Adaptive Optics Scanning Laser Ophthalmoscopy: A New Tool to Monitor Cones During Retinal Degeneration

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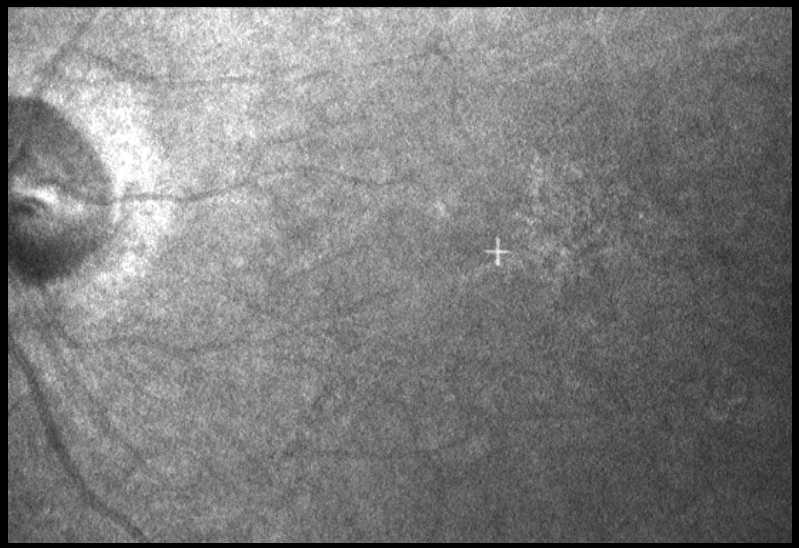
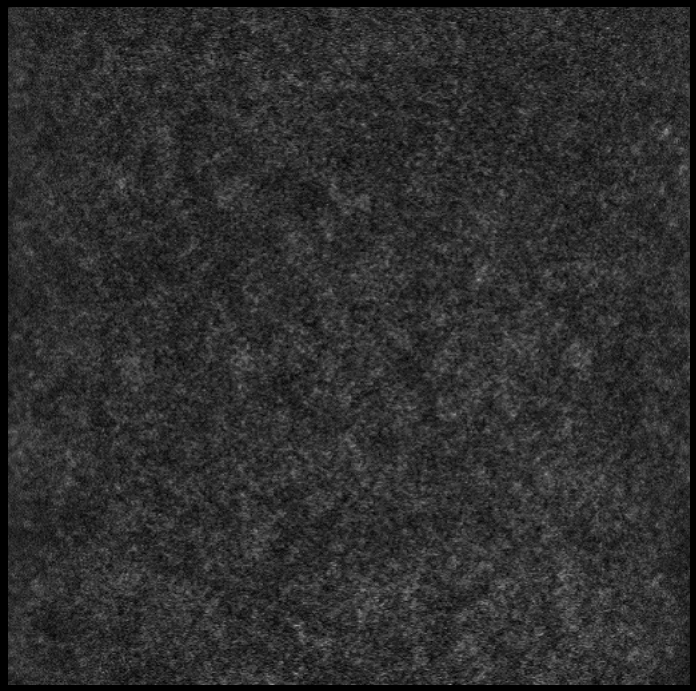
What Are Retinal Degenerations?

- Diverse group of inherited diseases, including Usher syndrome
- All associated with progressive loss of photoreceptors
- Today: update on new ways to study the vision cells (photoreceptors) in eyes with retinal degeneration

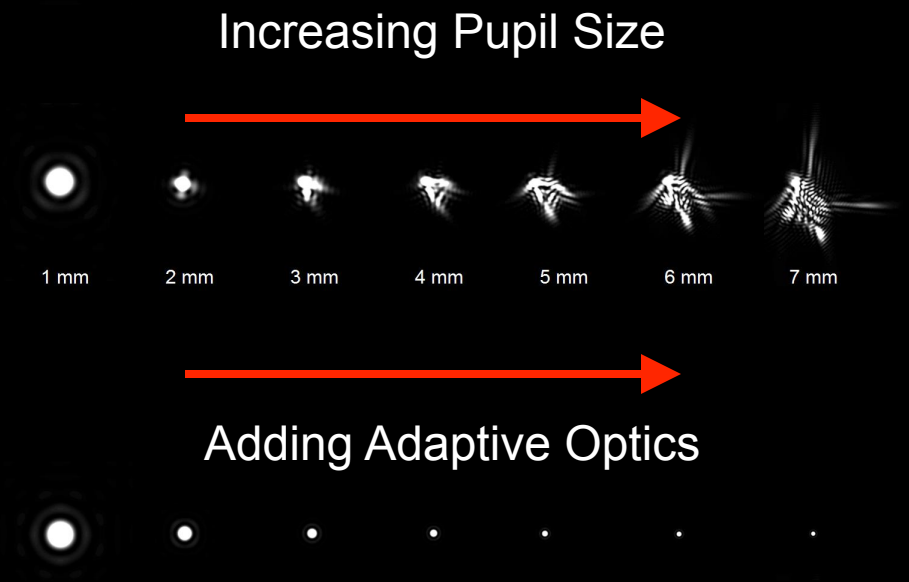
Scanning Laser Ophthalmoscopy (SLO)

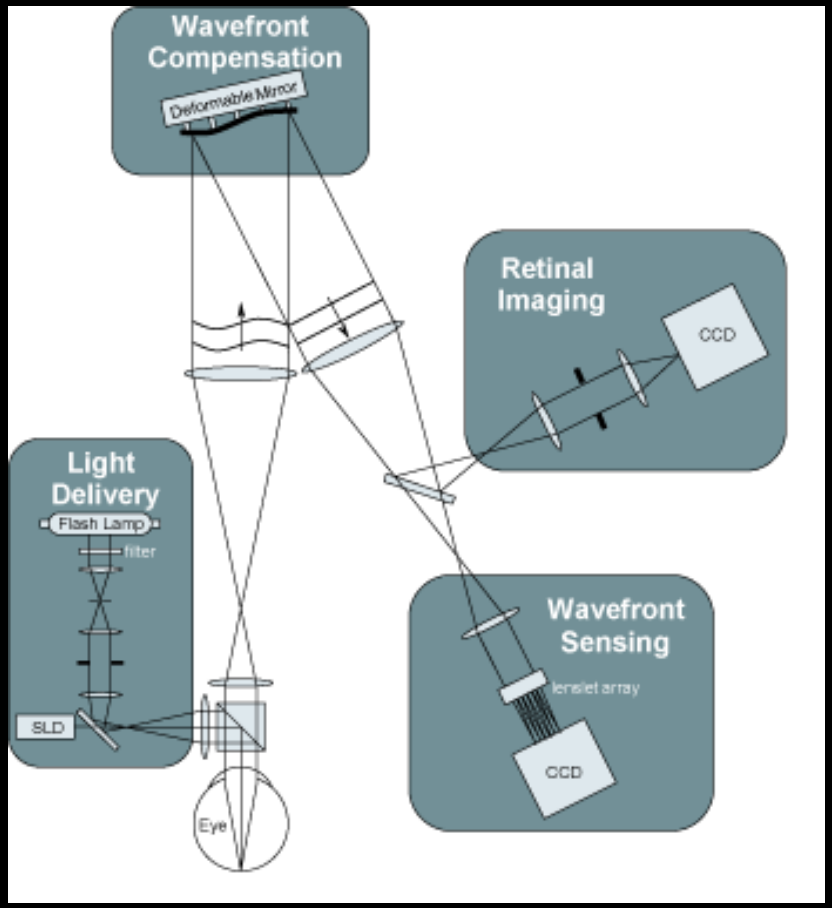
- Confocal images of retinal planes
- Poor axial resolution (300 μm)
- Lateral resolution limited by optics of cornea/lens





Adaptive Optics Correct Aberrations

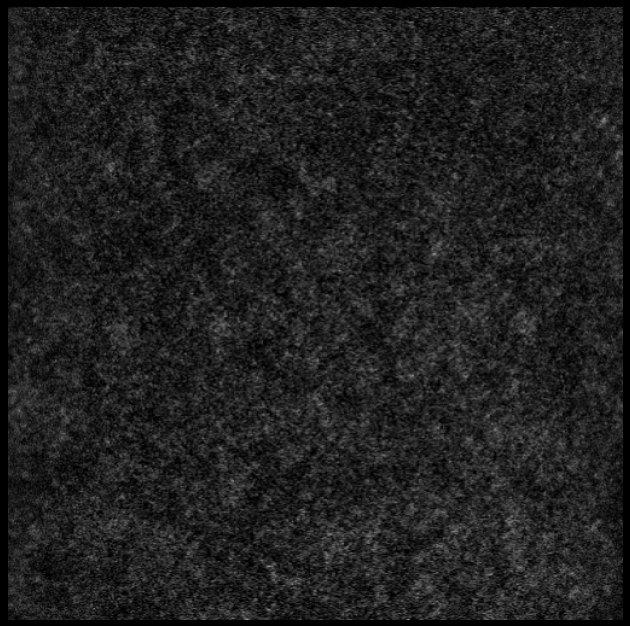




- Overcomes blur from optical aberrations
- Shack-Hartmann wavefront sensor
- Deformable mirror
- Image individual photoreceptors with high resolution

