Adaptive Optics and OCTA:
Update on Retinal Imaging

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Financial Disclosure

- Advisory Board
  - Alimera Science, Allergan, Bayer, Novartis
- Research Equipment
  - Optos, Notal Vision

- None related to this presentation
- Device for research use only and not yet FDA approved

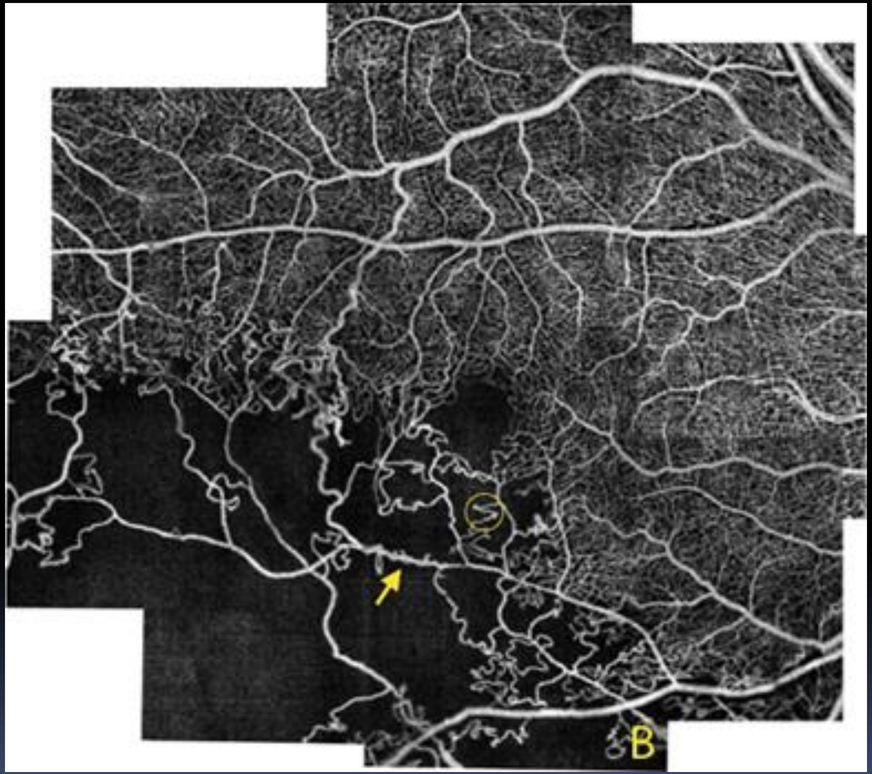
What is OCT Angiography?

- A non invasive way of performing retinal angiography without the use of extraneous dyes
- Done using newer generation OCT machines
- Takes 3-4 secs per eye

OCTA: How is it done?

Speed

Resolution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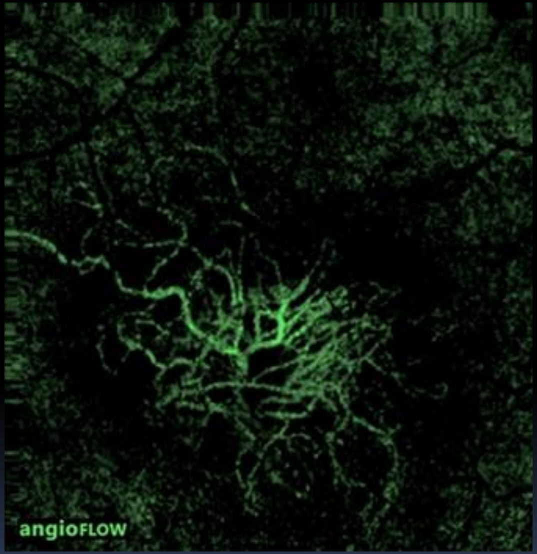
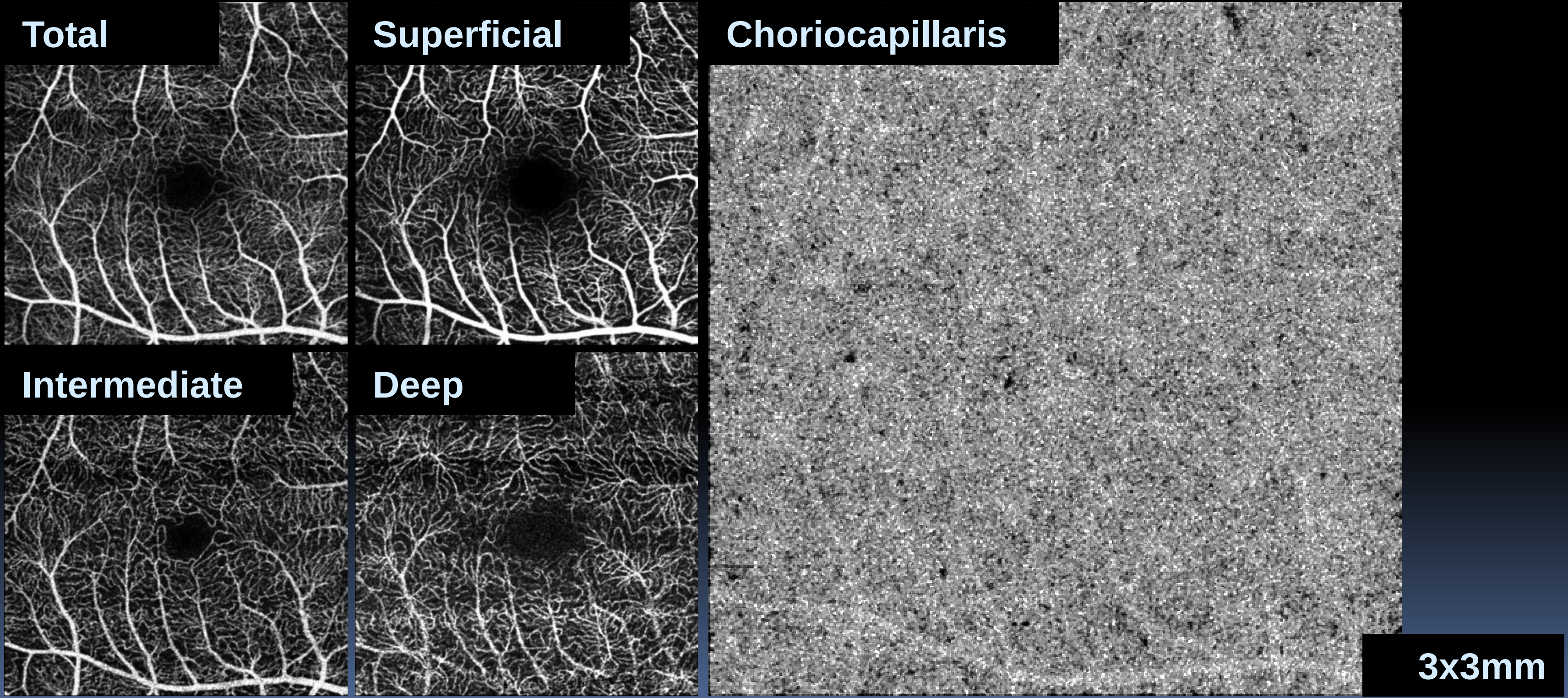

angioFLOW

Depth Resolved Microvasculature



Pressing Questions

- Where is OCTA clinically useful? What does it do better than what we have now?
  - Does it add to information from standard imaging modalities
  - Does it allow for better follow up
  - Does it drive better treatment options
  - Does it improve prognosis
  - What are the cost and time implications

Disease Modalities

- Diabetic retinopathy
- Choroidal neovascularization
  - Exudative AMD
  - Non-exudative AMD
- Other retinal vascular disease

OCTA in Diabetic Retinopathy

OCTA in Diabetic Retinopathy

Vessel Density

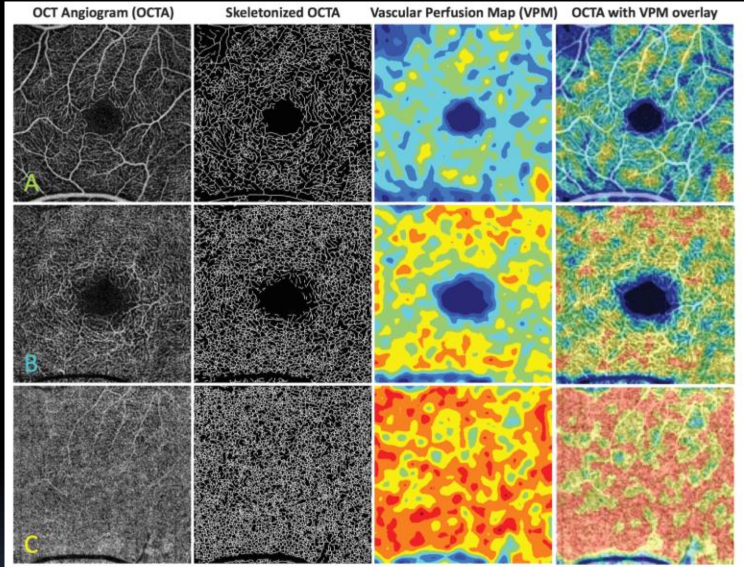


Fig. 1. An *en face* OCTA of a normal subject demonstrating the visualization of the (**A**) superficial retinal plexus, (**B**) the deep retinal plexus, and (**C**) the choriocapillaris. Skeletonized vessel maps, vascular perfusion maps (VPMs), and an overlay of the OCTA and VPMs (far right) are also included for each layer. Using these density maps, a CPD is calculated for each microvascular layer. The corresponding CPD values for the layers above are 0.1937, 0.2555, and 0.3343, respectively. The increased perfusion in the choriocapillaris compared with the superficial retinal plexus can be appreciated quantitatively with flow index and qualitatively with the color perfusion maps.

RETINAL VASCULAR PERFUSION DENSITY MAPPING USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN NORMALS AND DIABETIC RETINOPATHY PATIENTS

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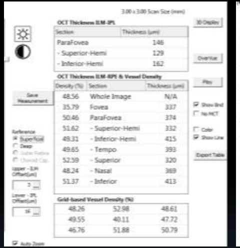
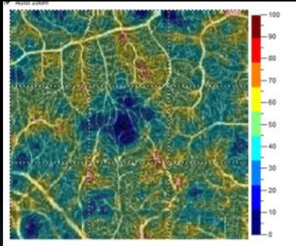
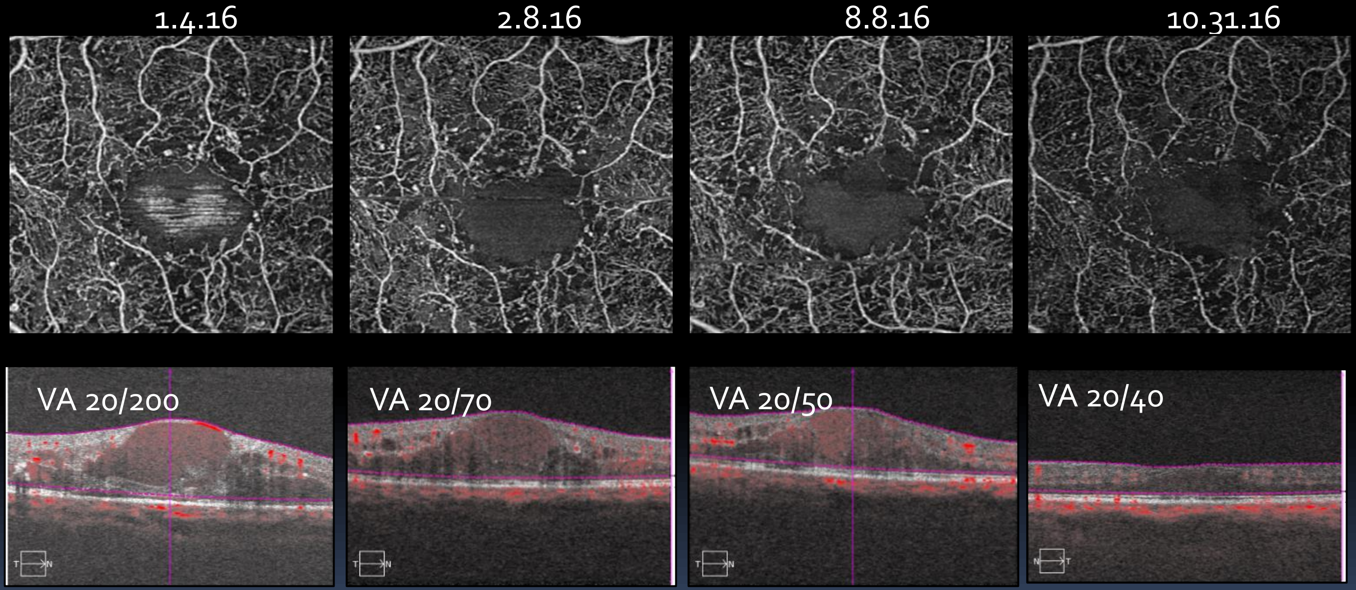


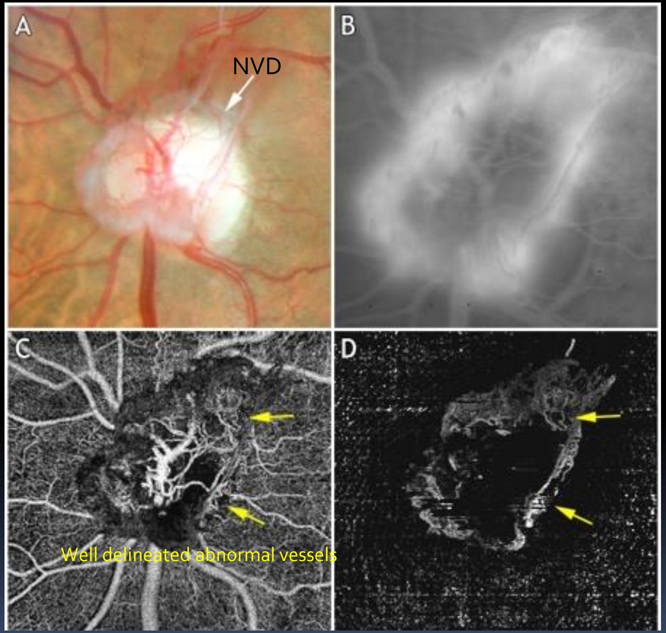


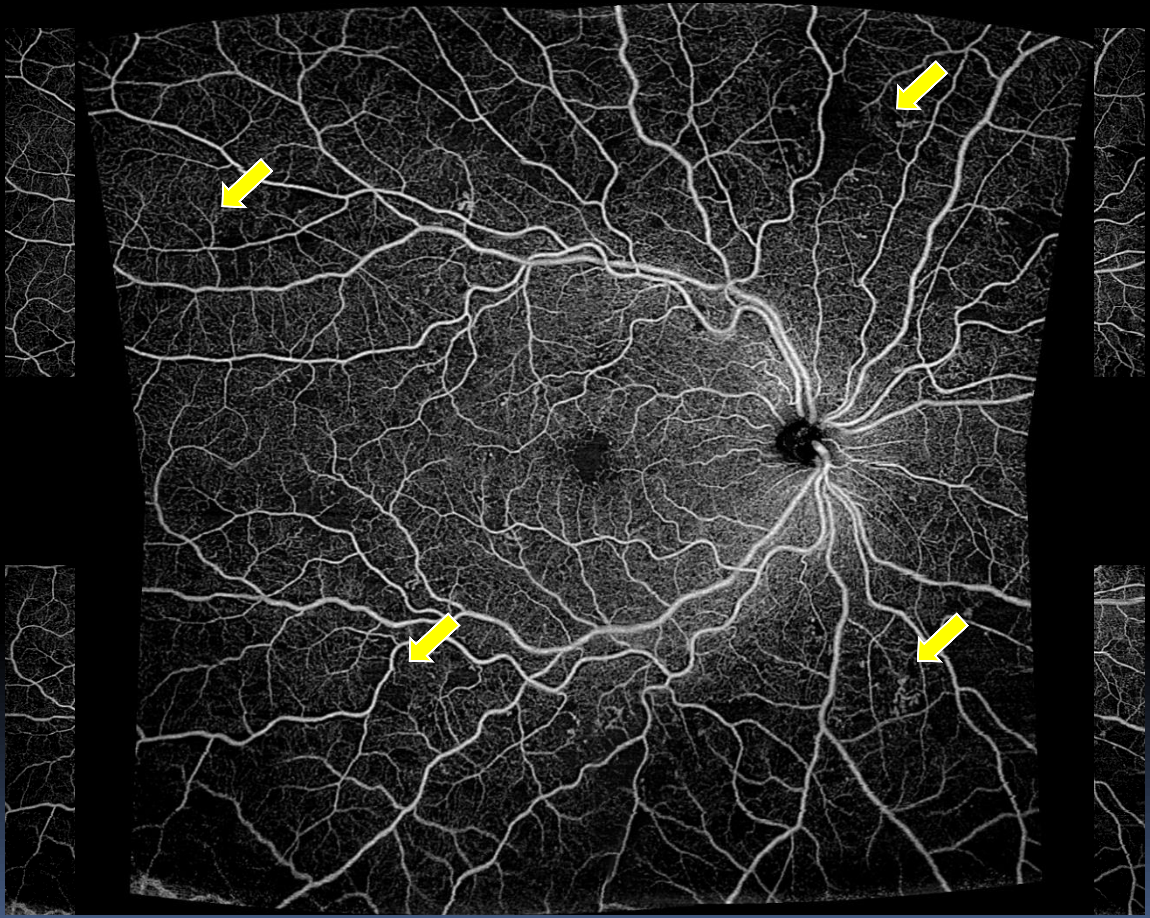
Vision Limiting Macular Ischemia



OCTA in PDR

- Identify NV
- Follow NV for regression
- Follow NV for re-growth

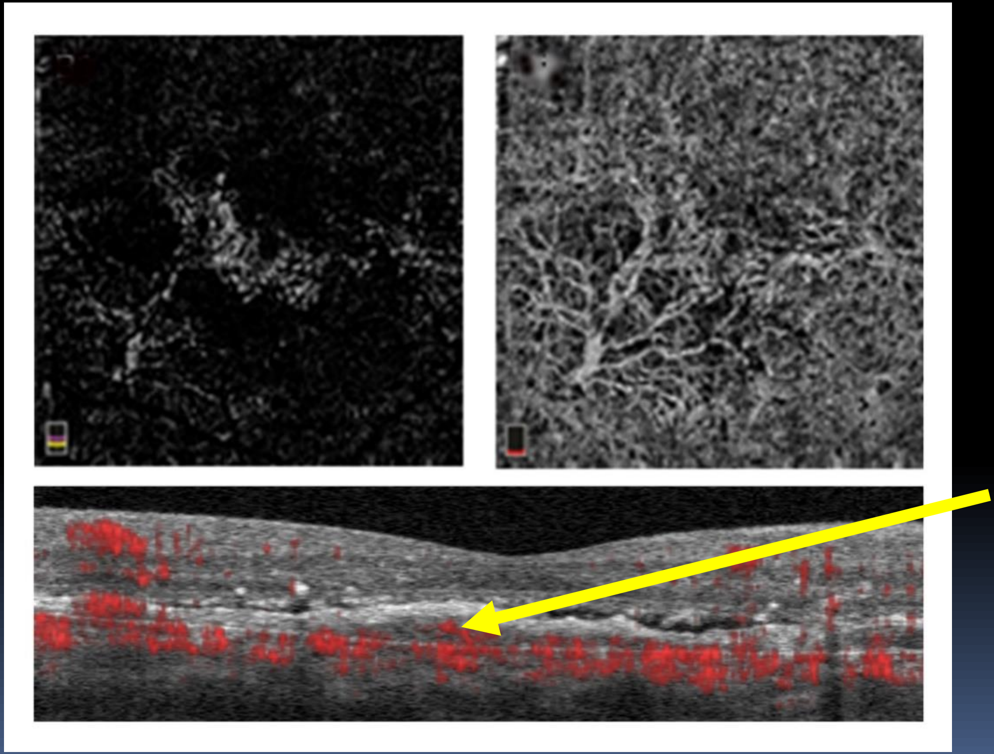




Disease Modalities

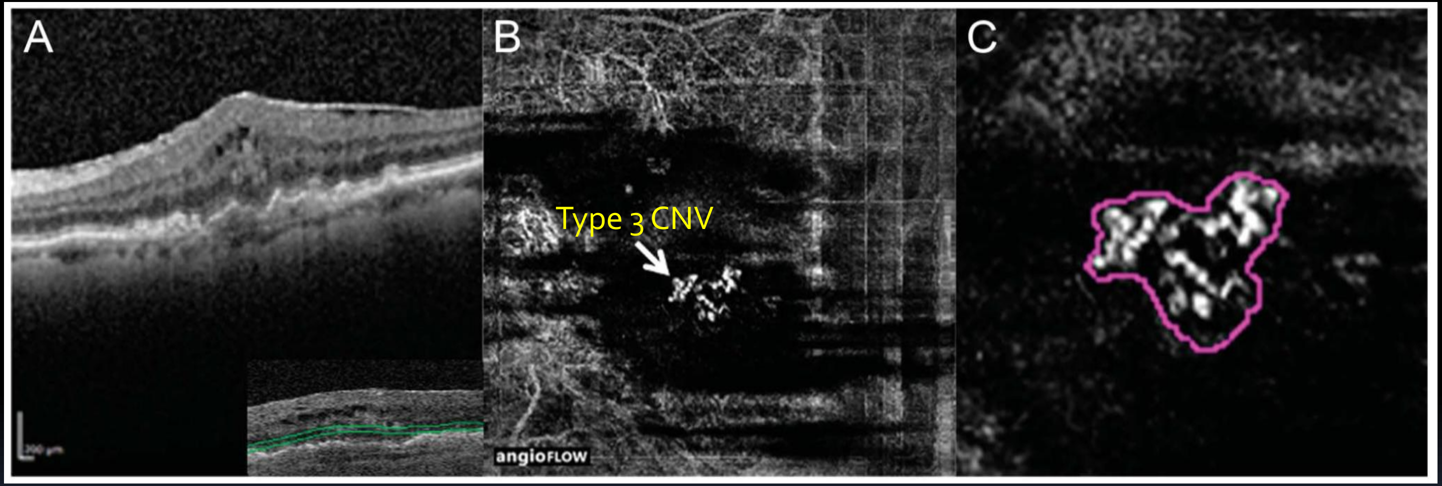
- Diabetic retinopathy
- Choroidal neovascularization
- Other retinal vascular disease

