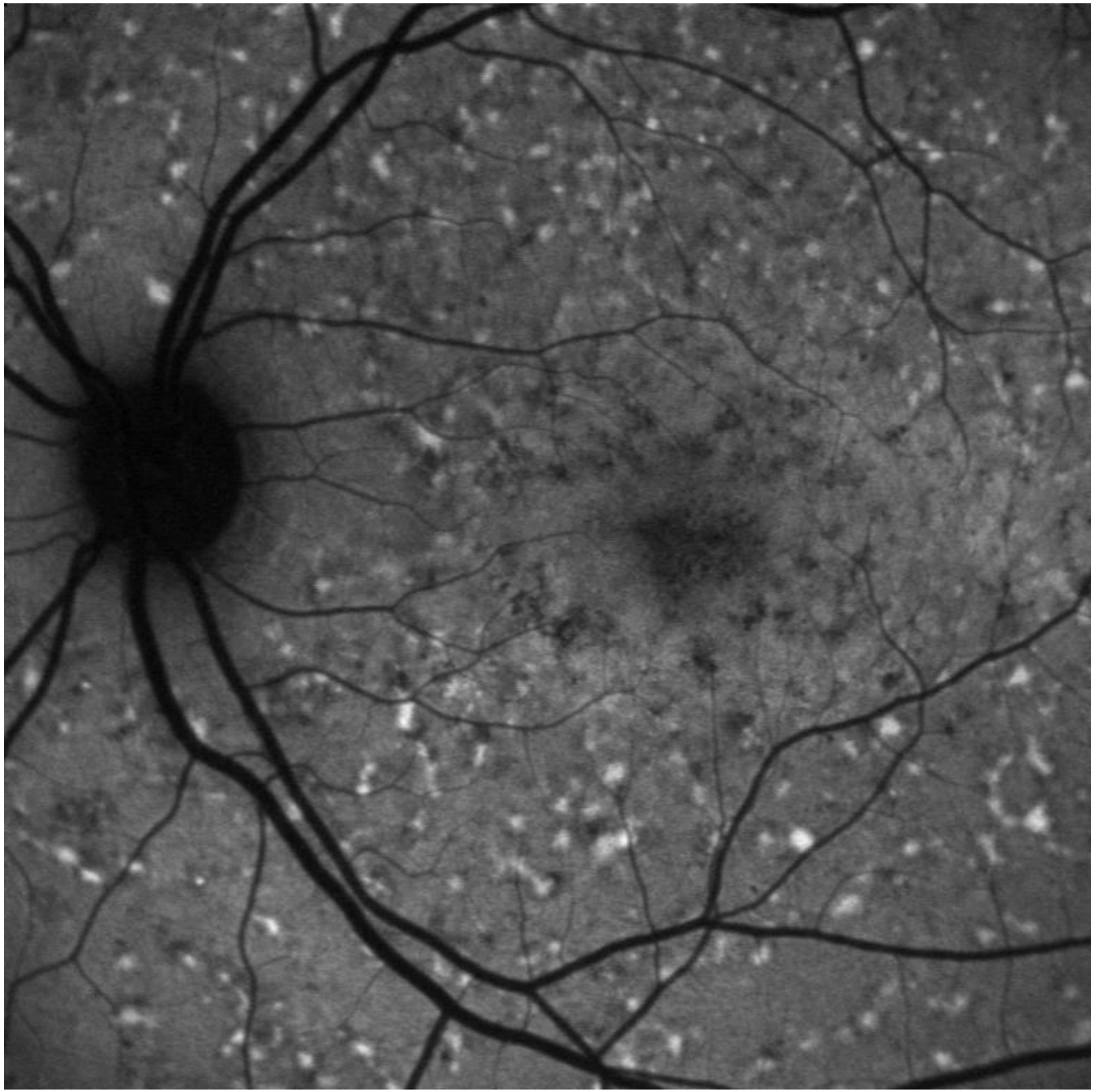


PIC

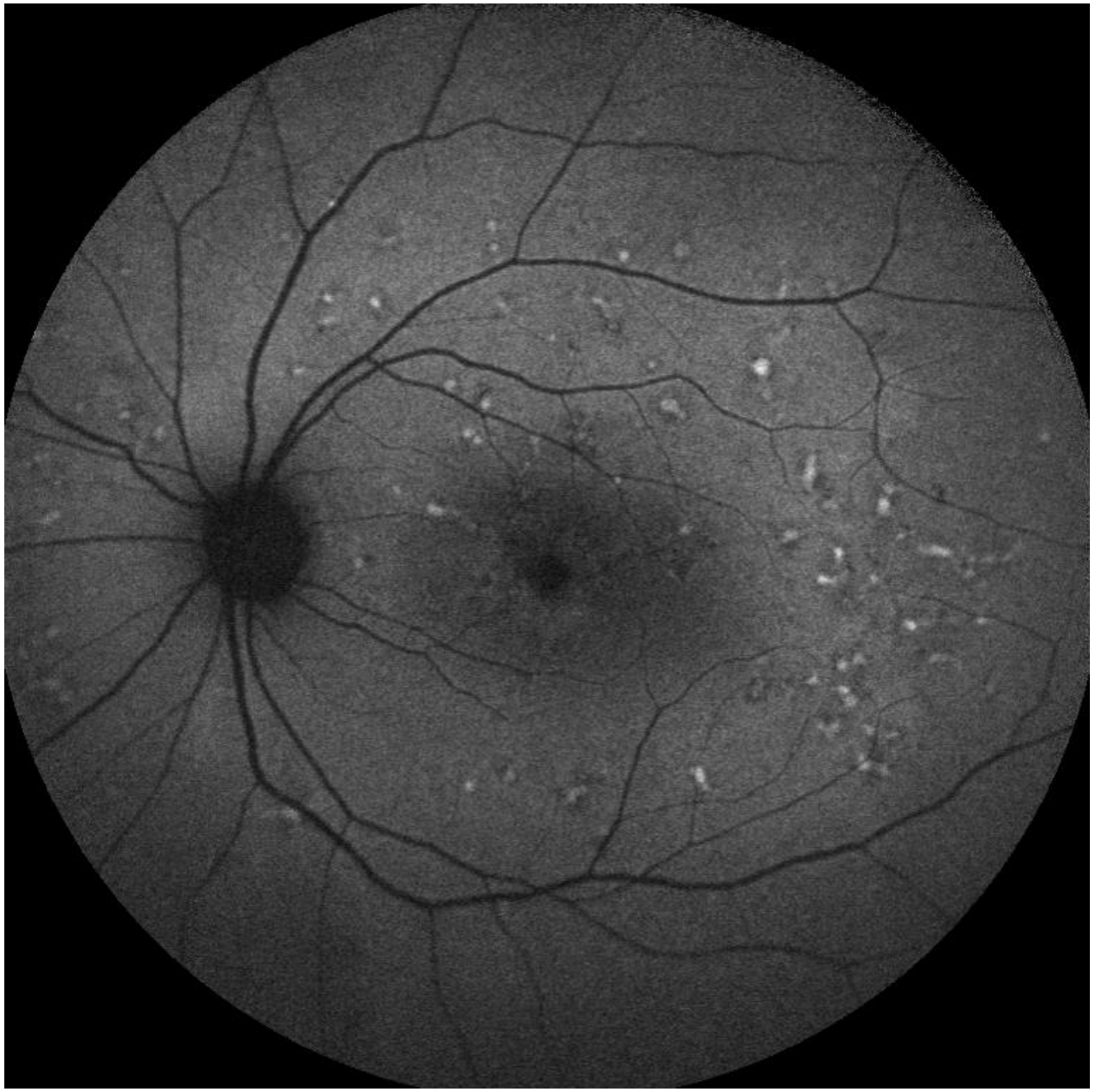


MEWDS

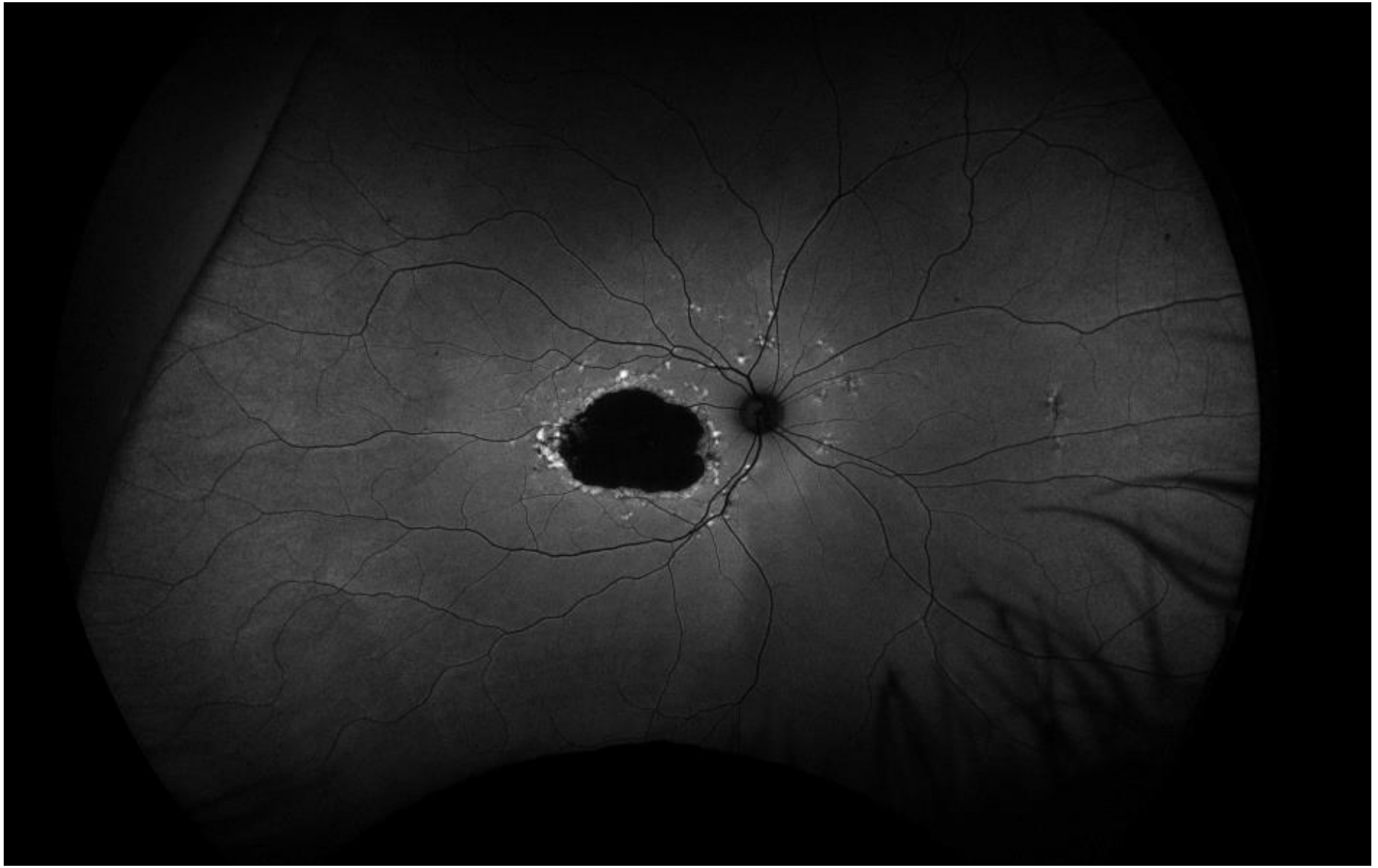
Yung *et al. Int J Retin Vitr* 2016



ABCA4
(Stargardt)



PRPH2



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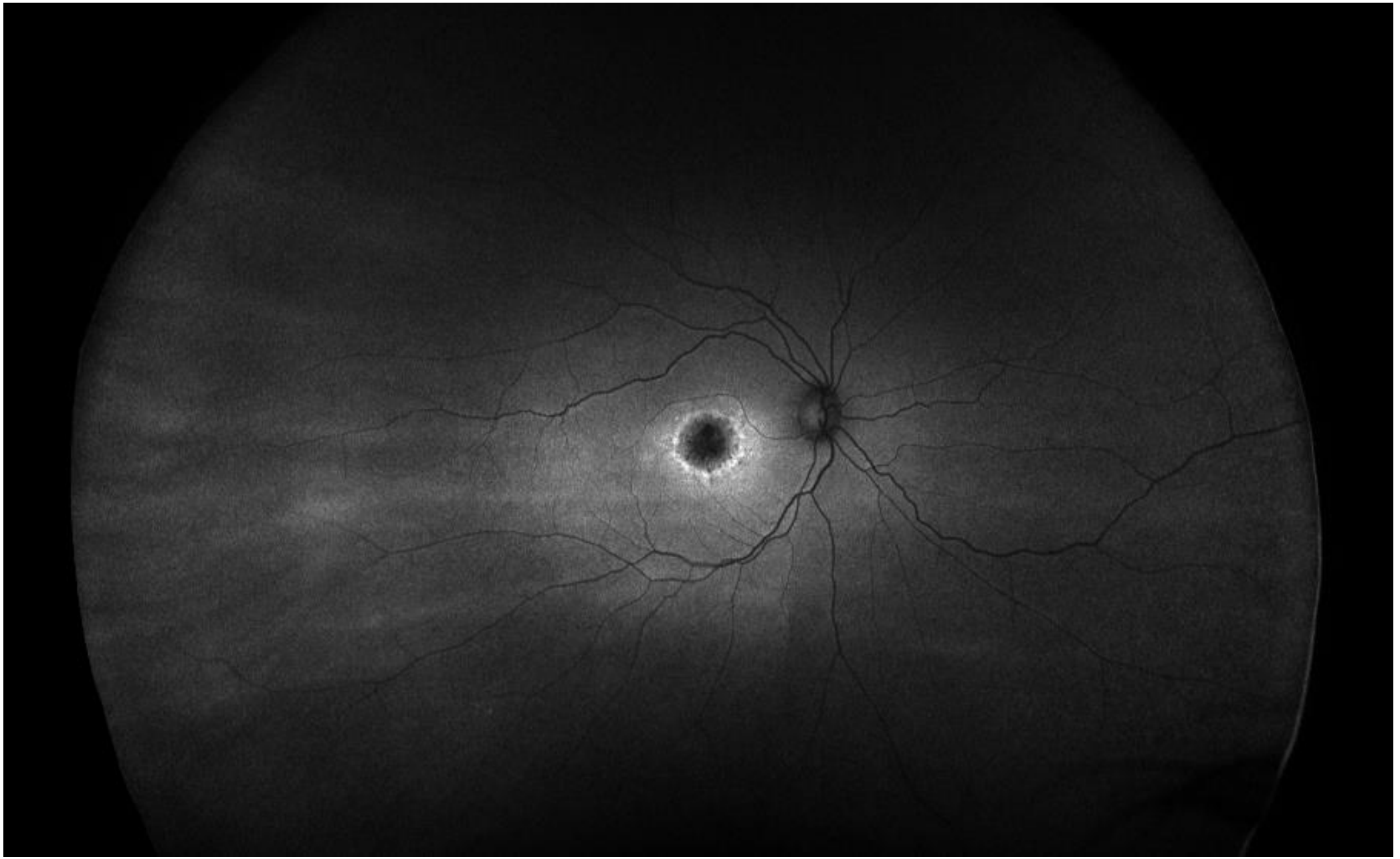