Adaptive Optics Makes it Possible to See Microscopic Retinal Features in Living Eyes

No AO
(defocus and astigmatism corrected)



AO + SLO = AOSLO

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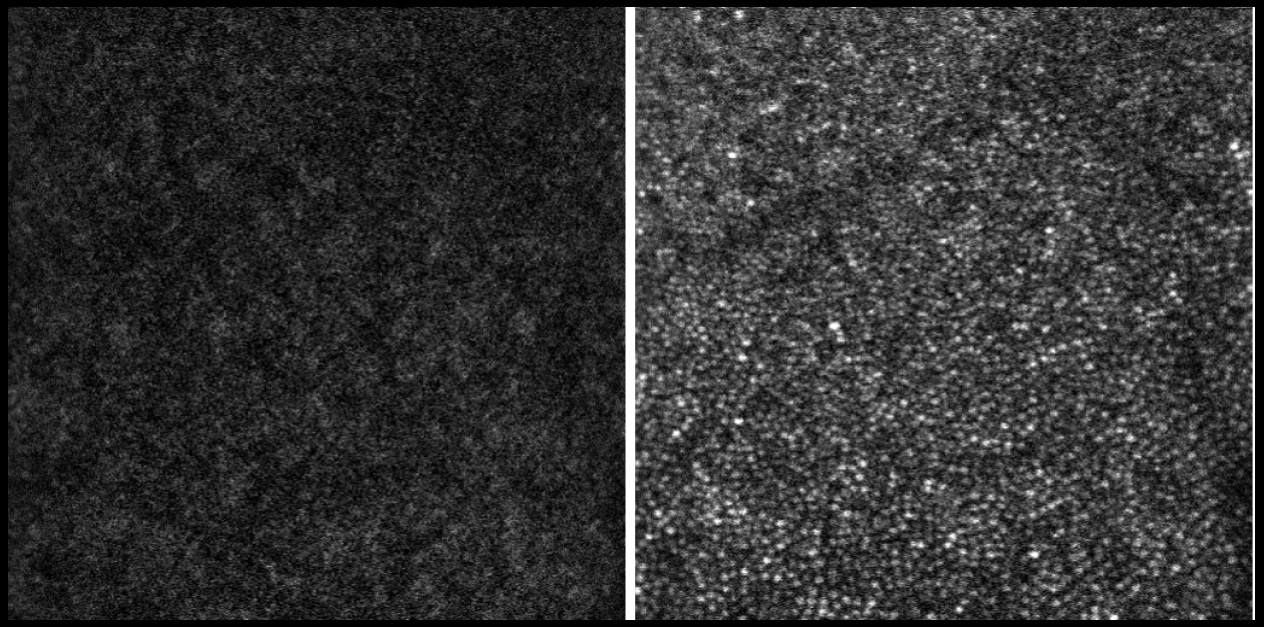
Single frame with AO



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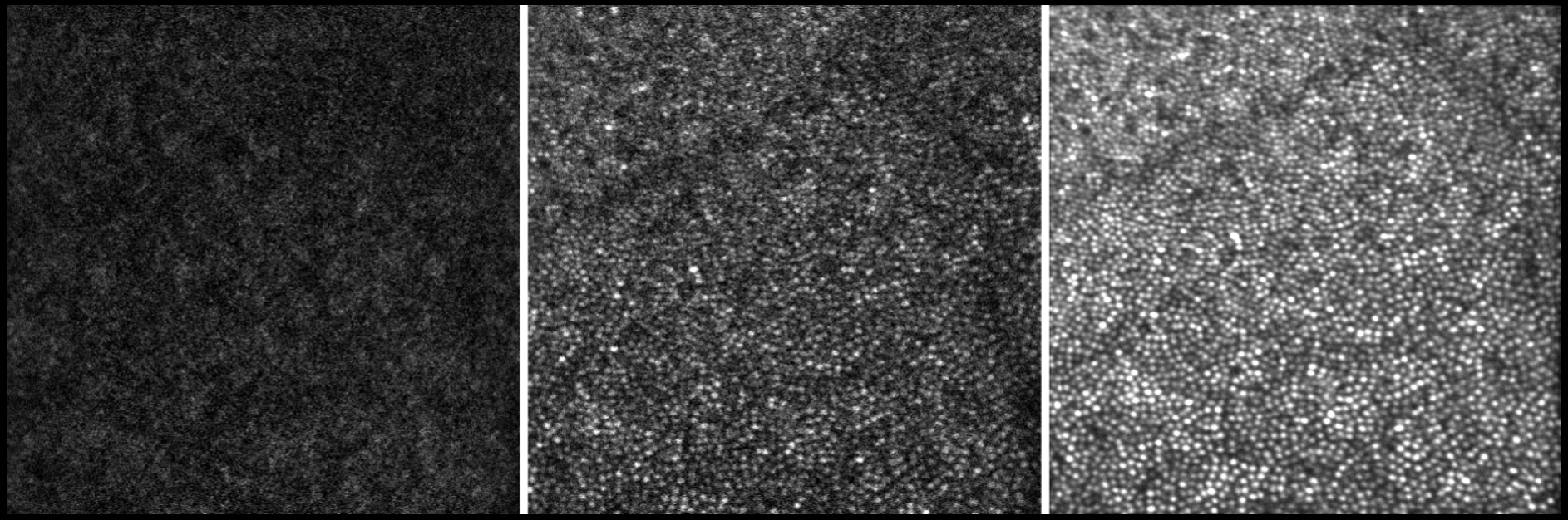
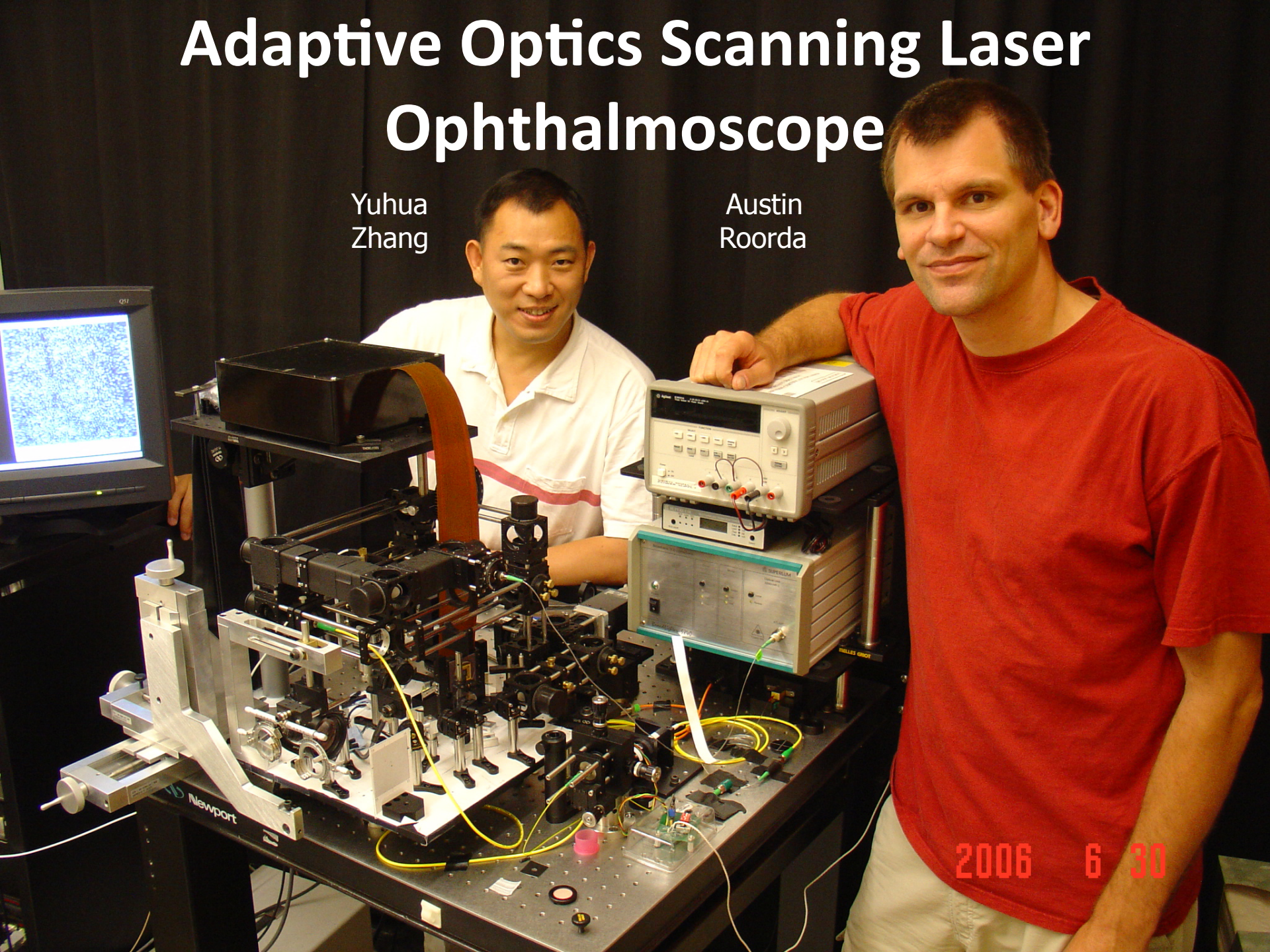
Single frame with AO