OCTA of CNV: Type 1



Flow under PED

OCTA of CNV: Type 3



Kuehlewein L, Dansingani KK, de Carlo TE, Bonini Filho MA, Iafe NA, Lenis TL, Freund KB, Waheed NK, Duker JS, Sadda SR, Sarraf D. OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF TYPE 3 NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION. Retina. 2015;35:2229-35.

OCTA: Sensitivity and Specificity

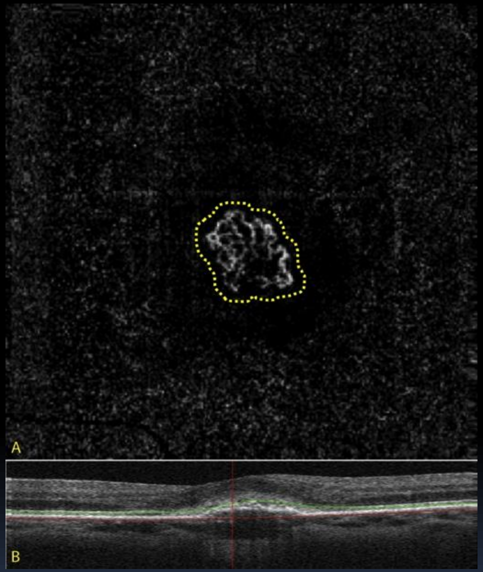
- Investigated CNV qualities on OCTA
- Sensitivity and specificity of CNV detection by OCTA using FA as the gold standard:
  - Sensitivity = 4/8 (50%)
  - Specificity = 20/22 (91%)

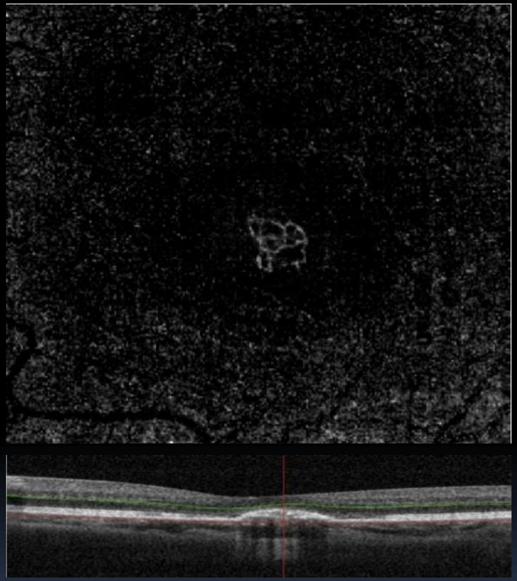
	CNV on FA	No CNV on FA	
CNV on OCTA	4	2	6
No CNV on OCTA	4	20	24
	8	22	30

- Sensitivity 70-100% in type 1 CNV

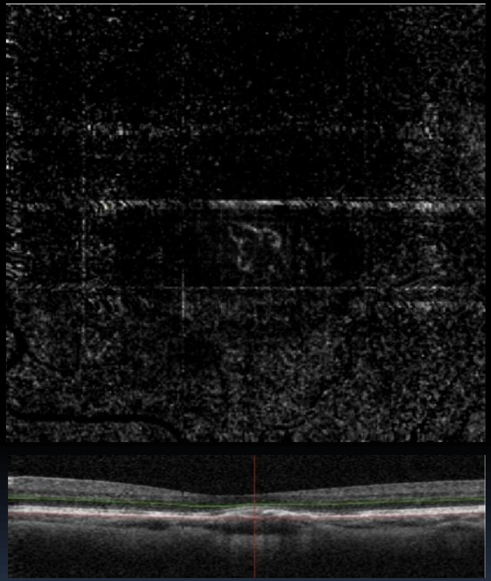
- de Carlo TE, Bonini Filho MA, Chin AT, Adhi M, Ferrara D, Baumal CR, Witkin AJ, Reichel E, Duker JS, Waheed NK. Ophthalmology. 2015 Jun;122(6):1228-38.
- Bonini Filho MA, de Carlo TE, Ferrara D, Adhi M, Baumal CR, Witkin AJ, Reichel E, Duker JS, Waheed NK.. JAMAOphthalmol. 2015 Aug;133(8):899-906.

OCTA: Size of Lesion





CNV 1 Week Post-Injection



CNV 3 Weeks Post-Injection

CNV Treatment Effect: Size of lesion

CHARACTERIZING THE EFFECT OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY ON TREATMENT-NAIVE CHOROIDAL NEOVASCULARIZATION USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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KENDRA A. KLEIN, MD,* CAROLINE R. BAUMAL, MD,* ANDRE J. WITKIN, MD,*
JAY S. DUKER, MD,* NADIA K. WAHEED, MD*

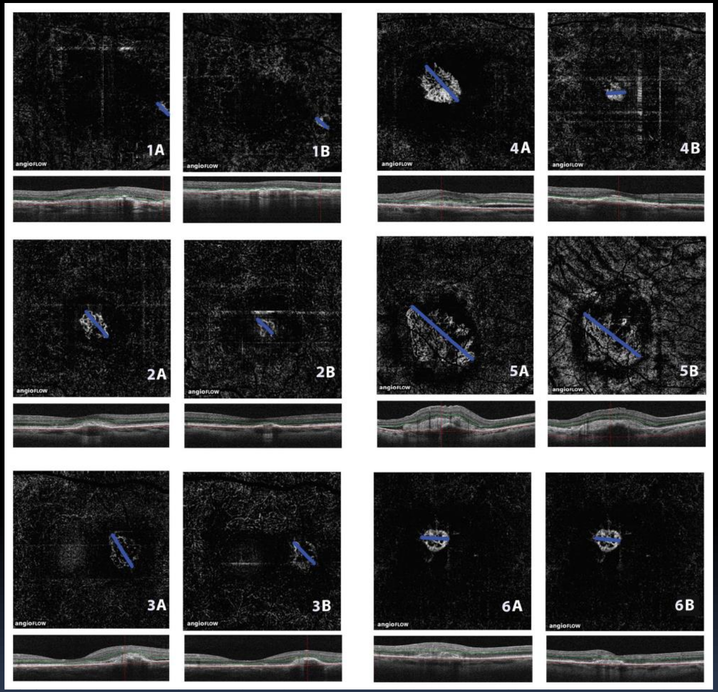
Purpose: To use optical coherence tomography angiography (OCTA) to characterize the effects of anti-VEGF injections on treatment-naive choroidal neovascularization (CNV).

Methods: From August 2014 to May 2015, treatment-naive eyes with CNV were scanned using a prototype OCTA system on a commercially available SD-OCT device (Optovue Inc, Fremont, CA). Optical coherence tomography angiography scans were obtained before anti-VEGF injection and at follow-up visits. The CNV area and greatest linear dimension (GLD) were measured along with the maximum retinal pigment epithelial detachment (RPED) height. Changes in subretinal and/or intraretinal fluid were also assessed.

Results: Six eyes of six patients with treatment-naive CNV were included. Diagnoses included neovascular age-related macular degeneration, idiopathic polypoidal choroidal vasculopathy, CNV secondary to central serous chorioretinopathy and multifocal choroiditis, and macular telangiectasia Type 2 with subretinal neovascularization. After treatment, all patients with fluid on OCT initially showed a decrease in the amount of fluid. Five of six patients demonstrated decreases in CNV GLD and area with an average reduction of 23.6% and 29.8% respectively.

Conclusion: Both CNV greatest linear dimension and area measured using OCTA decreased after anti-VEGF treatment in most patients. Optical coherence tomography angiography may be a useful tool for monitoring and quantifying the response of CNV to treatment.

RETINA 35:2252–2259, 2015

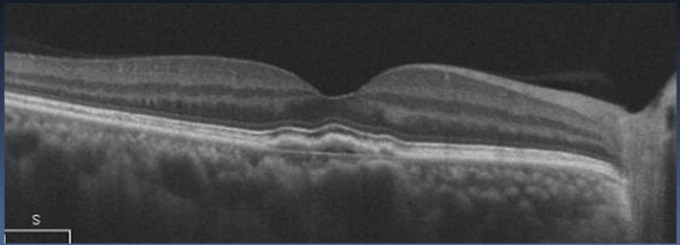


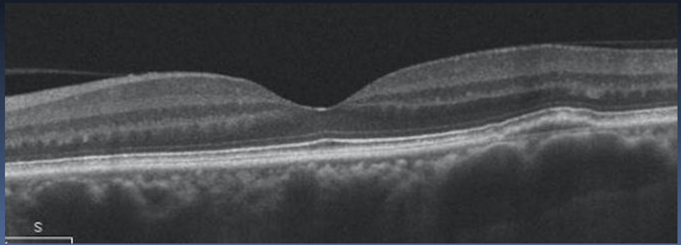
Case # 1

- 58-year-old Asian man followed for dry AMD

OD 20/50

OS 20/70+2





Neovascular 'Dry' AMD

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Optical Coherence Tomography Angiography of Asymptomatic Neovascularization in Intermediate Age-Related Macular Degeneration

Luiz Roisman, MD,[1,2] Qinqin Zhang, PhD,[3] Ruikang K. Wang, PhD,[3] Giovanni Gregori, PhD,[1] Anqi Zhang, PhD,[3] Chieh-Li Chen, PhD,[3] Mary K. Durbin, PhD,[4] Lin An, PhD,[4] Paul F. Stetson, PhD,[4] Gillian Robbins, MS,[1] Andrew Miller, BS,[1] Fang Zheng, MD,[1] Philip J. Rosenfeld, MD, PhD[1]

Purpose: To determine whether angiography with swept-source (SS) optical coherence tomography (OCT) identifies subclinical type 1 neovascularization in asymptomatic eyes with intermediate age-related macular degeneration (iAMD).

Design: Prospective, observational, consecutive case series.

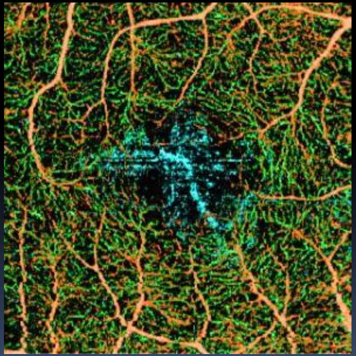
Participants: Patients with asymptomatic iAMD in one eye and neovascular age-related macular degeneration (AMD) in their fellow eye.

Methods: The patients underwent SS OCT angiography (OCTA), fluorescein angiography (FA), and indocyanine green angiography (ICGA), and the images from these 3 angiographic techniques were compared.

Main Outcome Measures: Identification of subclinical type 1 neovascularization with SS OCTA in asymptomatic eyes with iAMD.

Results: Eleven consecutive patients with iAMD in one eye and neovascular AMD in their fellow eye were imaged with FA, ICGA, and SS OCTA between August 2014 and September 2015. Clinical examination of the 11 eyes revealed drusen and pigmentary abnormalities in the central macula and no evidence of macular fluid on routine OCT imaging. Ten of the 11 eyes had no evidence of leakage on FA and 1 eye had questionable fluorescein leakage. Indocyanine green angiography revealed the presence of central macular plaques in 3 of the 11 asymptomatic eyes with iAMD, and SS OCTA revealed unambiguous type 1 neovascularization corresponding to the plaques in all 3 eyes. Optical coherence tomography angiography did not identify neovascularization in the remaining 8 eyes.

Conclusions: Swept-source OCTA identified type 1 neovascularization corresponding to ICGA plaques in asymptomatic eyes with iAMD. The ability of OCTA to provide noninvasive, fast, detailed, depth-resolved identification of nonexudative neovascular lesions in eyes with iAMD suggests the need for a new classification system that distinguishes between neovascular and nonneovascular iAMD. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology.*

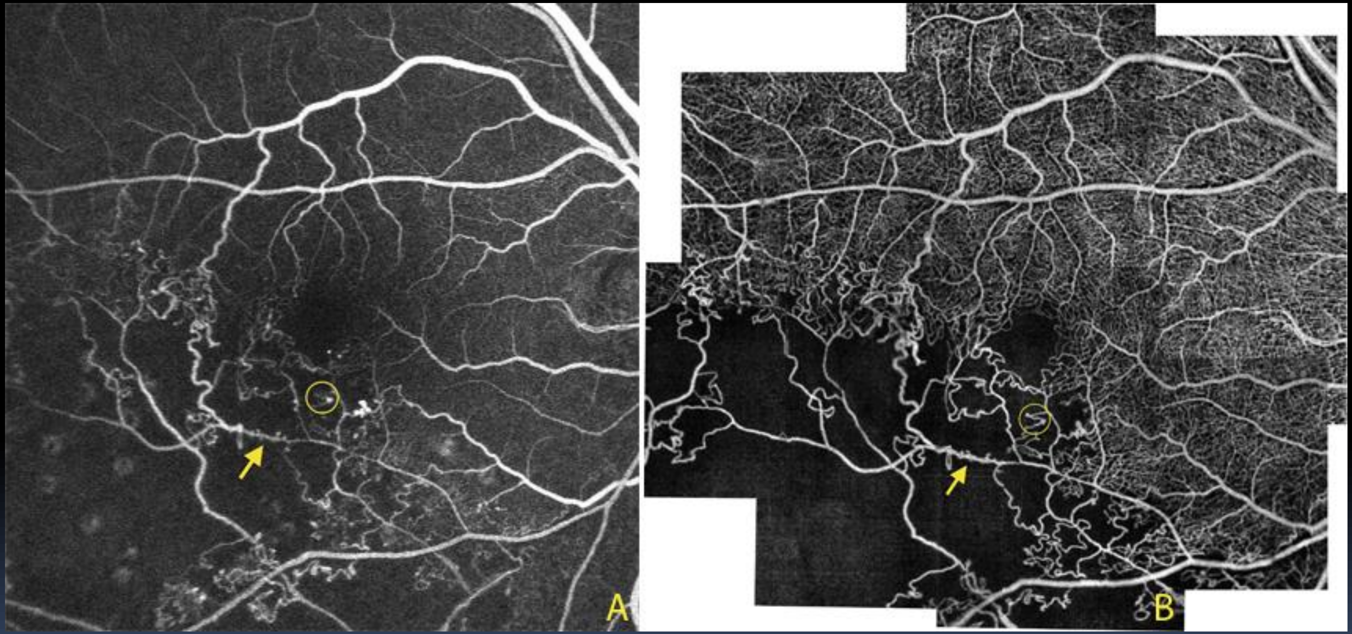


OD *Depth-encoded OCTA* OS

Disease Modalities

- Choroidal neovascularization
- Diabetic retinopathy
- Other retinal vascular disease

BRVO on OCTA



FA

OCTA Wide-Field Montage

Clinical Utility of OCTA

- Multidimensional imaging modality
  - OCTA provides all the information that you would get in a regular OCT, AND provides cross-registered vascular information
- Depth Resolved
  - Can separate out the superficial from the deep layers of vasculature
- Non-Invasive and Fast
  - Repeat at multiple visits and to closely monitor patients
  - Acquisition times are 3-4s per eye.
  - Total time in room is 10 mins
- OCTA is becoming a staple of retinal clinical practice in the diagnosis and management of AMD, DR and Retinal Vascular Disease

