



Overview of **Full-field Stimulus Testing (FST)**

Artur V. Cideciyan, Ph.D.

Center for Hereditary Retinal Degenerations
Scheie Eye Institute, University of Pennsylvania, Philadelphia, USA

No relevant disclosures

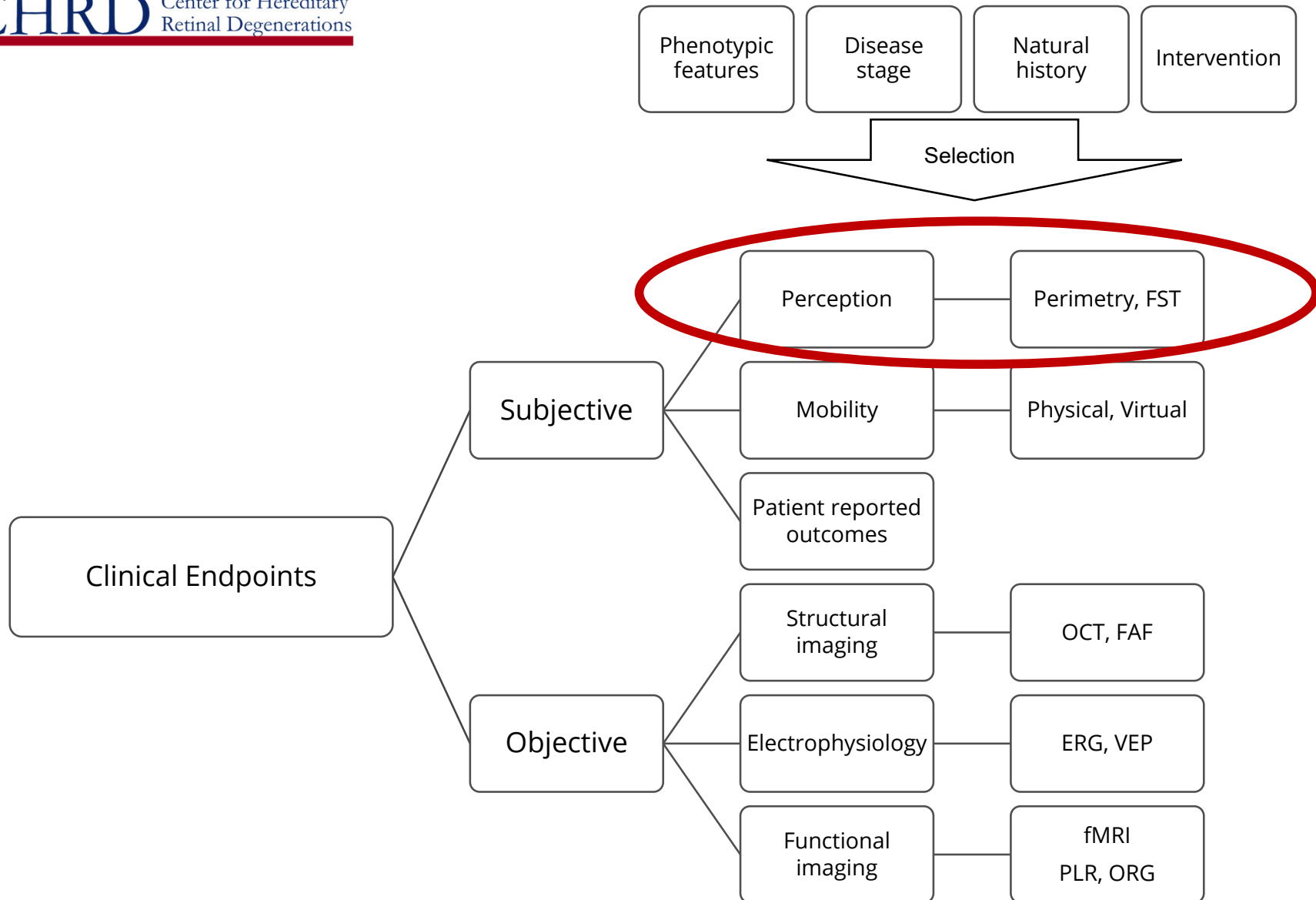


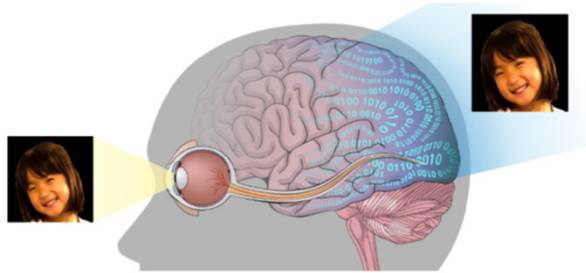
FST defined as = Full-field Stimulus Test

