Session 1

Potential primary visual functional endpoints for GA pivotal trials:

microperimetry, reading speed

Primer on human macular neuroanatomy

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University of Alabama at Birmingham

http://projectmacula

ALSTAR2
Alabama Study on Early Age-Related Macular Degeneration

Support

- National Eye Institute: R01EY029595, P30EY03039, R01EY027948
- Institutional: Research to Prevent Blindness, Inc; EyeSight Foundation of Alabama
- Private: Dorsett Davis Discovery Fund; Anonymous donor
- Past: R01EY06109, R01EY024378, R01028282; RPB AMD Catalyst; Thome Foundation, International retinal Research Foundation, Macula Society, Macula Foundation (NY); NEI P30 EY003039; Genentech

Disclosures

- Research support: Heidelberg Engineering, Genentech/ Roche
- Consult: Osanni, Genentech/ Roche, Boehringer-Ingelheim, Annexon, Mobius, Ripple, Sparing Vision, Roche, Heidelberg Engineering, Octant, Merck, Espansione, Sanofi, Topcon

Takeaway messages

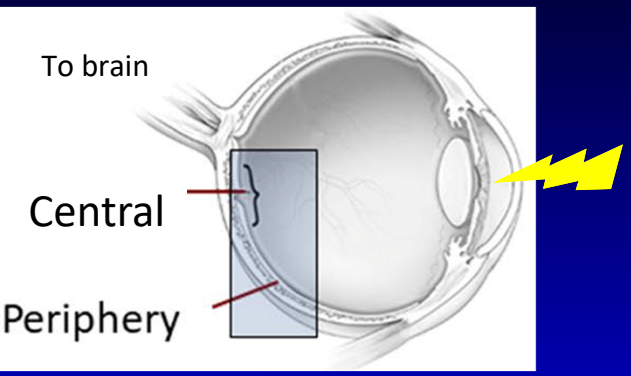
- AMD pathophysiology can be approached in the context of human retinal neuroanatomy
- The outer retina (photoreceptors, RPE) are a light-sensing chip – an engineering marvel
- Human fovea has high dynamic range of cell densities, unique to central neurodegenerations
- For trial outcome measures and functional vision - precision, precision, precision

Age-Related Macular Degeneration, a Mathematically Tractable Disease

2024 IOVS 65: 4

Christine A. Curcio,[1] Deepayan Kar,[1,*] Cynthia Owsley,[1] Kenneth R. Sloan,[1] and Thomas Ach[2]

Human central retina (area centralis), fovea, macula lutea



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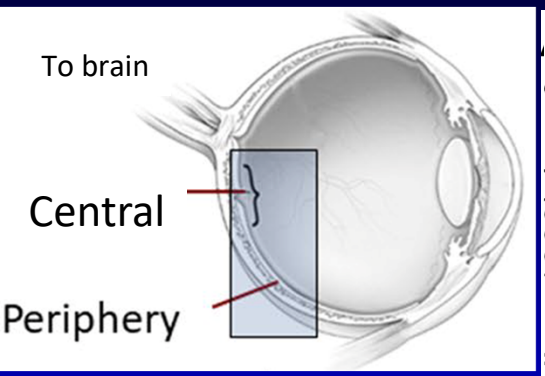

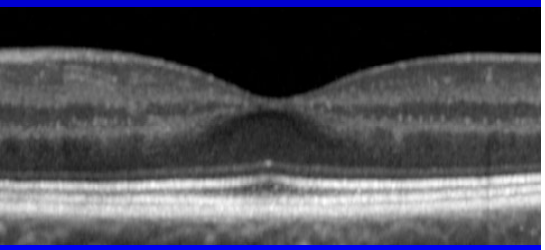

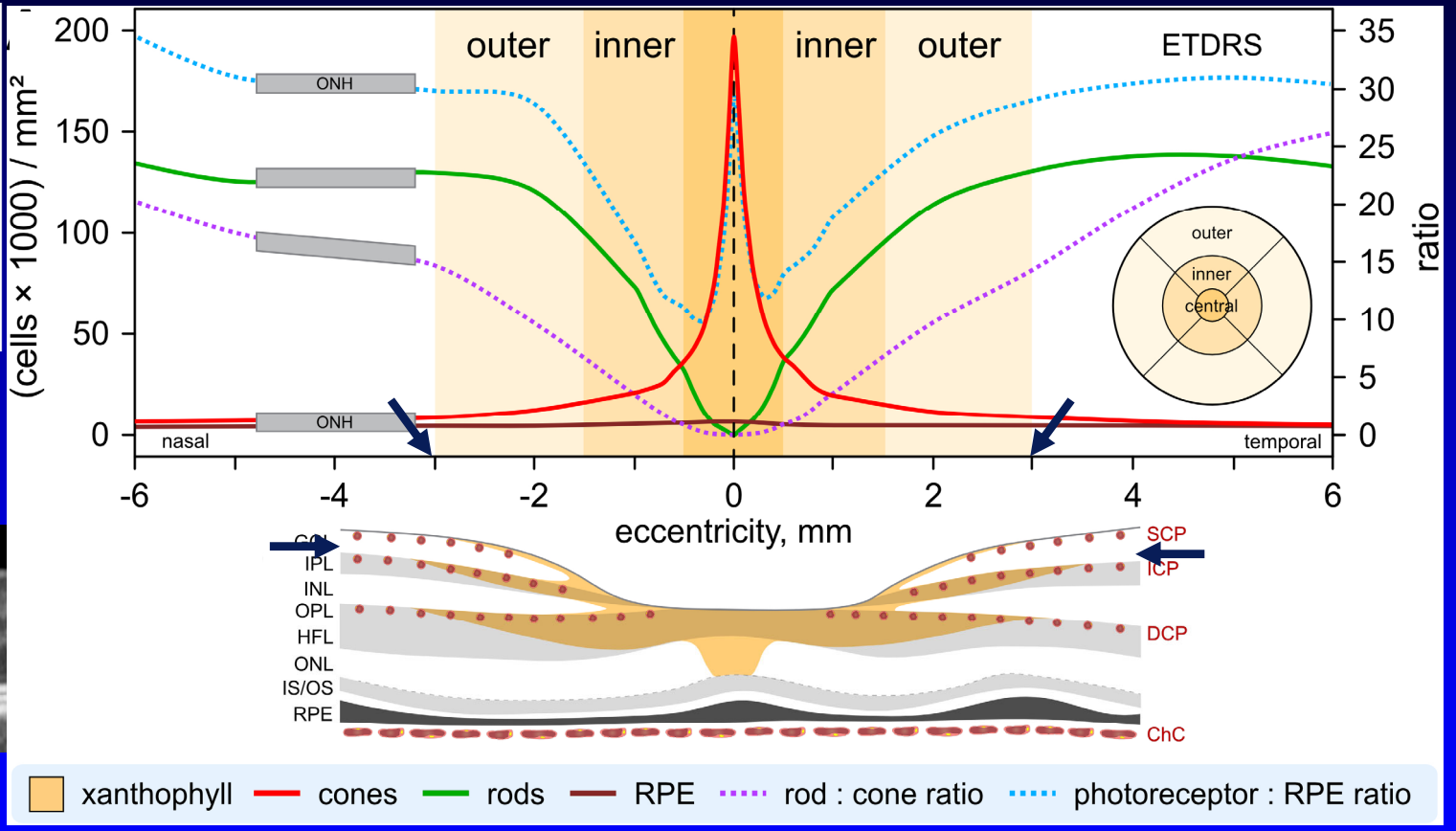

Curcio, Kar, Owsley, Sloan, Ach, 2024, IOVS 65:4

Photoreceptors: Curcio … Hendrickson, 1990; J Comp Neurol 292: 497;
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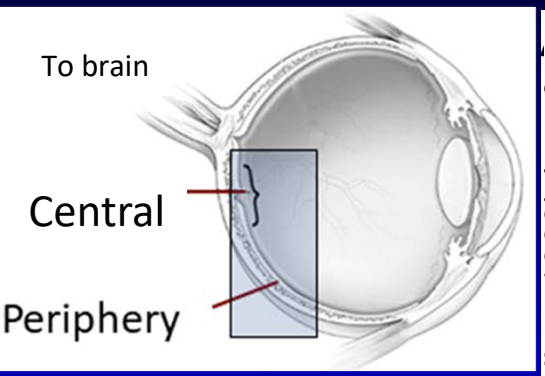