Adaptive Optics

ADVANCED OCULAR IMAGING PROGRAM

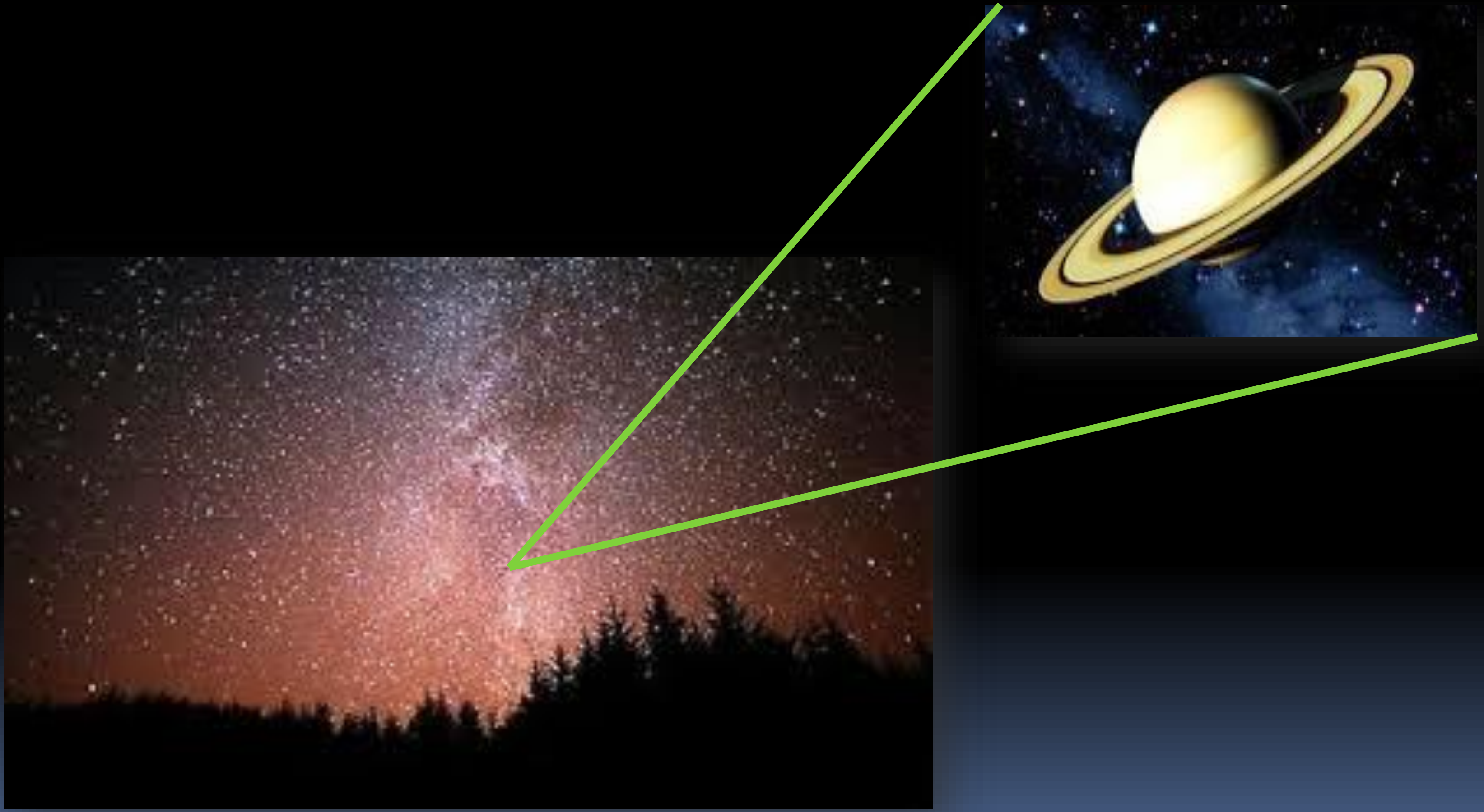
Joseph Carroll, PhD
Robert Cooper, PhD
Alfredo Dubra, PhD
Mara Goldberg
Brian Higgins
Chris Langlo
Drew Scoles, PhD
Yusufu Sulai, PhD
Phyllis Summerfelt
Melissa Wilk

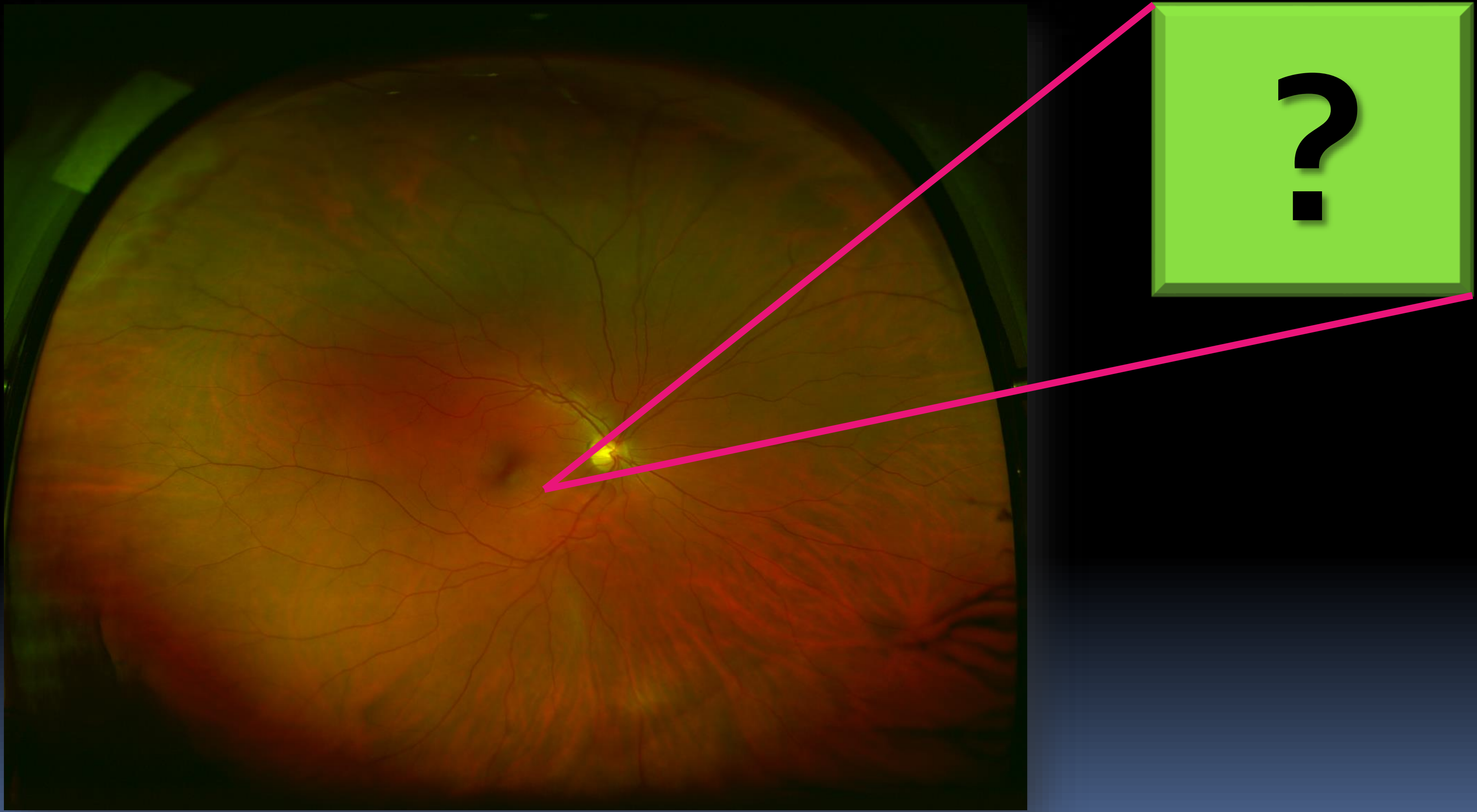
Tom Connor, Jr, MD
Dennis Han, MD
Judy Kim, MD
David Weinberg, MD
William Wirostko, MD

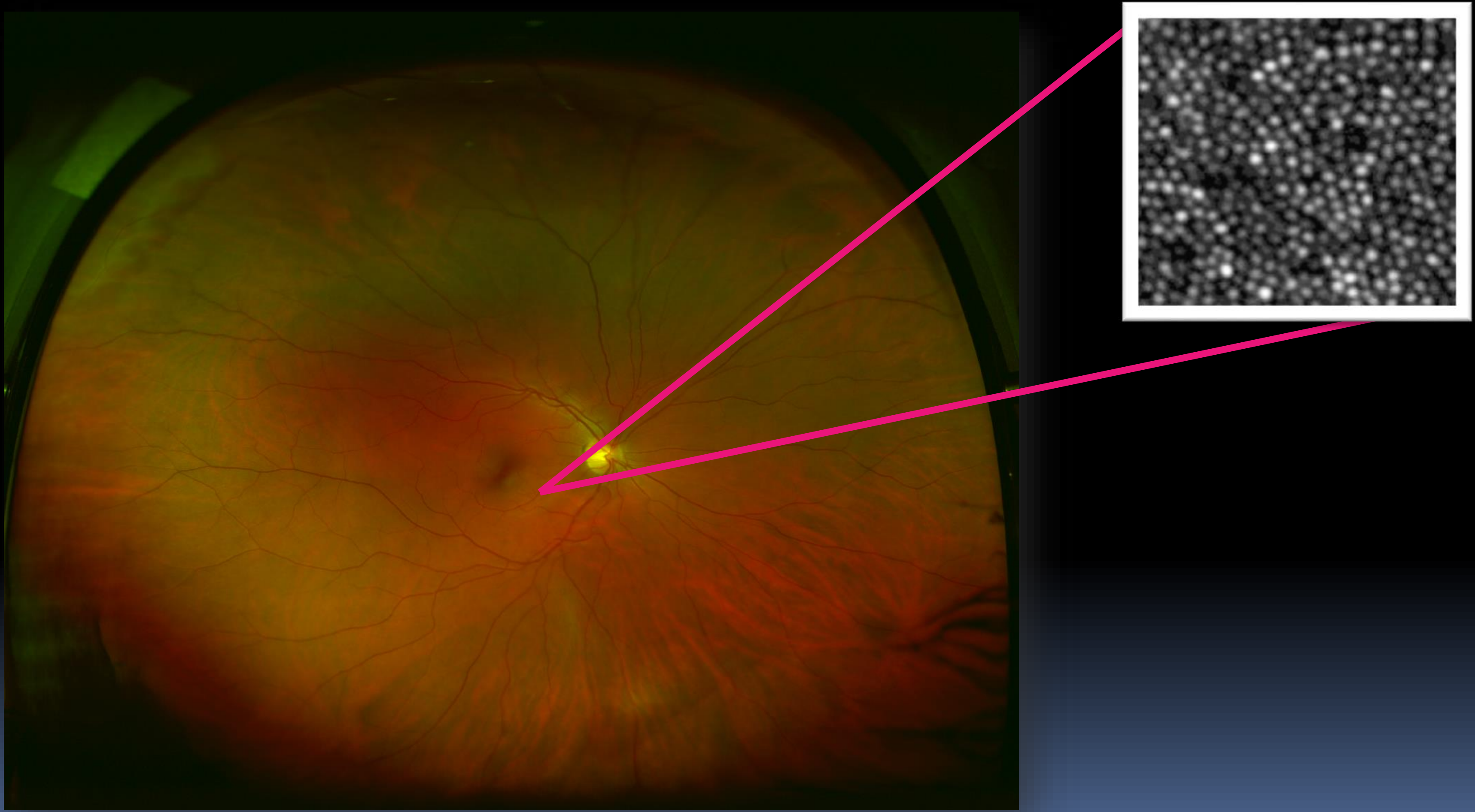
Shawn Batson
Shawn Hanson
Drew Davis, MD
Peter Karth, MD

MEDICAL COLLEGE OF WISCONSIN

Foundation Fighting Blindness
agtc
Greater Milwaukee Foundation
CTSI – Advancing Health Through Research and Discovery
Fight for Sight
The Medical Foundation – A division of Health Resources in Action
NIH National Eye Institute
wellcome trust
Alcon Research Institute
Glaucoma Research Foundation
RPB
The Vision for Tomorrow Foundation







Adaptive Optics

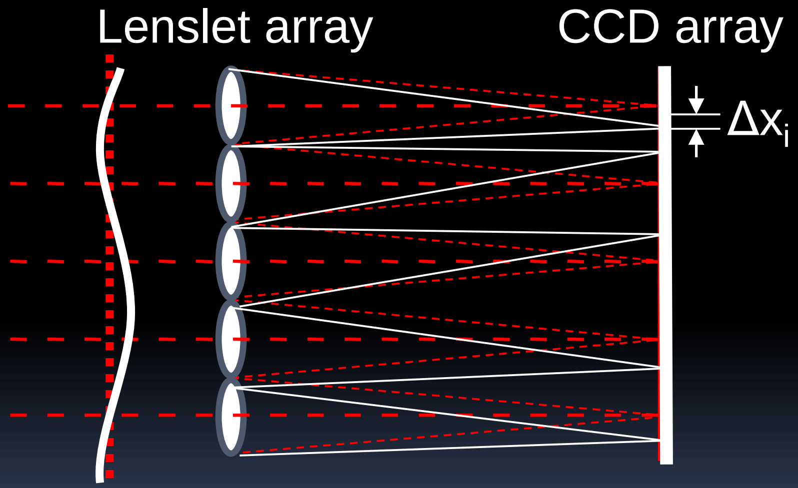
- Technology used to improve the performance of optical systems by reducing the effect of wave front distortions
- Corrects aberrations in lens and cornea that distort wavefront

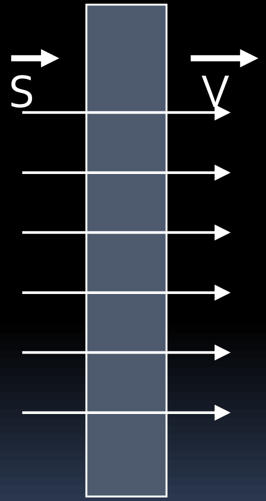
Components of Adaptive Optics

Wavefront Sensor

Controller

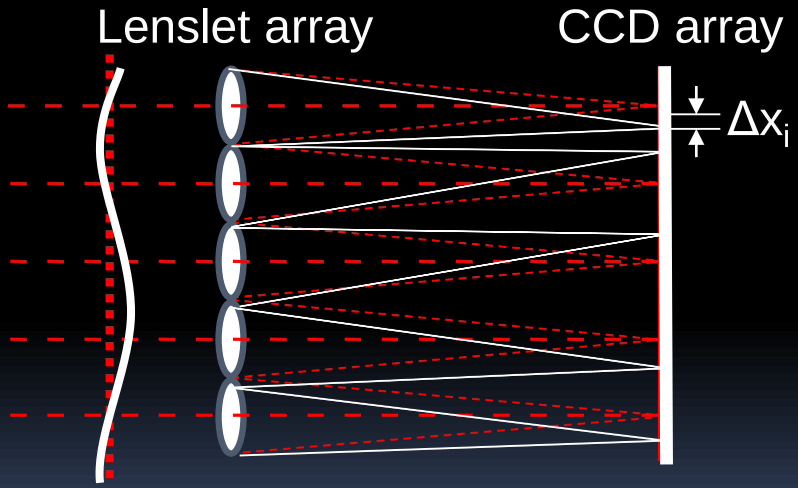
Wavefront Corrector



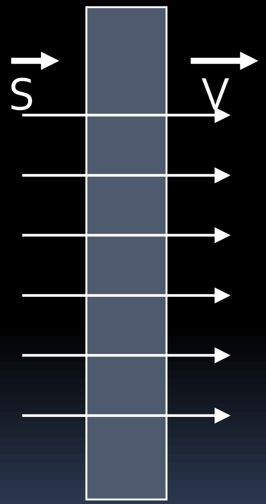


Components of Adaptive Optics

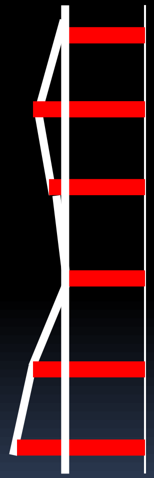
Wavefront Sensor



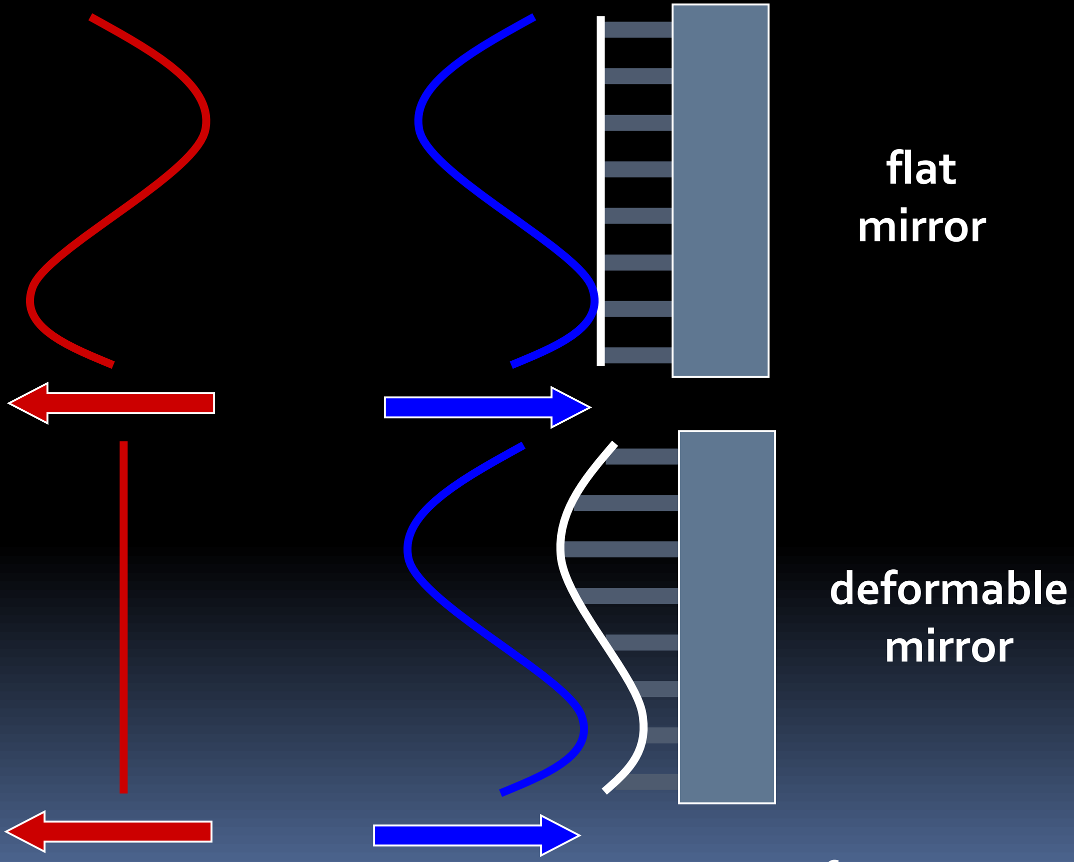
Controller



Wavefront Corrector

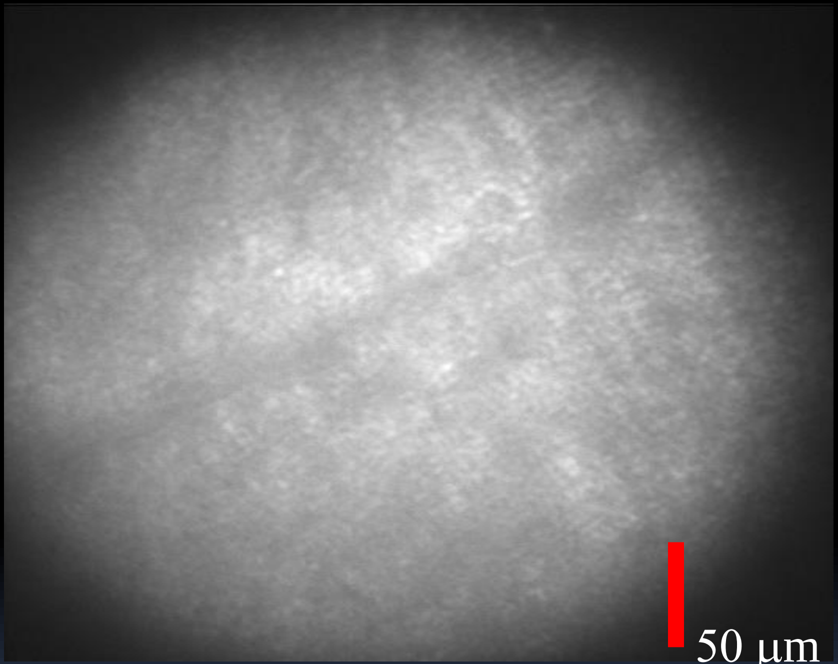


How does it work?