S ≠ Sensitivity

T ≠ Threshold

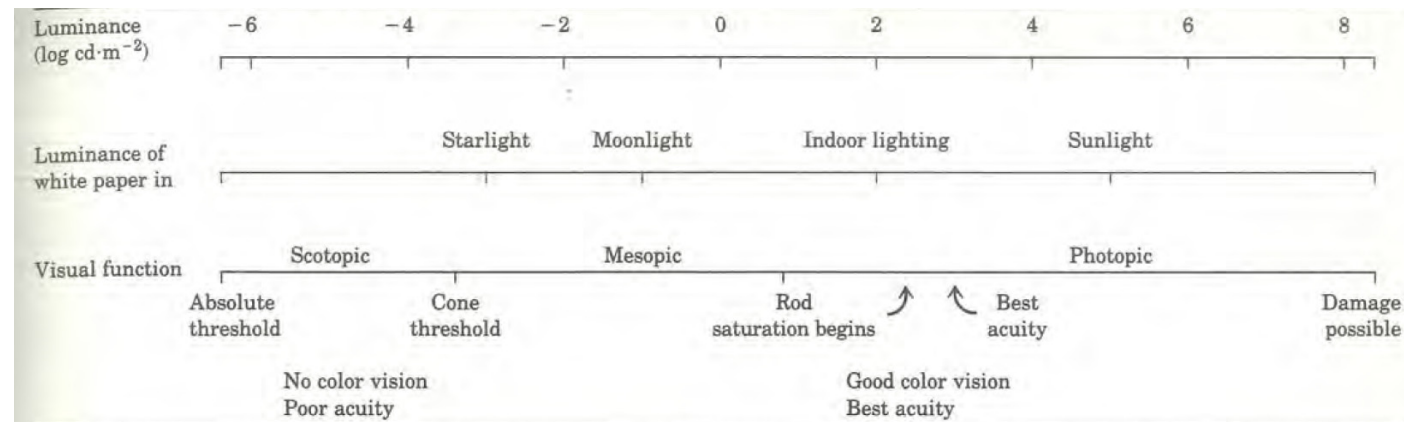
OK to qualify: DA-FST, LA-FST, Blue FST, Red FST,
FST Threshold, FST Sensitivity etc



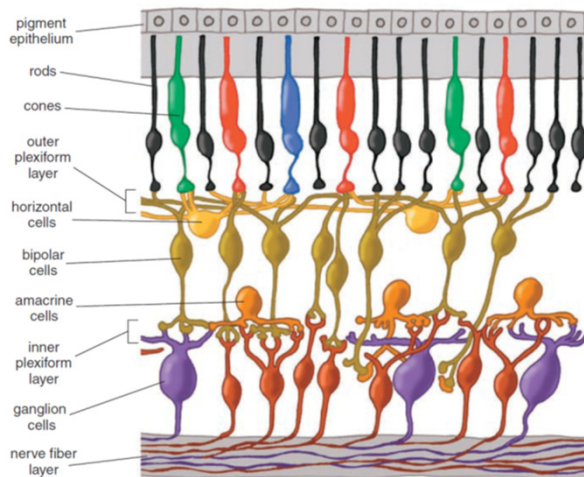


Kim et al., 2022

Human Visual Perception



Hood & Finkelstein, 1986



Vision starts at photoreceptor cells

What is the function of photoreceptors?

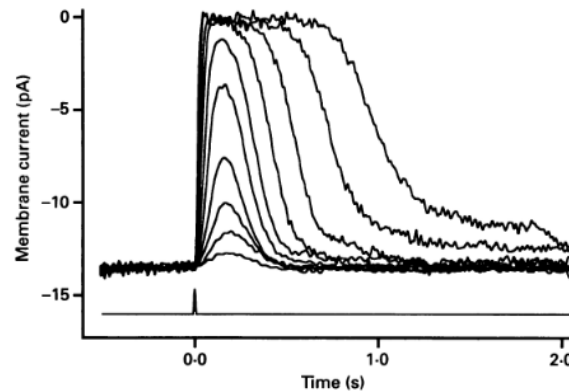
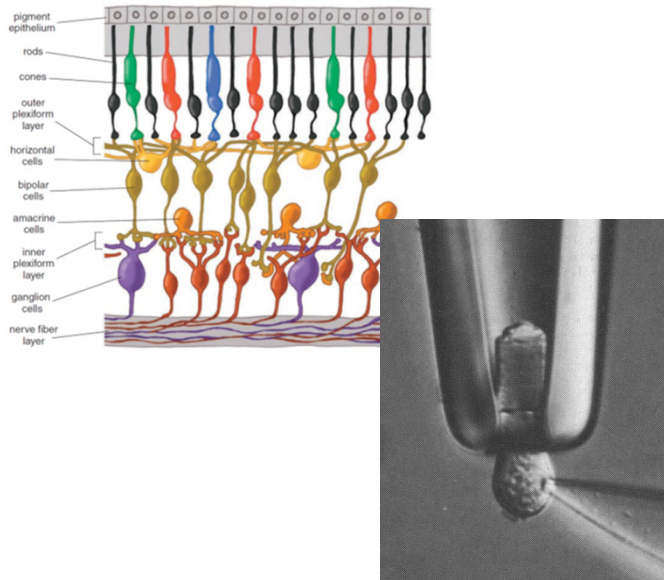


Fig. 1. Superimposed responses to 10 ms flashes of increasing strength in a human rod. Traces are averaged responses of 2–21 flashes. Membrane current is plotted as a function of time. Flash photon densities increased by roughly factors of 2 from 7 to 3060 photons μm^{-2} . Flash monitor shown below current traces. Bandwidth, DC–50 Hz.