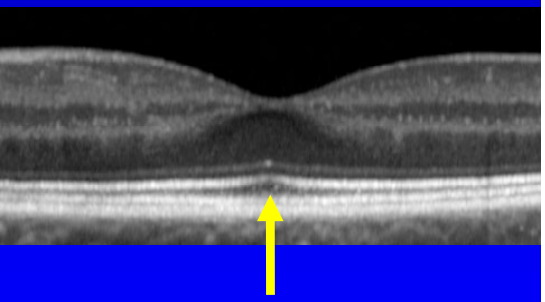

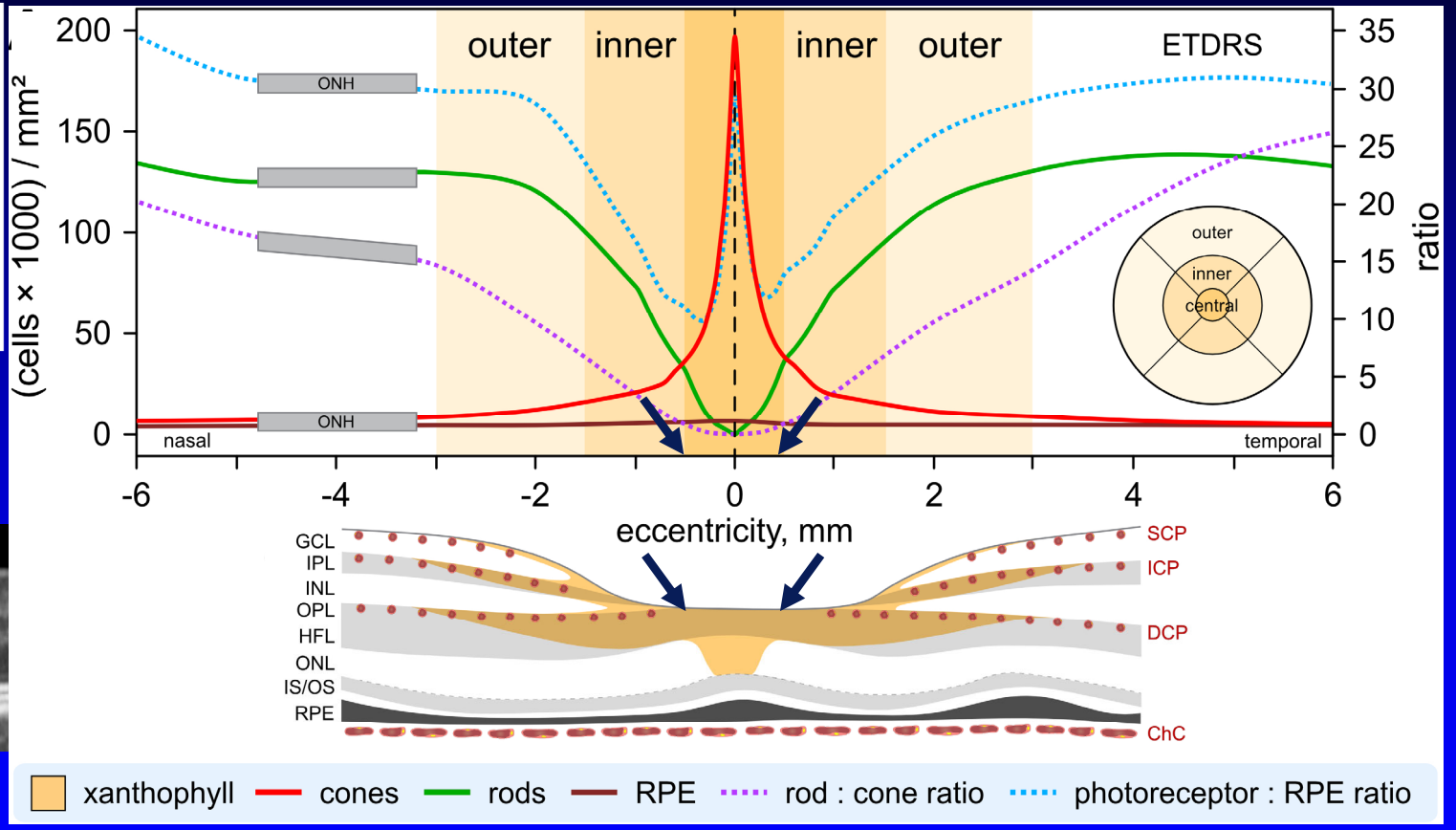

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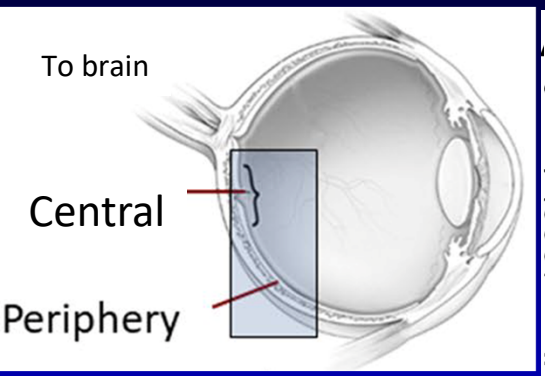

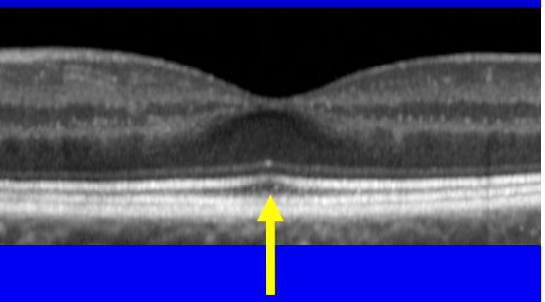

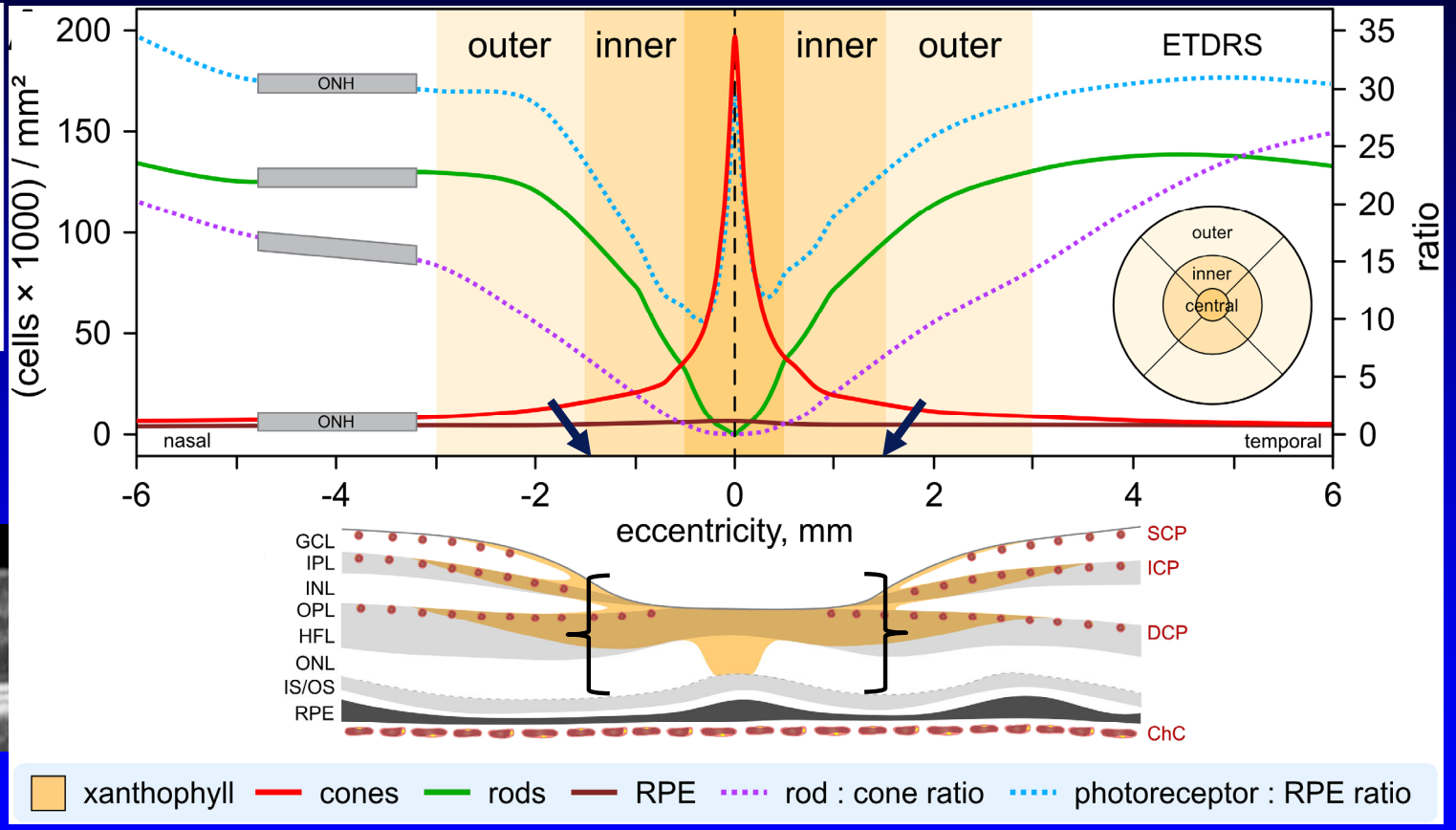

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Photoreceptors + RPE – sensing chip of brain, visible *in vivo,* sculpted by evolution