Multiple frames with AO



AO + SLO = AOSLO

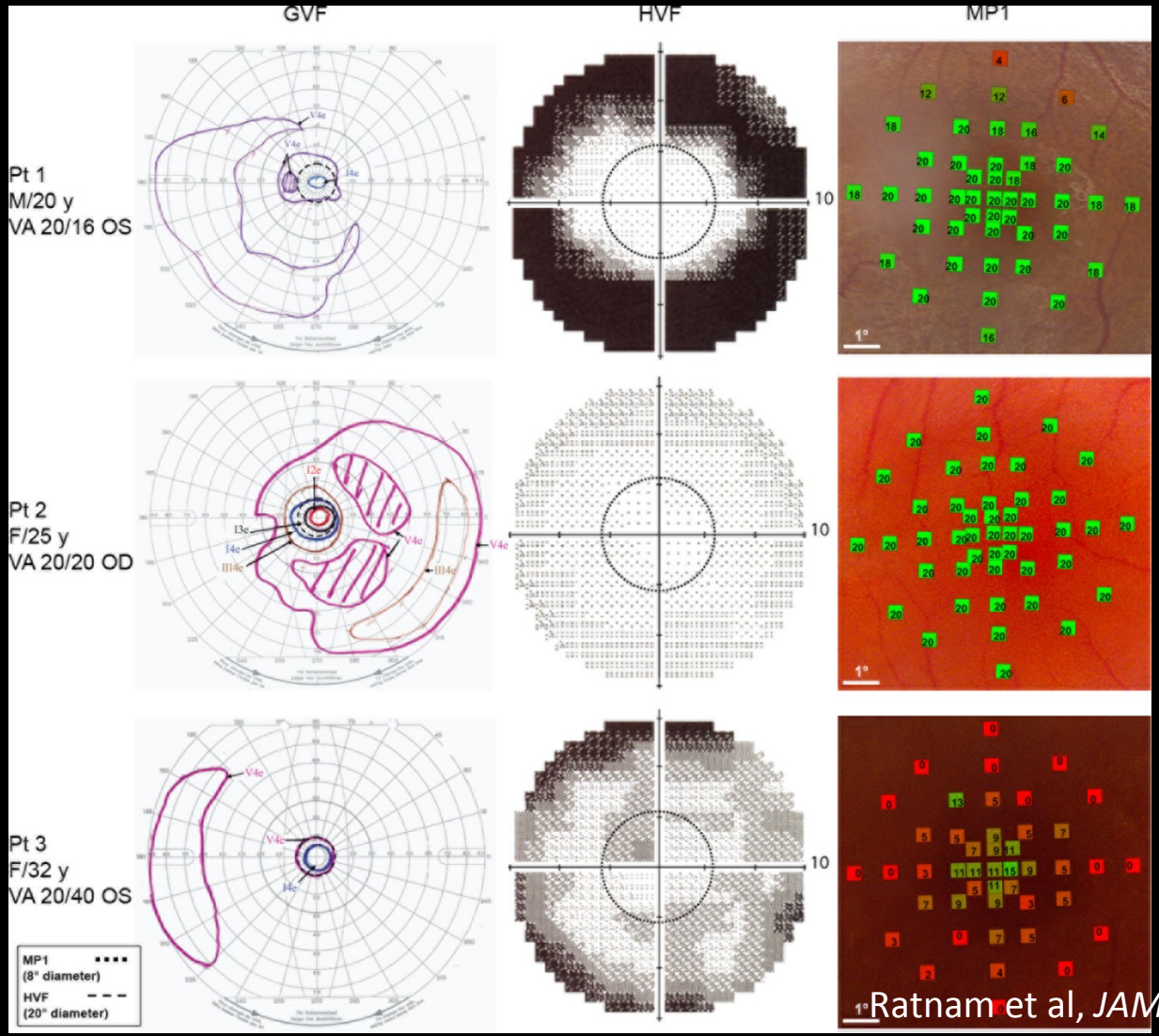
Adaptive Optics Scanning Laser Ophthalmoscope



AOSLO in Usher Syndrome Type 3

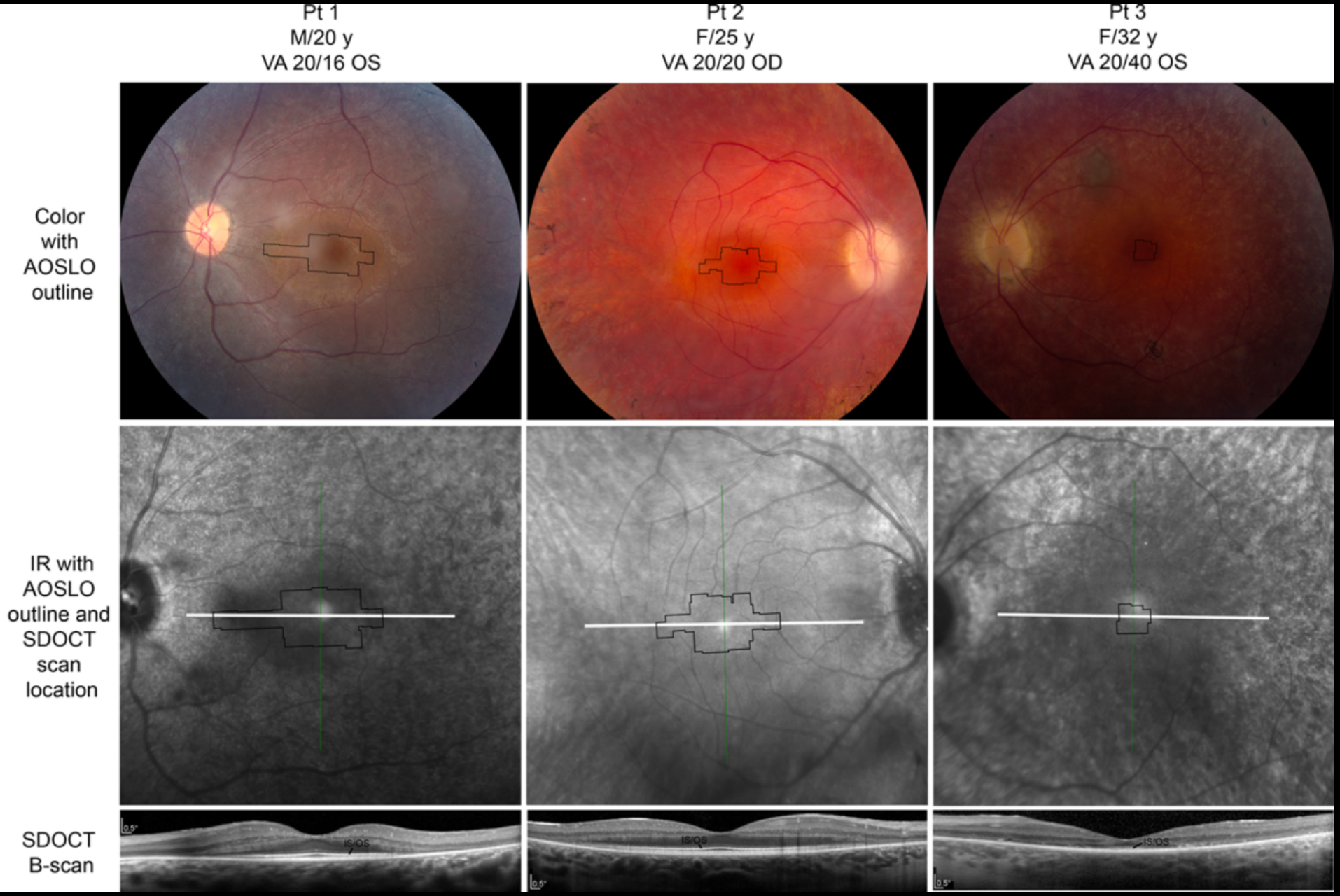
- Can we image cones in patients with diseased photoreceptors?