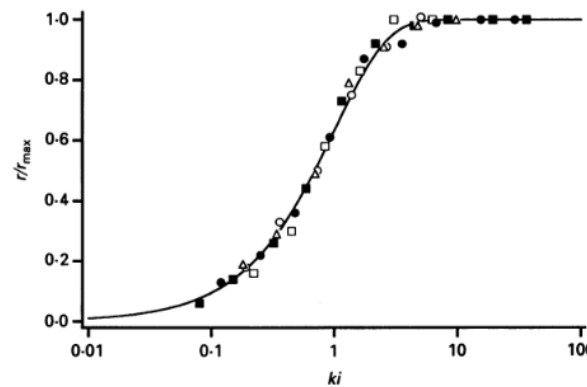
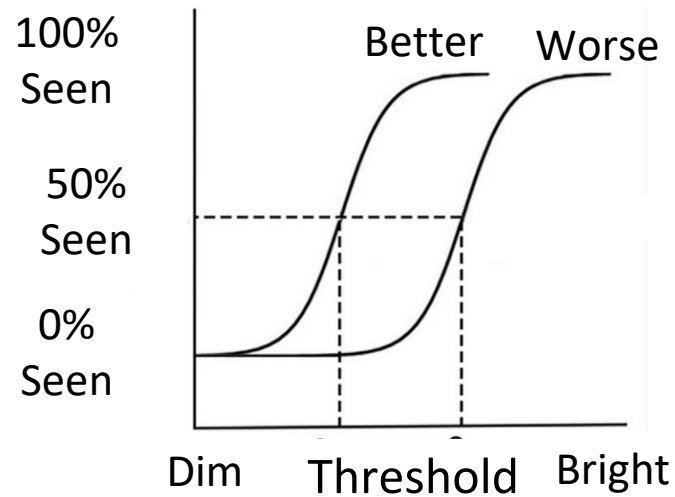


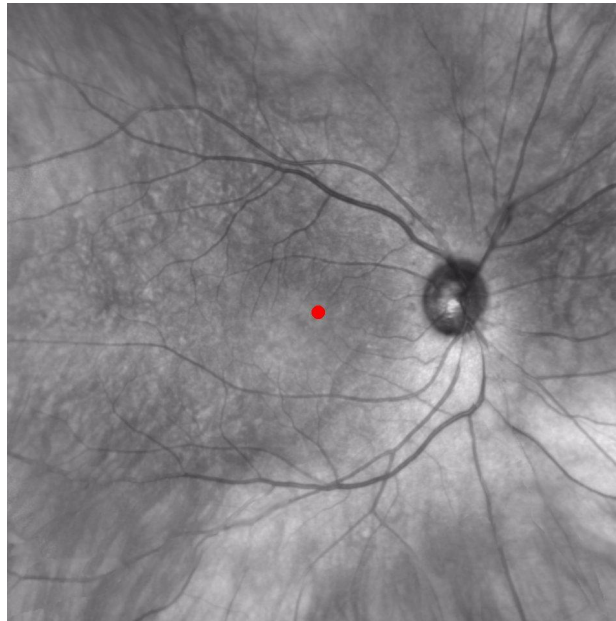
Fig. 2. Relationship between peak response amplitude and flash photon density on normalized axes. Symbols plot peak response amplitude measured in 5 rods; each rod represented by a different symbol. Smooth curve is eqn (1) in the text. Values of r_{max} ranged from 9 to 14 pA; values of k were in the range 0.016–0.028 photons $^{-1}\mu\text{m}^2$.

Response varies with
strength of the light

Perceptual consequences of photoreceptor function



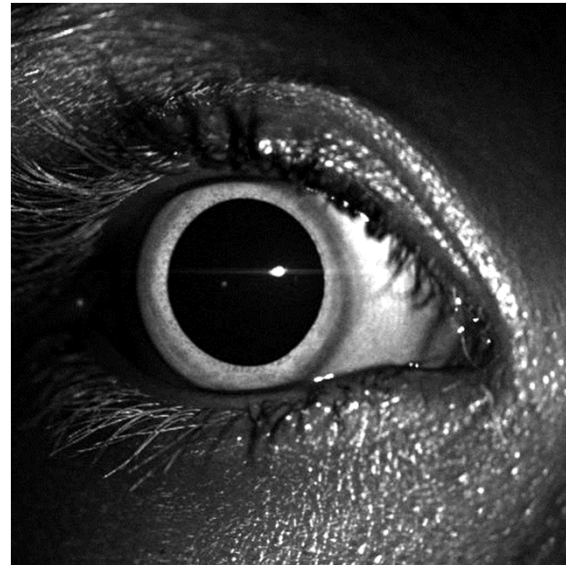
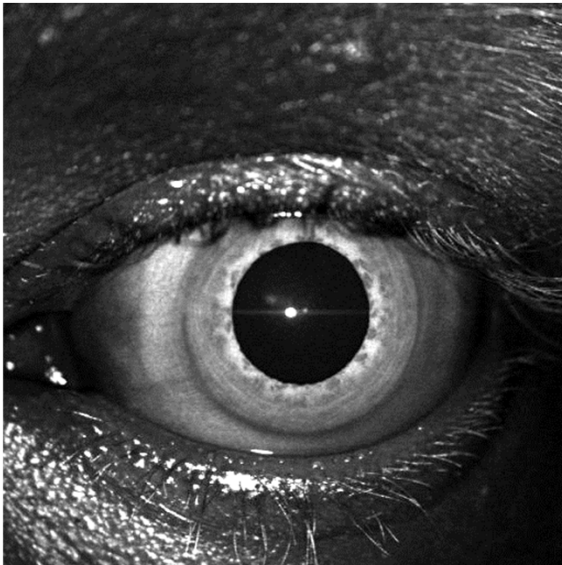
Perimetry/microperimetry



For severe vision loss due to inherited retinal diseases such as forms of Leber congenital amaurosis (LCA), there are two important considerations ...