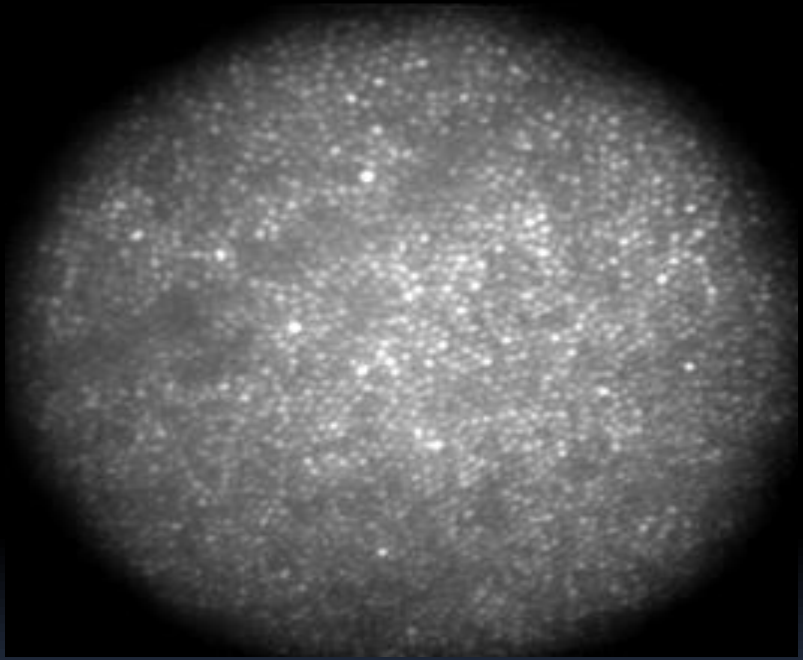


Courtesy of Geunyoung Yoon

Retinal Images



No AO correction



AO correction

Resolutions of Adaptive Optics Retinal Cameras

	Resolution	
	Lateral	Axial
AO-fundus camera	2 μm	60 μm
AO-confocal SLO	2 μm	20 μm
AO-SD OCT	2 μm	3 μm

Resolutions of Adaptive Optics Retinal Cameras

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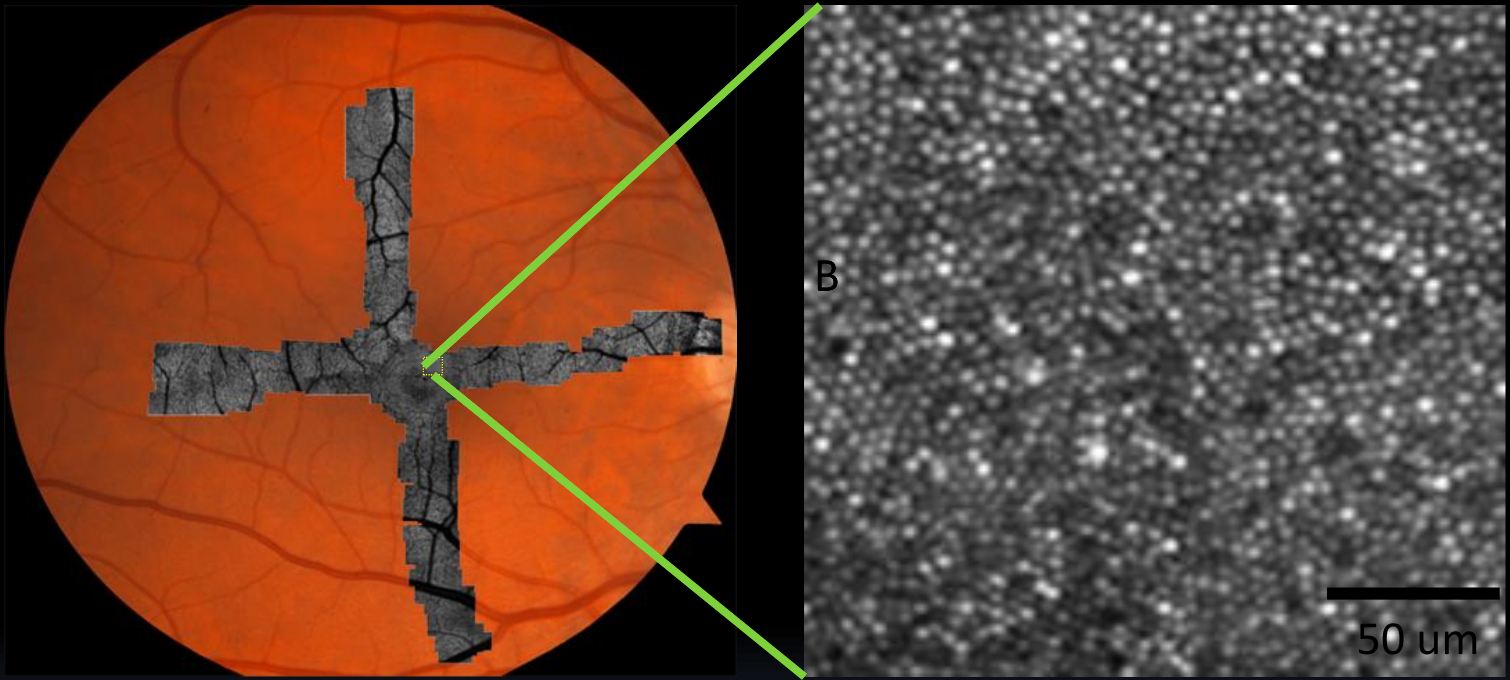


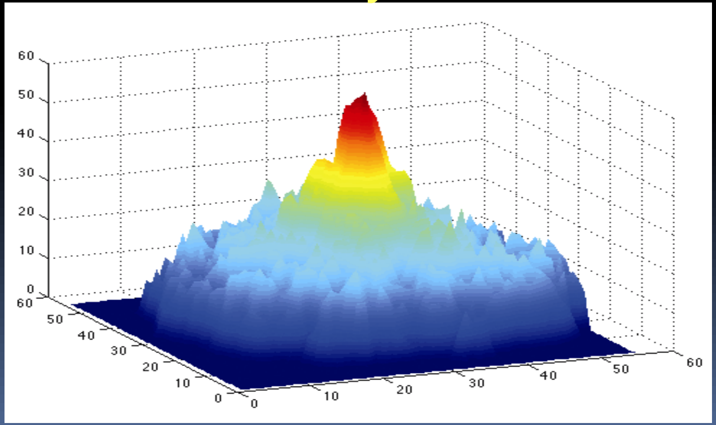
AOSLO montage overlaid on fundus photo

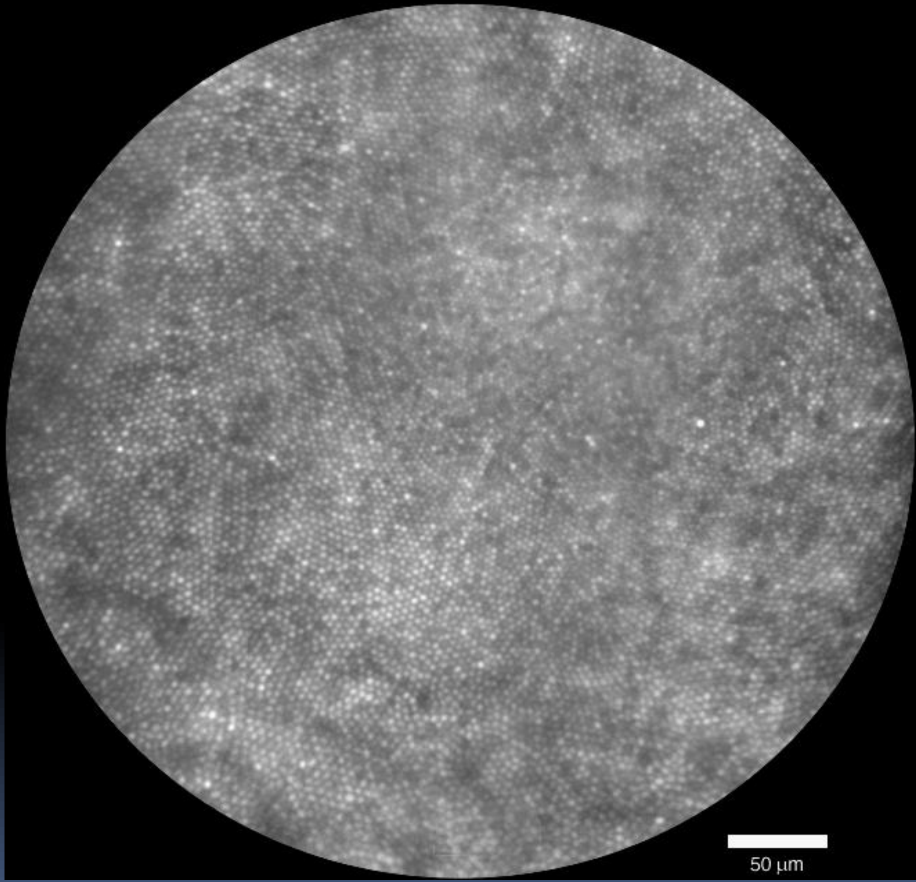
Cone mosaic 1^0 from foveal center

Courtesy: Mina Chung, MD

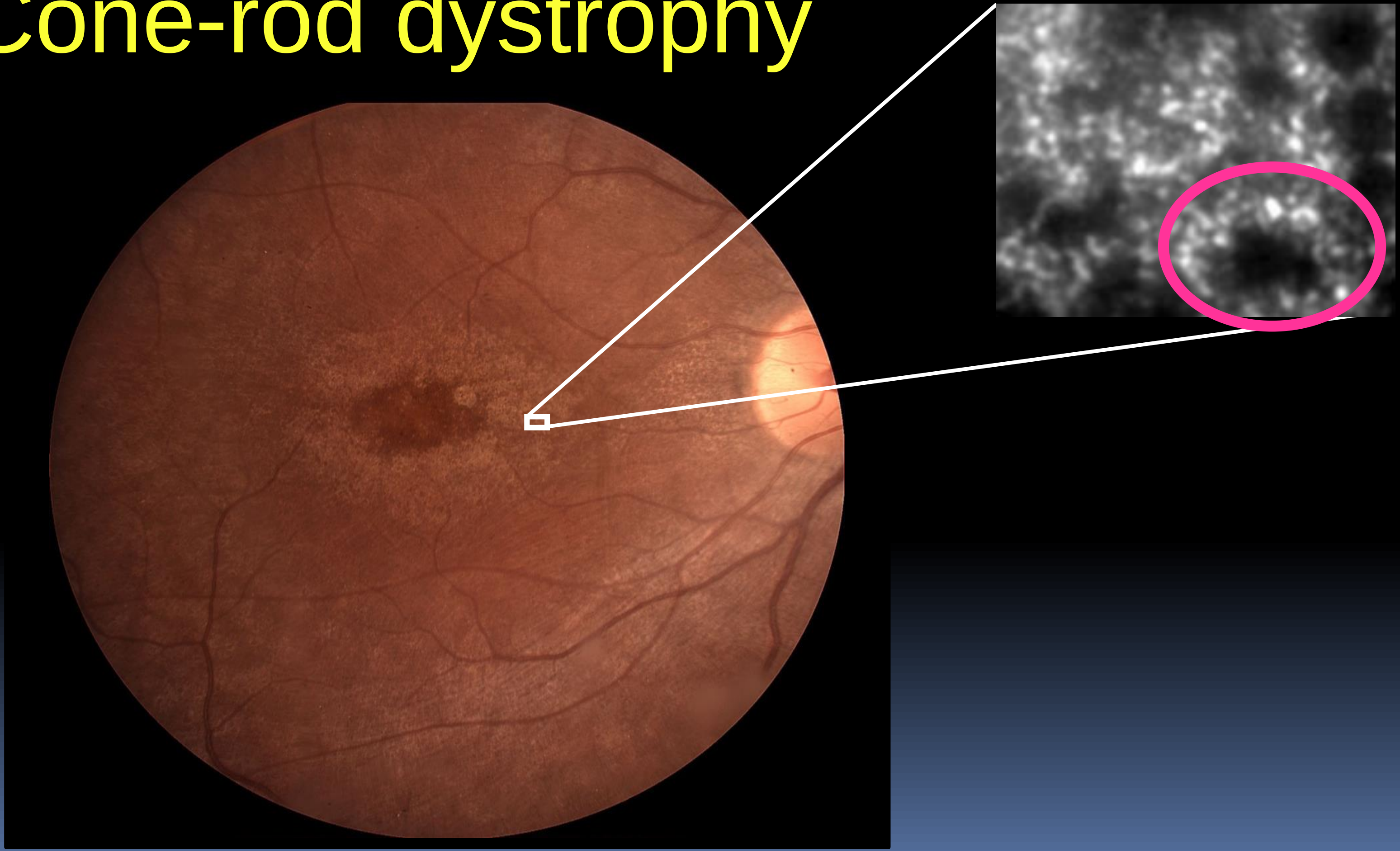
Create a montage from many locations

Cone Density Profile

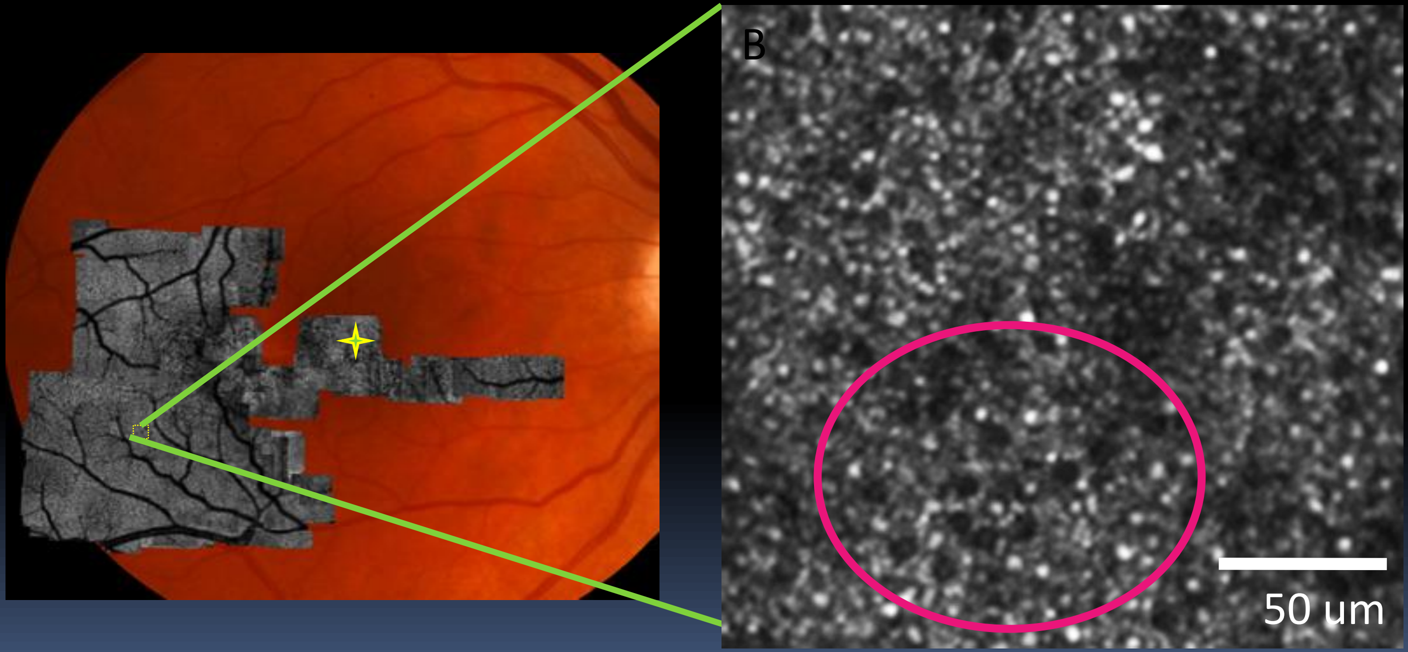




Cone-rod dystrophy



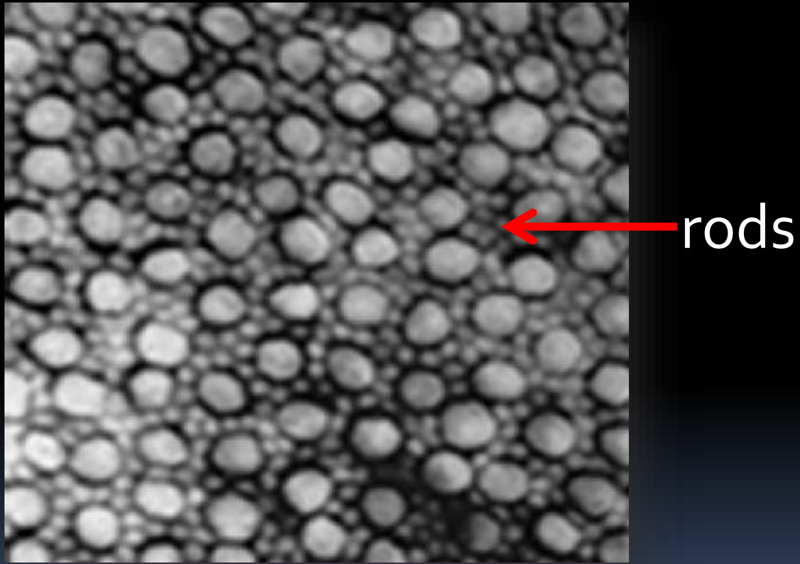
AOSLO montage overlaid on fundus photograph of a patient with MacTel : 10º from fovea



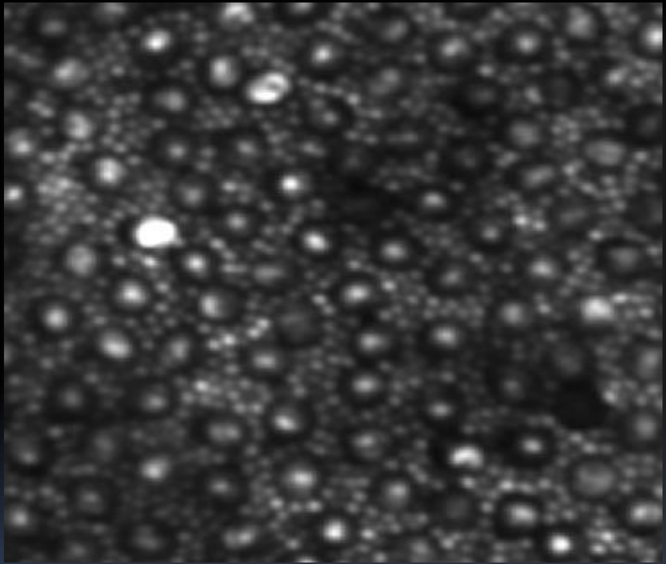
Courtesy: Hongxin Song, MD PhD and Mina Chung MD