3 Patients with Usher Syndrome Type 3



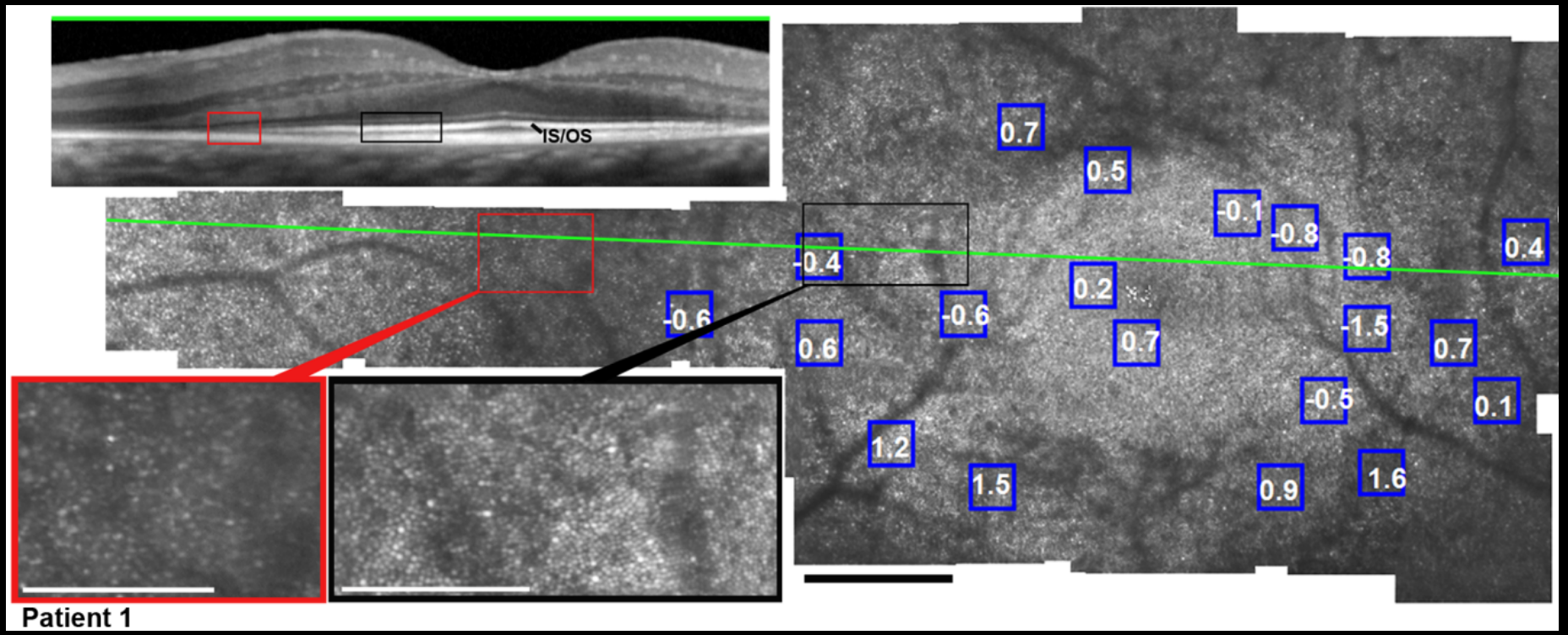
- Ages 20-32
- All with mutations in Clarin-1
- Range of visual field loss

Ratnam et al, *JAMA Ophthalmol* 2013; 131: 67-74



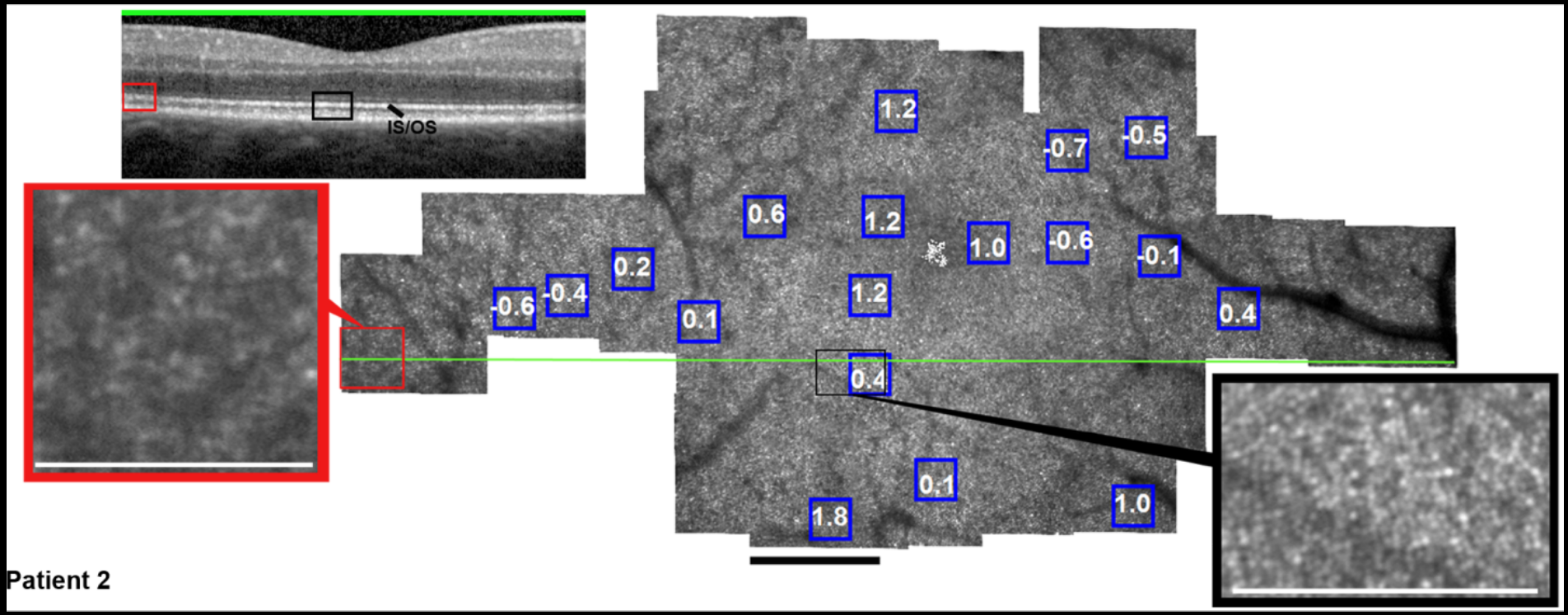
Ratnam et al, *JAMA Ophthalmol* 2013; 131: 67-74