Curcio, Kar, Owsley, Sloan, Ach; 2024, IOVS 65:4

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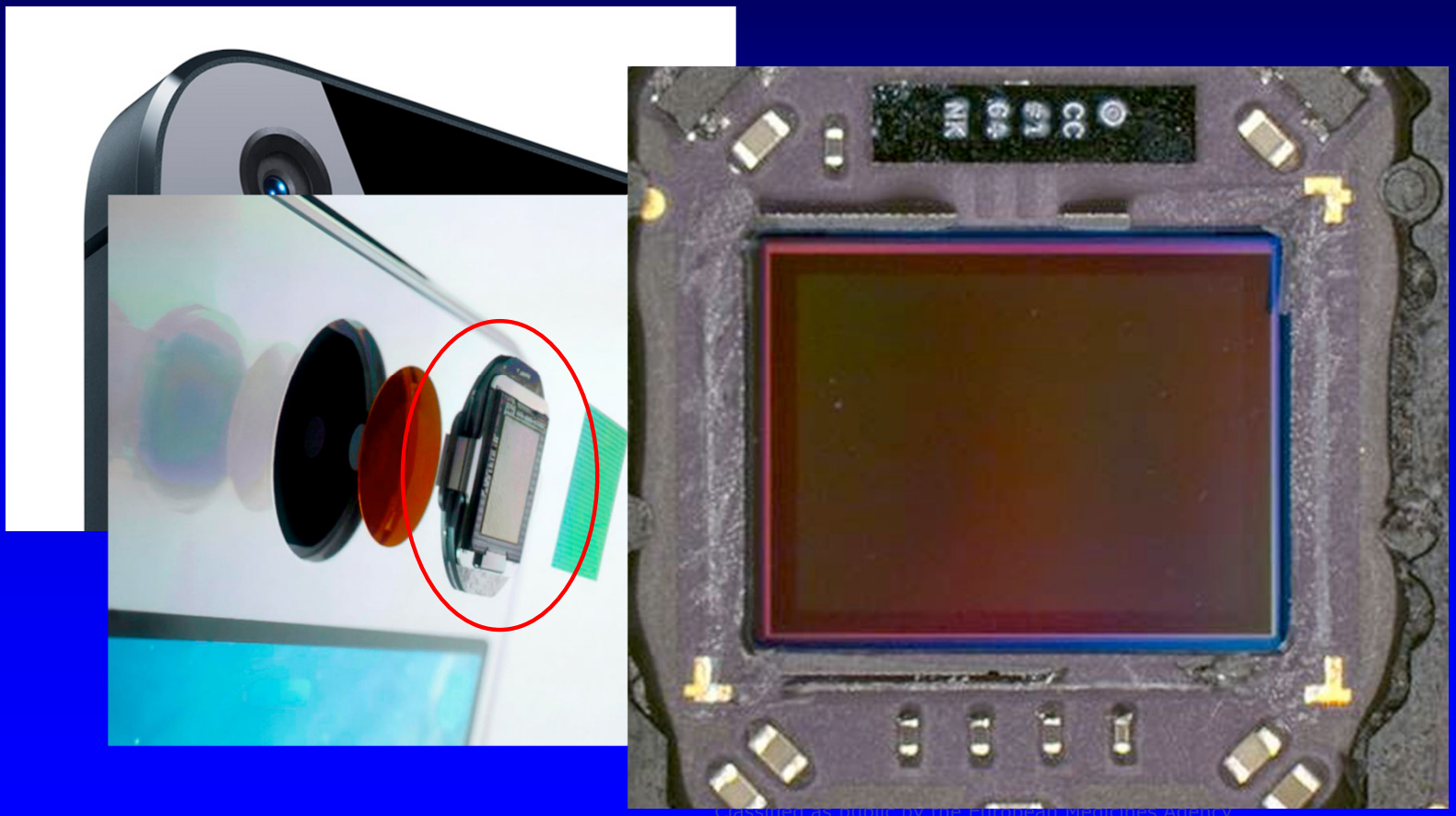

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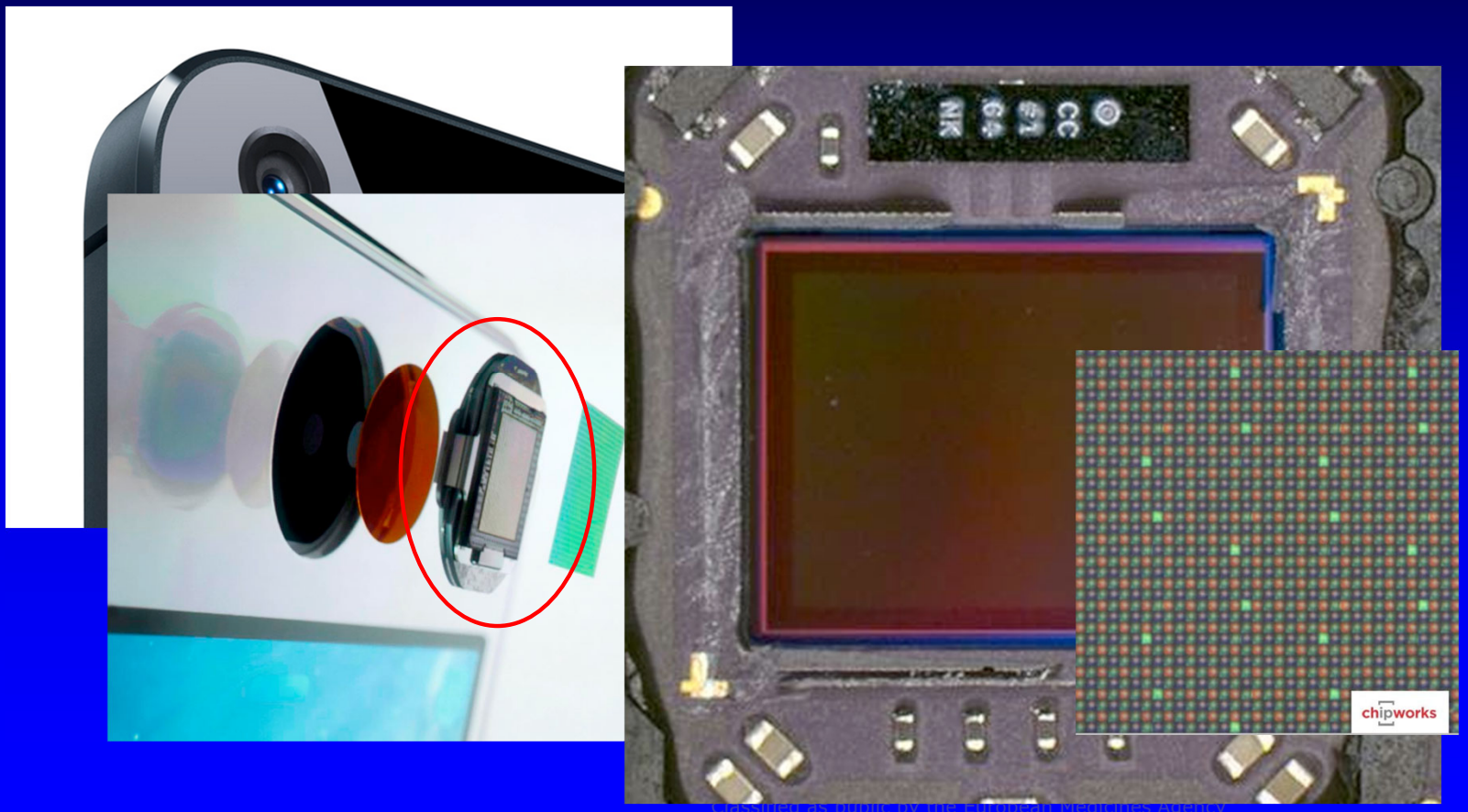