Rod Image @ 10 degree

Histology

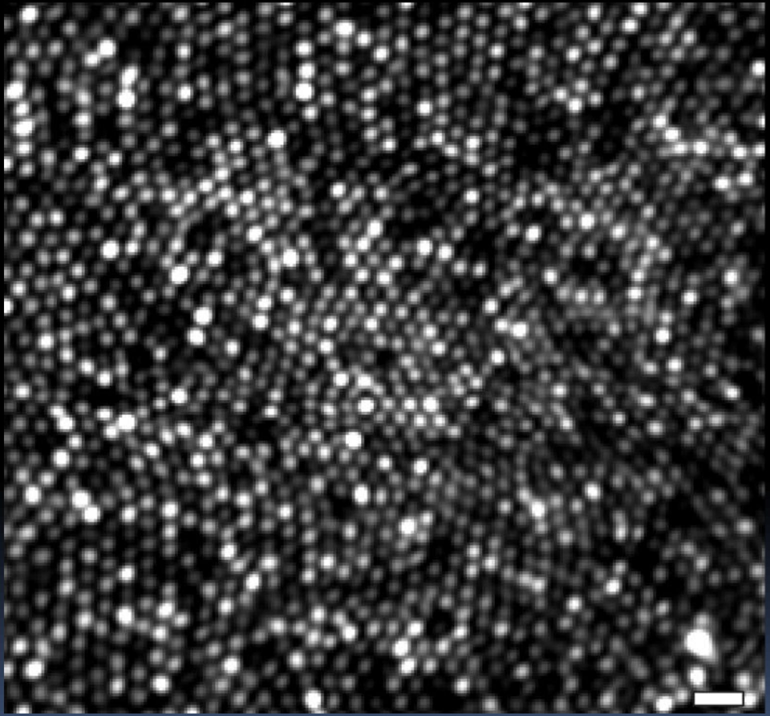


In vivo Image



A. Dubra, Y. Sulai, J.L. Norris, et al. ***Biomed. Opt. Express*** *2011; 2 (7): 1864-1876*

Foveal Cones

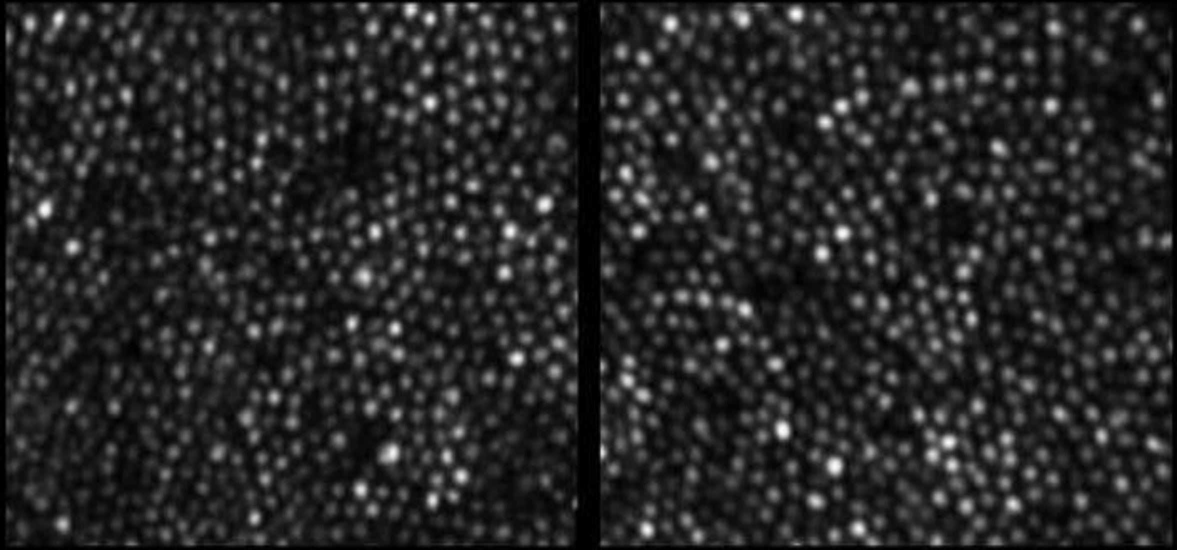


Scale bar: 10μm

A. Dubra, Y. Sulai, J.L. Norris, et al. ***Biomed. Opt. Express*** *2011; 2 (7): 1864-1876*

Cone Reflectance Variation Over Time

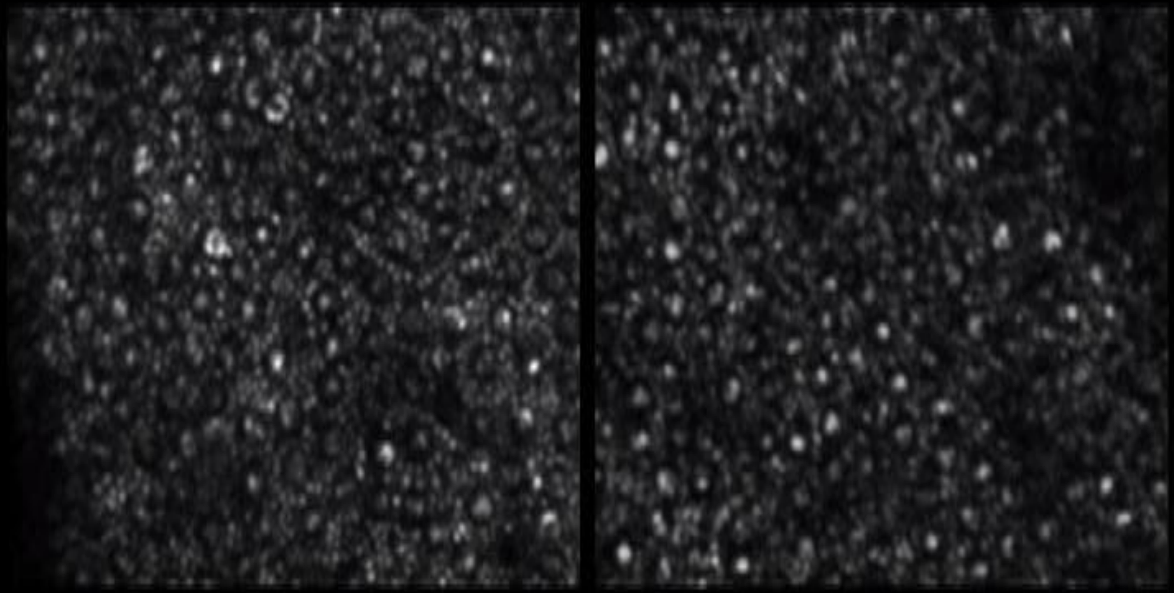
"Twinkle Twinkle Little Cones"



R.F. Cooper, A.M. Dubis, A. Pavaskar, J. Rha, A. Dubra , J. Carroll

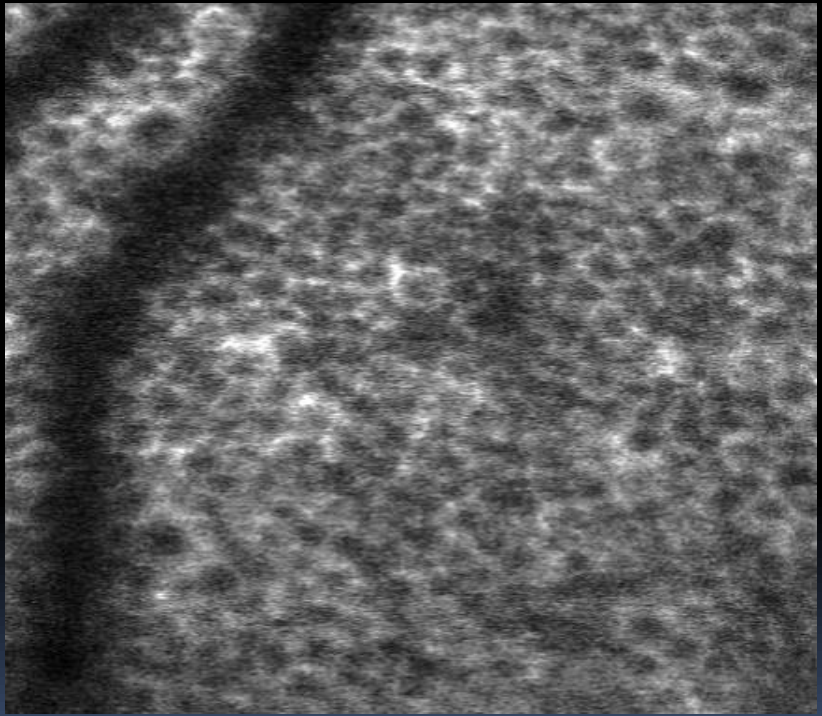
***Biomed. Opt. Express** 2011; 2(9): 2577-2589*

Rod Reflectance Variation Over Time



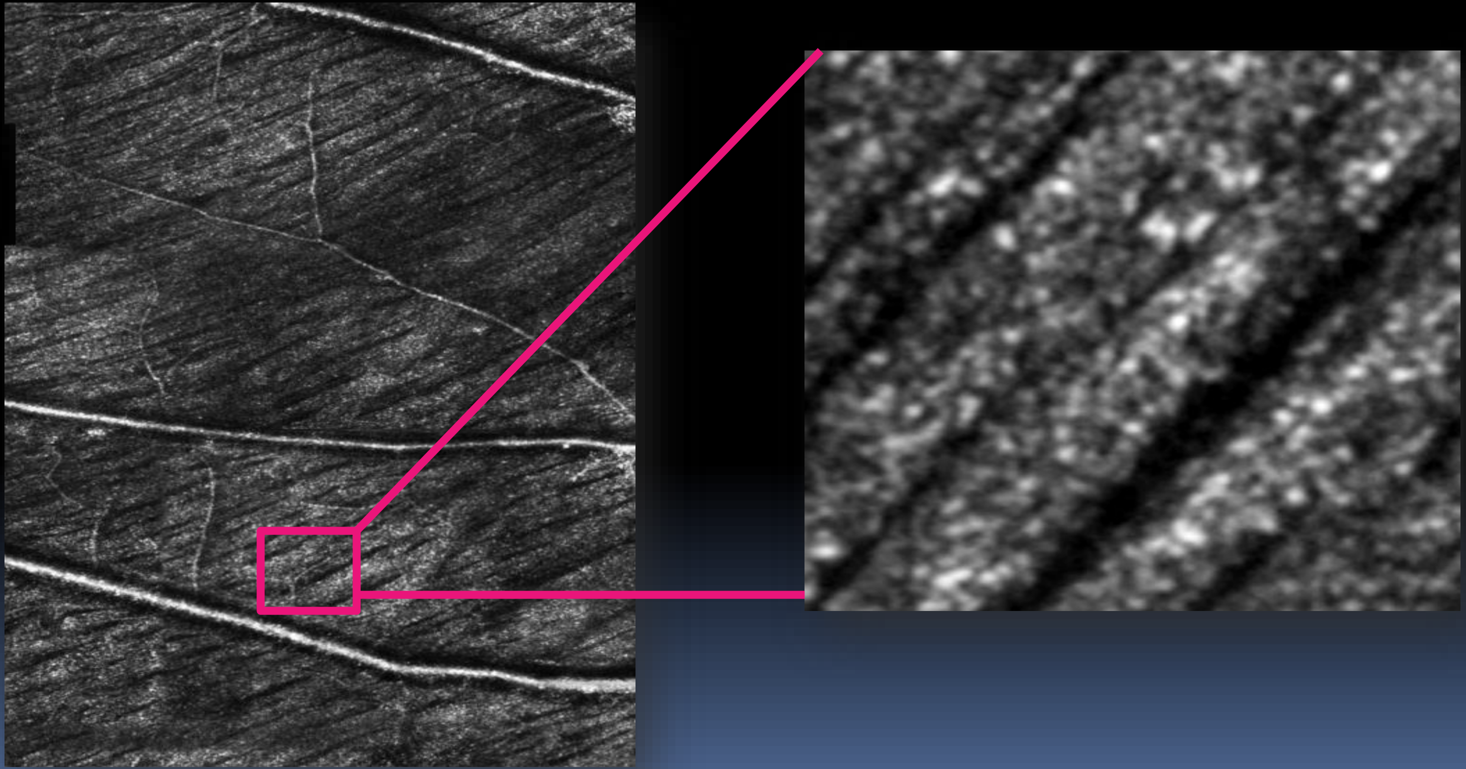
R.F. Cooper, A.M. Dubis, A. Pavaskar, J. Rha, A. Dubra and J. Carroll
***Biomed. Opt. Express* 2011;2(9)**: 2577-2589

Retinal Pigment Epithelial Cell Mosaic

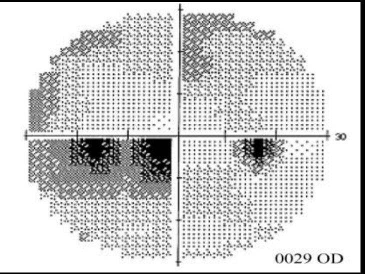


J.I. W. Morgan, A. Dubra, R. Wolfe, W.H. Merigan and D.R. Williams. ***IOVS*** *2009;50:1350-1359*

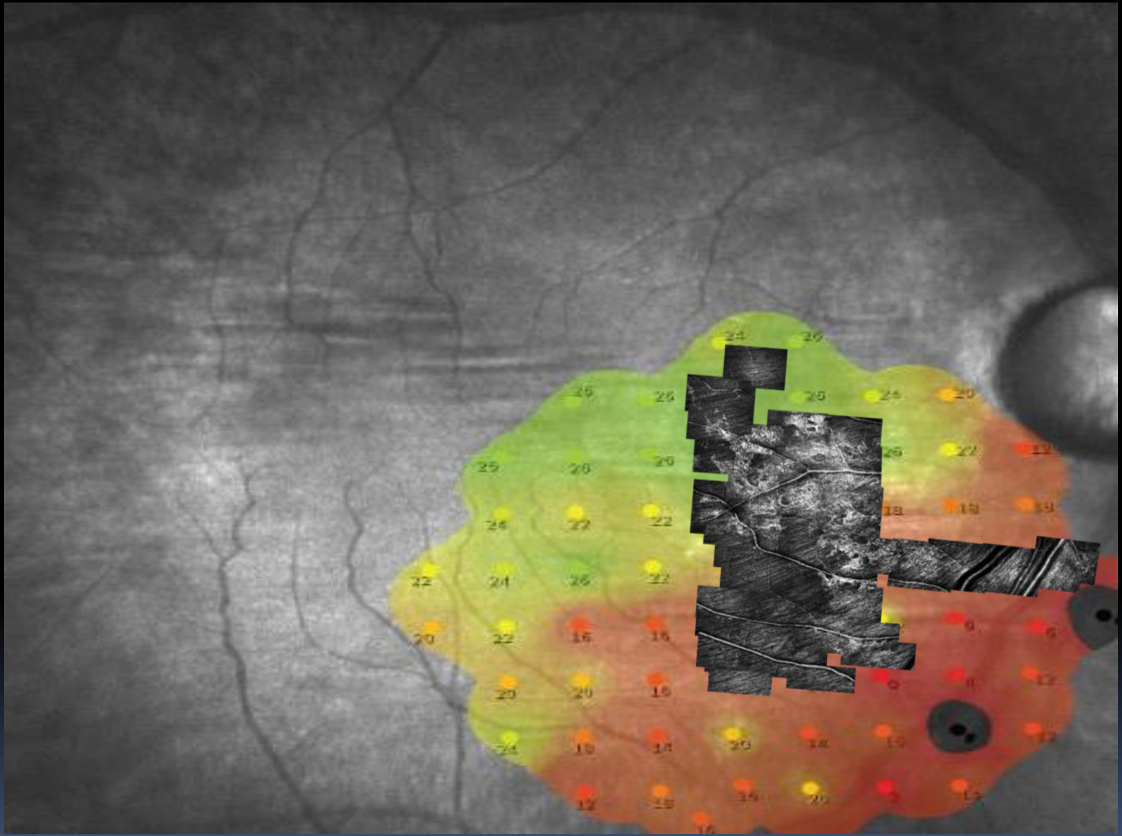
Nerve Fiber Layer



Glaucoma

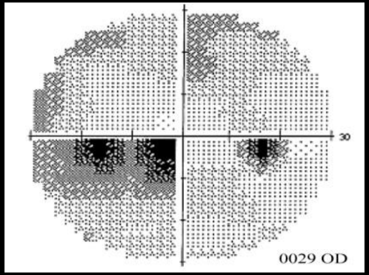


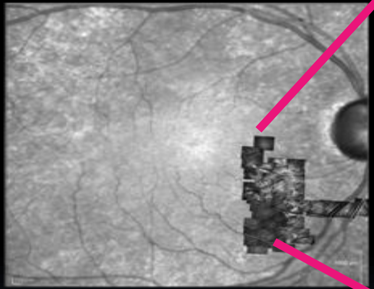
62 y.o. female

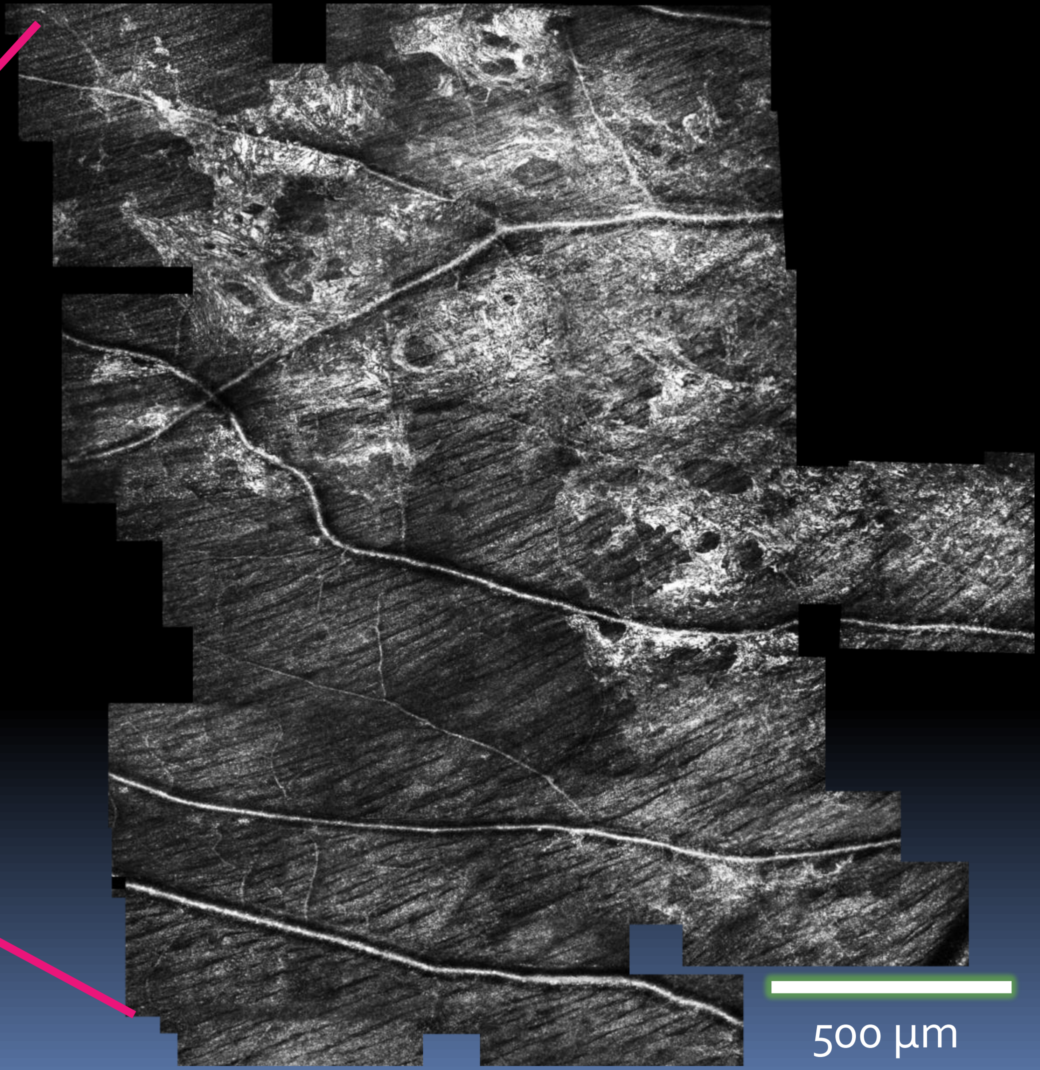


D.H. Scoles, Y.N. Sulai, A.D. Manguikian, S. Shareef and A. Dubra. ***2012 ARVO Meeting Abstract*** *53:6957*