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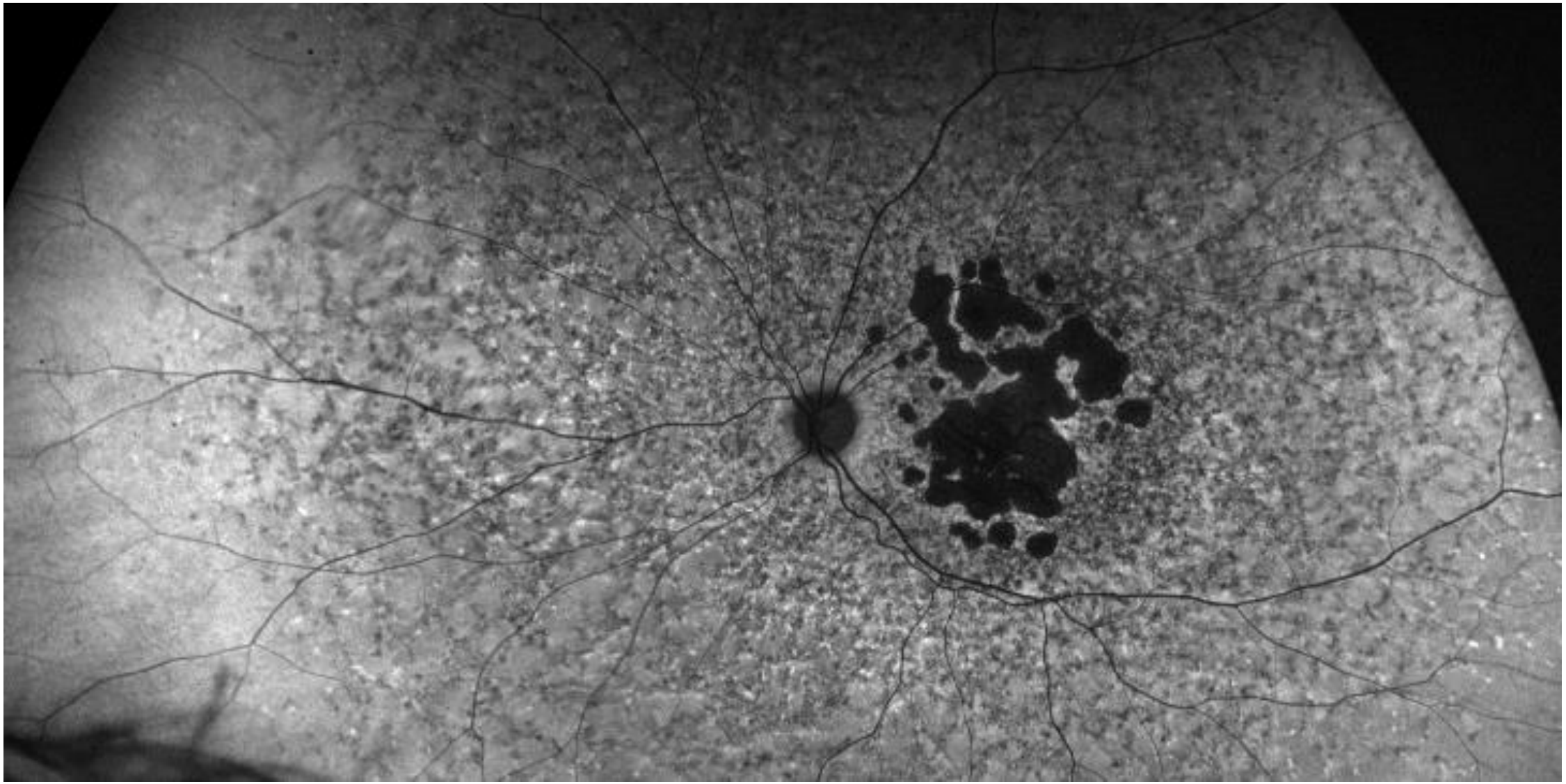

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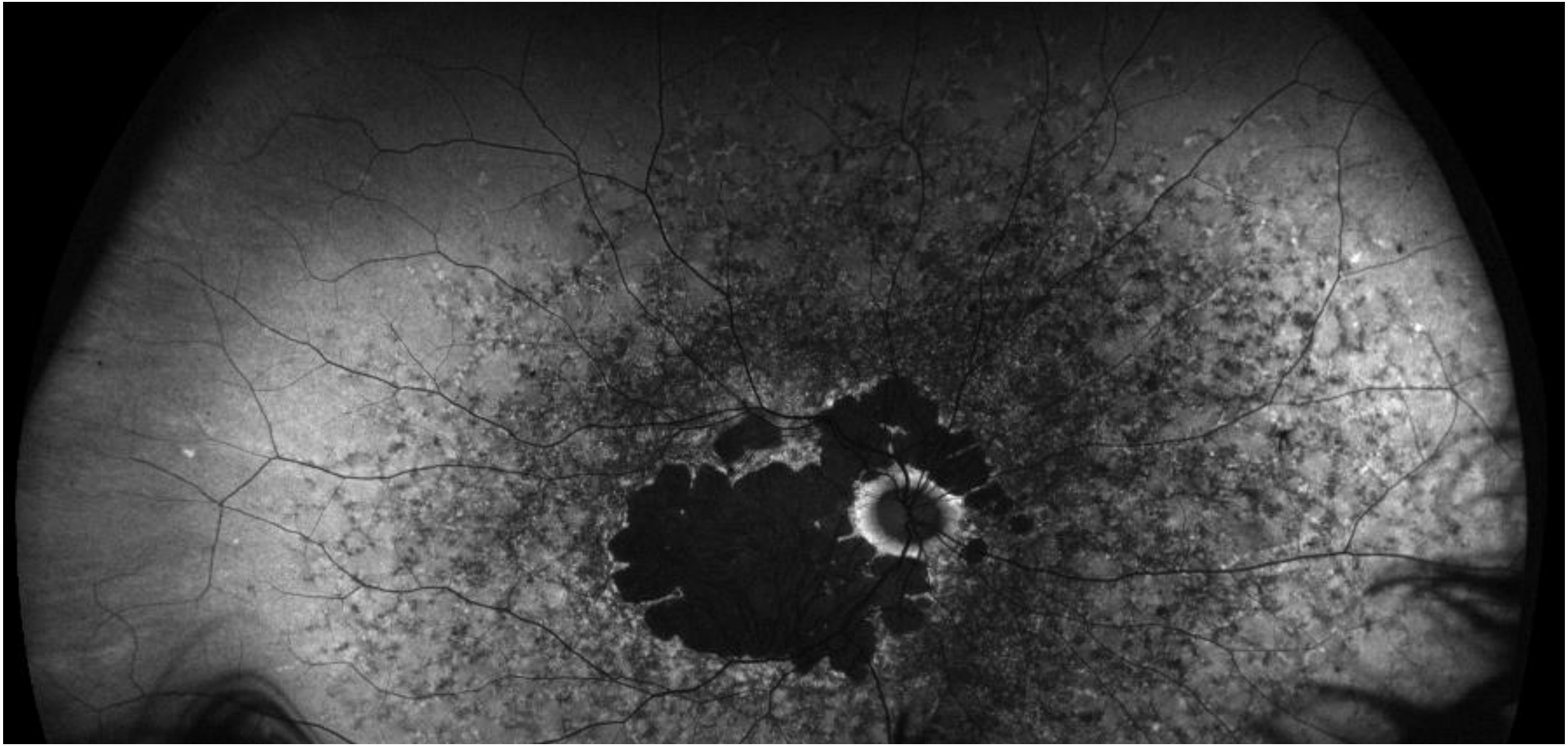