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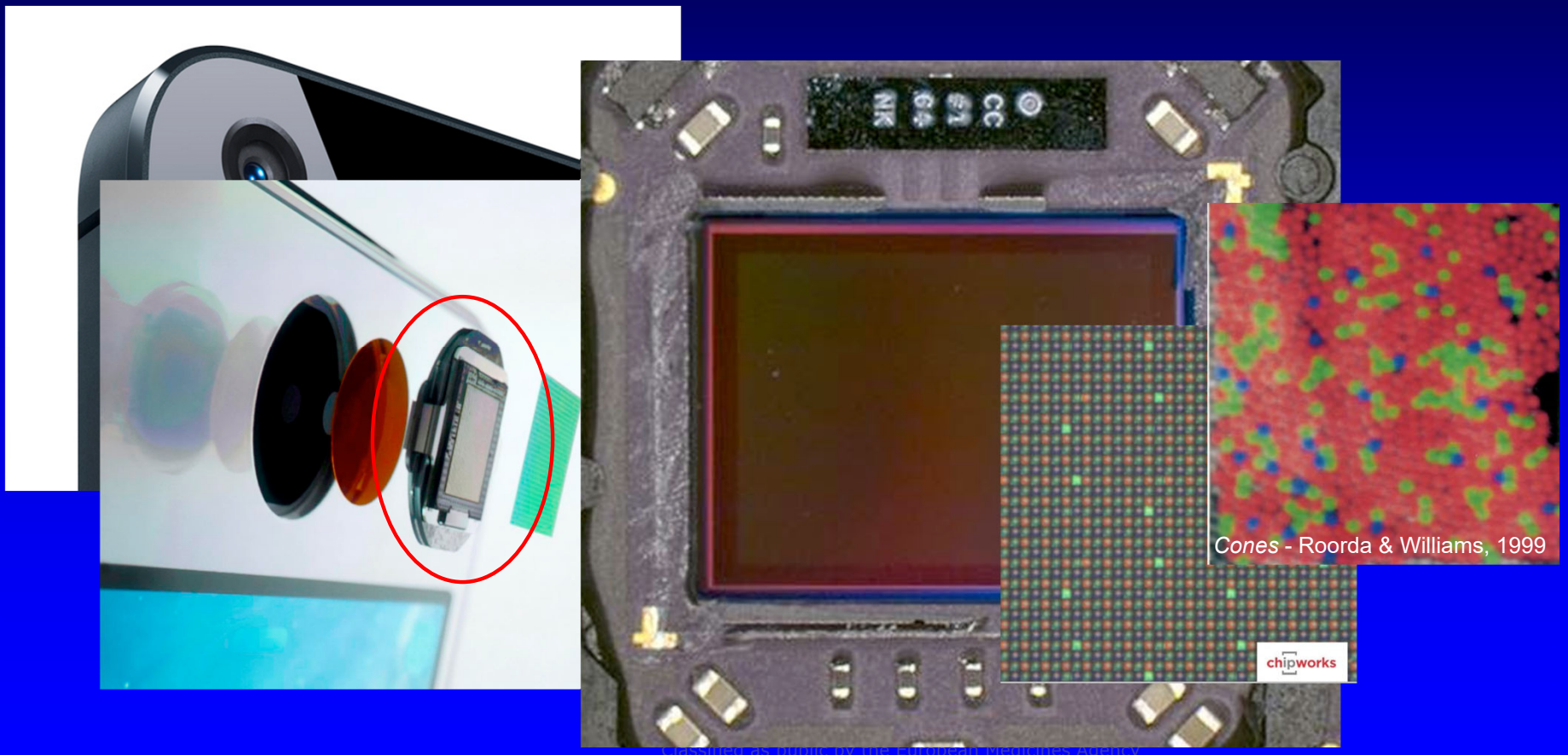

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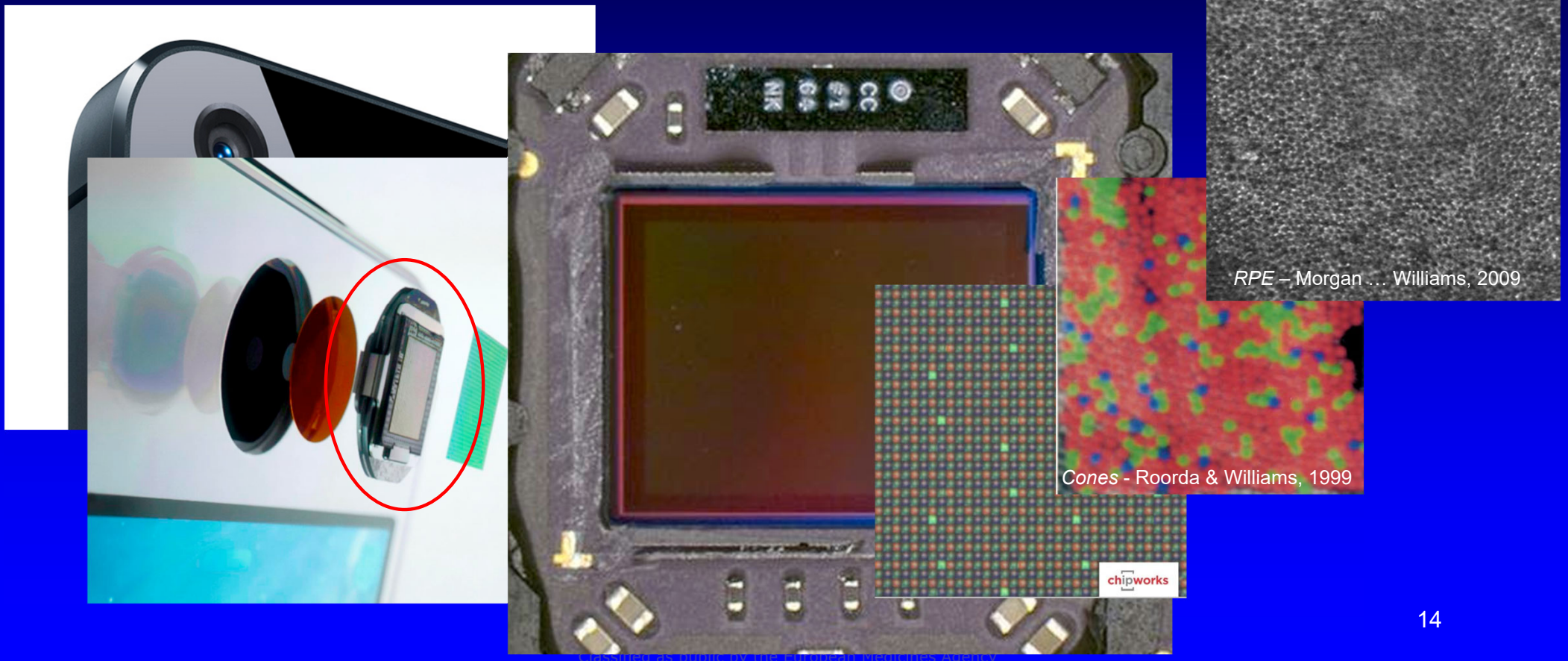
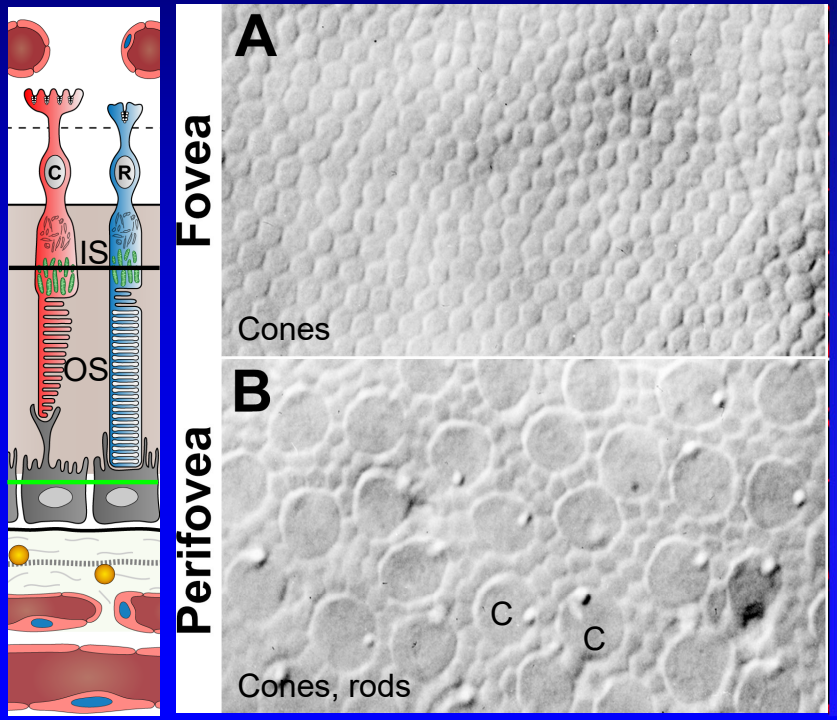


Cells of the brain's sensing chip, by microscopy

Curcio, Kar, Owsley, Sloan, Ach; 2024, IOVS 65:4

Inner segments

Differential interference contrast



originals (aged normal donors): Curcio, Medeiros, Millican, 1996. IOVS. 37: 1236; Ach … Sloan, Curcio, 2014. IOVS 55: 4832.