Patient 1: Vision 20/16



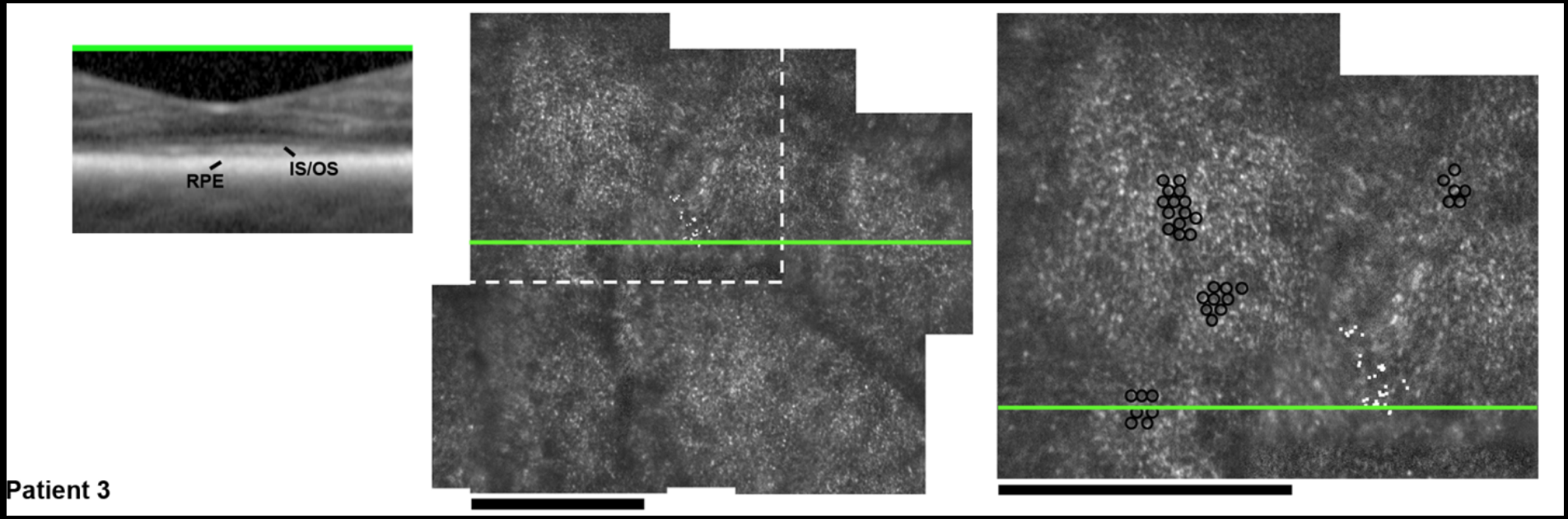
Ratnam et al, *JAMA Ophthalmol* 2013; 131: 67-74

Patient 2: Vision 20/20



Ratnam et al, *JAMA Ophthalmol* 2013; 131: 67-74

Patient 3: Vision 20/40



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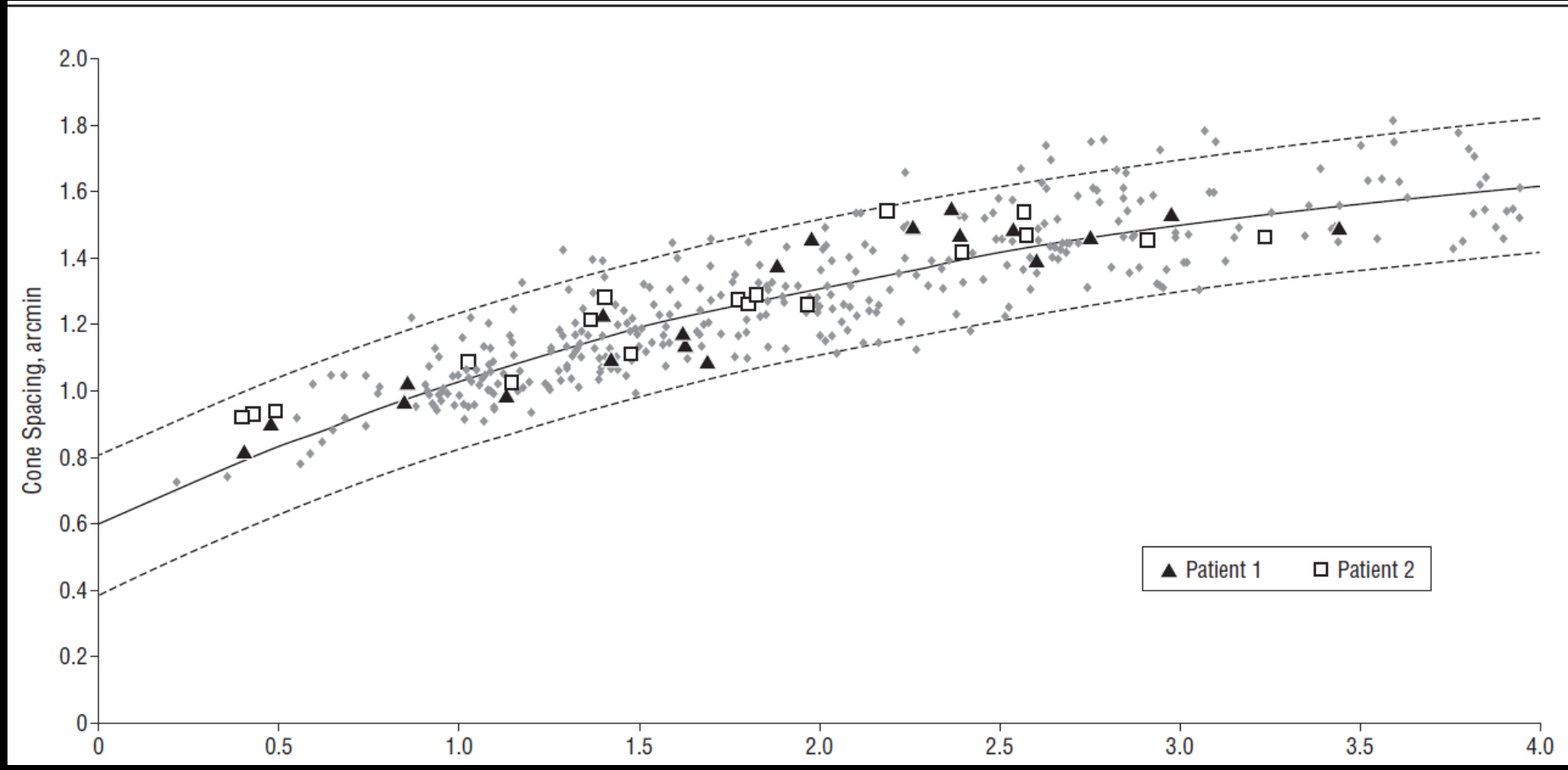
Usher 3 Patients Show Normal Cone Spacing Where Cones are Clearly Seen



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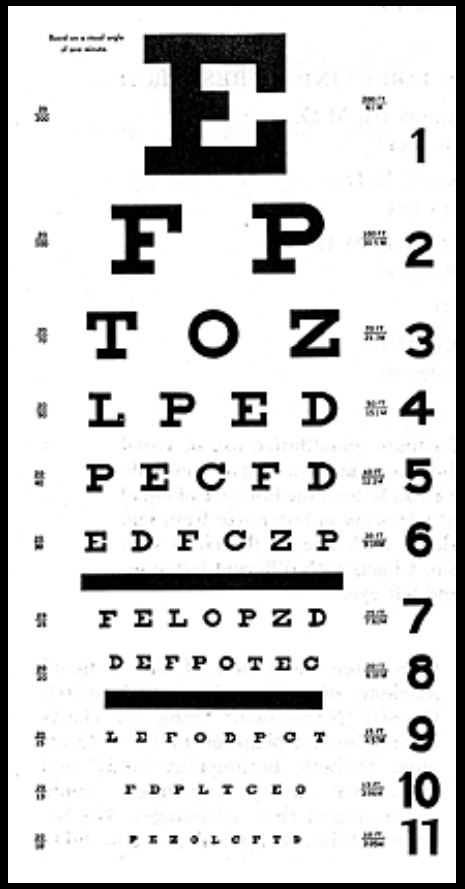
How can we keep the vision cells alive longer?

Neurotrophic Factors

- CNTF: Ciliary NeuroTrophic Factor
  - Shown effective in at least 4 species with retinal degeneration
  - Encapsulated Cell Technology: ECT
    - Sustained delivery from transformed RPE cells
    - 6 month NEI study reported safety in patients with advanced RP and atrophic macular degeneration

As treatments are developed, how should we measure response?