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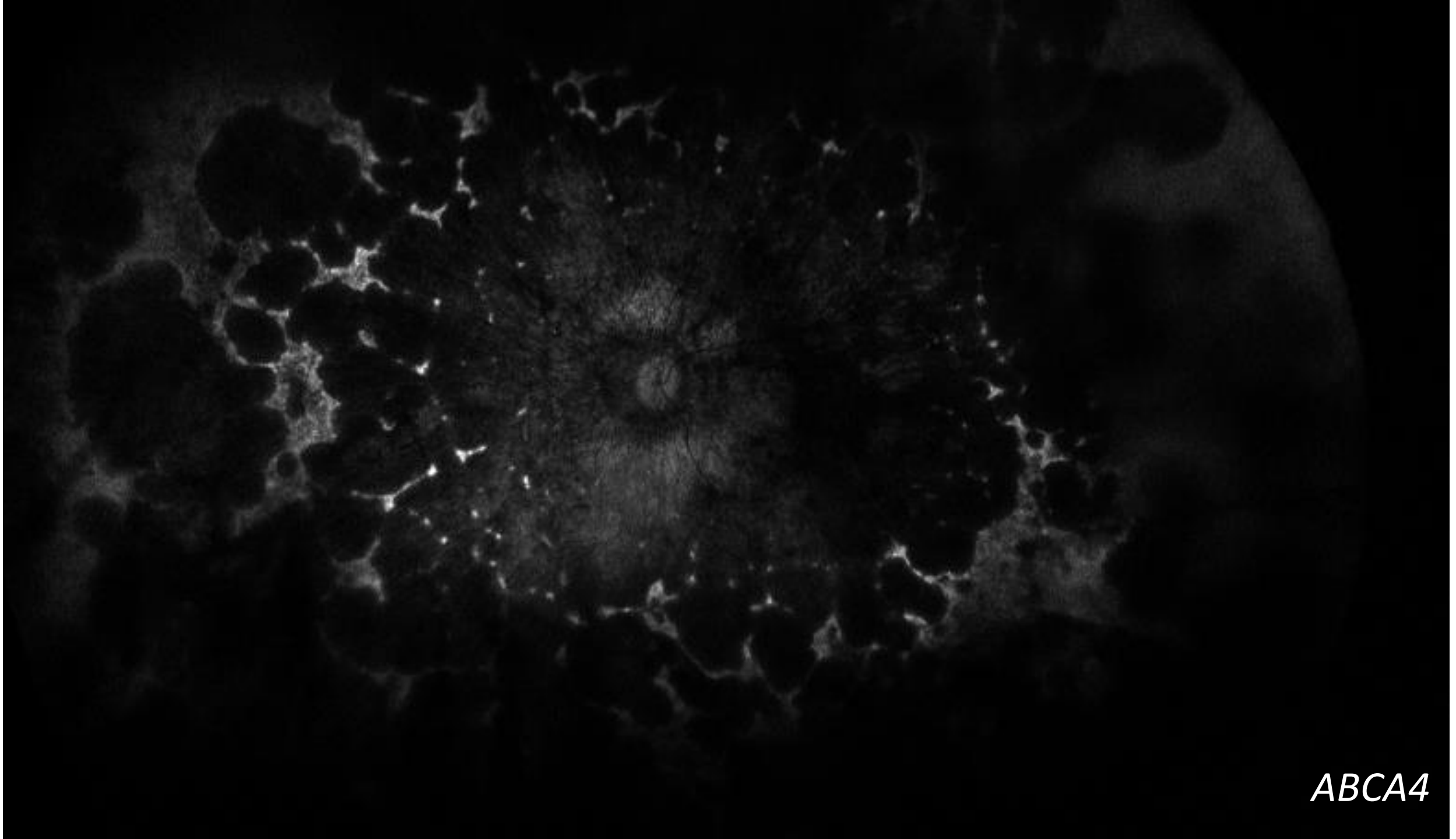
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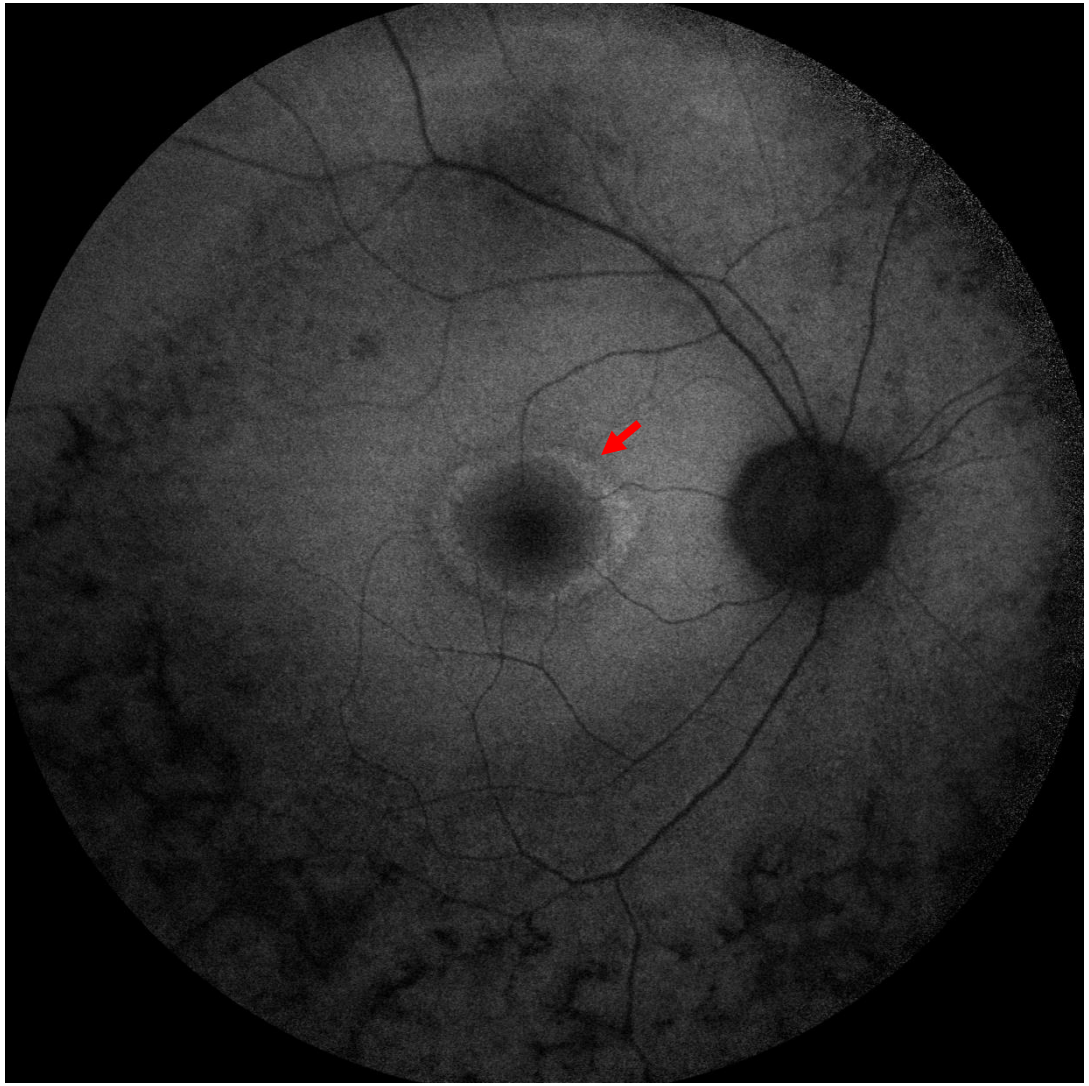
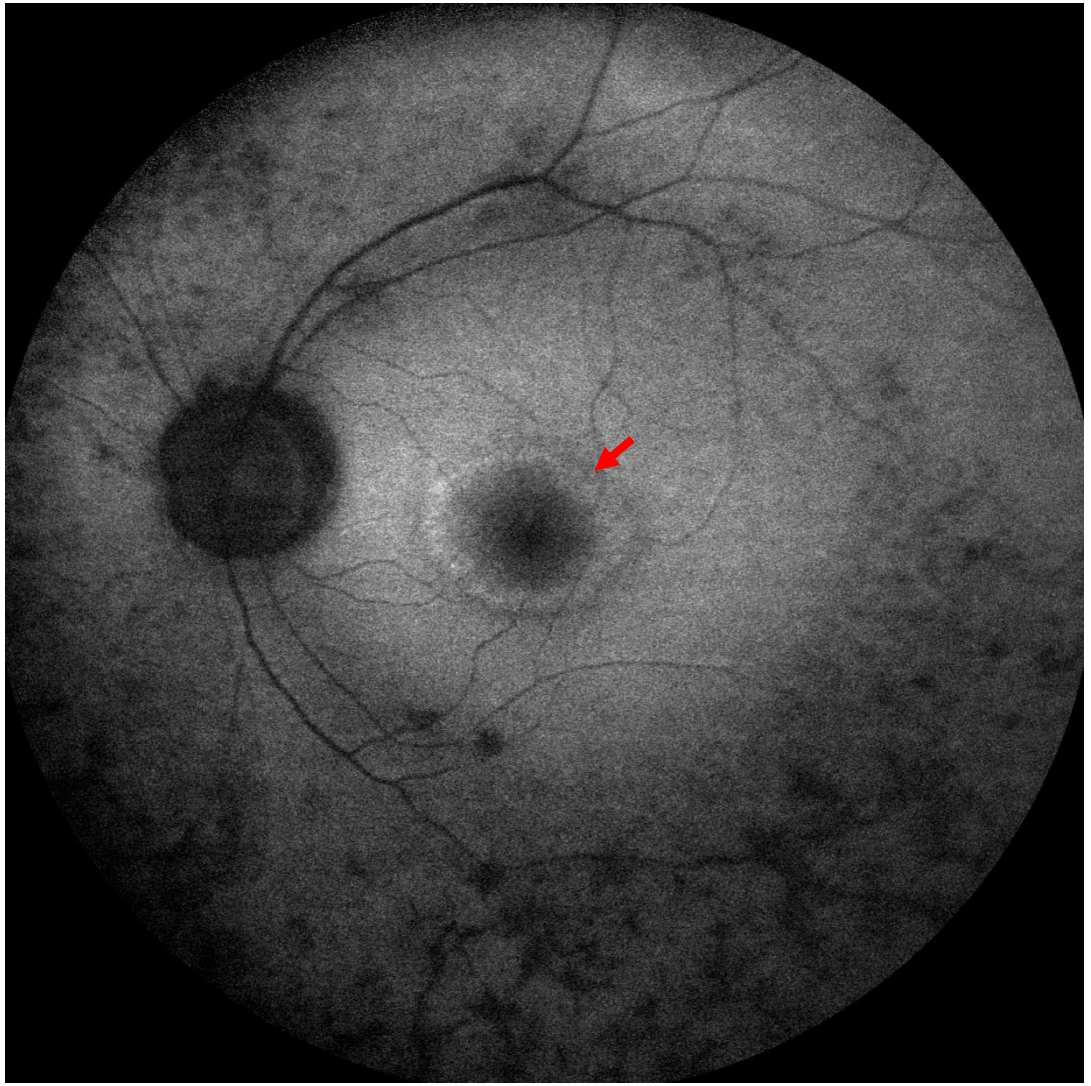
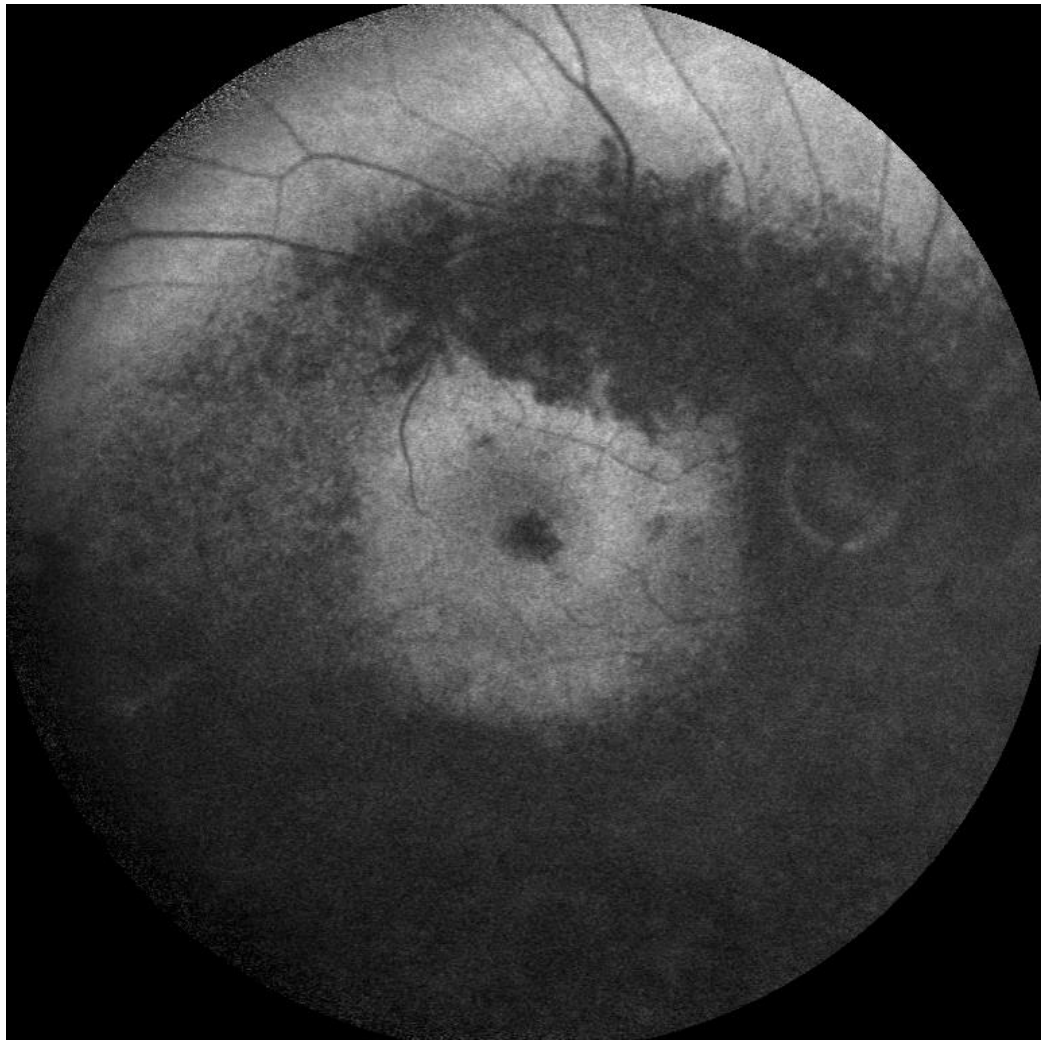
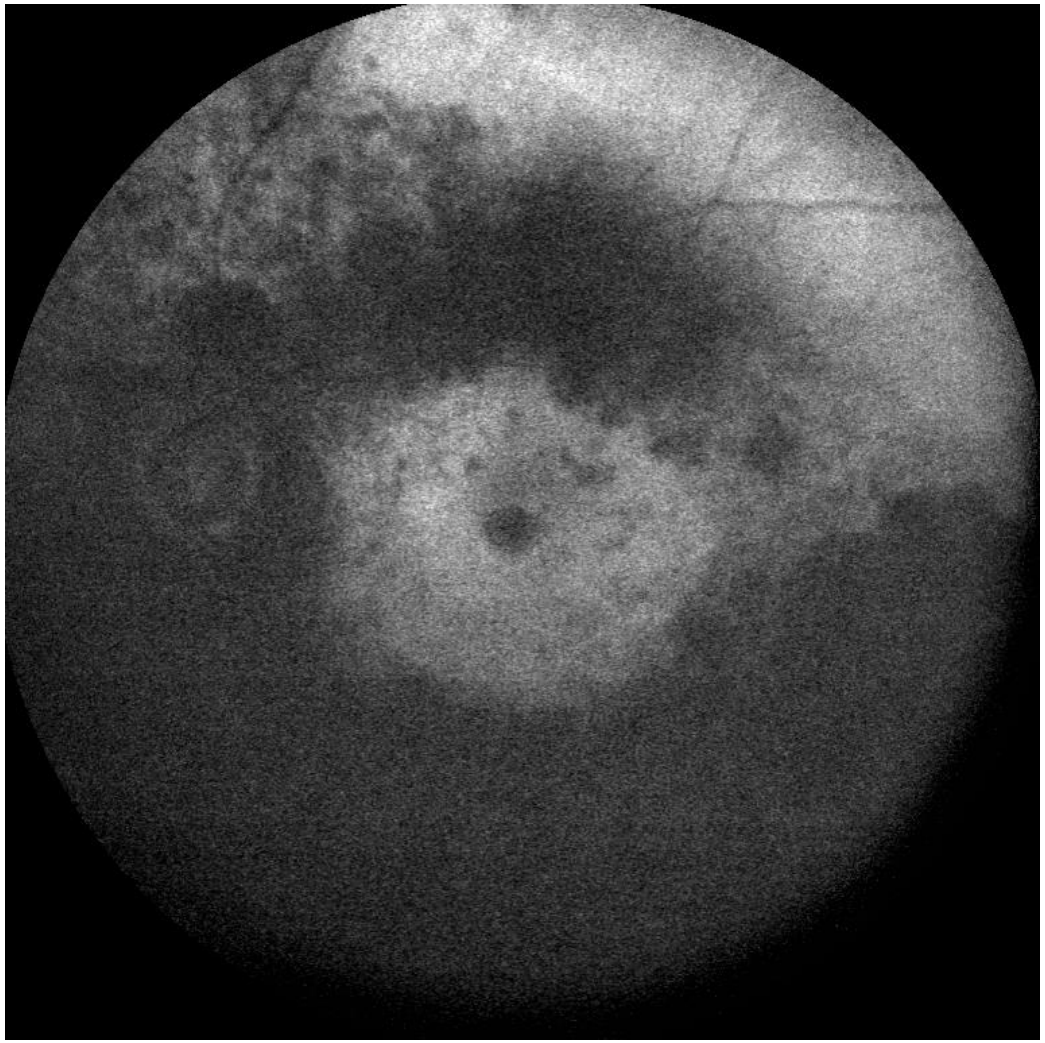