Glaucoma







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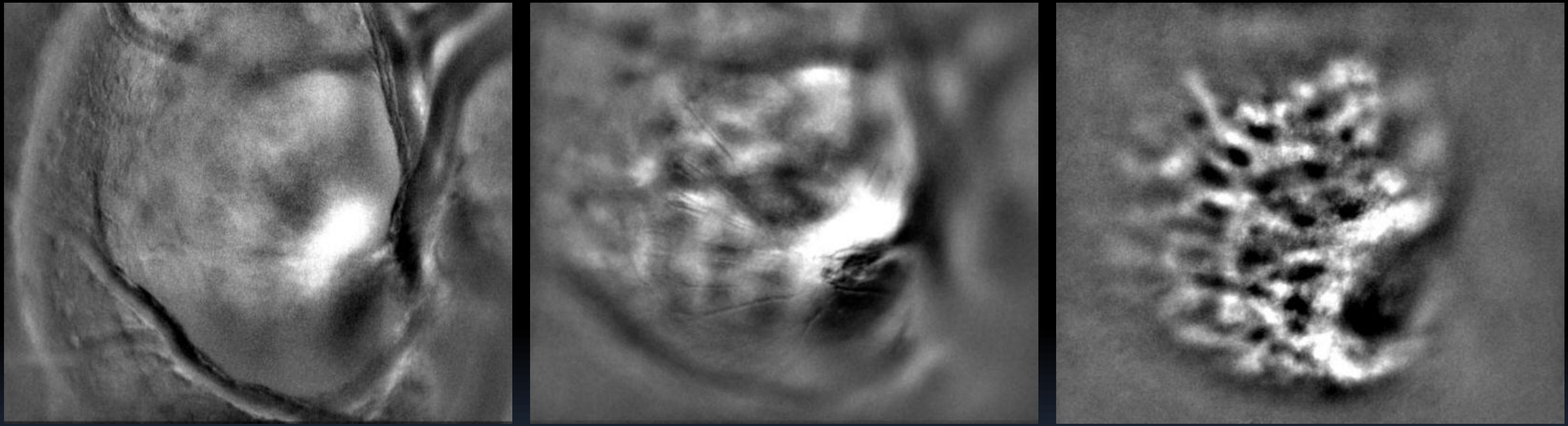
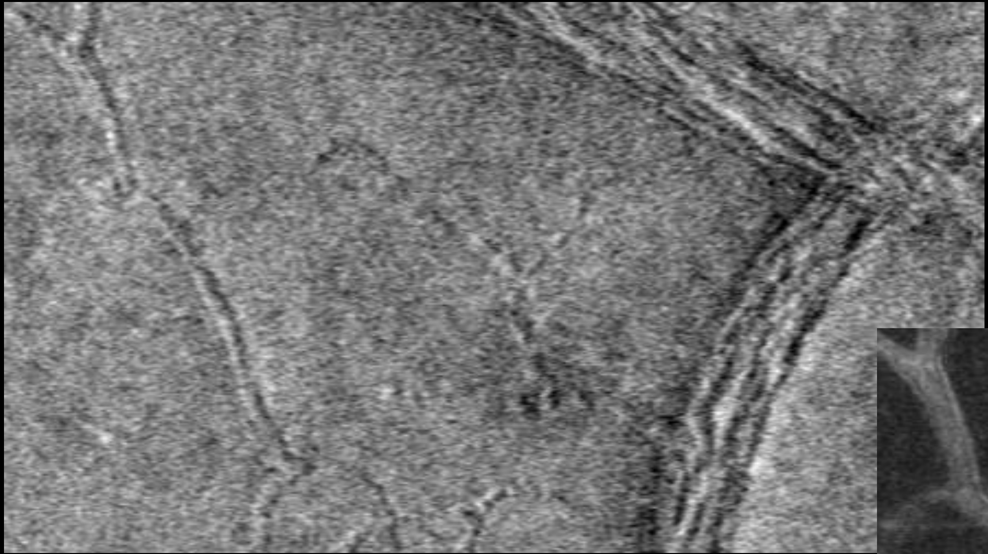
***2012 ARVO Abstract** 53:6957*

Optic Nerve Imaging: Lamina Cribrosa

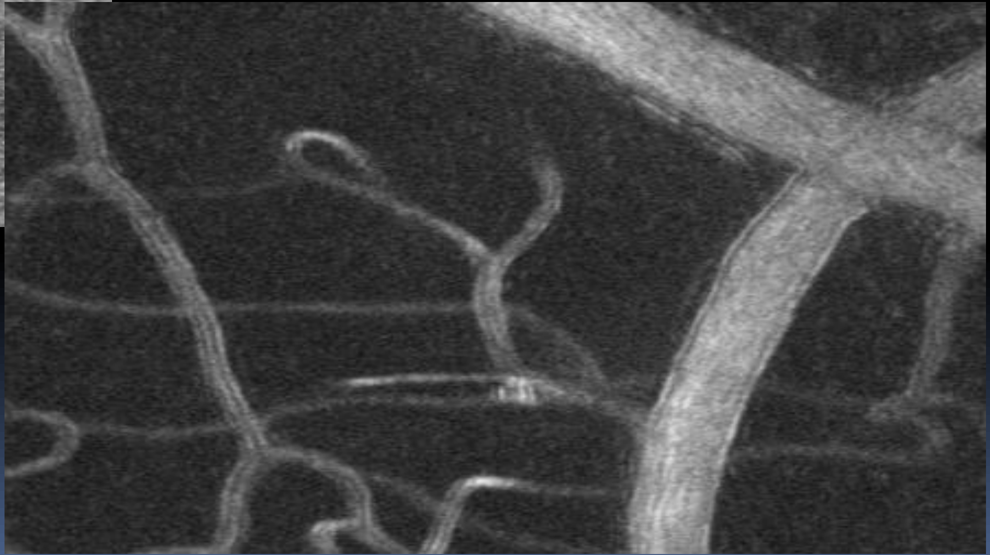


Courtesy: Imagine Eyes

Vascular Imaging and Perfusion Maps:

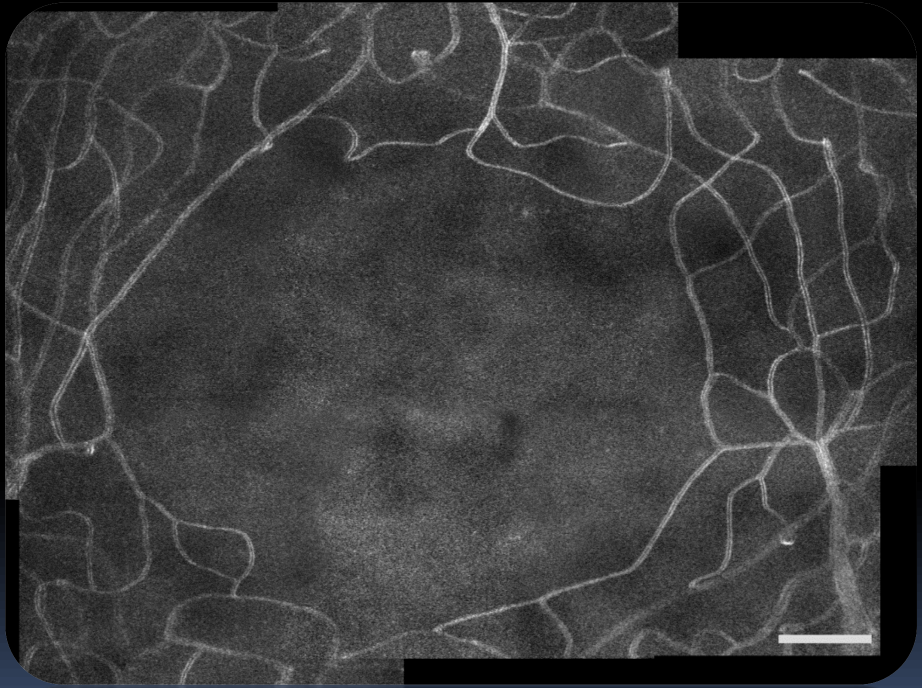


50 µm



Foveal Perfusion Map: Normal Subject

Without Fluorescein Dye



Scale bar: 100 µm

- Despite macular hole (MH) closure following pars plana vitrectomy (PPV) surgery, vision loss or metamorphopsia may persist

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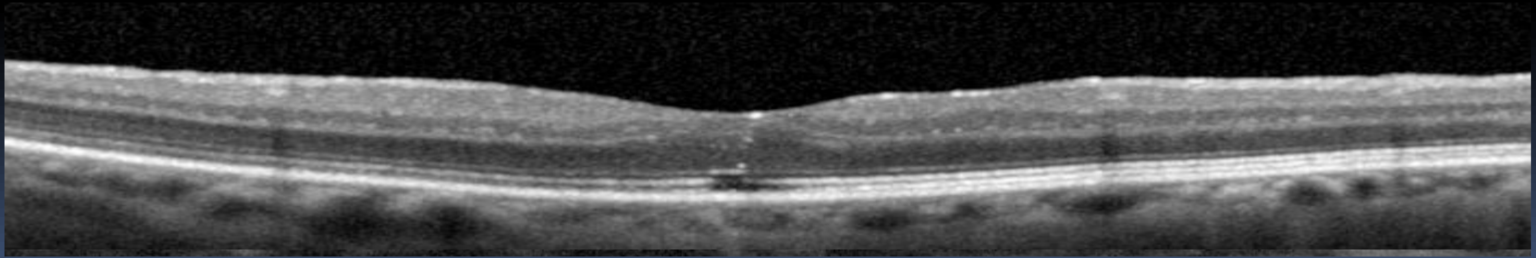
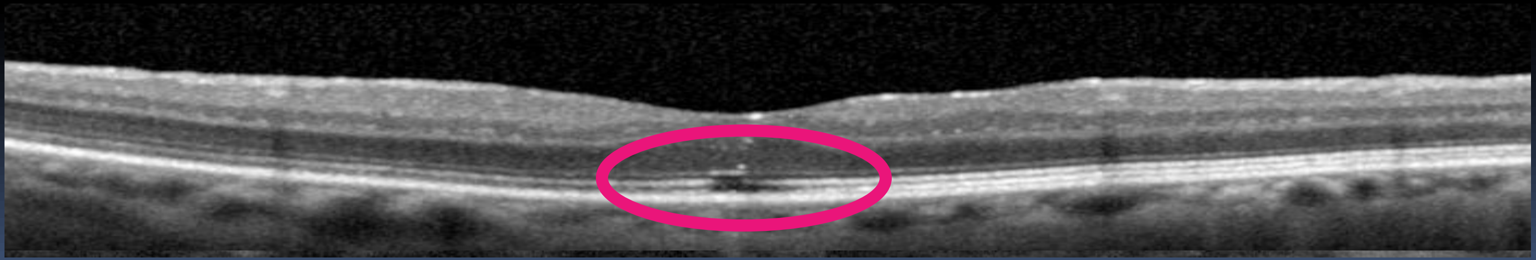


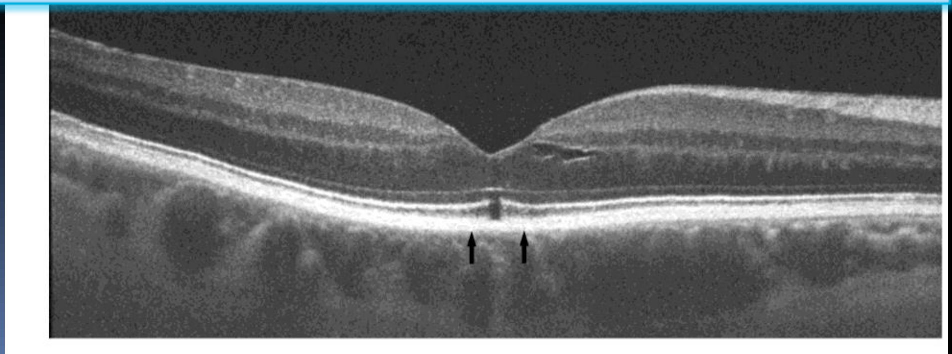
- SD-OCT studies have shown that mild outer segment changes are common in the early post-operative course



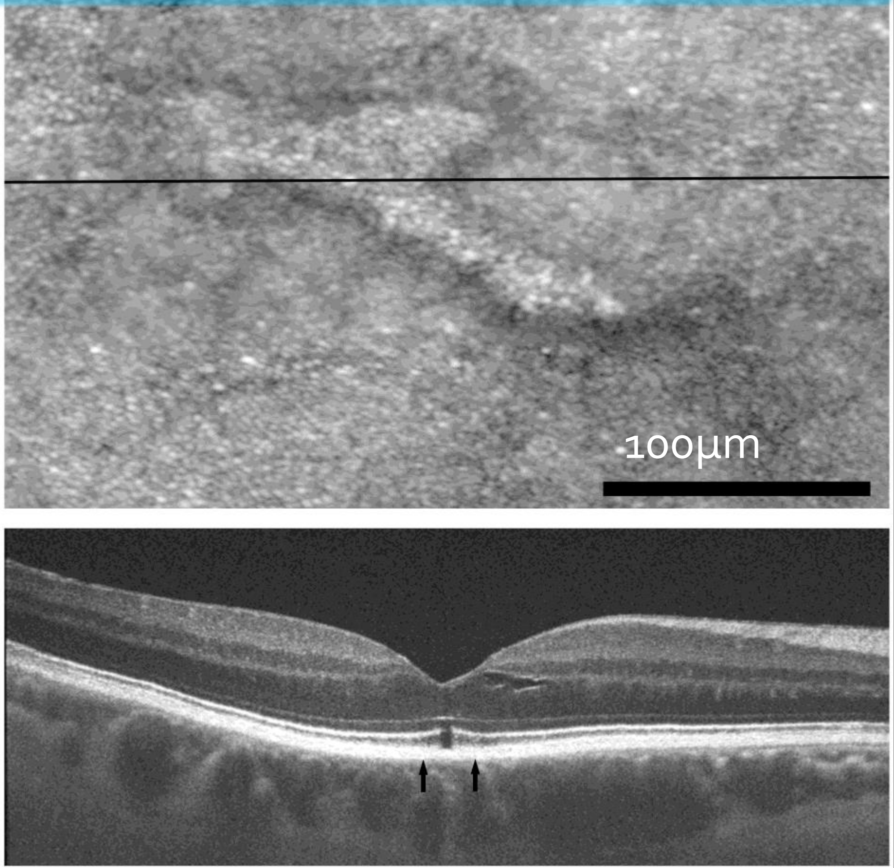
Macular Hole Closure

- What is going on at the photoreceptor layer at the fovea following surgery?
- Why are there differences in VA even when MH is closed?

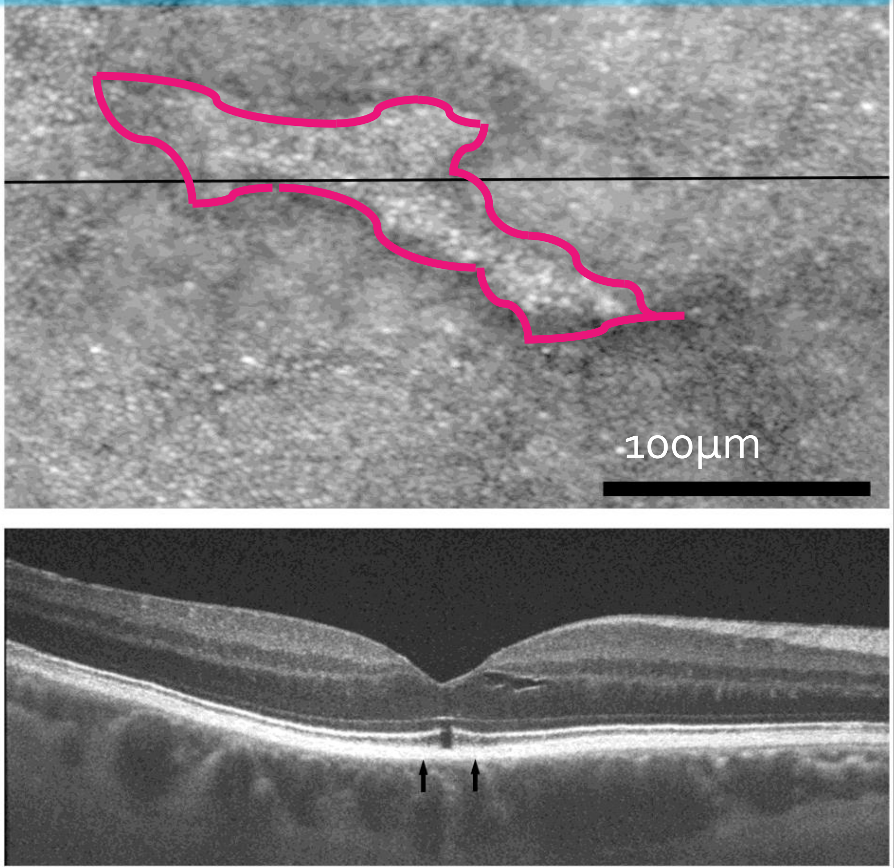
Case 1: 3 months post-op
VA $20/50^{-2}$



Case 1: 3 months post-op VA 20/50^{-2}



Case 1: 3 months post-op VA $20/50^{-2}$



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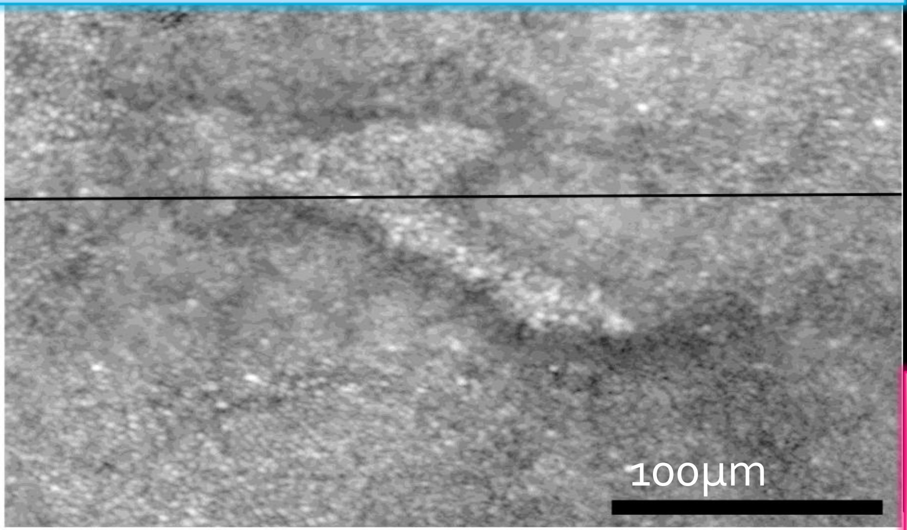
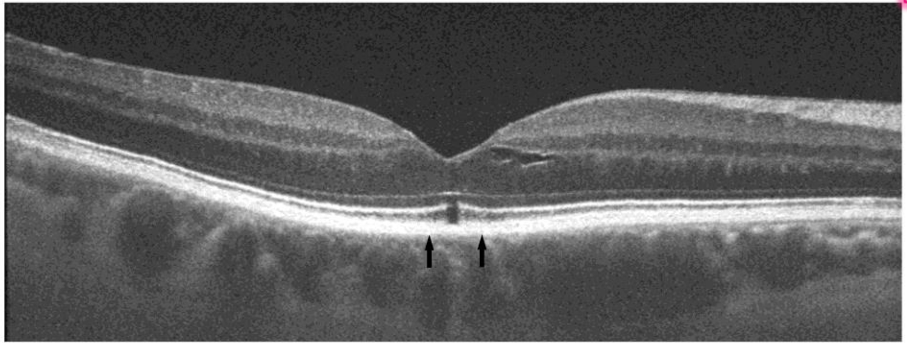
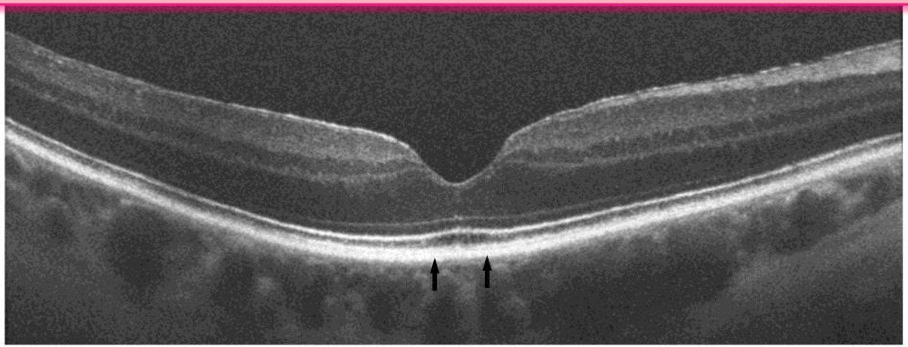