- Can't see vision cells
- Typically: Measure visual acuity, visual field sensitivity
- These take 7-10 years to change significantly
- New tools
  - AOSLO: image individual cone vision cells in living eyes



Grover, *Ophthalmology* 1997
Iannaconne, *IOVS* 2004
Fishman, *Retina* 2007

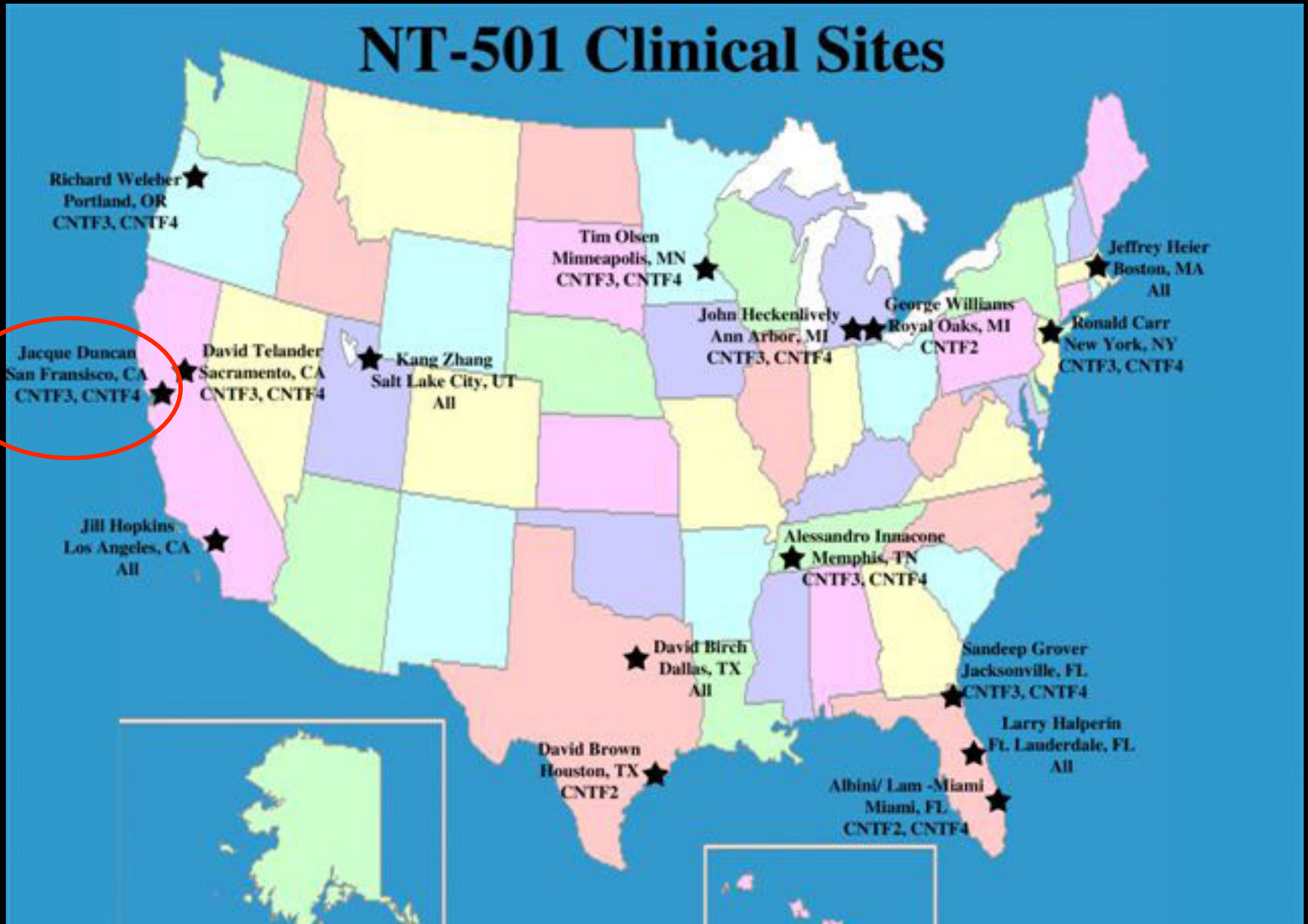
Case Study: Neurotech CNTF3 and 4 Trials in RP Patients:

Outcomes over 12-24 months

- No adverse events
- Dose-dependent increase in retinal thickness in CNTF-treated eyes
- No significant changes in visual acuity
- Significant decline in central 30 degrees of visual field, reversible upon CNTF removal
- What happened to macular cones?