Autosomal Dominant RP





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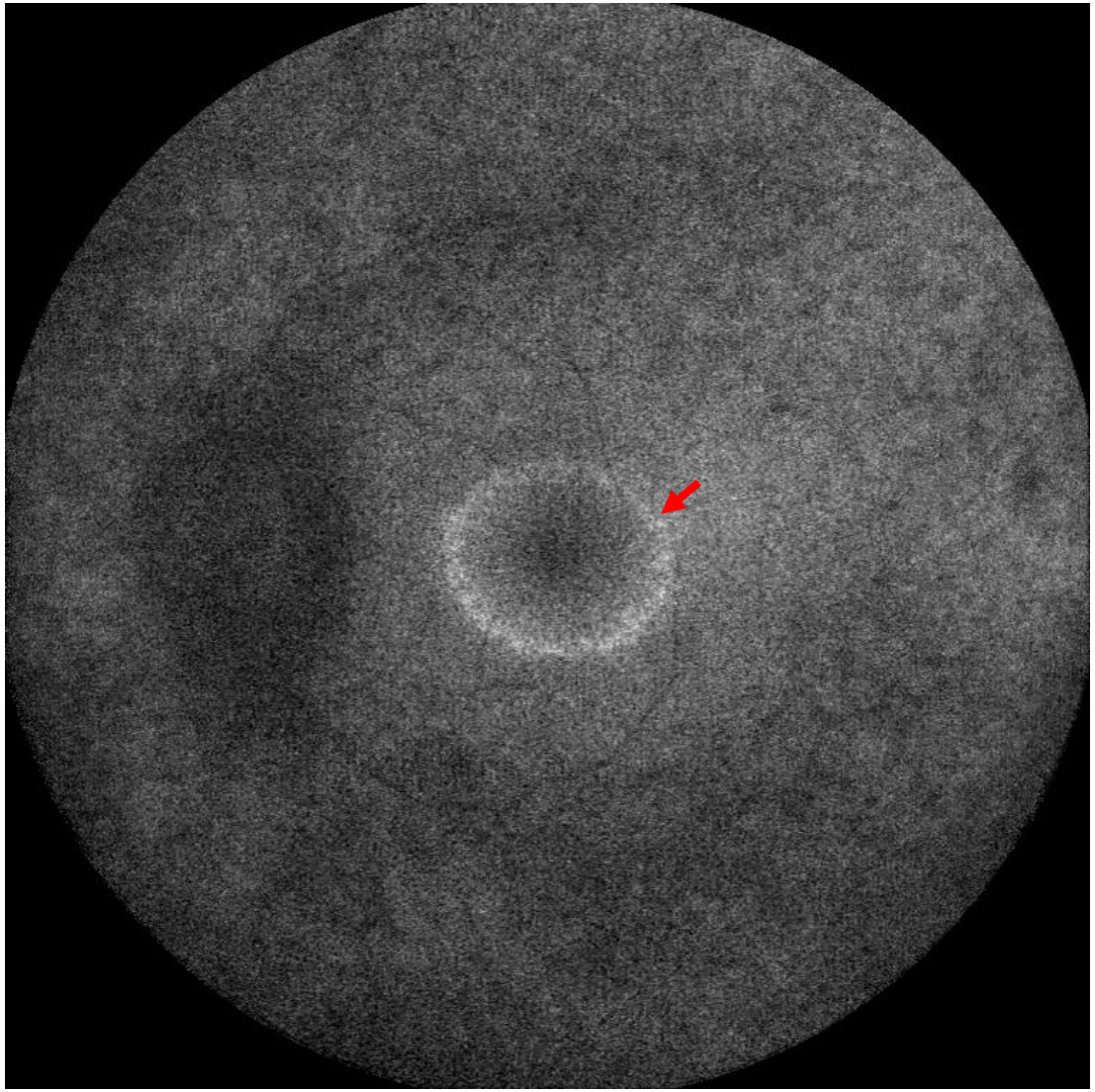
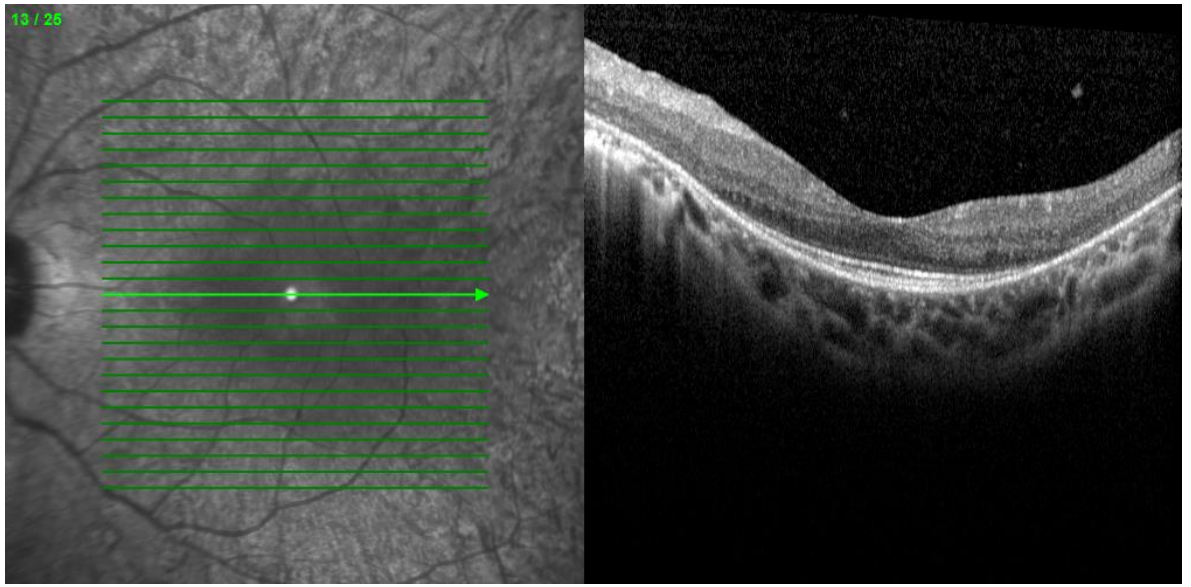
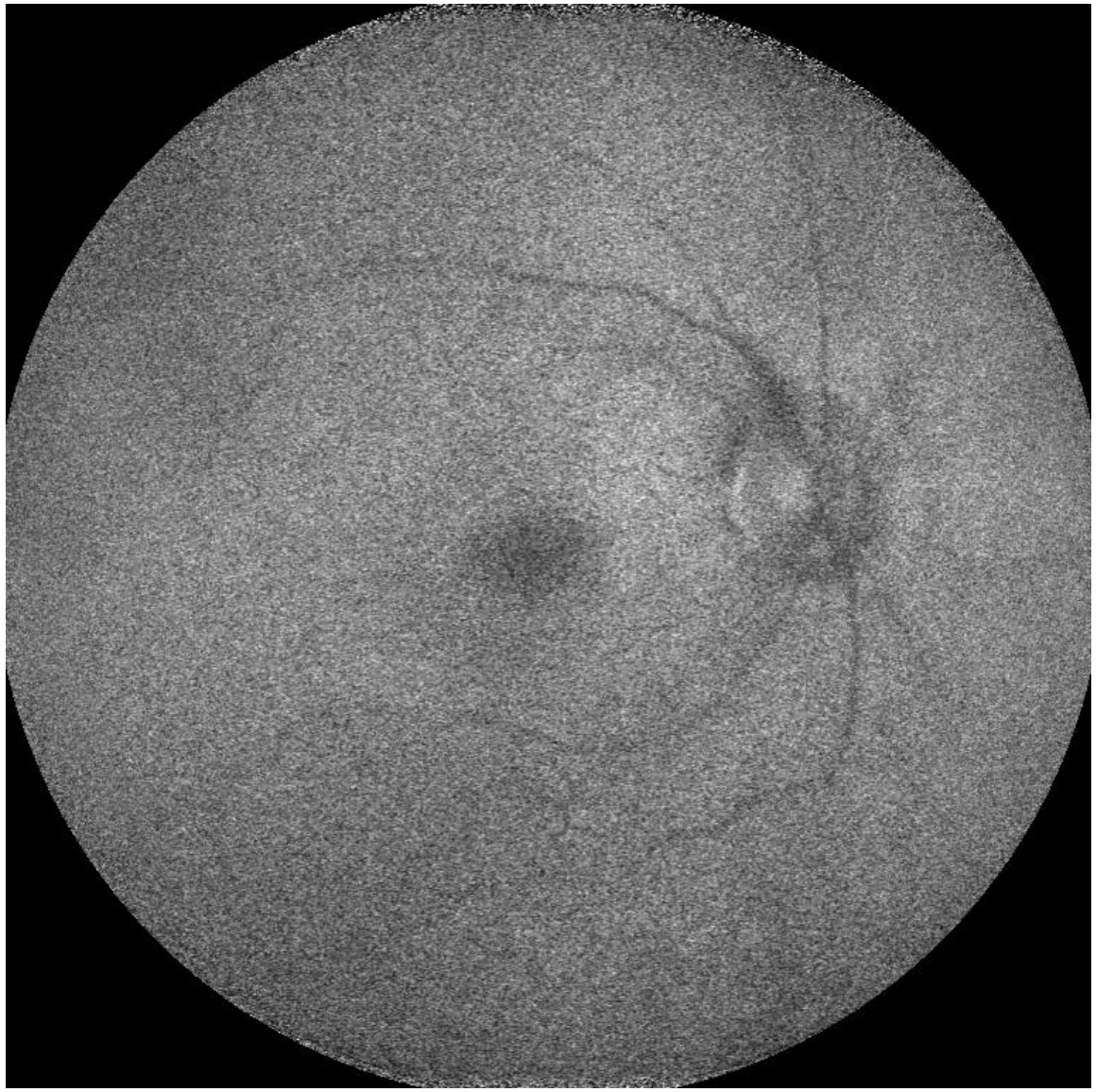
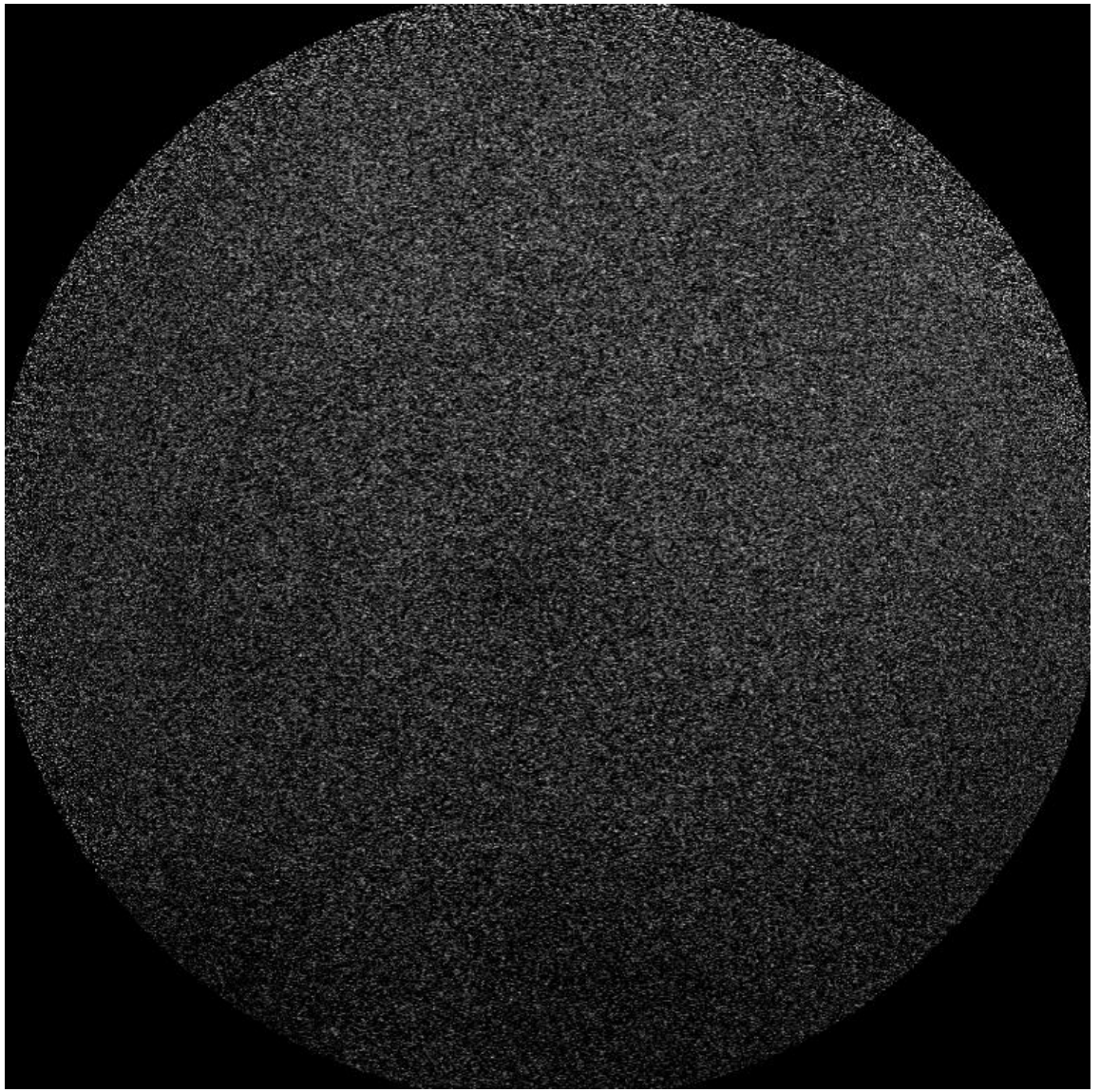
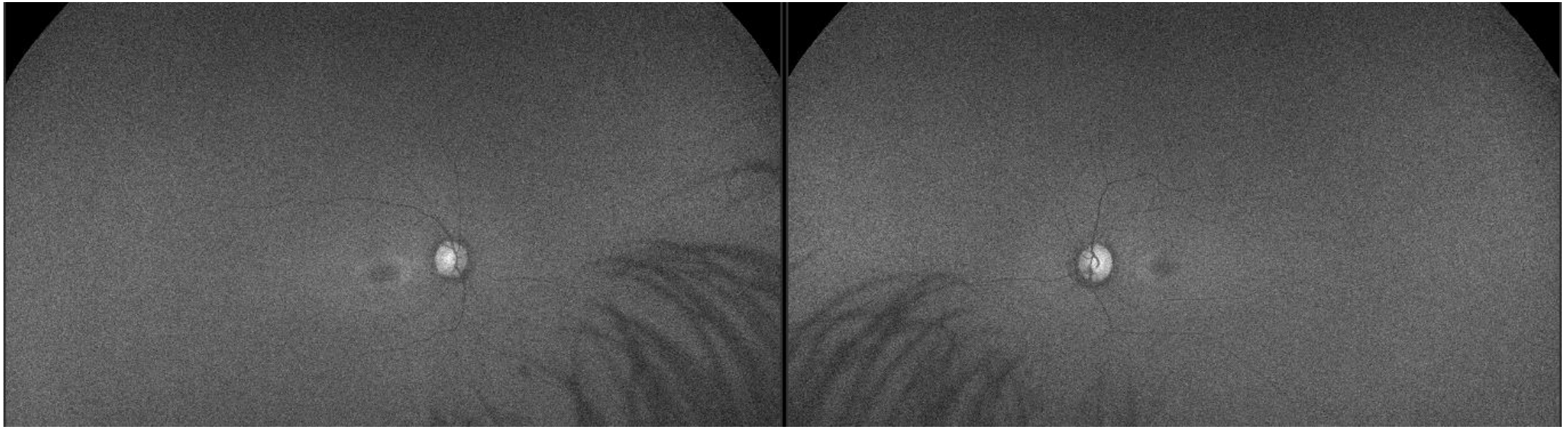