17 months post-op VA $20/30^{-2}$



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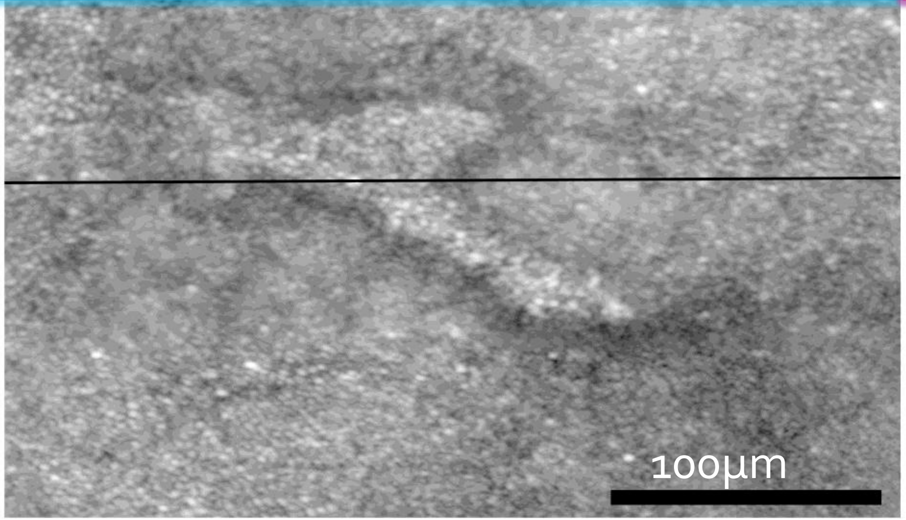

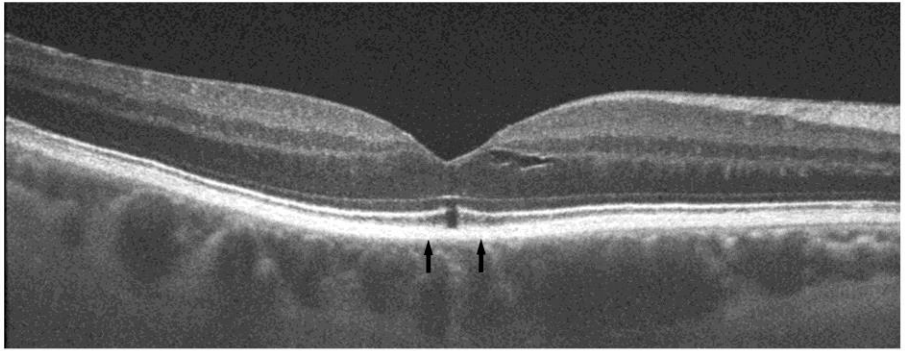

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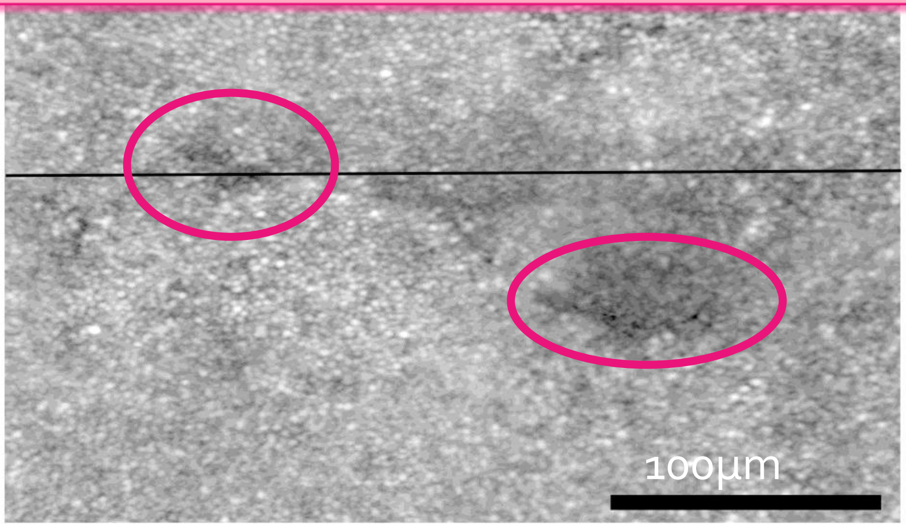
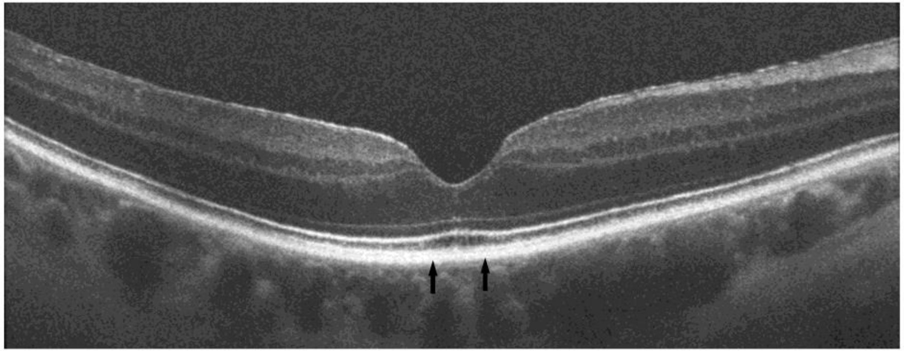
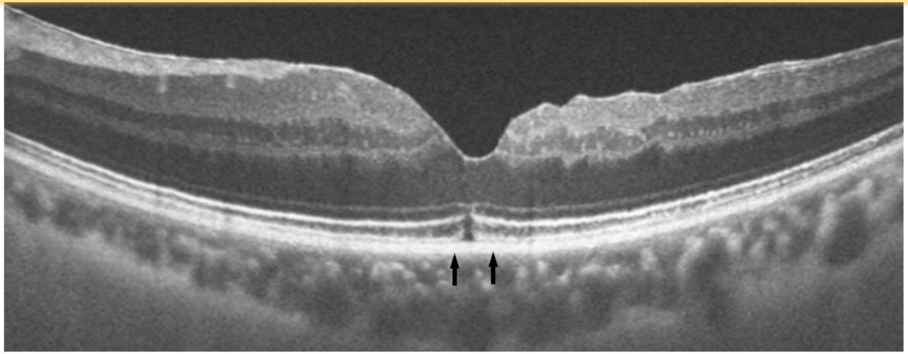




Case 2: 3 months post-op
VA 20/80



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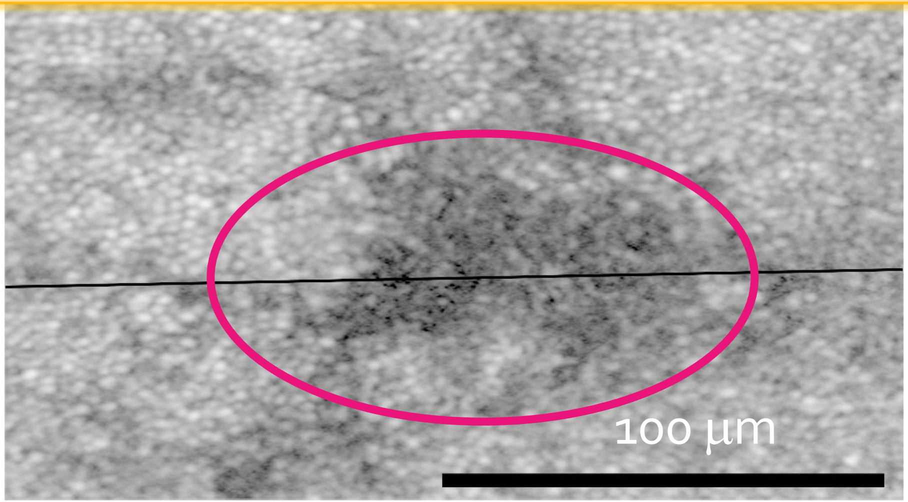
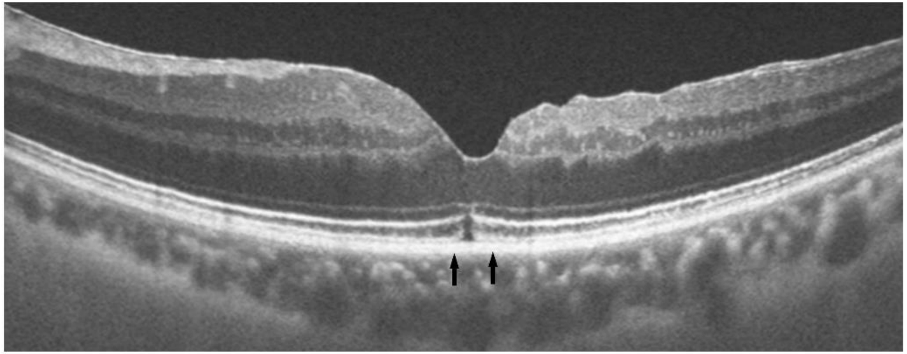
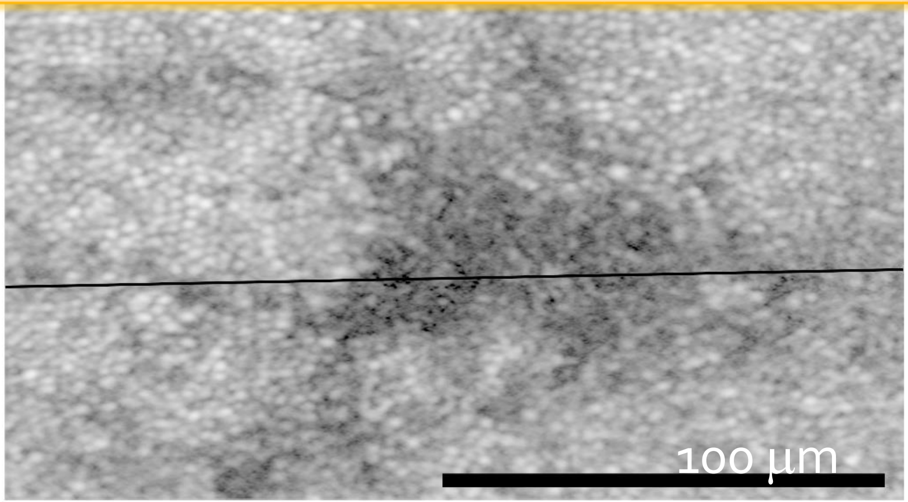
VA 20/80

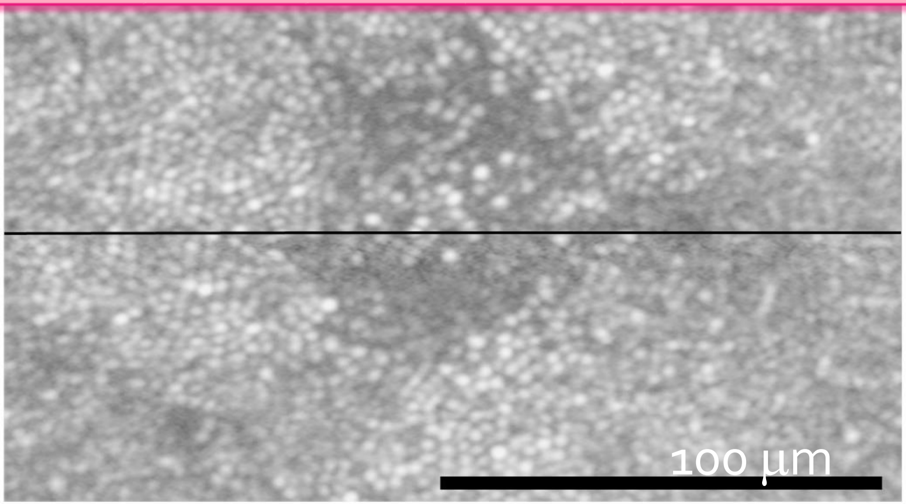


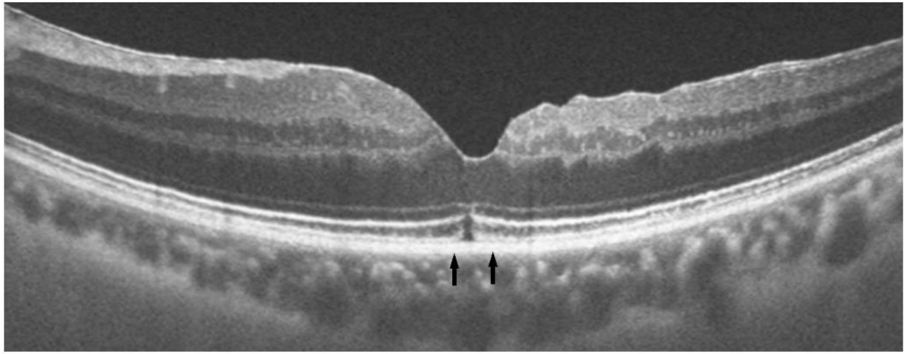


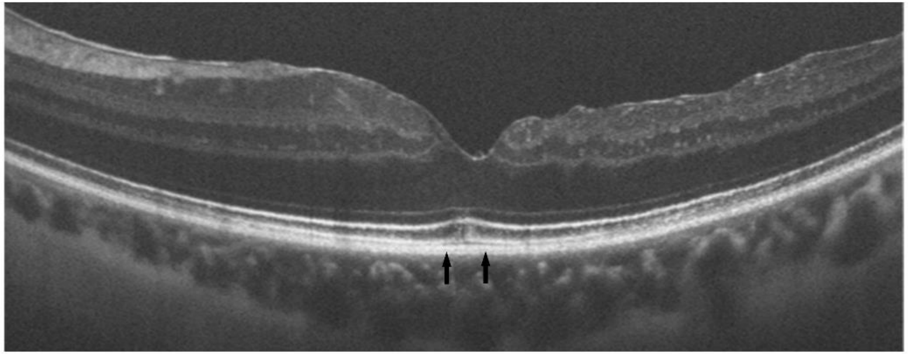
Case 2: 3 months post-op
VA 20/80

12 months post-op
VA 20/30



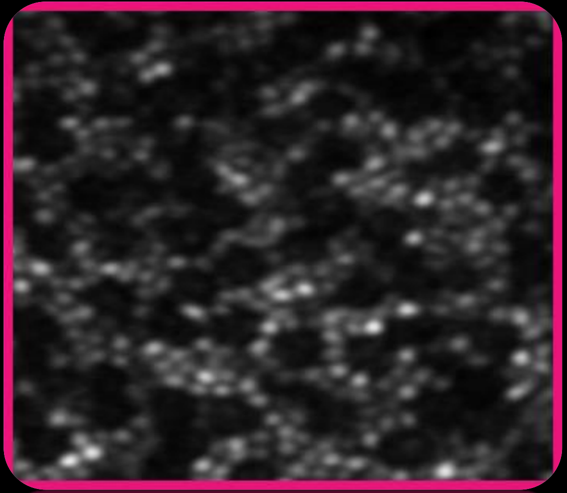






- Significant photoreceptor disruption appears to exist following MH closure
- Remodeling of the foveal cone mosaic can continue following surgery, perhaps accounting for the delayed post-operative VA improvements

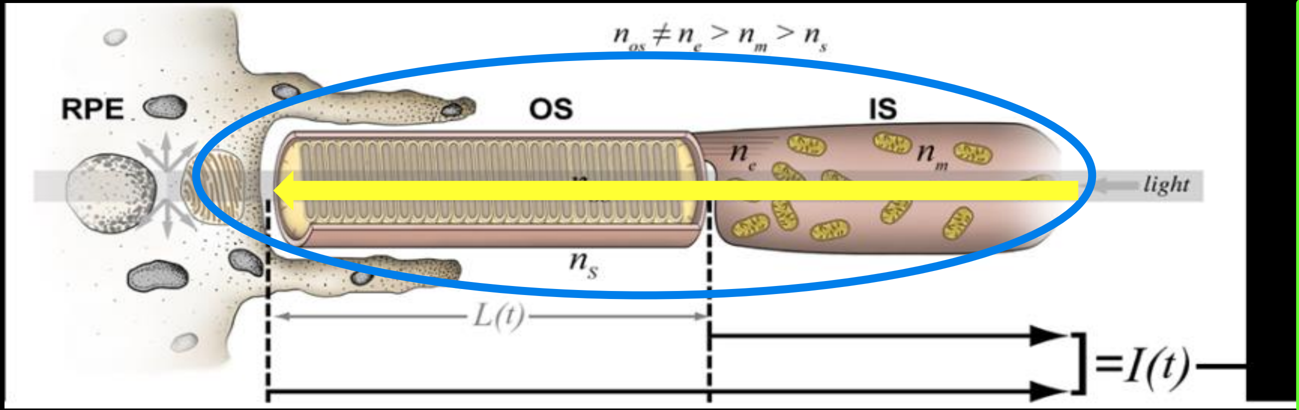
“Dark Cones”

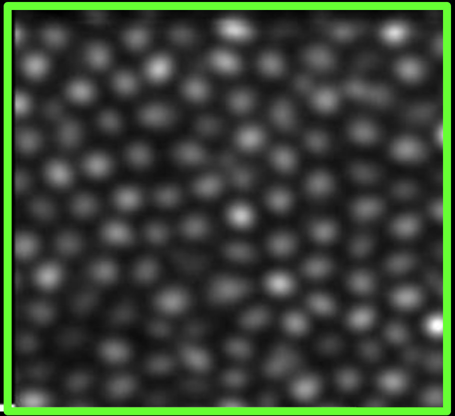


Cones present
but not wave-guiding

Cones are absent

AO SLO Imaging of Photoreceptors





Visualization of cone structure with confocal AOSLO relies on IS/OS alignment and intact outer segment structure

Scoles D, et al., In vivo imaging of human cone photoreceptor inner segments, IOVS 2014:6;55(7):4244-51

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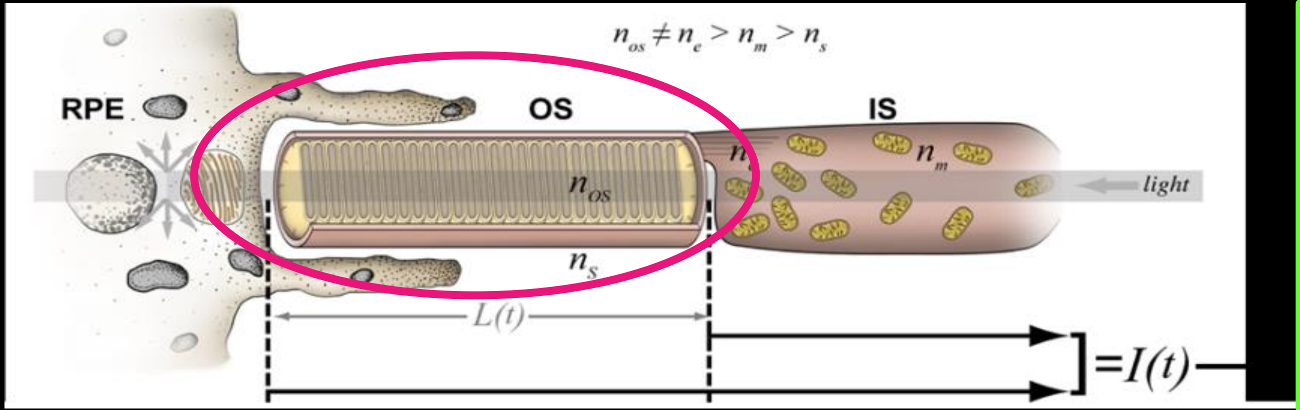