Cells of the brain's sensing chip, by microscopy

Curcio, Kar, Owsley, Sloan, Ach; 2024, IOVS 65:4

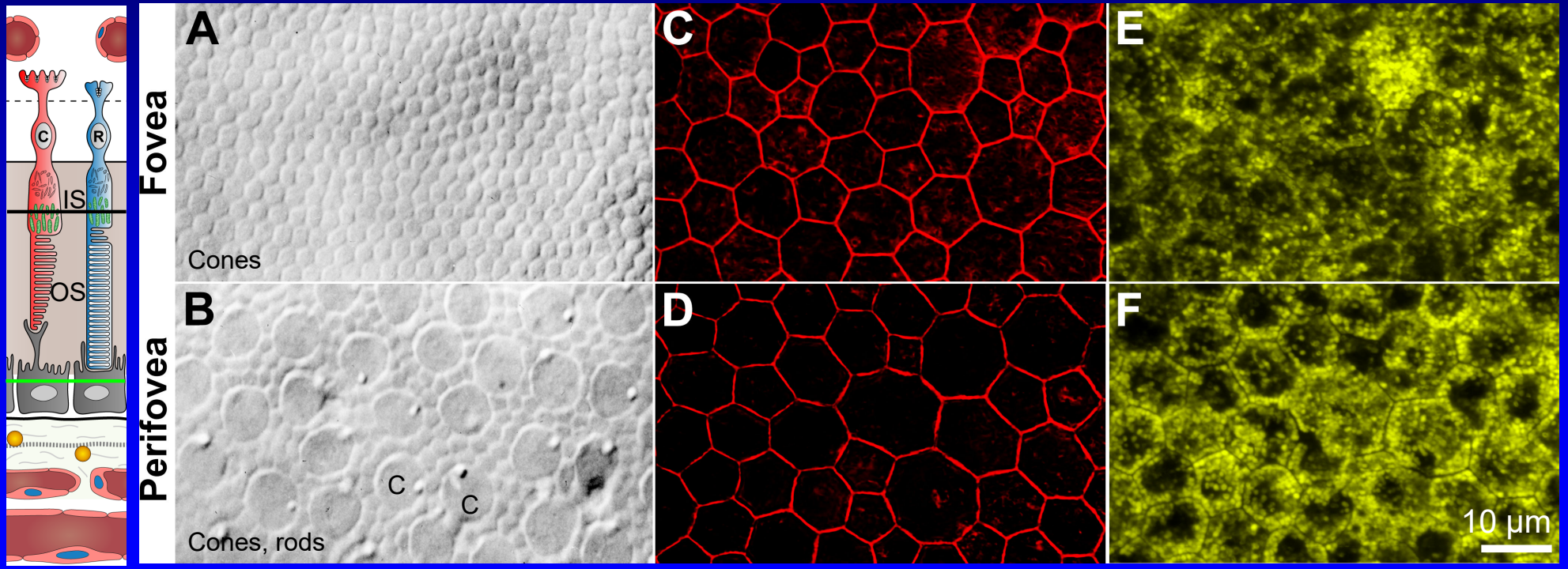
Inner segments

Retinal pigment epithelium

Differential interference contrast

Phalloidin bound actin cytoskeleton

Autofluorescence, λ_{ex} = 488 nm



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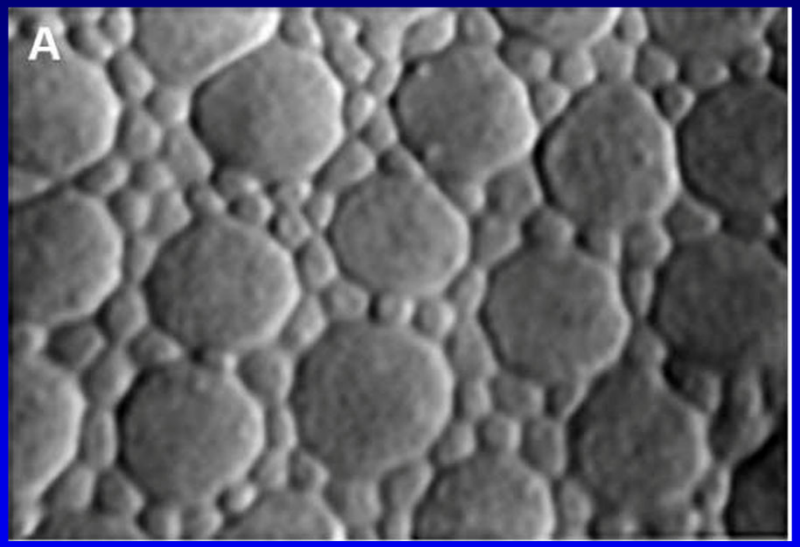
Photoreceptor mosaic → single-cell imaging, 2D continuous maps

Curcio, Kar, Owsley, Sloan, Ach; 2024, IOVS 65:4



Video-enhanced differential interference microscopy
Curcio, Sloan, Kalina, Hendrickson, 1990.
J. Comp. Neurol. 292: 497

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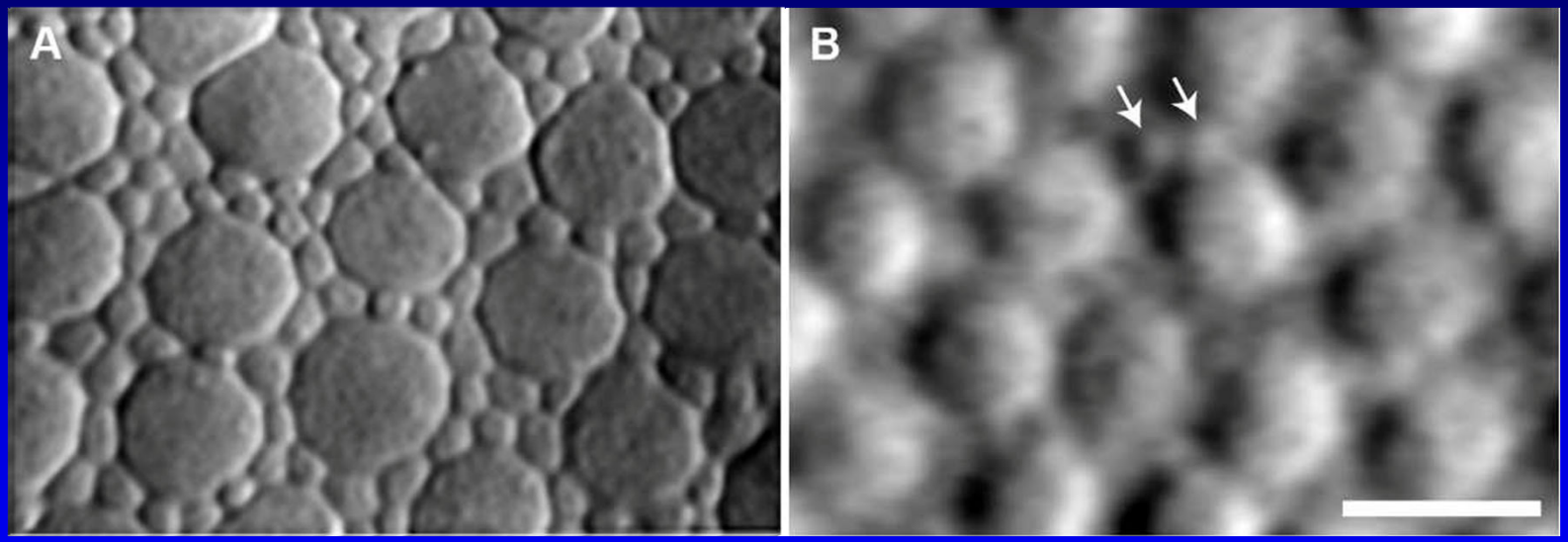

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Split-detection AO-assisted SLO
Scoles, Sulai, Langlo, Fishman, Curcio, Carroll, Dubra, 2014.
IOVS 55: 4244.

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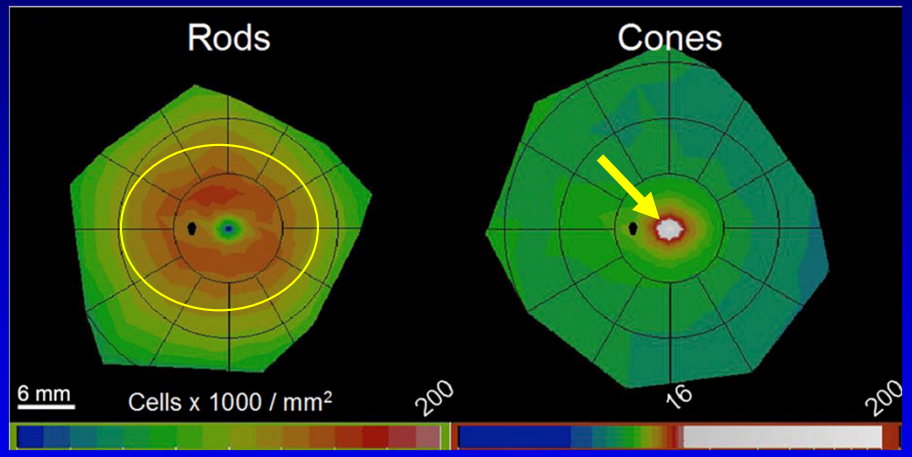

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J. Comp. Neurol. 292: 497; *3498 citations*

Human retina is rod-dominated (20:1), even the 6-mm-diameter central area (9:1)

Cone-only foveola is 0.8 mm in diameter

Cone streak, rod ring, rod hot-spot

Photoreceptor mosaic → single-cell imaging, 2D continuous maps

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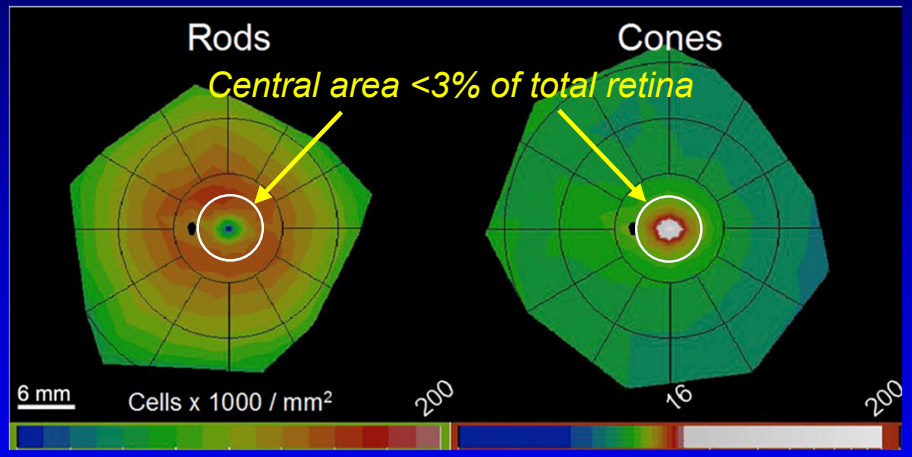