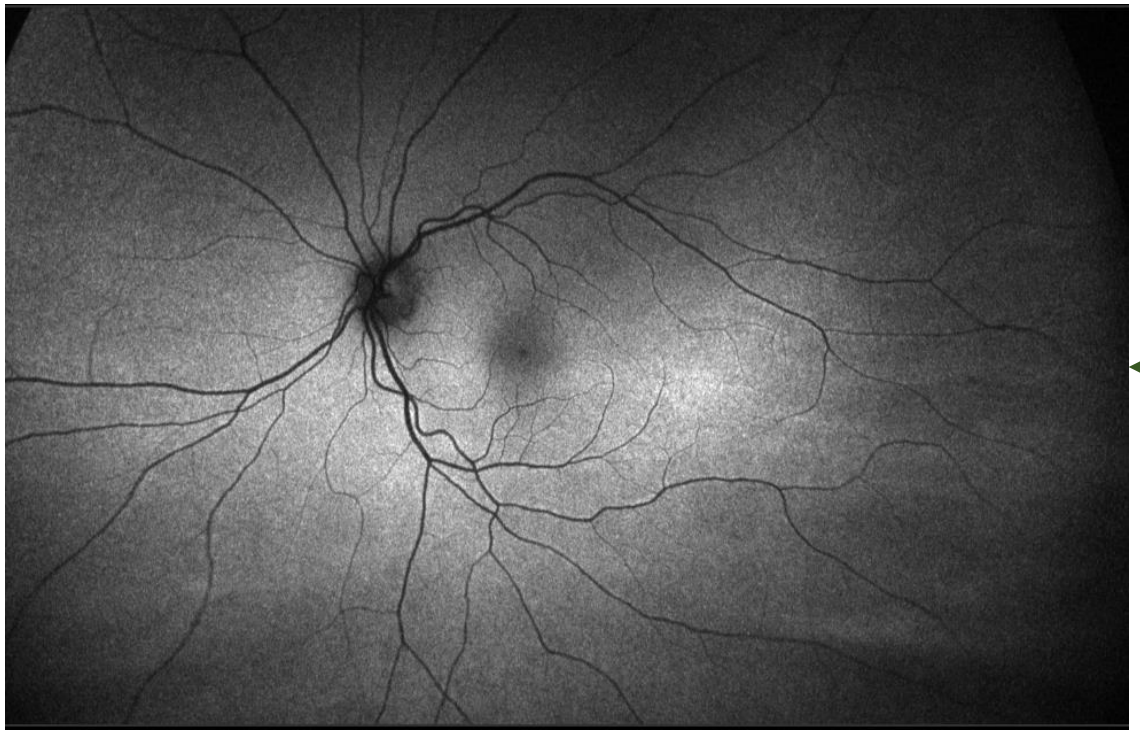
Usher syndrome





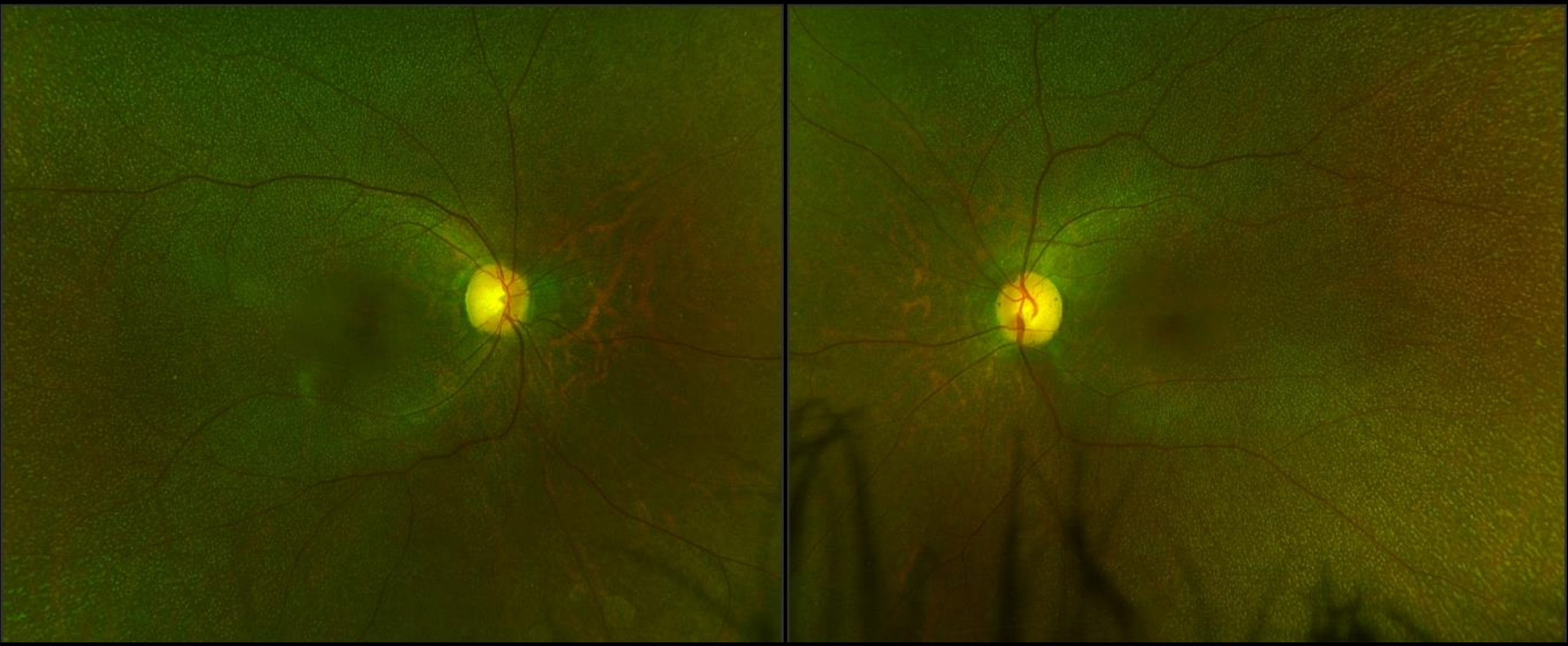






Very low autofluorescence
Impairment of synthesis of fluorophores

Control subject



Infra red autofluorescence imaging…

Am J Ophthalmol. 2018 Oct;194:120-125. doi: 10.1016/j.ajo.2018.07.012. Epub 2018 Jul 24.

Quantitative Comparison of Near-infrared Versus Short-wave Autofluorescence Imaging in Monitoring Progression of Retinitis Pigmentosa.

Jauregui R[1], Park KS[2], Duong JK[3], Sparrow JR[4], Tsang SH[5].

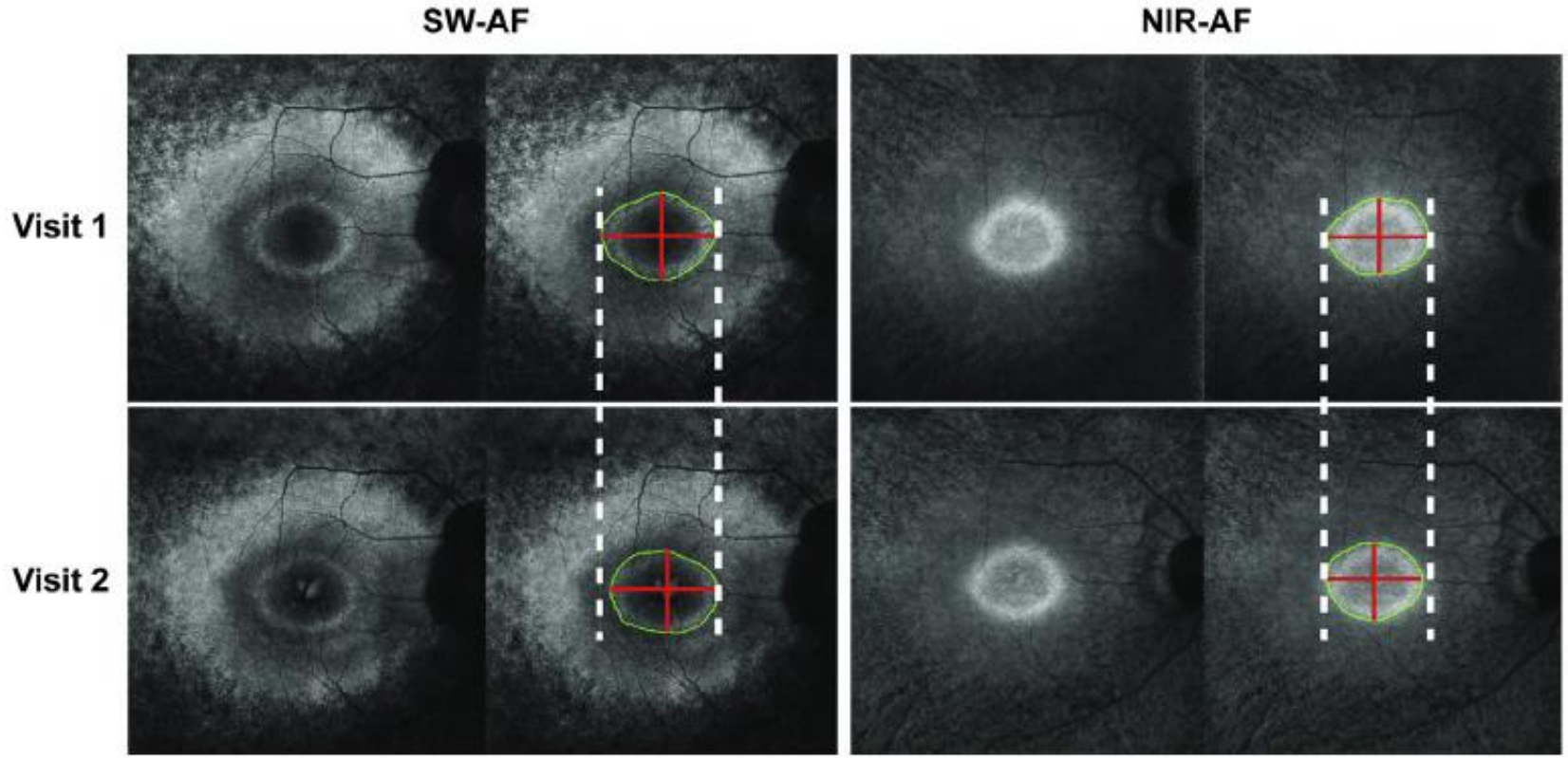
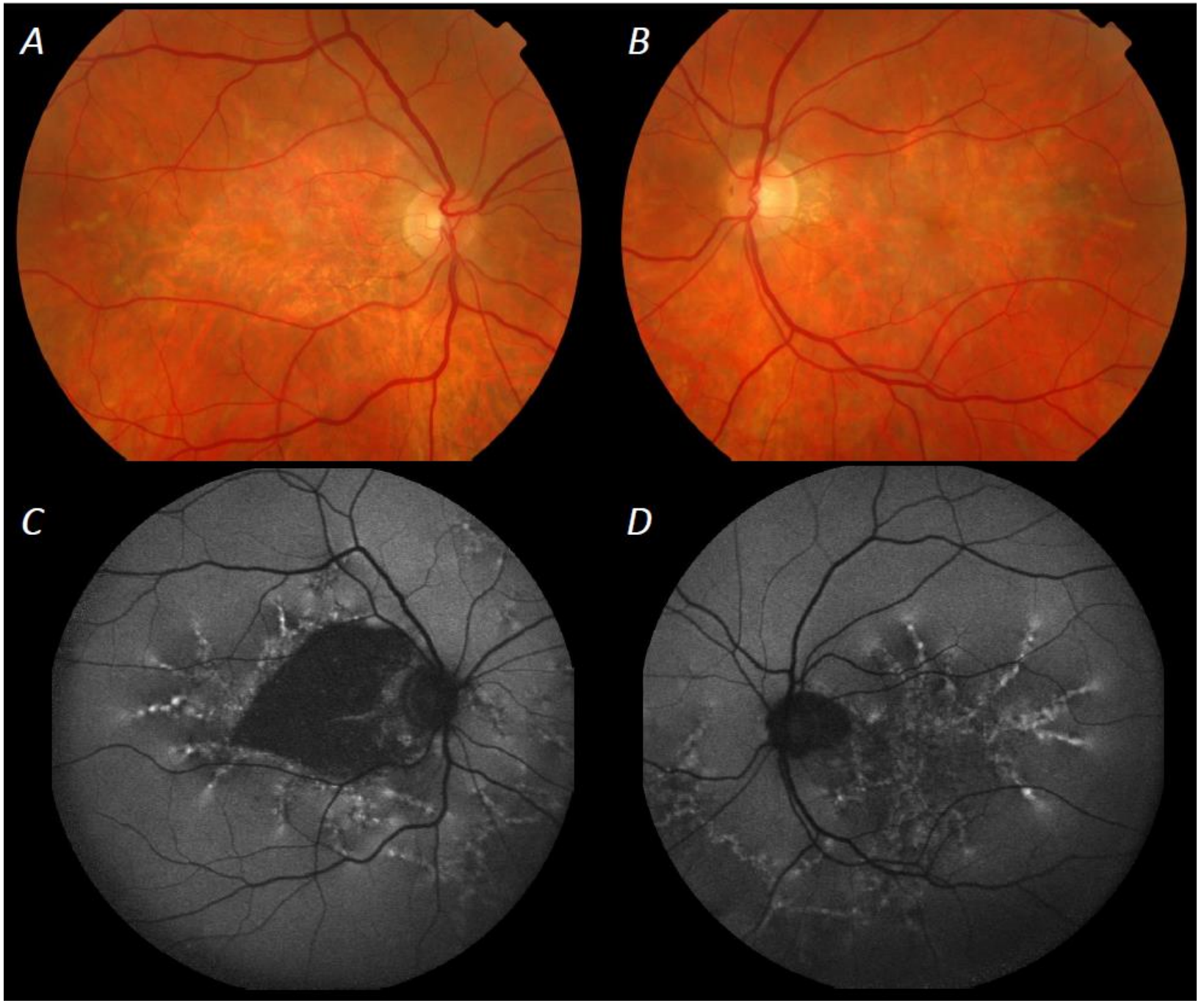


FIGURE. Hyperautofluorescent ring progression in short-wave (SW-AF) vs near-infrared autofluorescence (NIR-AF) imaging of a patient with retinitis pigmentosa. SW-AF and NIR-AF images of a patient with autosomal dominant retinitis pigmentosa caused by the gene *KLHL7*. The left panel displays SW-AF images, while the right displays NIR-AF images. (Top row) Images obtained at the first visit. (Bottom row) Images obtained at the follow-up visit approximately 3 years later. Dashed white lines are tangent to the horizontal-most edges of the hyperautofluorescent ring from visit 1. The outer border of the ring is outlined in green, while red lines span the length of the horizontal and vertical diameters. While both SW-AF and NIR-AF images reveal decreases in ring size over time, the difference in size is seen more clearly in the SW-AF images.

New characterisations…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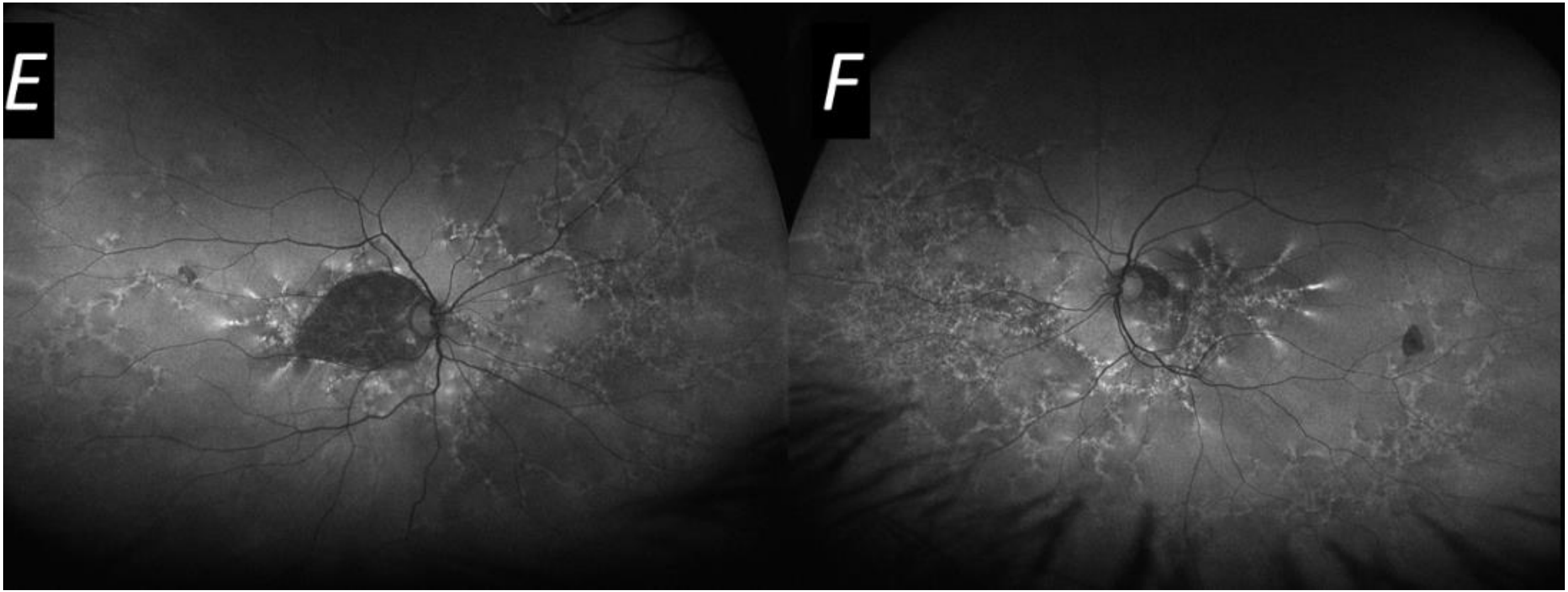
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Pattern Dystrophy of the Retinal Pigment Epithelium in a Patient With McArdle's Disease

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McArdle's disease is a rare glycogen storage disease (type V) in which a deficiency of myophosphorylase inhibits the ability of muscle to use its stored glycogen.[1] We recently examined a patient with McArdle's disease who also had a pattern retinal dystrophy.