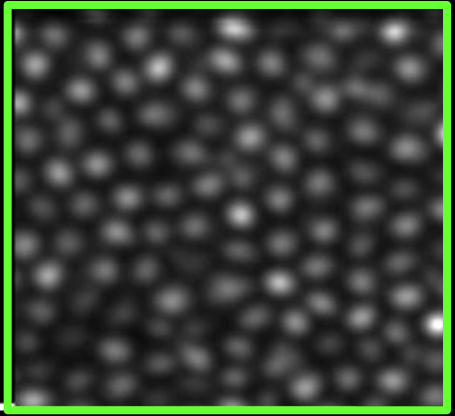

Visualization of cone structure with confocal AOSLO relies on IS/OS alignment and intact outer segment structure

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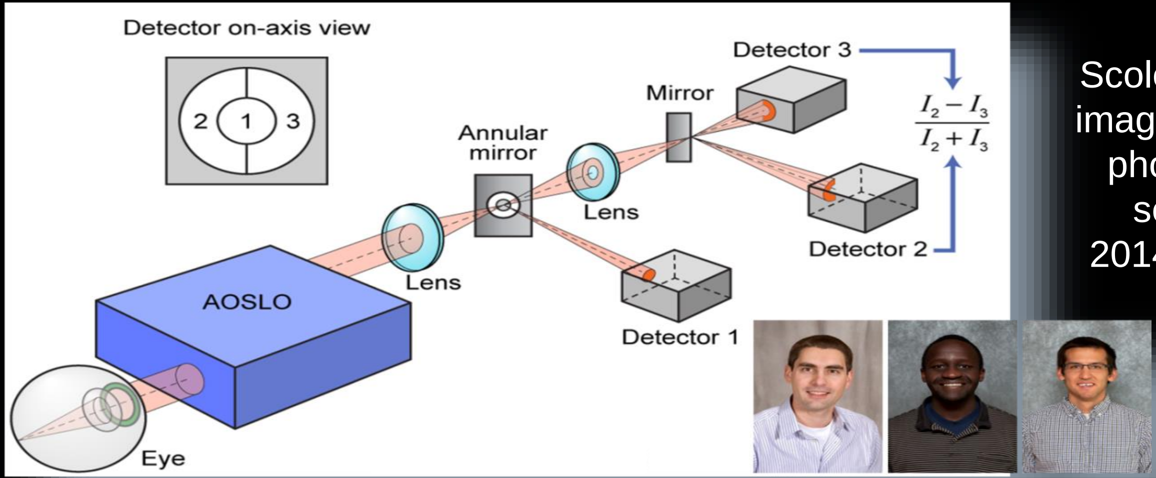
Split Detector AOSLO

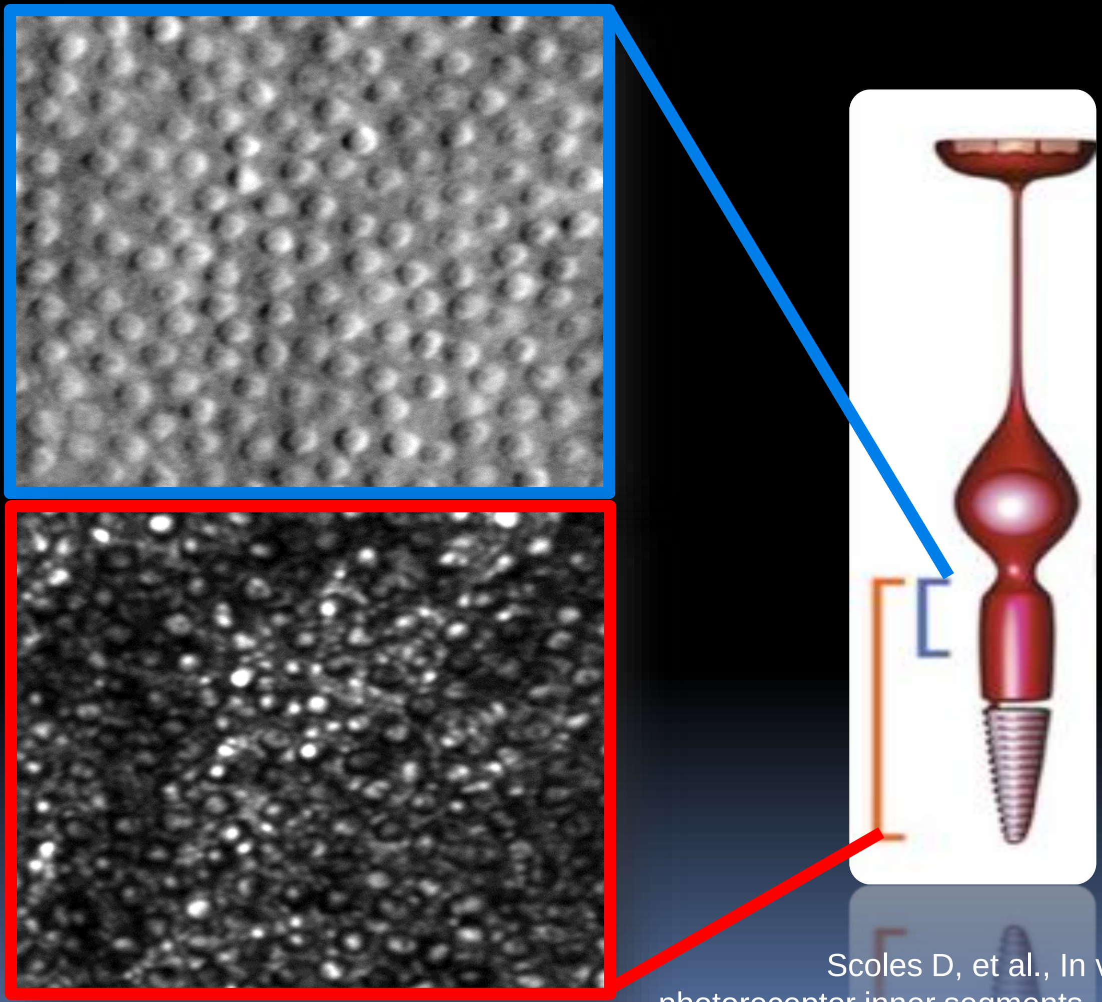


Scoles D, et al., In vivo imaging of human cone photoreceptor inner segments, IOVS 2014:6;55(7):4244-51

- Captures the non-confocal light and divides it spatially
- Creates good contrast for structures that scatter light
  - Blood vessels
  - Rounded pole of photoreceptor inner segments

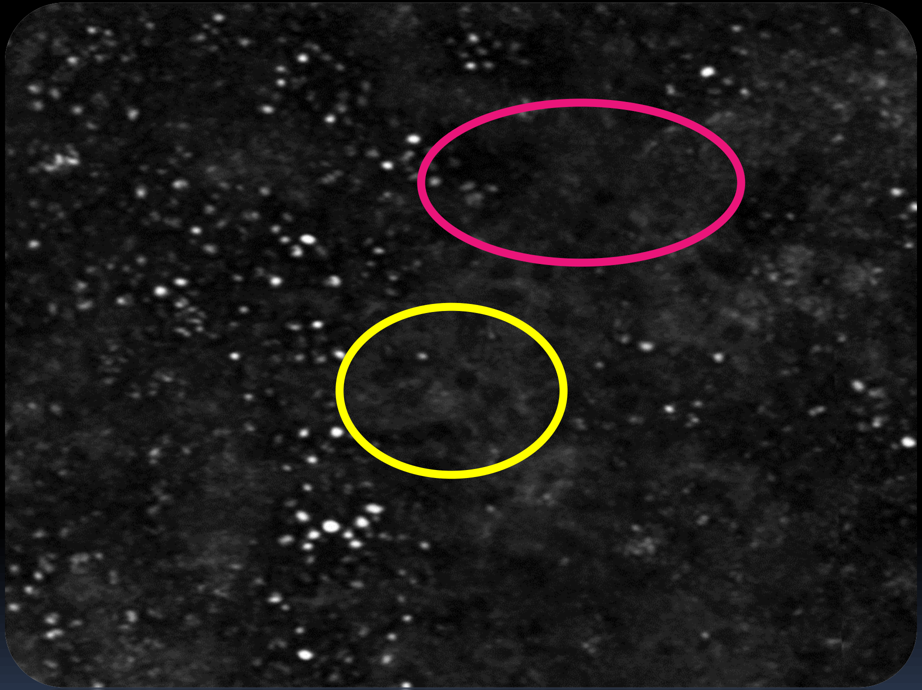
Split Detector
AOSLO

Confocal
AOSLO

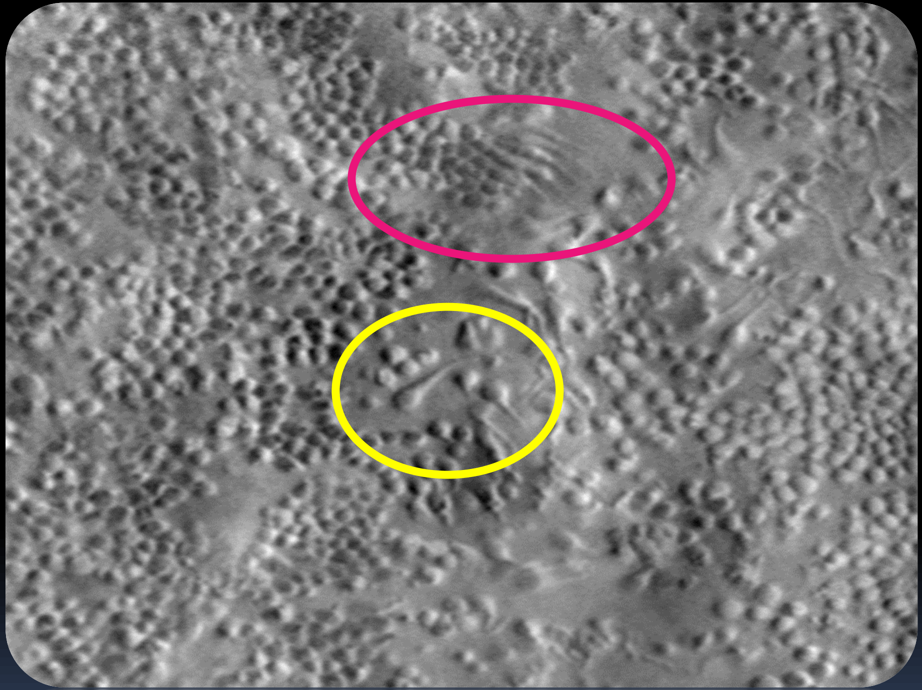


Scoles D, et al., In vivo imaging of human cone photoreceptor inner segments, IOVS 2014:6;55(7):4244-51

Confocal AO



Split detector AO



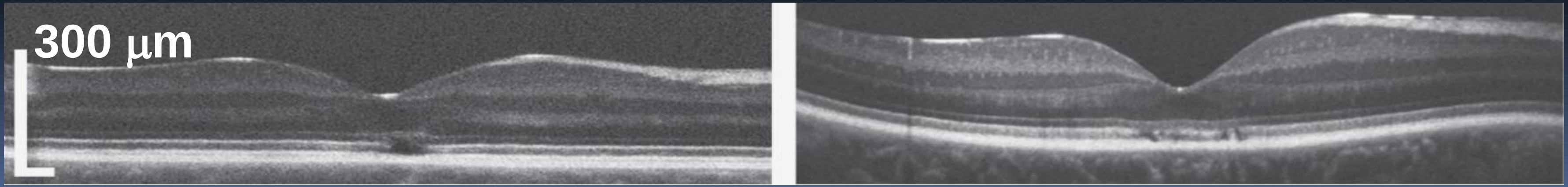
100 µm

Scoles *et al*. (submitted)

Variable Foveal Cone Structure in *Achromatopsia*

CNGB3
c.1148 delC: p.Thr383fs
c.983T>A: p.Met328Lys

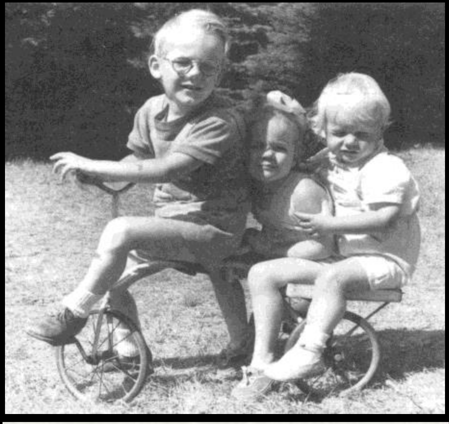
CNGB3
c.1148 delC: p.Thr383fs
c.1255G>T: p.Glu419stop

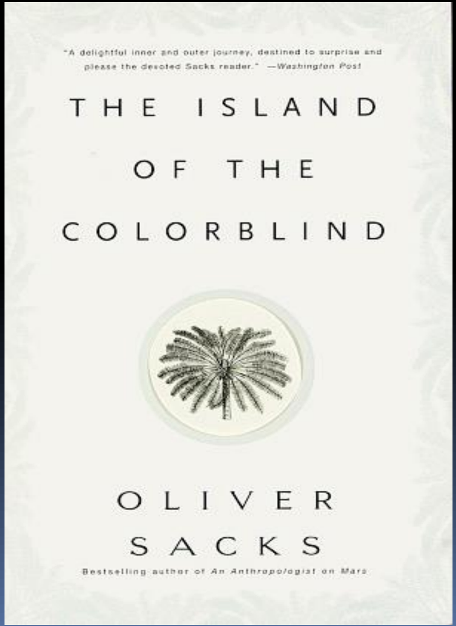


Achromatopsia (ACHM)

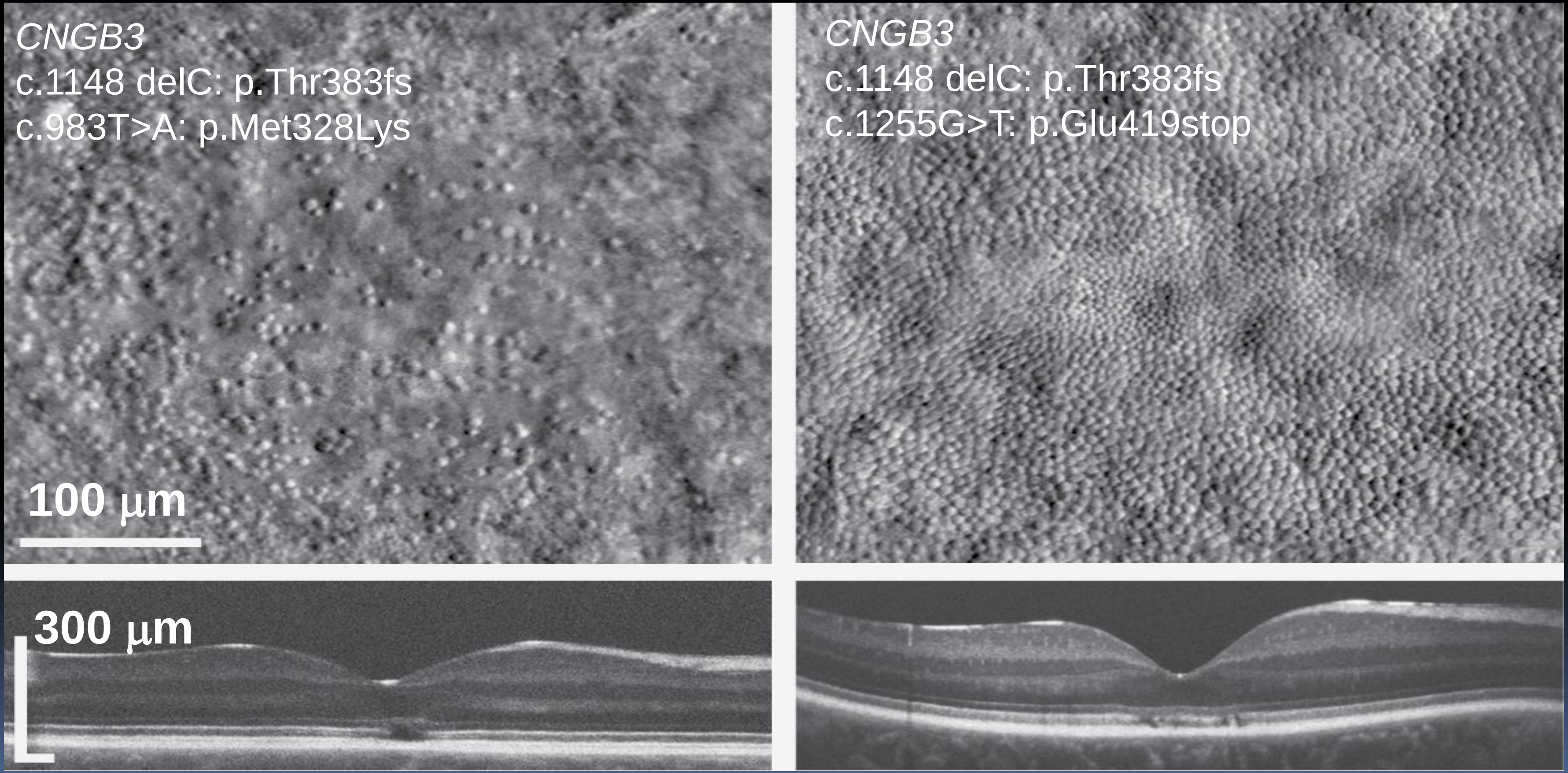
Autosomal recessive; ≈1 in 33,000 incidence

- Caused by defects in *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H, or ATF6*
- Affected individuals are thought to have no cone function (though see Nishiguchi, *et al*., 2005)
- Photophobia, reduced acuity, nystagmus
- Histological data concerning remnant cone structure is variable, ranging from normal numbers in the fovea (Falls *et al*., 1965) to reduced numbers throughout (Larsen, 1921)





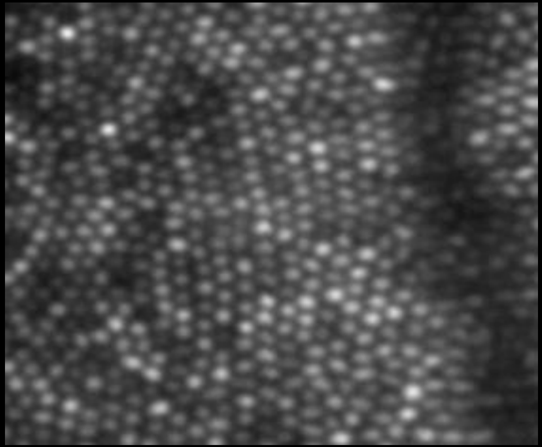
Variable Foveal Cone Structure in Achromatopsia



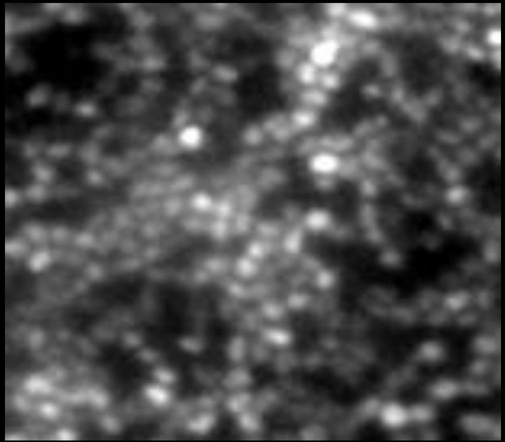
- Recent success in retinal gene therapy
- May be possible to restore cone function in some retinal disorders

"…identifying and then targeting retinal locations with retained photoreceptors will be a prerequisite for successful gene therapy in humans…" Jacobson *et al.* (2005)

Why is AO needed?



20/20



20/20

- Necessary to detect photoreceptor loss early
- Assist in selection of candidates for therapies
- Earlier detection of treatment effect

AO Imaging

- Assist in better understanding of photoreceptor structure and vessels
- Allow assessment of the therapeutic potential and outcomes in patients with retinal disorders