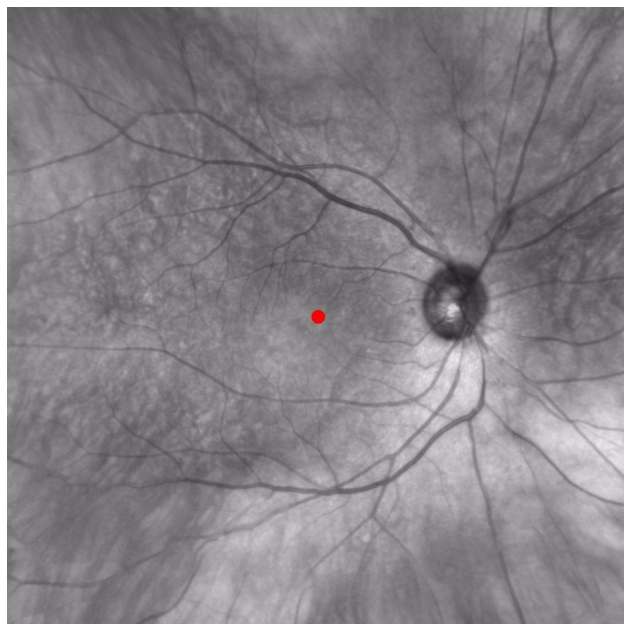
Large loss of light sensitivity

Oculo-motor instability



Development of the FST

Perimetry/microperimetry (localized)



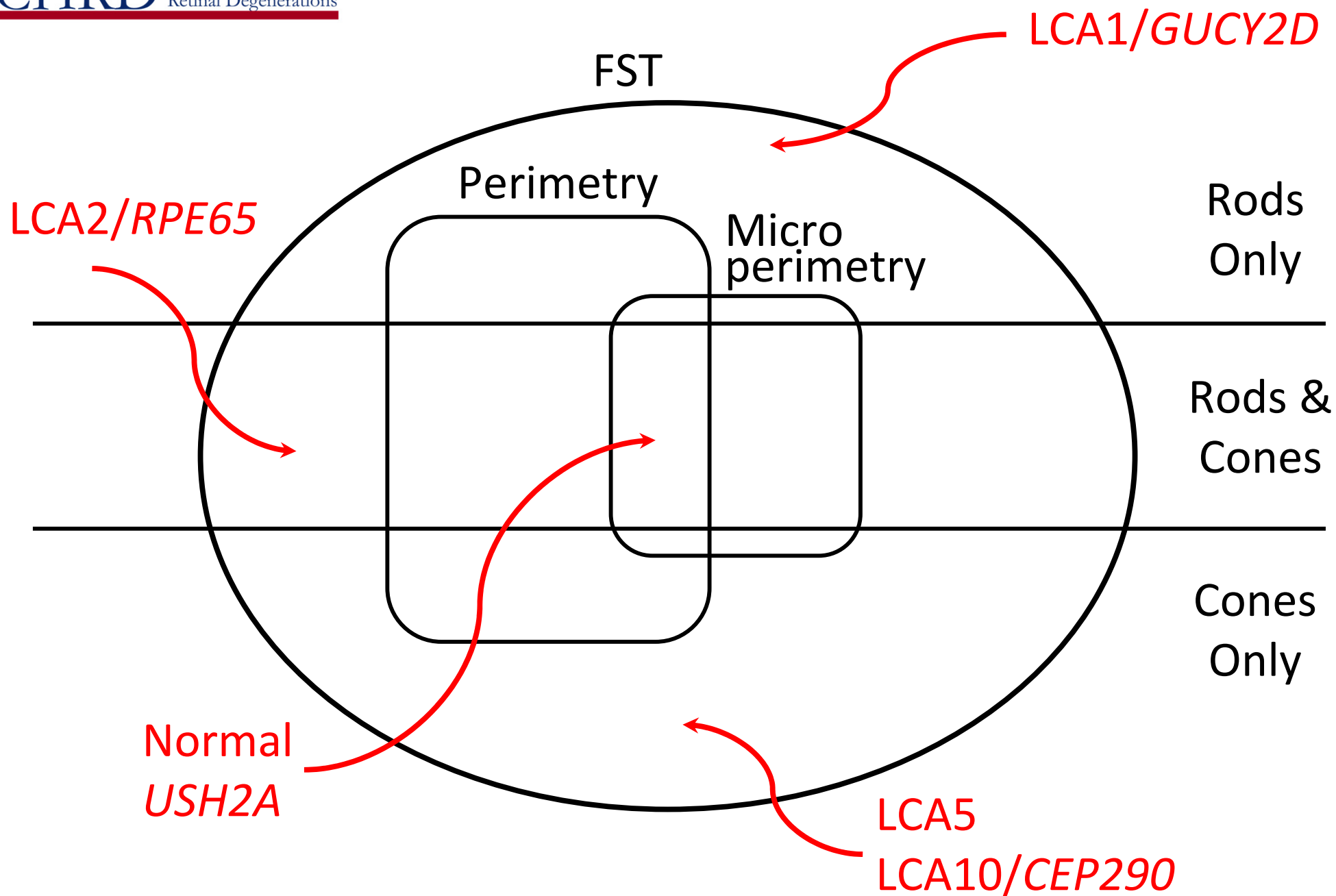
Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials

Alejandro J Roman, Artur V Cideciyan, Tomas S Aleman
and Samuel G Jacobson

Physiol. Meas. **28** (2007) N51–N56

FST (full field)





How does FST quantitatively compare to ...
Perimetry

Where does FST come from?