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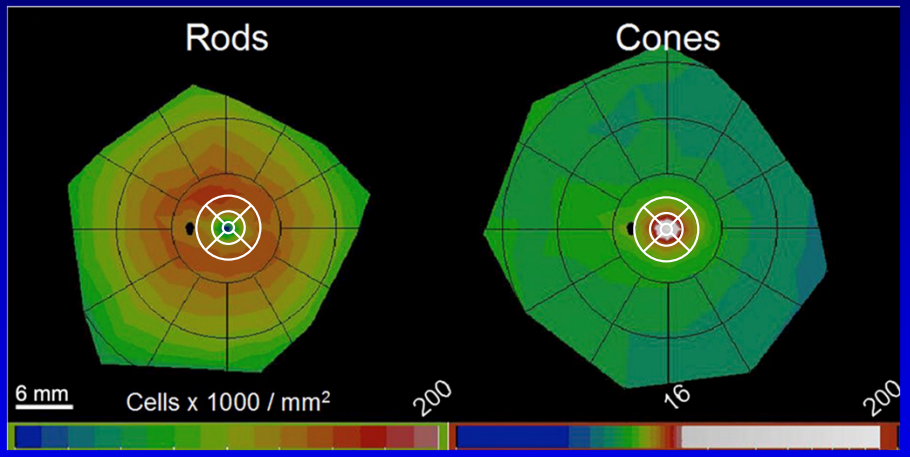

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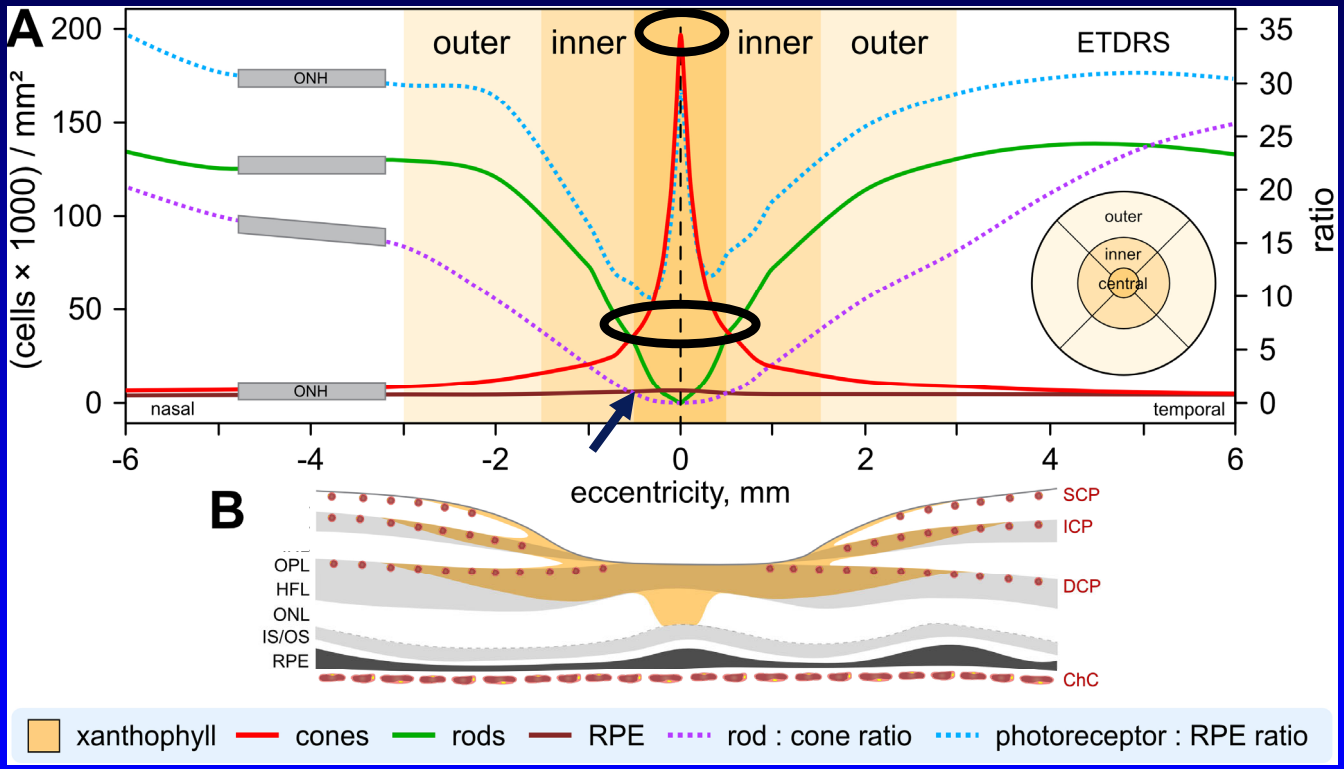
Photoreceptor topography → high dynamic range for spatially precise assays

In central ETDRS

Cones/mm^2
200K to 35K

Rods/mm^2
0 to 35K

RPE/mm^2
6.7K to 6.2K



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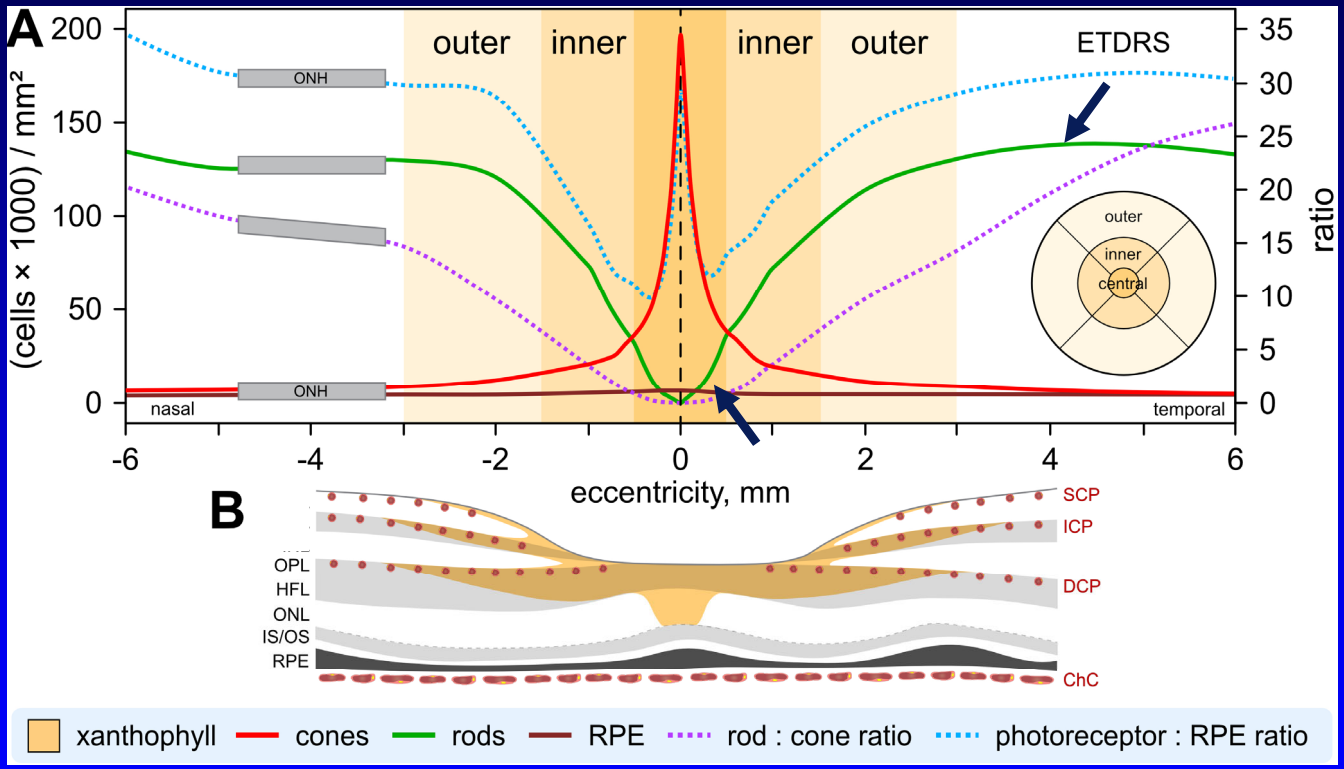