The patient, a 39-year-old white man with McArdle's disease, complained of decreased vision in areas of poor illumination. He had no family history of ophthalmic disease. Visual acuity was 20/20 in both eyes with normal color vision. Amsler grid disclosed metamorphopsia in both eyes. Ophthalmoscopy demonstrated bilateral macular lesions with focal areas of hyperpigmentation surrounded by a thin rim of hypopigmentation (Fig. 1); comparison with color photographs from two years earlier suggested that there had been some resolution of deposited material with resultant loss of pigment epithelial cells. The retinal periphery in both eyes showed irregular reticular pigmentary changes. On fluorescein angiography, the macular lesions were hypofluorescent spots surrounded by irregular, thin rings of hyperfluorescence that appeared early in the transit phase (Fig. 2) and were consistent with the hypopigmented areas seen clinically. The pig-

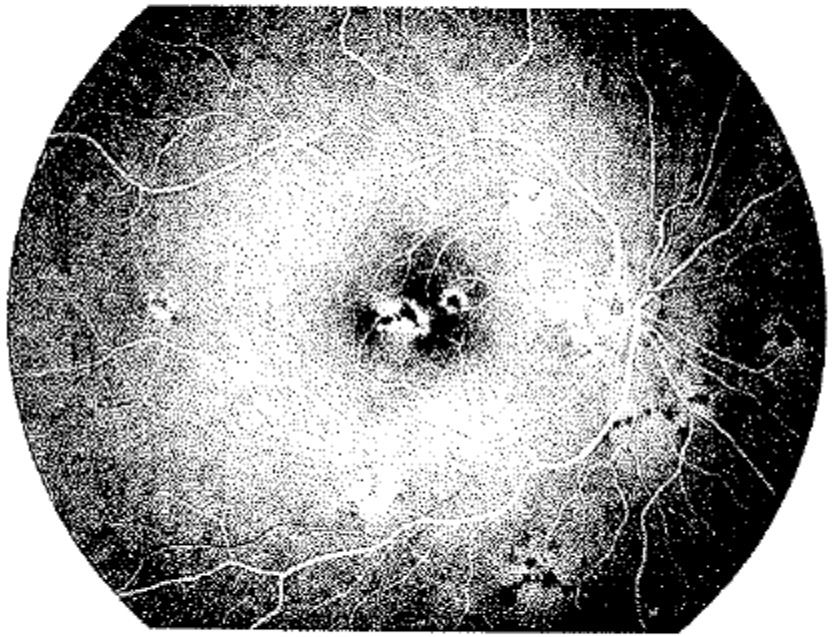


Fig. 1 (Leonardy, Harbin, and Sternberg). Fluorescein angiography of right eye demonstrates hypofluorescent macular lesions surrounded by thin, irregular rings of hyperfluorescence.

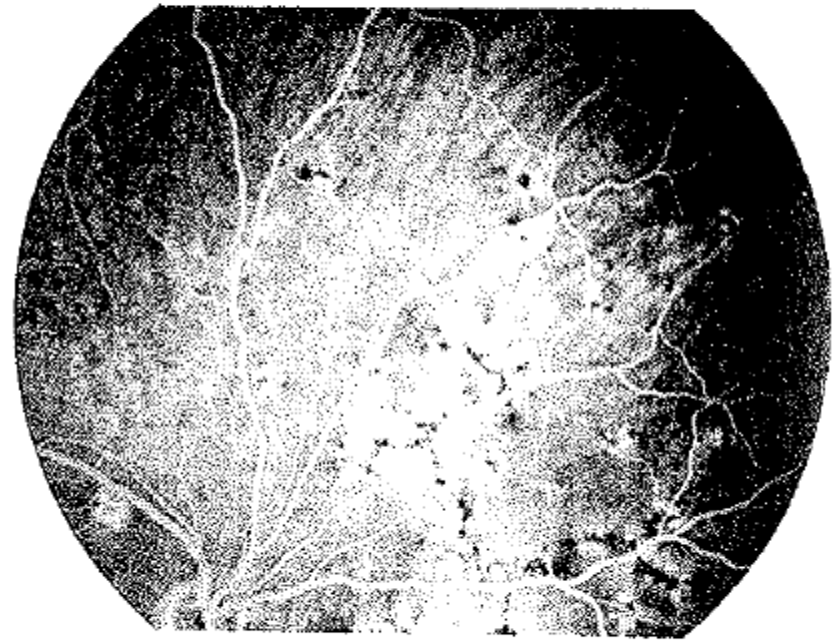
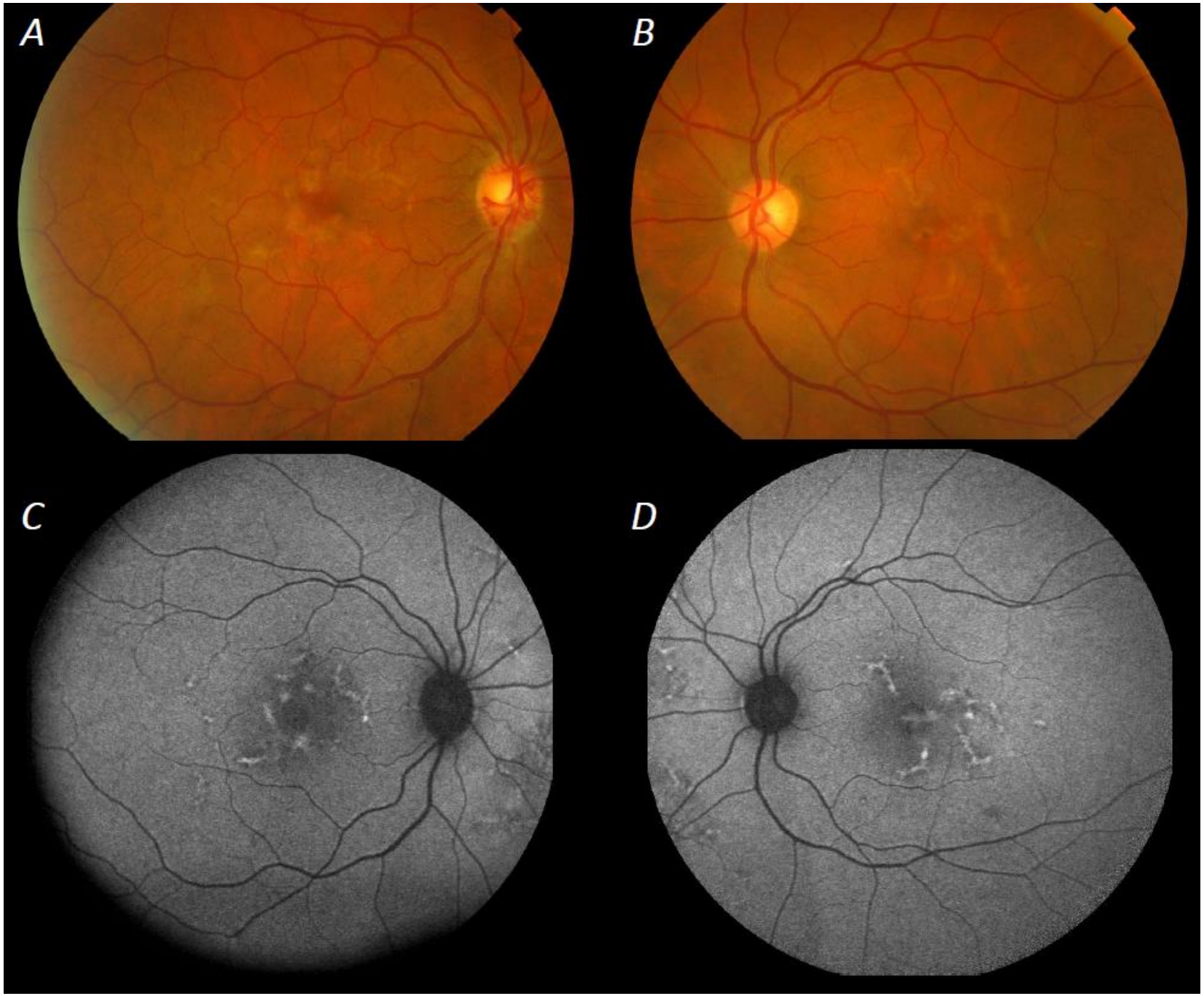