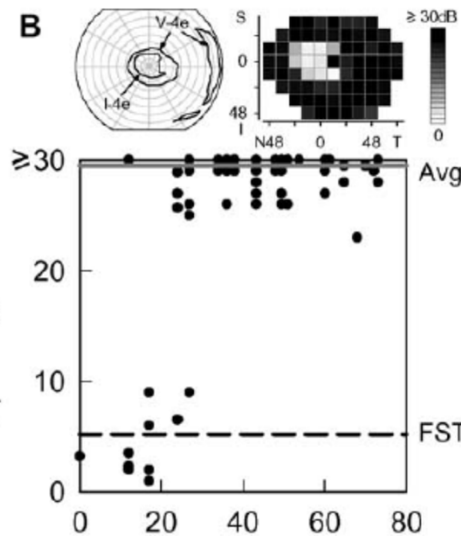
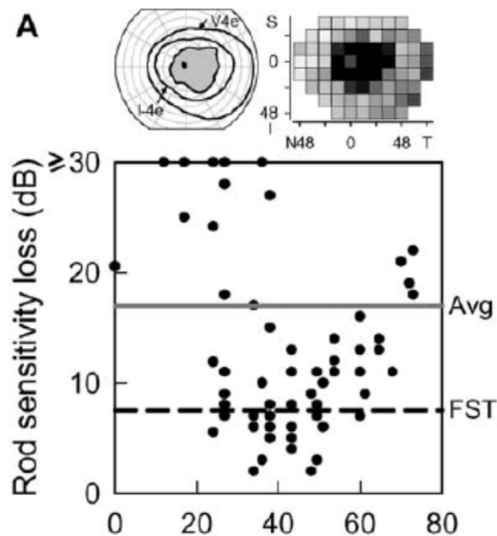


Table 1
Subject characteristics

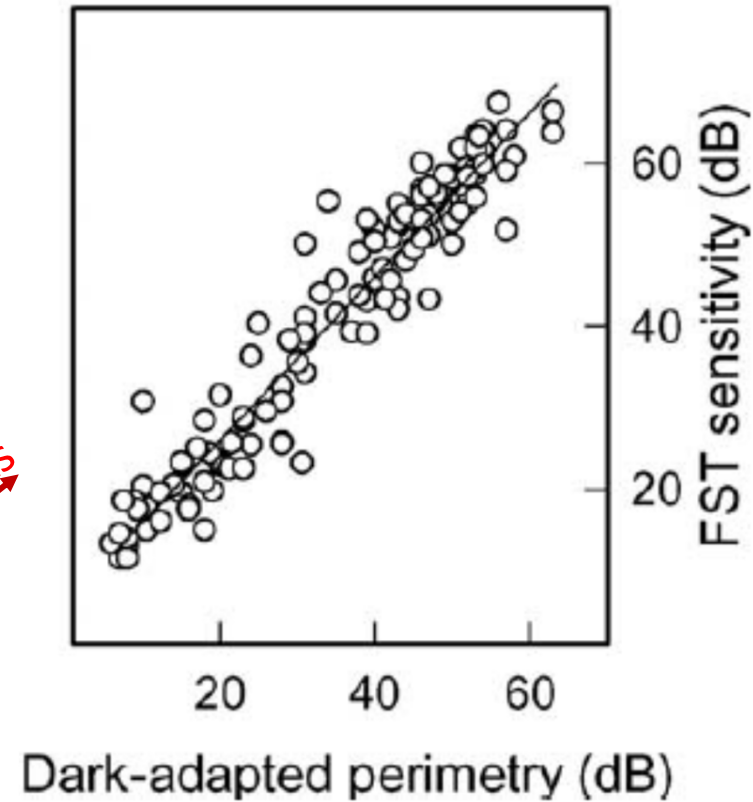
Clinical diagnosis	Subjects (n)	Gender (F/M)	Age range (mean)	Subjects with two visits ^a (n)
<i>Experiment 1</i>				
Retinal degeneration ^b	35	13/19	11–61 (34)	35
<i>Experiment 2</i>				
Retinal degeneration ^c	112	59/53	9–81 (39)	26
Cone-rod dystrophy	16	5/11	9–66 (30)	6
Maculopathy ^d	18	11/7	18–63 (43)	9

^a Fifteen subjects are included in both Experiments 1 and 2.

^b Includes retinitis pigmentosa ($n=24$), Usher syndrome types I, II ($n=3$), cone-rod dystrophy ($n=2$), choroideremia ($n=6$).

^c Includes retinitis pigmentosa ($n=78$), Leber congenital amaurosis or early onset retinal degeneration ($n=15$), Usher syndrome types I, II ($n=8$), Bardet-Biedl syndrome ($n=3$), choroideremia ($n=8$).

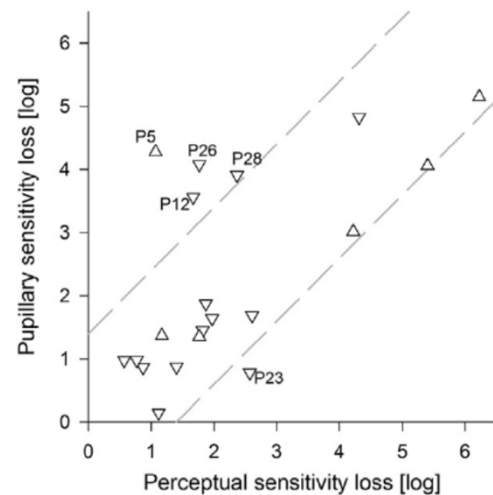
^d Includes Stargardt disease ($n=13$), autosomal dominant macular degeneration ($n=3$), early onset macular drusen ($n=2$).