Birch DG et al, *Am J Ophthalmol* 2013; 156:283-292

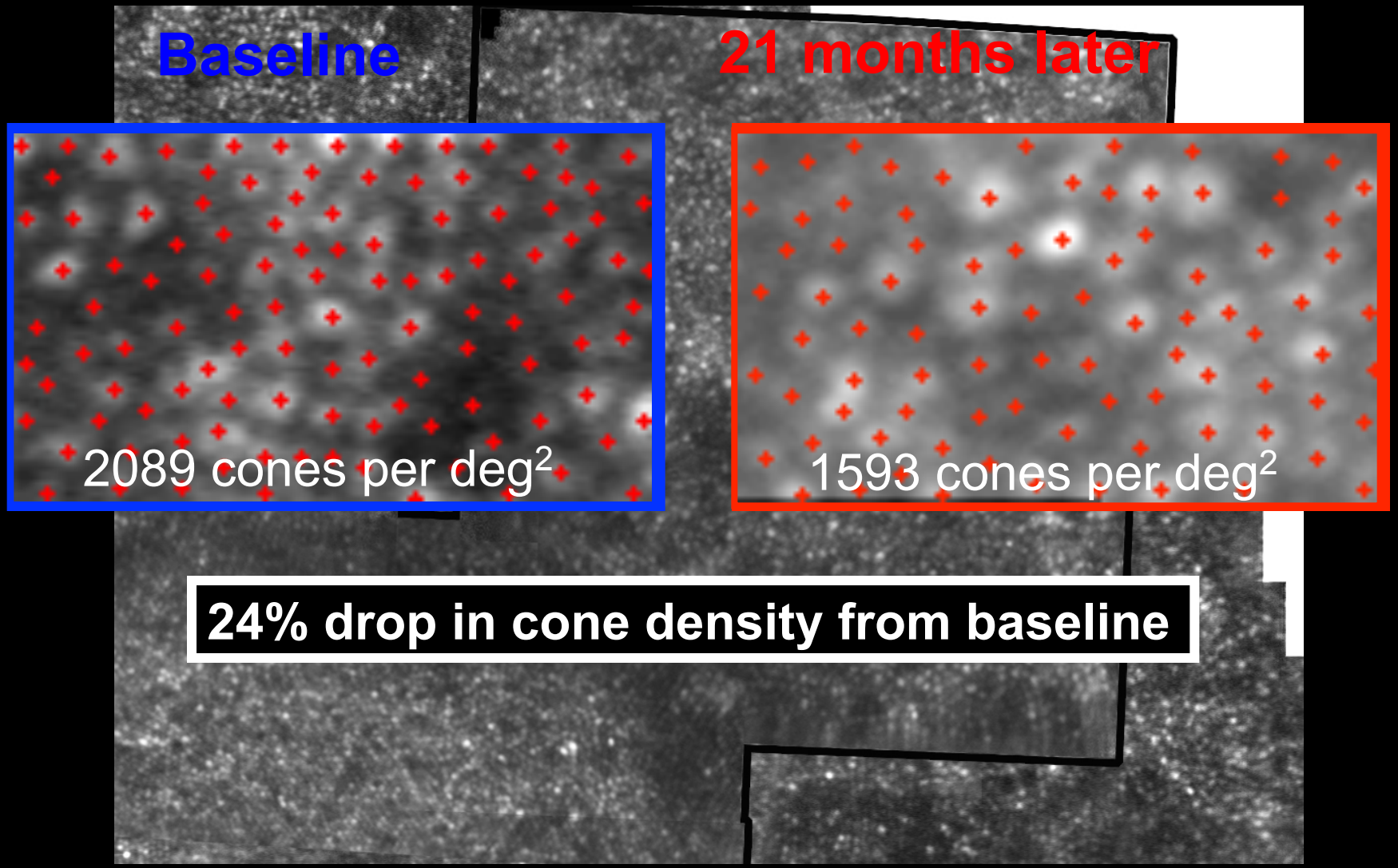
2007: 3 Multicenter Trials of CNTF



CNTF3 and CNTF4 Trials: Outcomes

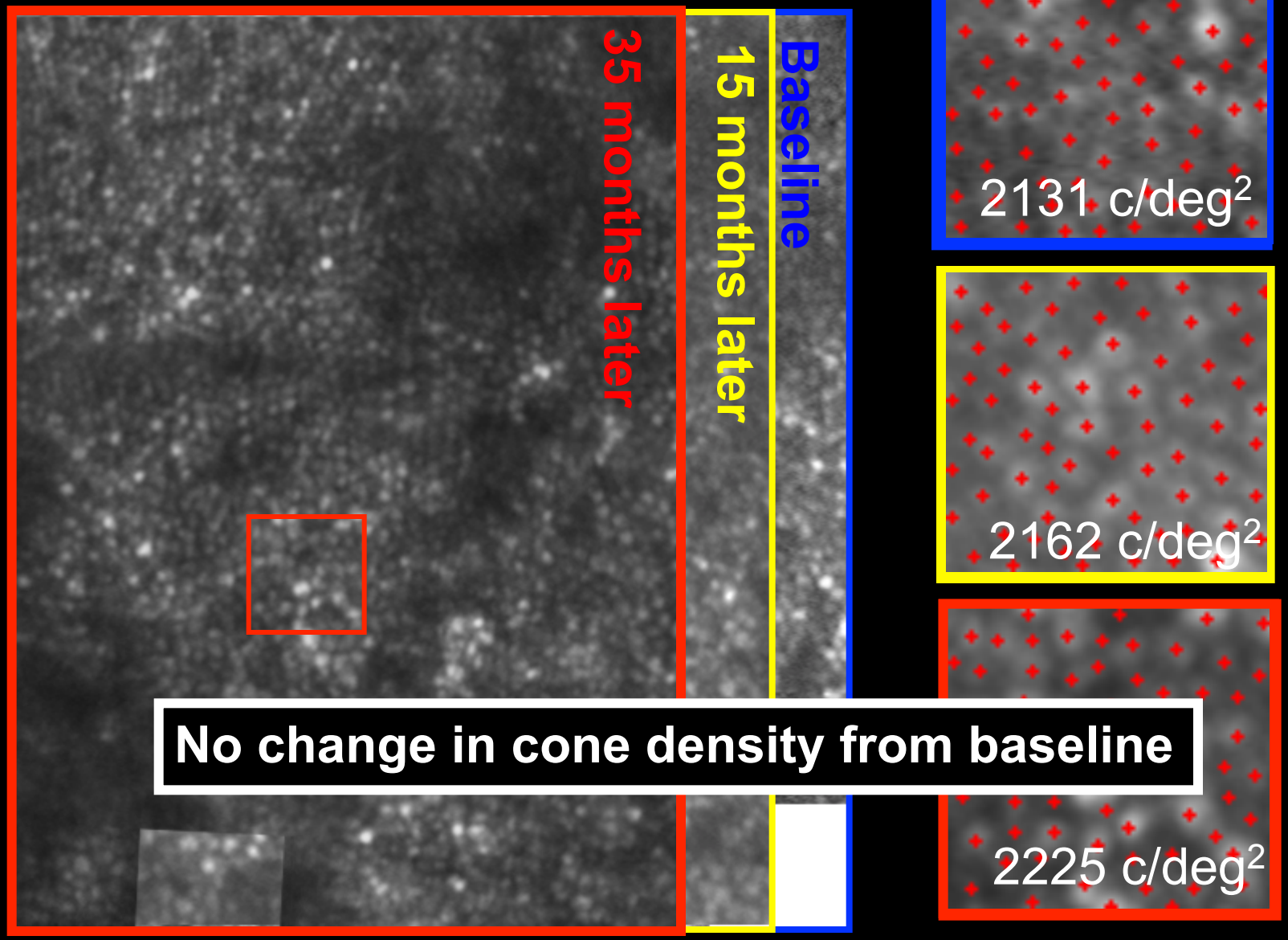
- No adverse events
- No significant changes in visual acuity
- No clinically significant changes in visual field
- Statistically significant increase in retinal thickness