Rods/mm² 0-130,000 just outside ETDRS

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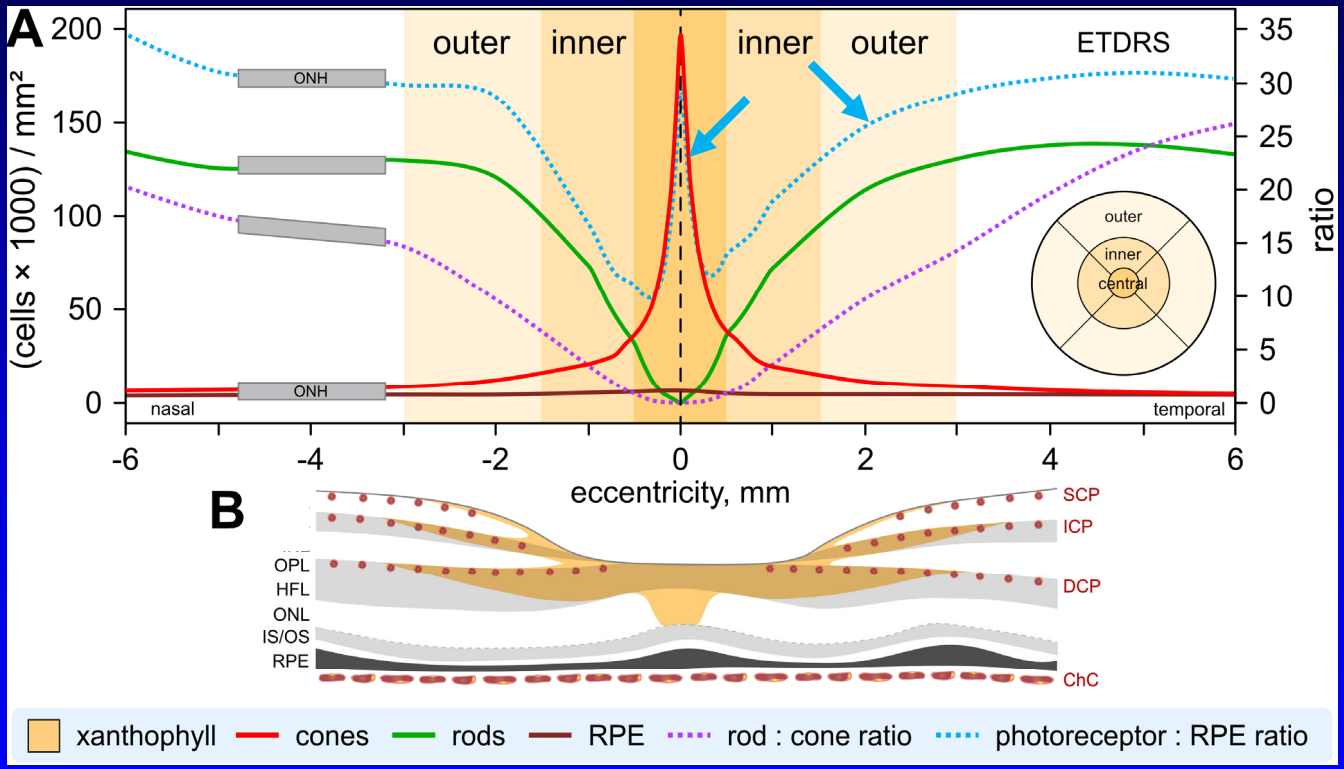

Degradative load on RPE is biphasic

Curcio, Kar, Owsley, Sloan, Ach, 2024, IOVS 65:4

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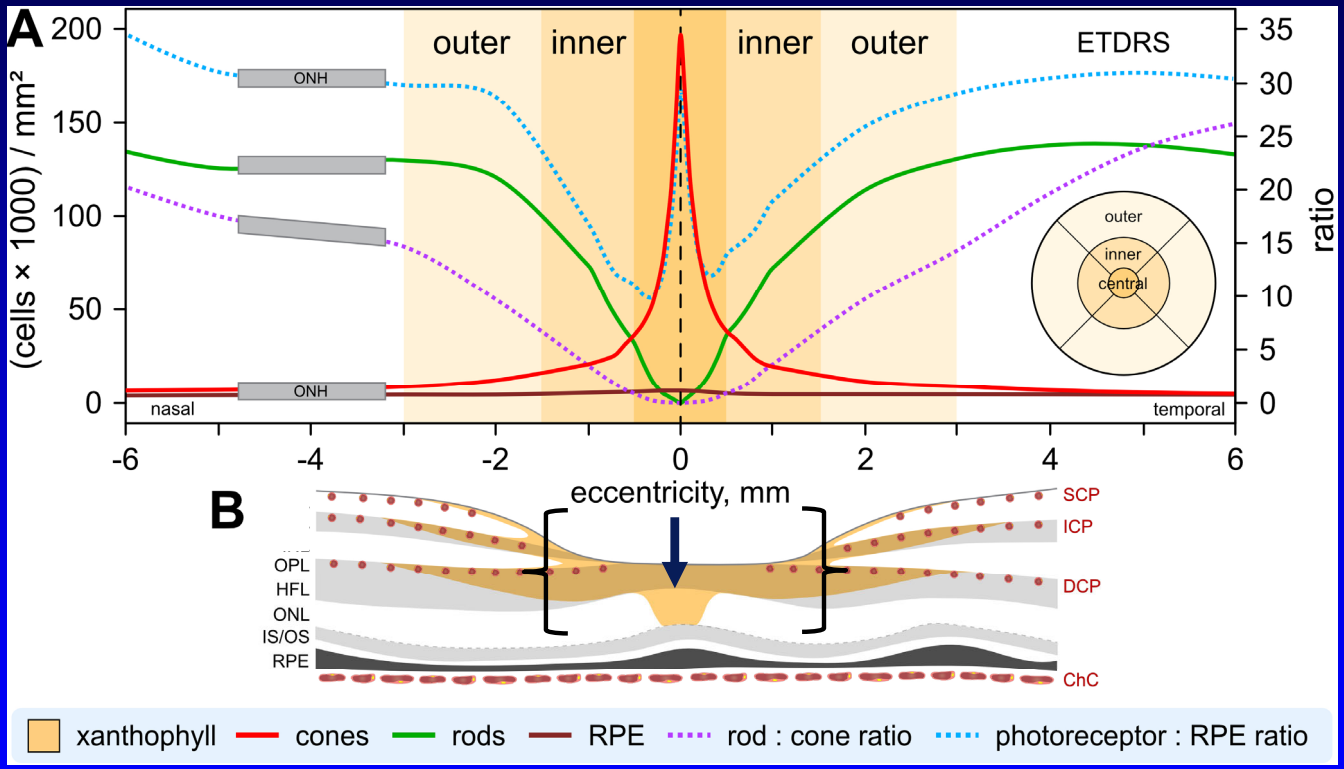

AMD risk is concentrated in 3-mm-diameter macula lutea

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Functional outcome measures

RETINAL NEUROANATOMY MATTERS

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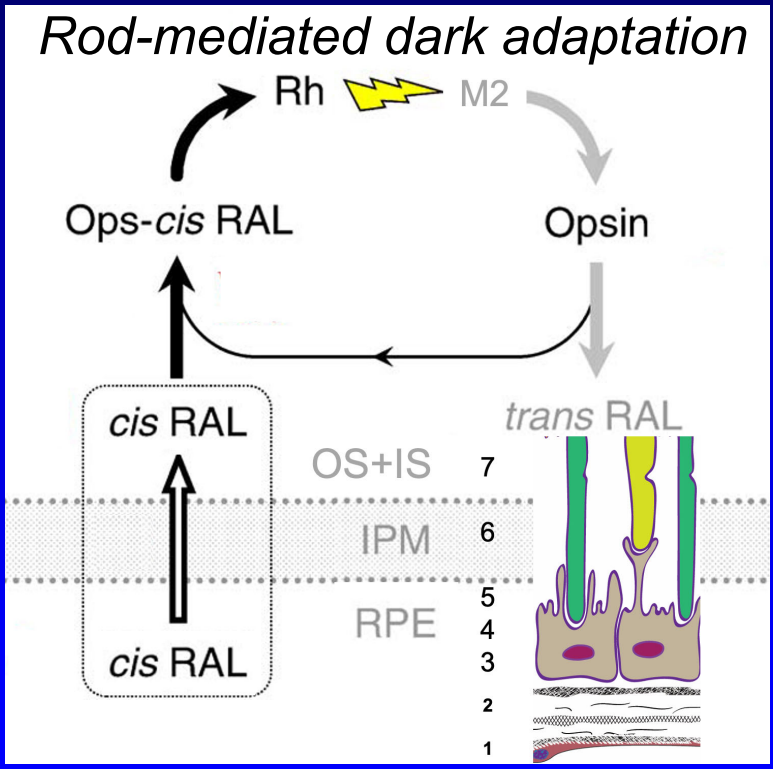
Alabama Study on Early Age-Related Macular Degeneration