146 patients

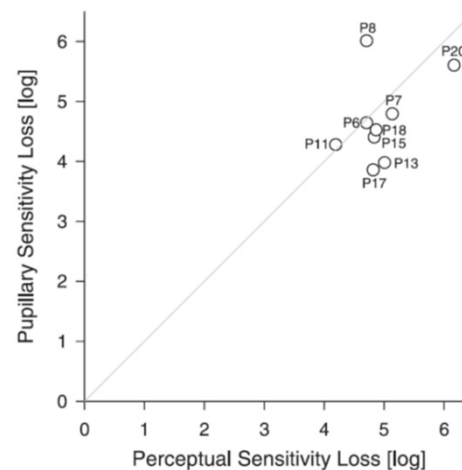


How does FST quantitatively compare to ...
Pupillary light reflex (PLR)



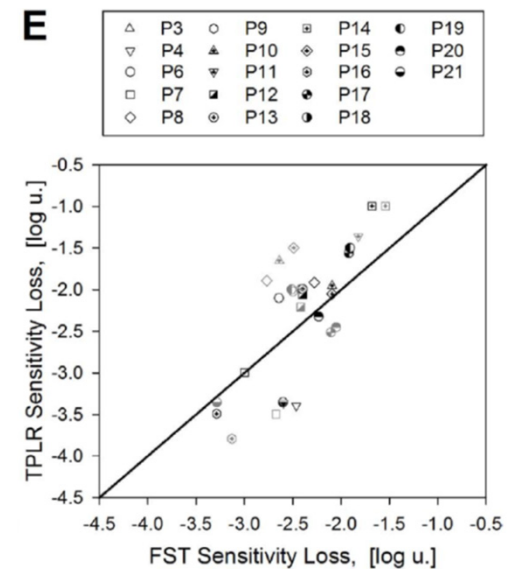
Defining Outcomes for Clinical Trials of Leber Congenital Amaurosis Caused by *GUCY2D* Mutations

SAMUEL G. JACOBSON,¹ ARTUR V. CIDECIYAN,¹ ALEXANDER SUMAROKA,¹ ALEJANDRO J. ROMAN,¹ JASON CHANG,¹ MONICA LU,¹ SHREYASI CHOUDHURY,¹ SHARON B. SCHWARTZ,¹ ELISE HEON,¹ GERALD A. FISHMAN,¹ AND SHANNON E. BOYE¹



Outcome Measures for Clinical Trials of Leber Congenital Amaurosis Caused by the Intronic Mutation in the *CEP290* Gene

Samuel G. Jacobson,¹ Artur V. Cideciyan,¹ Alexander Sumaroka,¹ Alejandro J. Roman,¹ Jason Chang,¹ Monica Lu,¹ Windy Choi,¹ Rebecca Sheplock,¹ Malgorzata Swider,¹ Mychajlo S. Kosyk,¹ Sharon B. Schwartz,¹ Edwin M. Stone,² and Gerald A. Fishman³



RDH12 Mutations Cause a Severe Retinal Degeneration With Relatively Spared Rod Function

Tomas S. Aleman,^{1,2} Katherine E. Uyhazi,¹ Leona W. Serrano,¹ Vidyullatha Vasireddy,² Scott J. Bowman,¹ Michael J. Ammar,¹ Denise J. Pearson,¹ Albert M. Maguire,^{1,2} and Jean Bennett^{1,2}

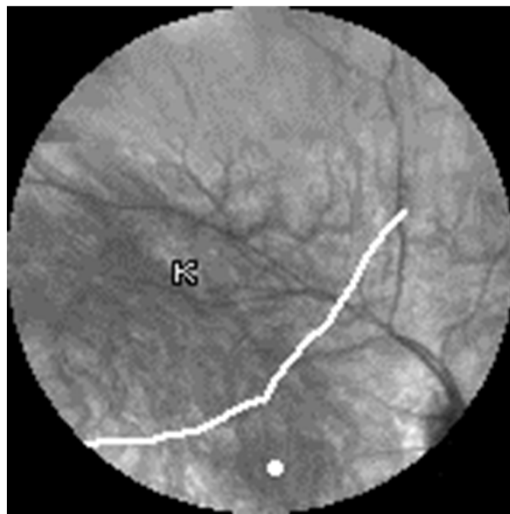
FST as outcome measure in clinical trials

- *RPE65*-LCA: Jacobson, 2008 (NIH)
- *RPE65*-LCA: Banin, 2010 (MVRF)
- *RPE65*-LCA: Bennett, 2012 (CHOP/Spark)
- End-stage RP: Ahuja, 2013 (Second Sight)
- RP: Bittner, 2014 (NIH)
- *MERTK*-RD: Ghazi, 2016 (King Salman Center)
- End-stage RP: Edwards, 2018 (Retina Implant Alpha AMS)
- *CEP290*-LCA: Cideciyan, 2019 (ProQR)
- *CNGA3*-ACHM: Fischer, 2020 (RD-CURE)
- *GUCY2D*-LCA: Jacobson, 2021 (Sanofi/Atsena)
- *CEP290*-LCA: Pierce, 2024 (Editas)
- *RLBP1*-RD: Kvanta, 2024 (Novartis)

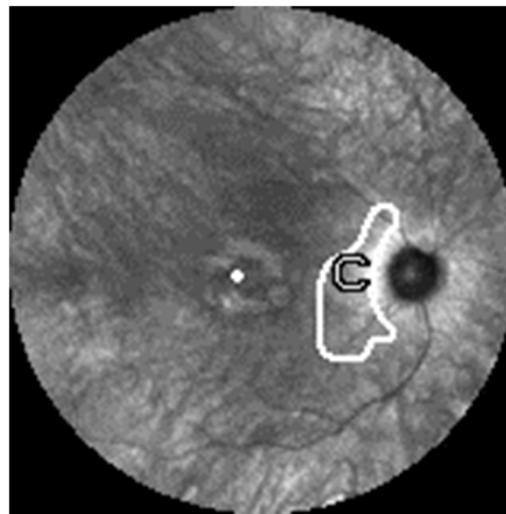
FST is not localized on the retina ...