Patient 1, Autosomal Dominant RP: Sham-treated eye

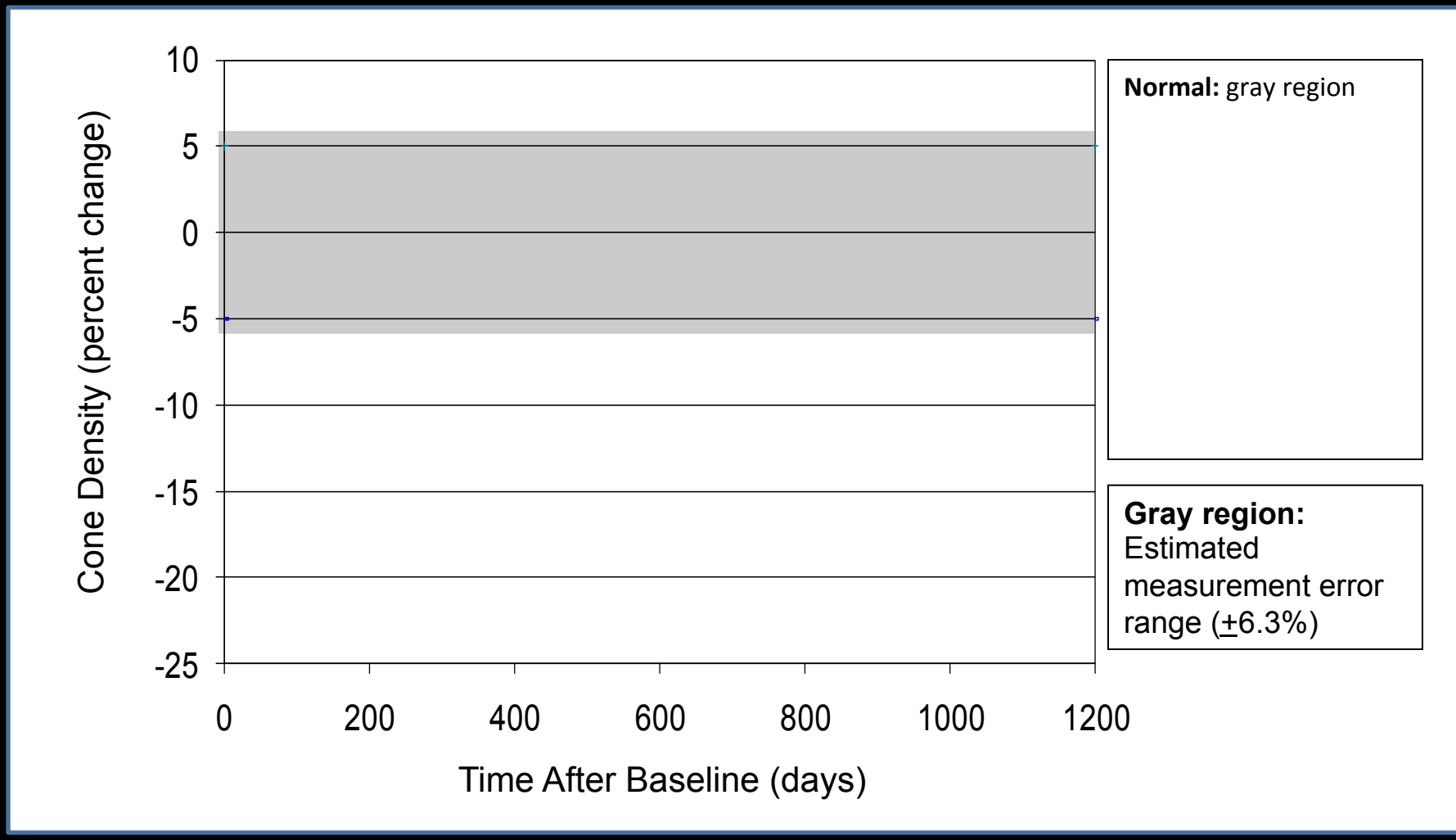


Talcott KA et al, *Invest Ophthalmol Vis Sci 2011*: 52; 2219-2226

Patient 1, Autosomal Dominant RP: CNTF-treated eye



Cone Density Decreased More in Sham-treated Eyes than CNTF-treated Eyes



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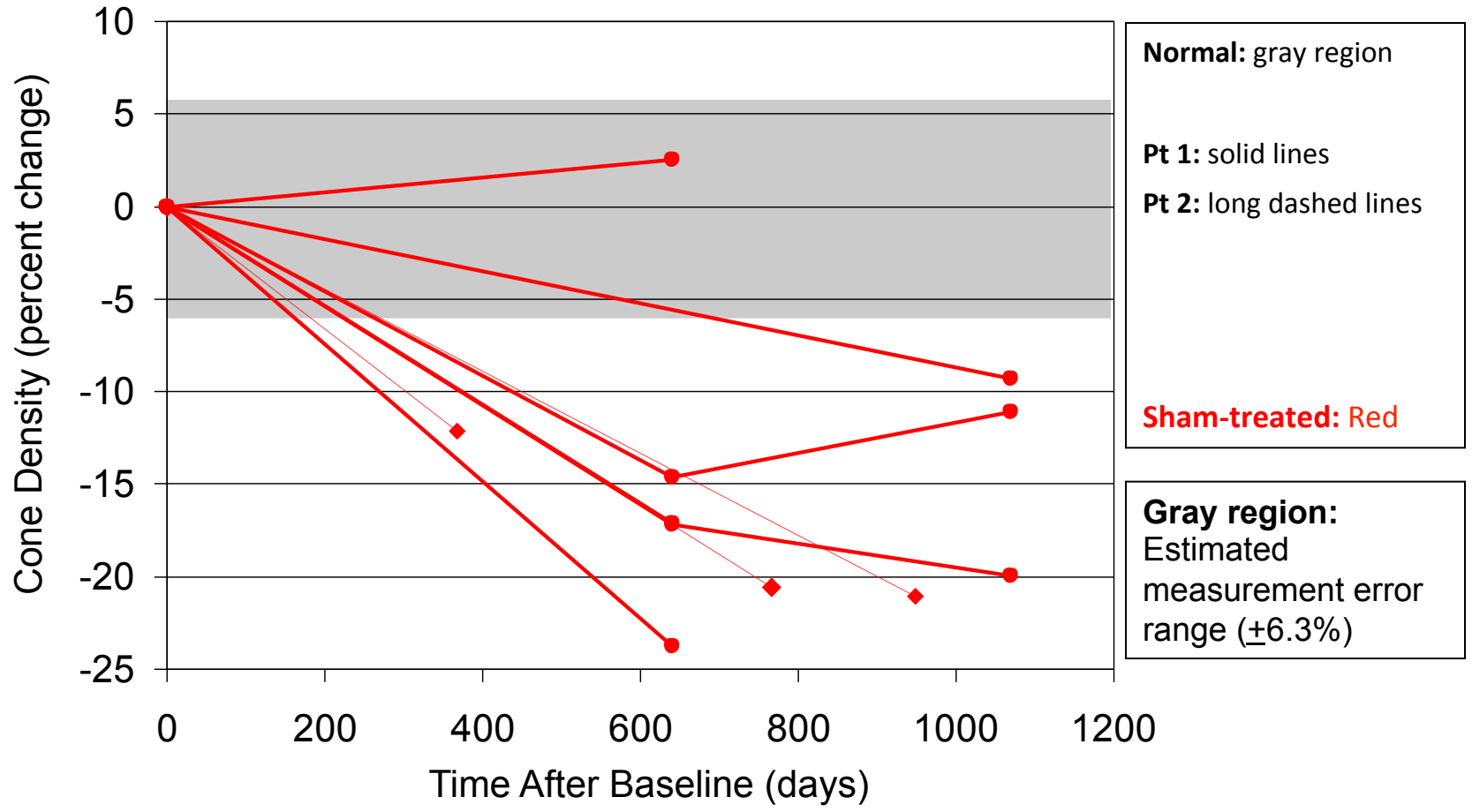

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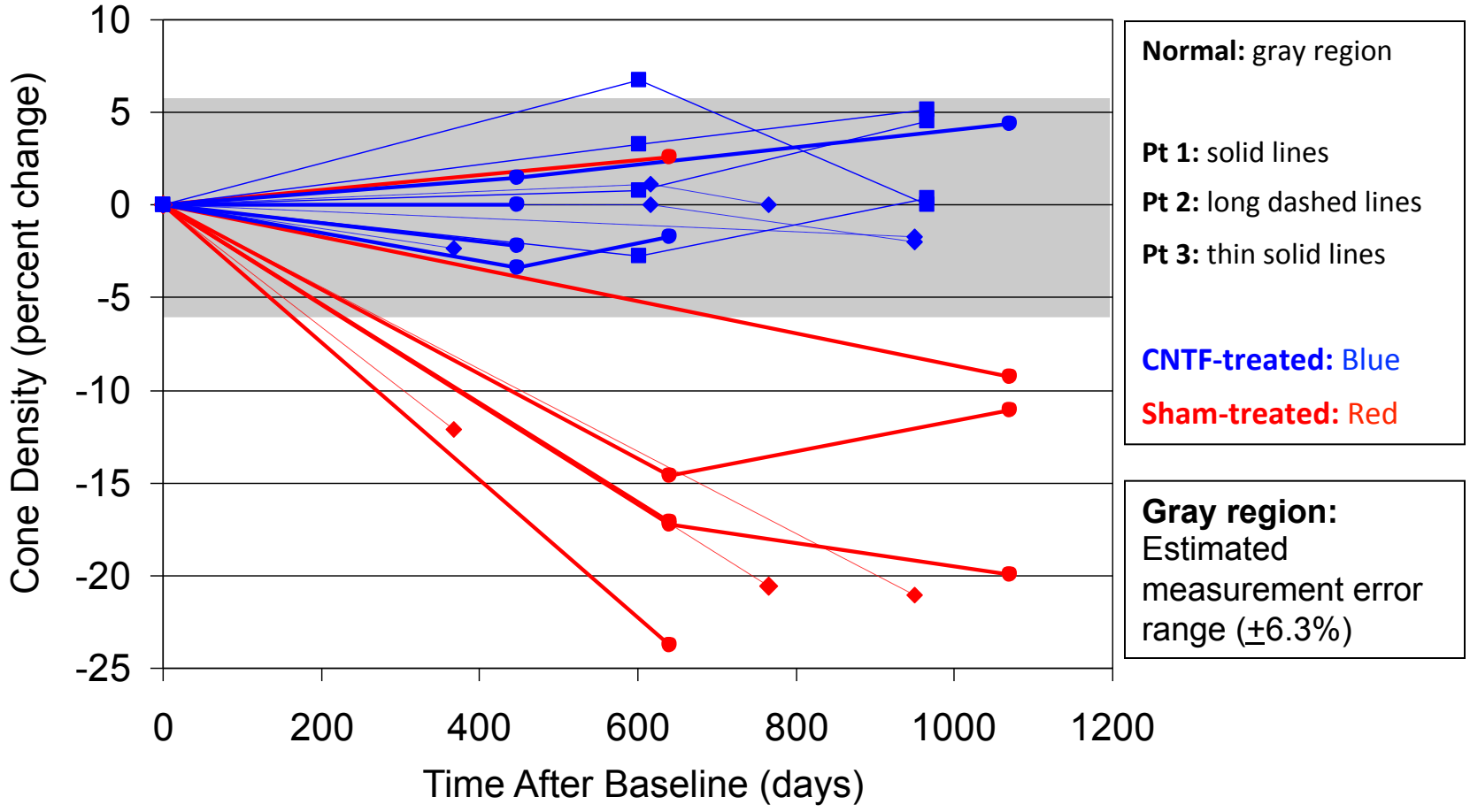

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Cone Density Analysis Results: CNTF vs Sham treatment over 30 months

- Cone density decreased by 9.3% per year more in sham-treated vs CNTF-treated eyes (*P* = 0.002)
- CNTF-treated eyes showed less cone loss
- AOSLO may be a sensitive way to measure disease progression and treatment response
- Larger studies using AOSLO are required to evaluate the effect of CNTF on cone structure

Talcott et al, *IOVS* 2011; 52: 2219-26

New CNTF Clinical Trials:

- Funding from FFB and USFDA supports 3 year study of in RP patients using AOSLO to measure cones over time
- Recruiting now to study how cones change over time
  - Vision must be better than 20/40, no cataract or edema
  - Email duncanj@vision.ucsf.edu for more information

Adaptive Optics in Retinal Degeneration Trials: Advantages

- Image photoreceptor structure with high resolution
- Retinal landmarks enable precise tracking over time
- Interocular symmetry makes it possible to use of contralateral eye as internal control
- AOSLO permits simultaneous high-resolution imaging and visual function testing

Tuten et al, *OVS* 2012; 89(5): 563-574

Adaptive Optics in Retinal Degeneration Trials: Challenges

- Difficult in patients with:
  - advanced disease
  - unstable fixation
  - nystagmus
  - media opacity
  - high refractive error
  - cystoid macular edema
- Image quality affects variability of measures
- Rods are small and hard to see

Adaptive Optics in Retinal Degeneration Trials: Challenges

- Few commercially-available, standard systems
- Each system needs normative data, information on repeatability, validation
- Labor intensive, time-consuming acquisition and analysis
- Natural history of retinal degeneration is not well-characterized
- Centralized interpretation by a Reading Center may reduce variability in measures to use AO metrics as clinical trial endpoints

Conclusions: Adaptive Optics Imaging for Clinical Trials in Retinal Degenerations

- Noninvasive, objective means of evaluating photoreceptors
- May provide sensitive outcome measures for treatment trials, in select patients with central cones
- Synergy: Combining different imaging approaches increases sensitivity of each imaging tool

Acknowledgements

- The Foundation Fighting Blindness
- The US FDA Office of Orphan Product Development
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