Retinal topography impacts outcome measures

Inspired by Lamb & Pugh, 2004 PRER 23:307



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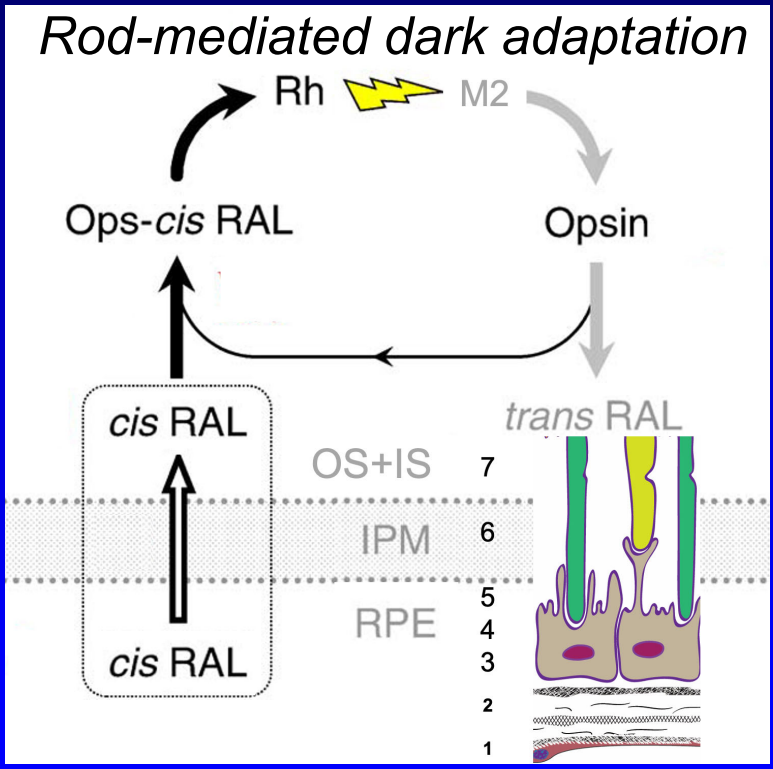

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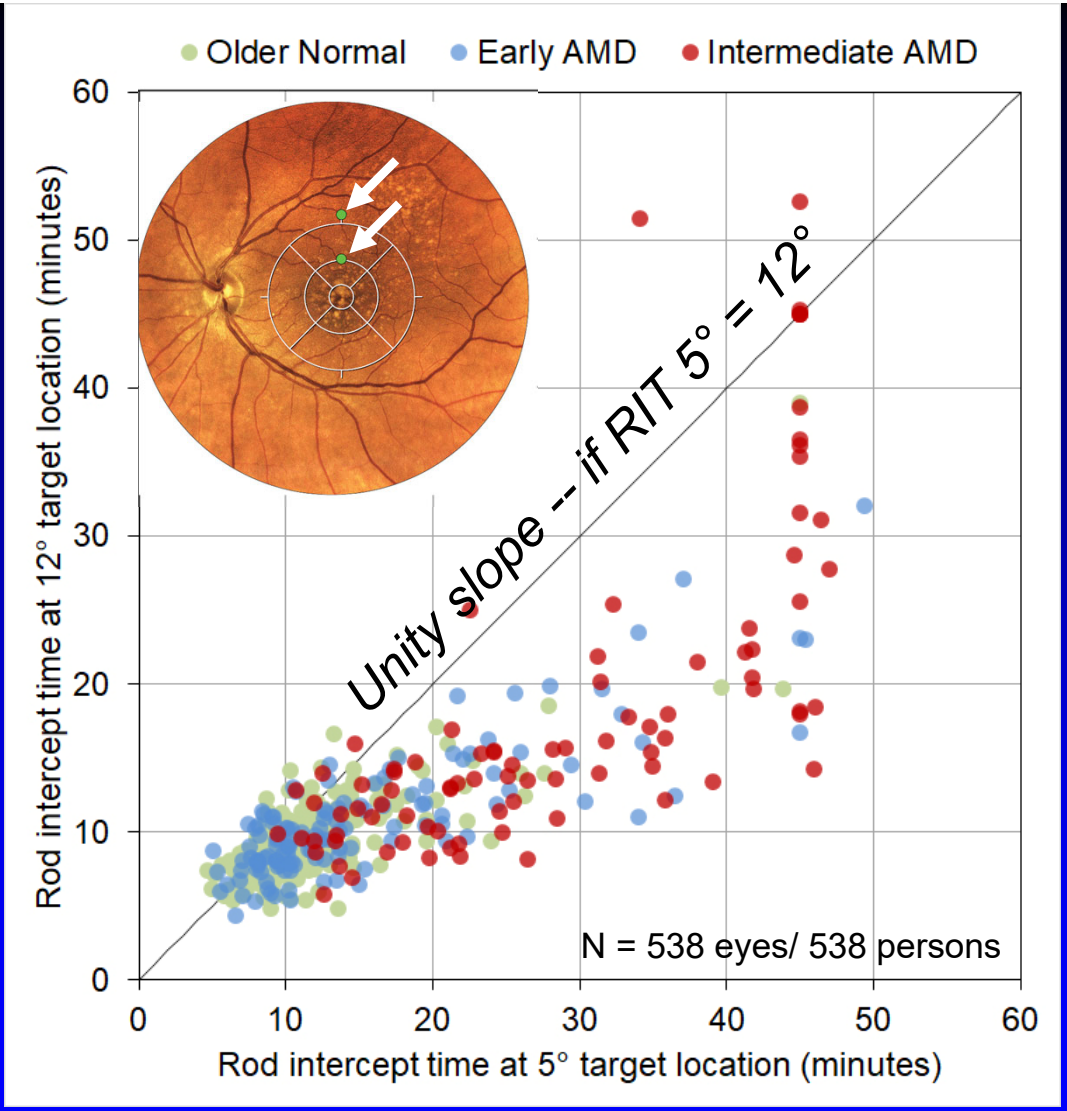

Owsley … Curcio, 2023. Ophthalmology Science 3:100274

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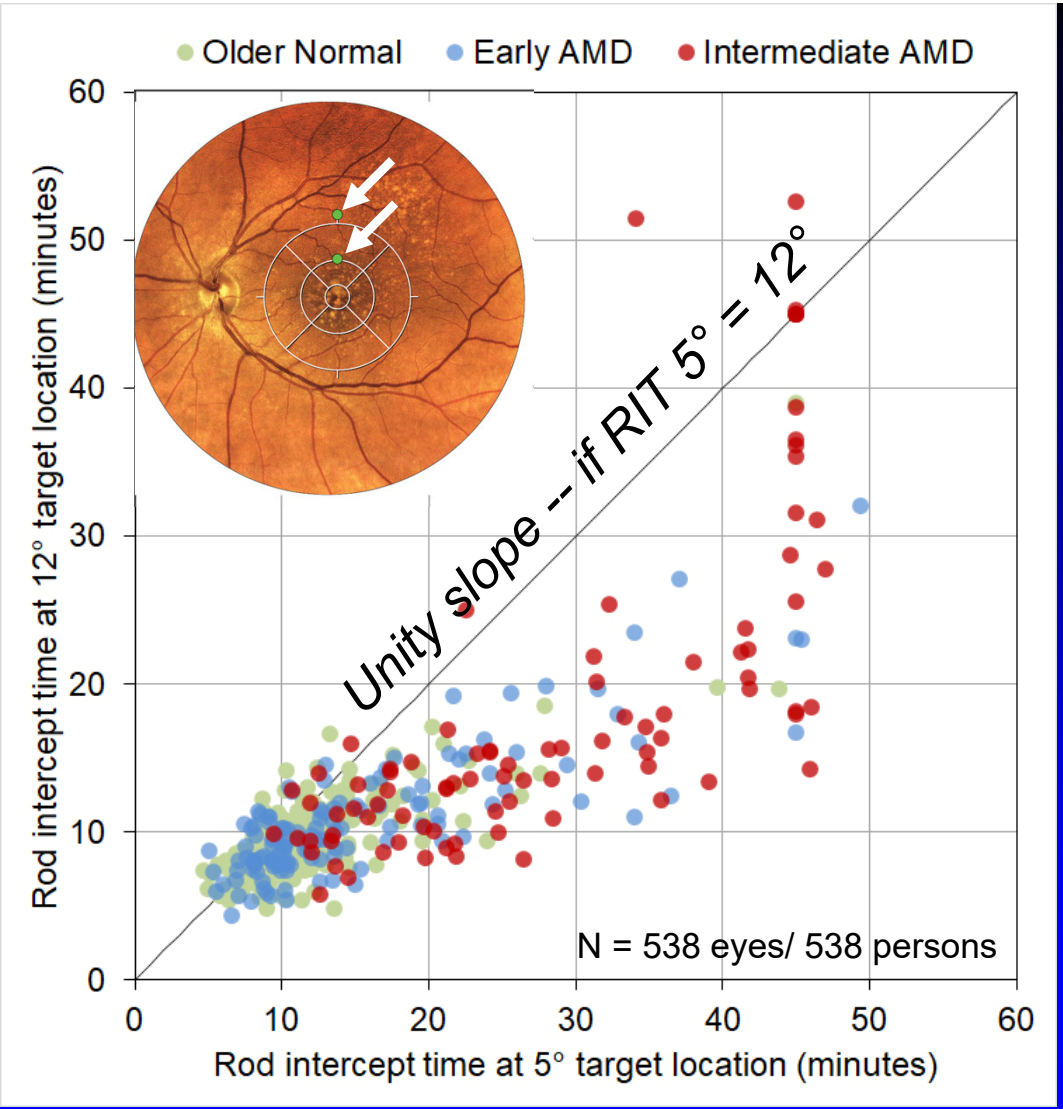
Retinal topography impacts outcome measures

Worse RMDA near fovea
✓ *5 different groups*



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Preventing atrophy from starting will also prevent its expansion
Preventing neovascularization will also prevent fluid and fibrosis

Thanks for your attention!

cacurcio@gmail.com

2025 Proctor Medal
Association for Research in Vision and Ophthalmology

Jointly awarded with
Cynthia Owsley PhD