True but neither is visual acuity when $<20/50$

Visual acuity (under retinal imaging) in *RPE65*-LCA



1.6° ~20/400

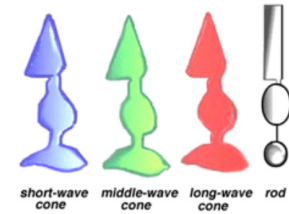


3.3° ~20/800



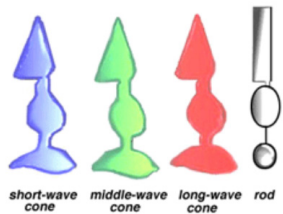
3.3° ~20/800

Key consideration:
Which type of photoreceptor driving FST?

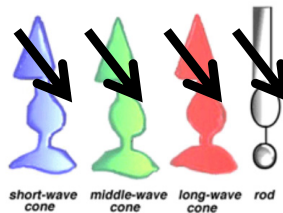


From webvision.med.utah.edu

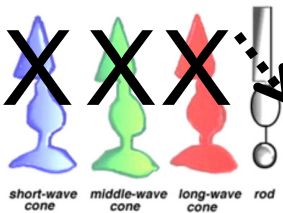
Photoreceptor types can be differentially susceptible to pathological processes and can exhibit distinct responses to therapeutic interventions.



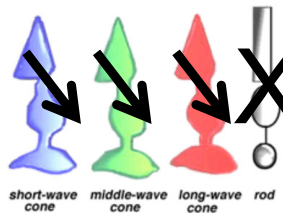
Normal



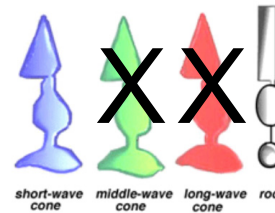
RPE65-LCA



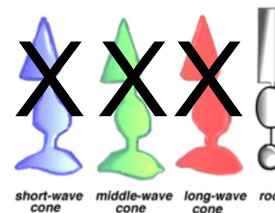
GUCY2D-LCA



CEP290-LCA



BCM



Complete ACHM

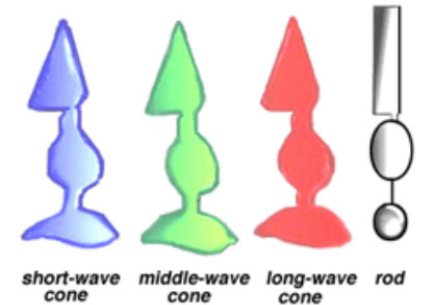
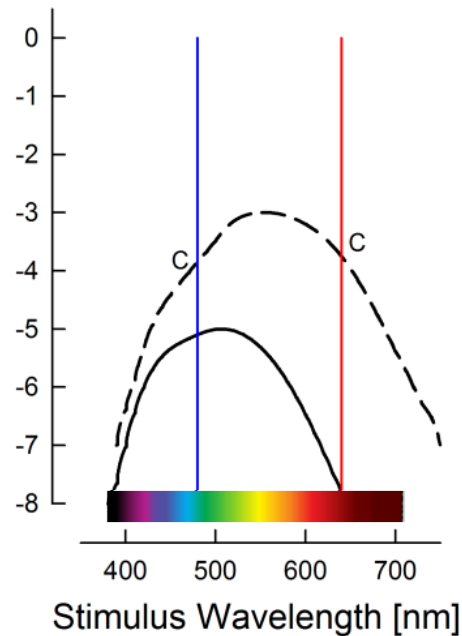
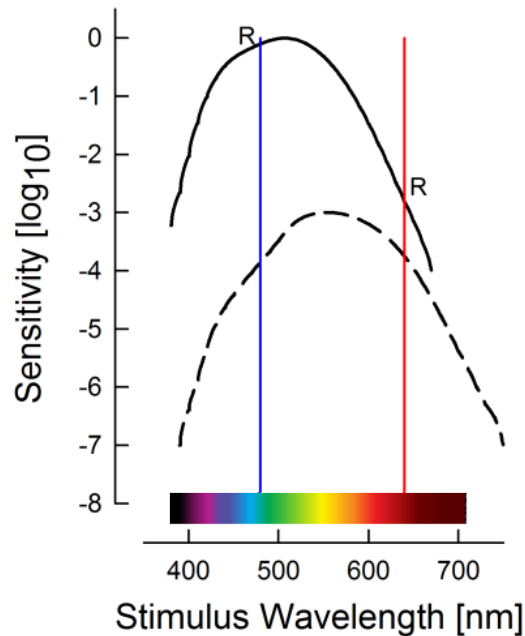