Fig. 2 (Leonardy, Harbin, and Sternberg). Hypofluorescent peripheral lesions with surrounding hyperfluorescence were consistent with areas of irregular reticular peripheral changes seen clinically.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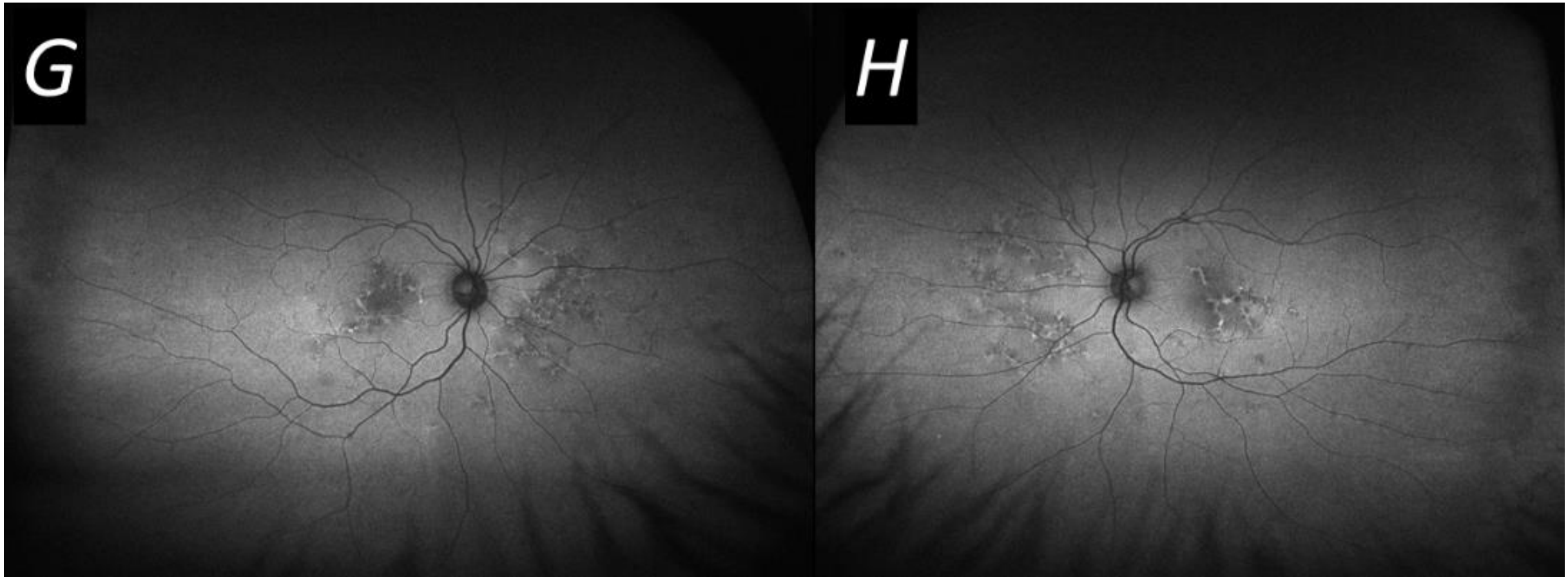
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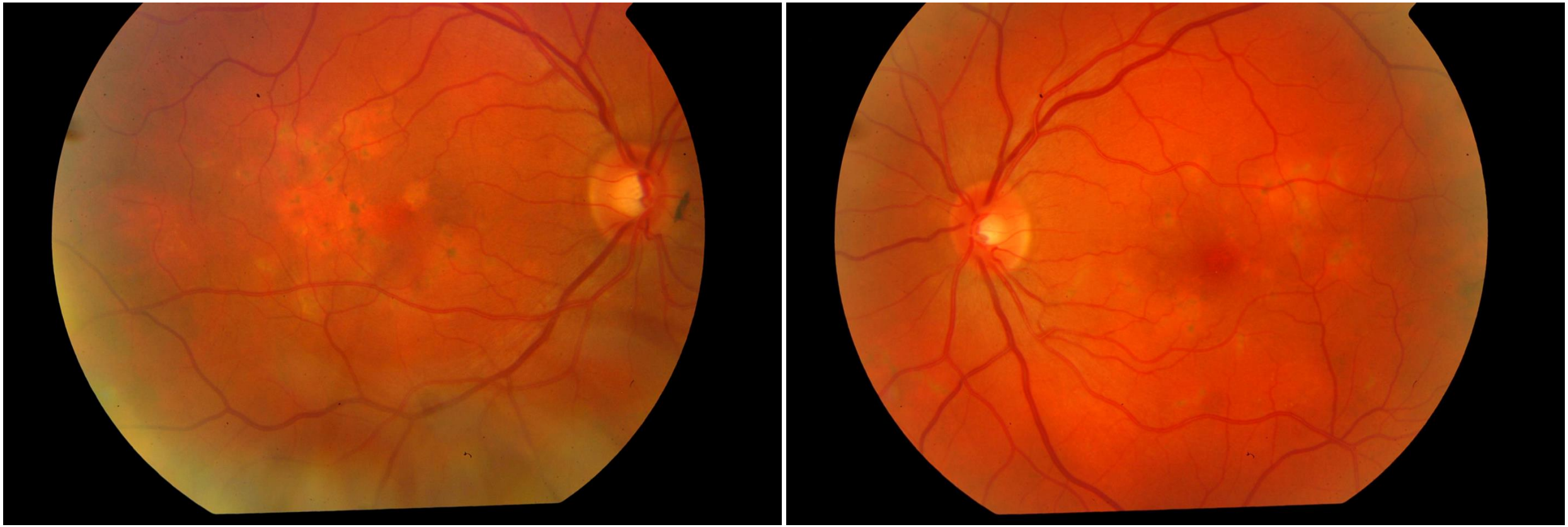
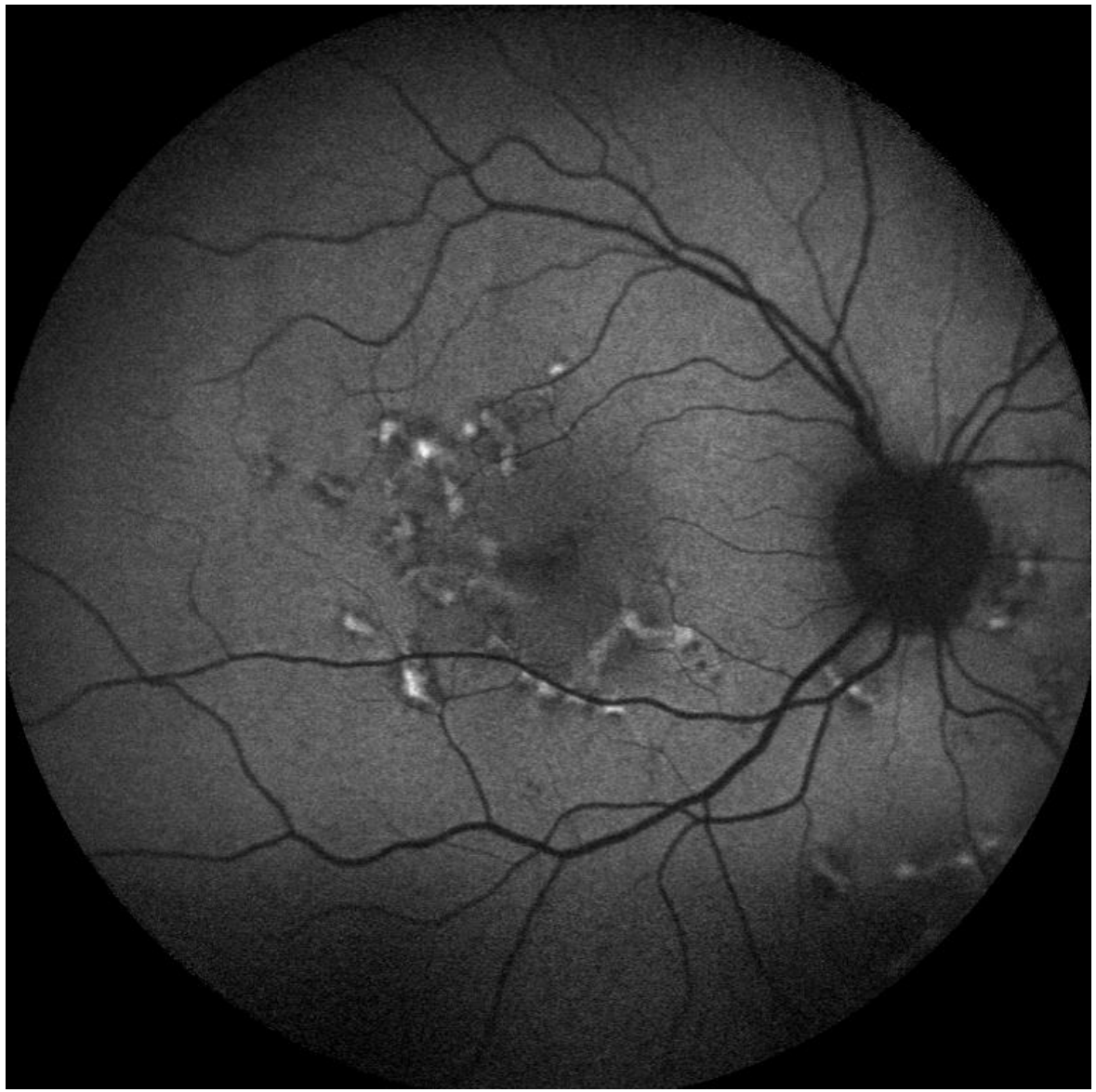
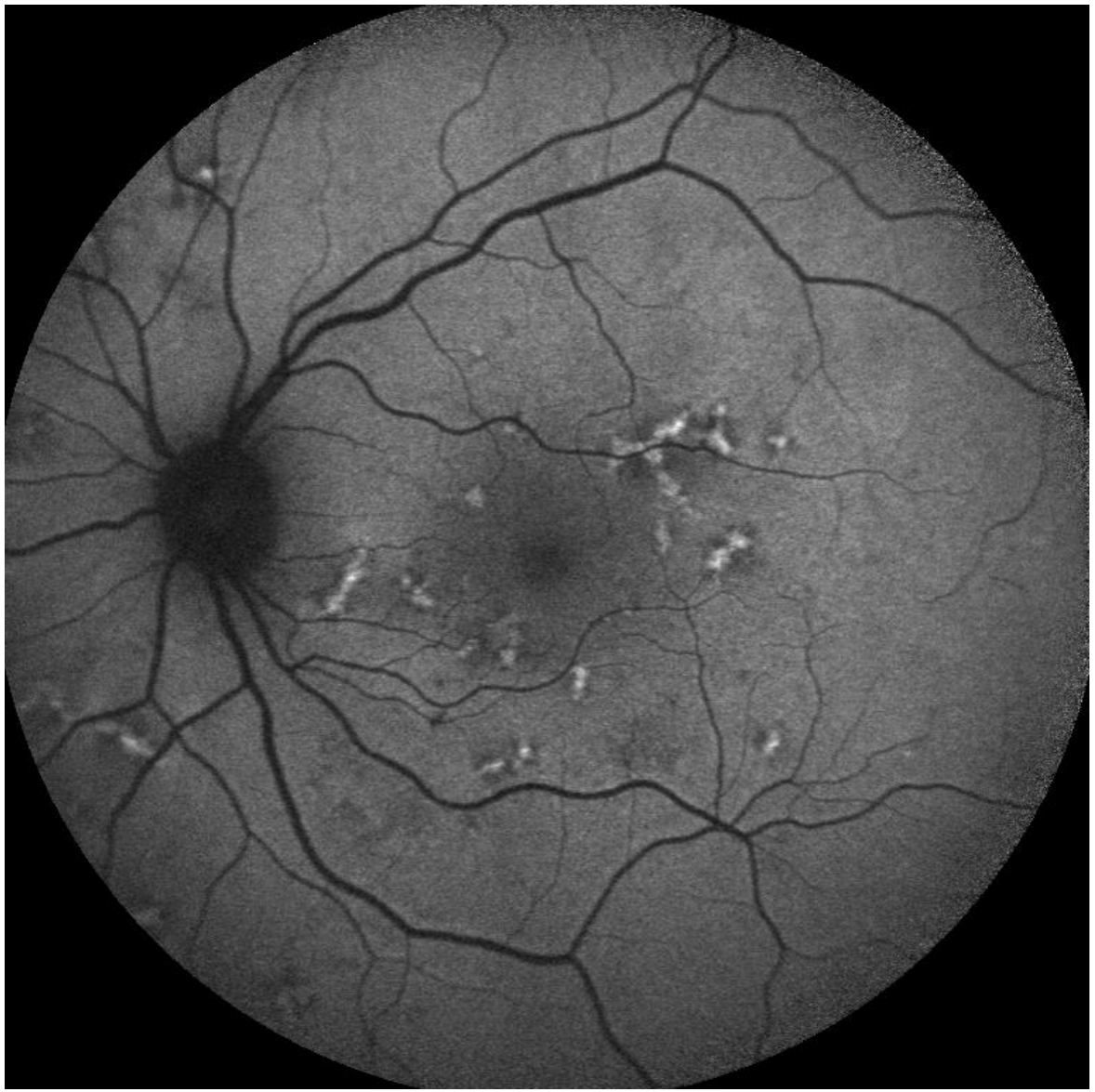
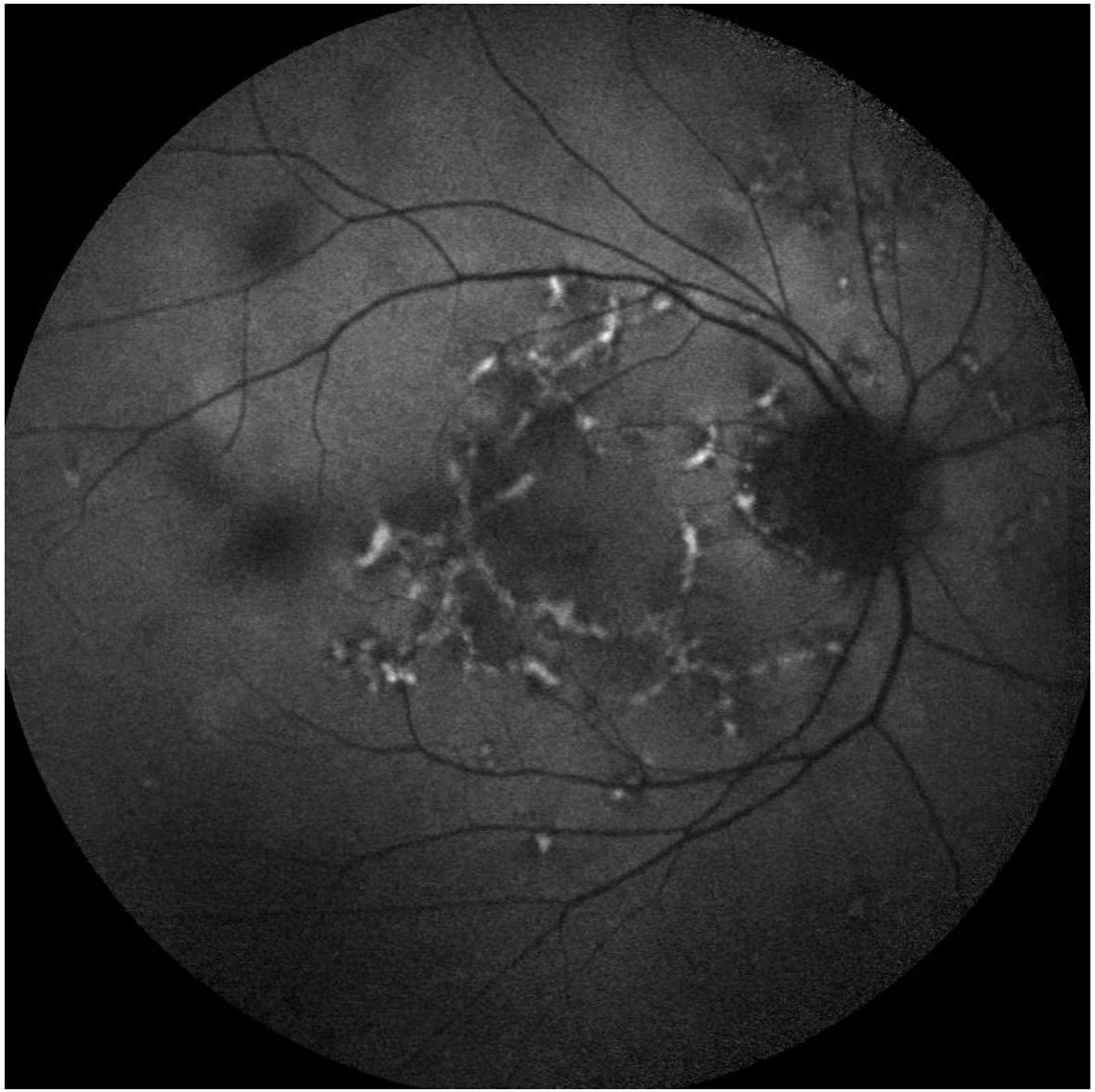
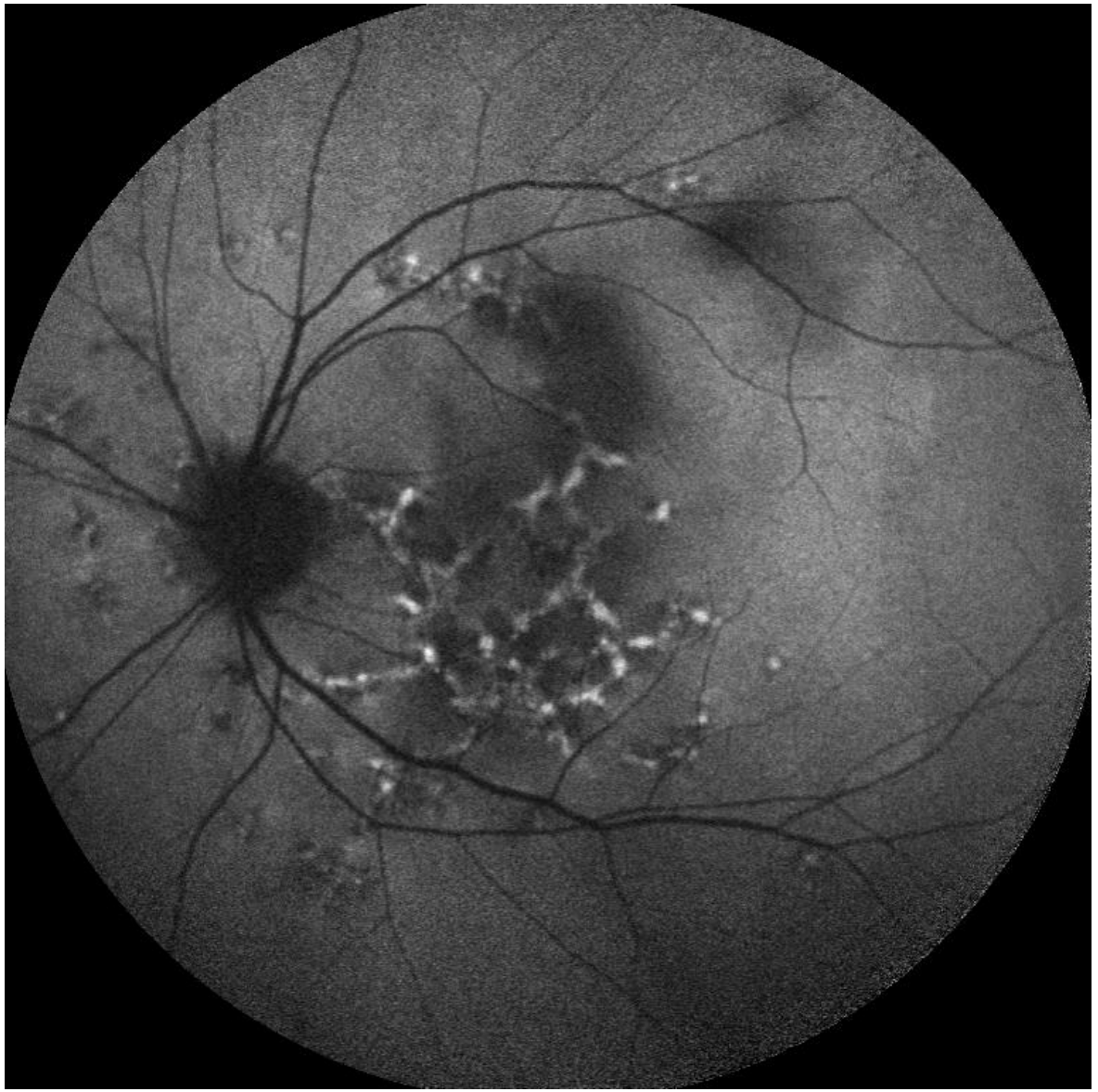








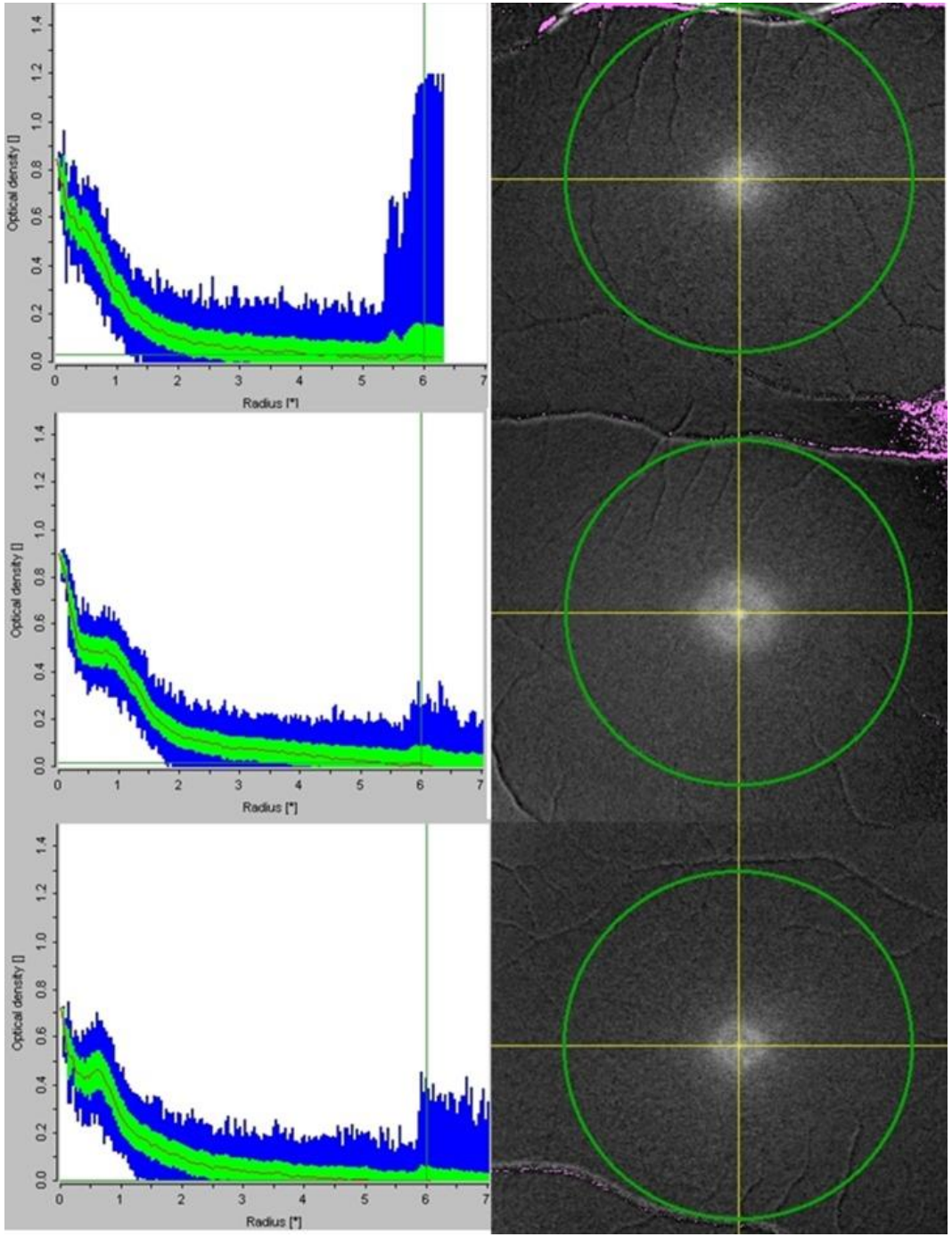


Outline

- Definition
- Historical perspective
- Some current devices
- Clinical applications: examples
  - AMD; CSCR; hydroxychloroquine
  - Inflammatory disease
  - Inherited retinal disease
  - New characterisations
- Further developments
  - Two wavelength autofluorescence
  - Photopigment bleaching and regeneration
  - Quantitative autofluorescence

Dual wavelength autofluorescence

- Objective quantification of macular luteal pigment
- Excitation at 488 and 514 nm



Clinical and Epidemiologic Research

The Heritability of the Ring-Like Distribution of Macular Pigment Assessed in a Twin Study

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AT and OAM contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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Purpose. It has been suggested that ring-like patterns of macular pigment, as measured with dual wavelength autofluorescence, are observed less frequently in subjects with age-related maculopathy. We explored relative contributions of genetic and environmental factors in macular pigment optical density (MPOD) distributions using a classic twin study.

Methods. As part of a previous nutritional study, 322 healthy Caucasian female twins, aged 16 to 50 (mean 40) years, underwent measurement of MPOD optical density by two-wavelength fundus autofluorescence. In the present study, the right eye MPOD profile was assessed for the presence of a ring-like pattern by two graders independently, using common criteria, with a third grader arbitrating in cases of disagreement. Concordance was calculated as $2C/(2C + D)$, where C is the number of twin pairs concordant, and D the number discordant, for the ring-like pattern. Also, heritability was calculated using maximum-likelihood structural equation modeling.

Results. Images and zygosity data were available for 314 twins (88 monozygotic [MZ] and 69 dizygotic [DZ] pairs). The overall prevalence of the ring pattern was 25.8%. Respective concordances for MZ and DZ twins were 0.75 and 0.22. Additive genetic factors were estimated to contribute to 84.0% of the total variance (95% confidence intervals, 63.7%–94.6%).

Photopigment bleaching and regeneration

PLoS One. 2015; 10(7): e0131881. PMCID: PMC4510609
Published online 2015 Jul 21. doi: 10.1371/journal.pone.0131881

Modeling Photo-Bleaching Kinetics to Create High Resolution Maps of Rod Rhodopsin in the Human Retina

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Invest Ophthalmol Vis Sci. 2013 Mar 1;54(3):2048-59. doi: 10.1167/iovs.12-11089.

Scanning laser ophthalmoscope measurement of local fundus reflectance and autofluorescence changes arising from rhodopsin bleaching and regeneration.

Morgan JI[1], Pugh EN Jr.

Quantitative autofluorescence (qAF)

Retina

Quantitative Measurements of Autofluorescence with the Scanning Laser Ophthalmoscope

François Delori,[1,2] *Jonathan P. Greenberg,*[3] *Russell L. Woods,*[1,2] *Jörg Fischer,*[4] *Tobias Duncker,*[3] *Janet Sparrow,*[3] *and R. Theodore Smith*[3,5]

Purpose. To evaluate the feasibility and reliability of a standardized approach for quantitative measurements of fundus autofluorescence (AF) in images obtained with a confocal scanning laser ophthalmoscope (cSLO).

Methods. AF images (30°) were acquired in 34 normal subjects (age range, 20–55 years) with two different cSLOs (488-nm excitation) equipped with an internal fluorescent reference to account for variable laser power and detector sensitivity. The gray levels (GLs) of each image were calibrated to the reference, the zero GL, and the magnification, to give quantified autofluorescence (qAF). Images from subjects and fixed patterns were used to test detector linearity with respect to fluorescence intensity, the stability of qAF with change in detector gain, field uniformity, effect of refractive error, and repeatability.

(including A2E) and their oxidized forms.[2] Defects in photoreceptor genes can have a direct impact on RPE lipofuscin levels, such as is the case for ABCA4-related retinal disorders.[3–5] Several adverse effects of RPE lipofuscin has been demonstrated in vitro, including generation of free radicals,[6,7] lysing of cell membrane,[8,9] photoinduced apoptosis,[10,11] and photooxidation-associated complement activation.[12] These deleterious effects may play a role in the pathogenesis of age-related macular degeneration (AMD) and some retinal dystrophies.[13]

Fundus AF has been quantified noninvasively by fluorometry[14] in normal subjects,[1,15] patients with AMD,[16] and those with recessive Stargardt's disease.[17] However, fluorometry did not enjoy broad clinical use, in part because of its restricted availability, but also because of the difficulty in obtaining measurements from discrete areas of pathology in the presence of

Delori *et al.*, *IOVS* 2011

Retina

Monoallelic *ABCA4* Mutations Appear Insufficient to Cause Retinopathy: A Quantitative Autofluorescence Study

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PLM and MG contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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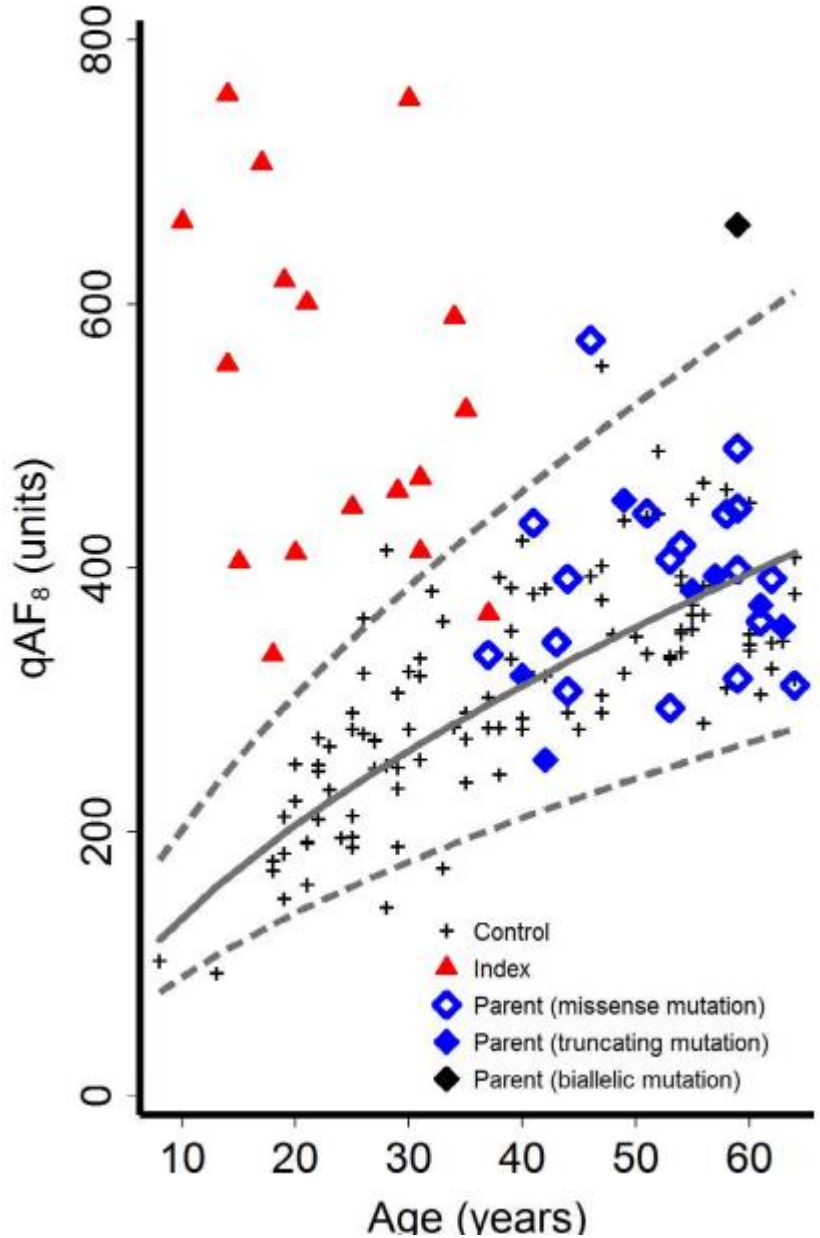
Purpose. To investigate the effect of *ABCA4* mutation status on lipofuscin-related quantitative autofluorescence (qAF) in humans and on bisretinoid accumulation in mice.

Methods. Genotyped parents (n = 26; age 37–64 years) of patients with biallelic *ABCA4*-related retinopathy underwent in-depth retinal phenotyping including qAF imaging as a surrogate measure for RPE lipofuscin accumulation. In addition, bisretinoids as the main components of autofluorescent lipofuscin at the ocular fundus were quantified in *Abca4*$^{-/-}$, *Abca4*$^{+/-}$, and wild-type mice.

Results. Index patients showed a retinal phenotype characteristic for *ABCA4*-related retinopathy, including increased qAF levels. In contrast, qAF measures in carriers of only one *ABCA4* mutation were not different from age-matched controls in this sample, and there was no difference between truncating and missense mutations. Also, none of these carriers presented an abnormal phenotype on conventional imaging. One parent with *ABCA4*-related retinopathy and increased qAF carried an additional *ABCA4* mutation, explaining the phenotype under a recessive disease model (pseudodominance). Biochemical analysis in the mouse model revealed direct downstream products (A2PE-H_2, *at*-RALdimer-PE) of the ABCA4 substrate *N*-Ret-PE to be similar in wild-type and *Abca4*$^{+/-}$ mice. Both bisretinoids were 12- to 18-fold increased in *Abca4*$^{-/-}$ mice. Levels of A2E and A2PE in *Abca4*$^{+/-}$ mice were in



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Quantitative Fundus Autofluorescence in Best Vitelliform Macular Dystrophy: RPE Lipofuscin is not Increased in Non-Lesion Areas of Retina

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Original Investigation

December 2017

Quantitative Autofluorescence Intensities in Acute Zonal Occult Outer Retinopathy vs Healthy Eyes

Katherine Boudreault, MD[1]; Kaspar Schuerch, MD[1]; Jin Zhao, PhD[1]; et al

» Author Affiliations

JAMA Ophthalmol. 2017;135(12):1330-1338. doi:10.1001/jamaophthalmol.2017.4499

Concluding Remarks

- Fundus autofluorescence imaging is an **important modality for assessing retinal disease**, more sensitive in many conditions than colour fundus photography or clinical examination

- **Patterns of autofluorescence** emerge in different conditions, permitting better diagnosis and monitoring, particularly when correlated with OCT

- **Quantitative measures** are being developed to permit objective assessments that will allow better distinction between phenotypes and insights into pathogenesis of disease