Partial loss of function



Complete loss of function

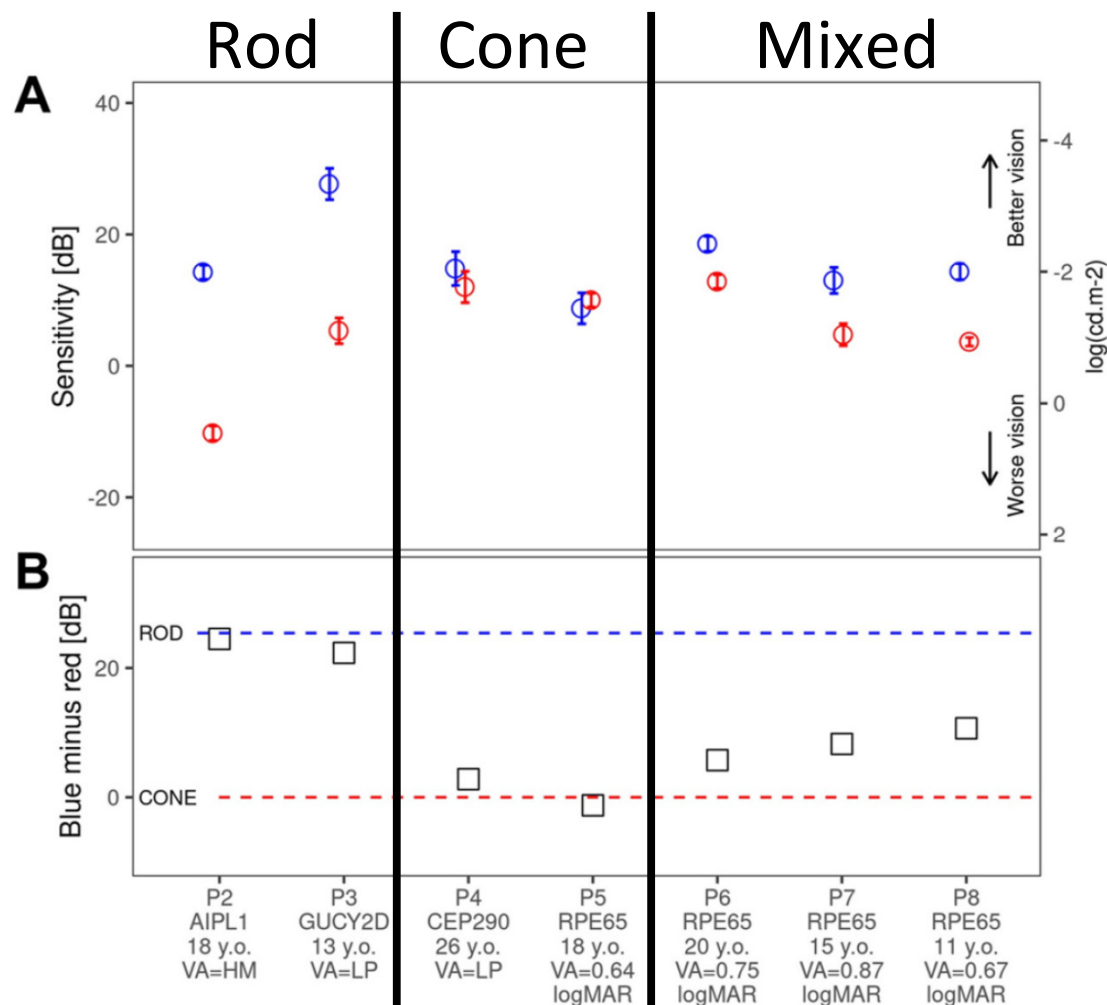
Distinguishing between rods and cones



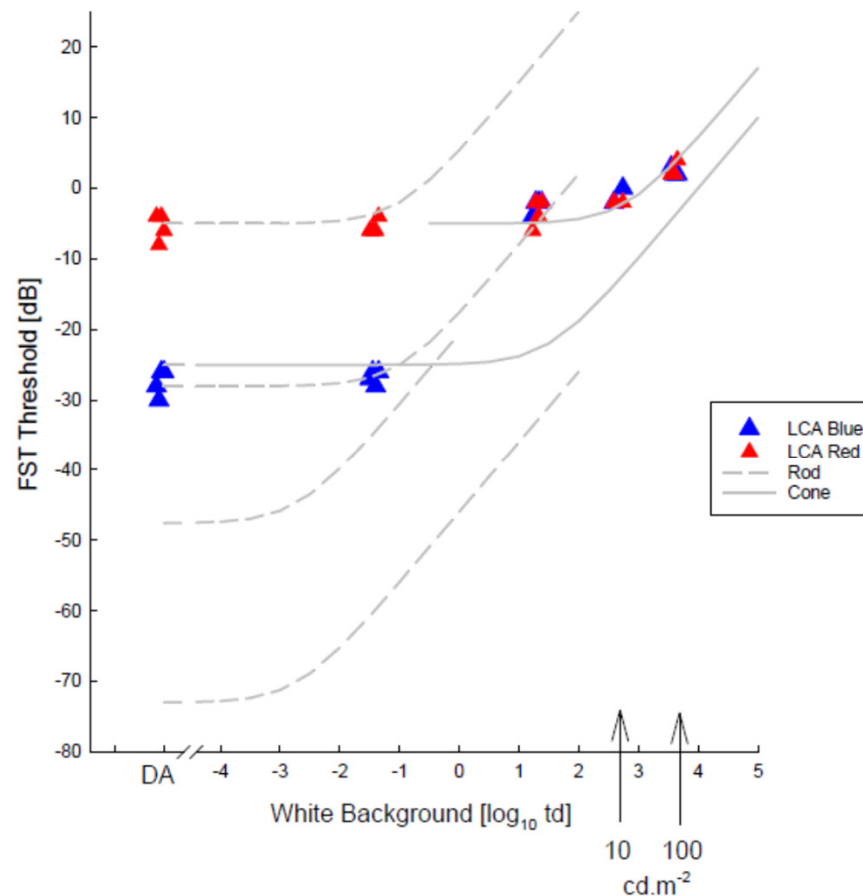
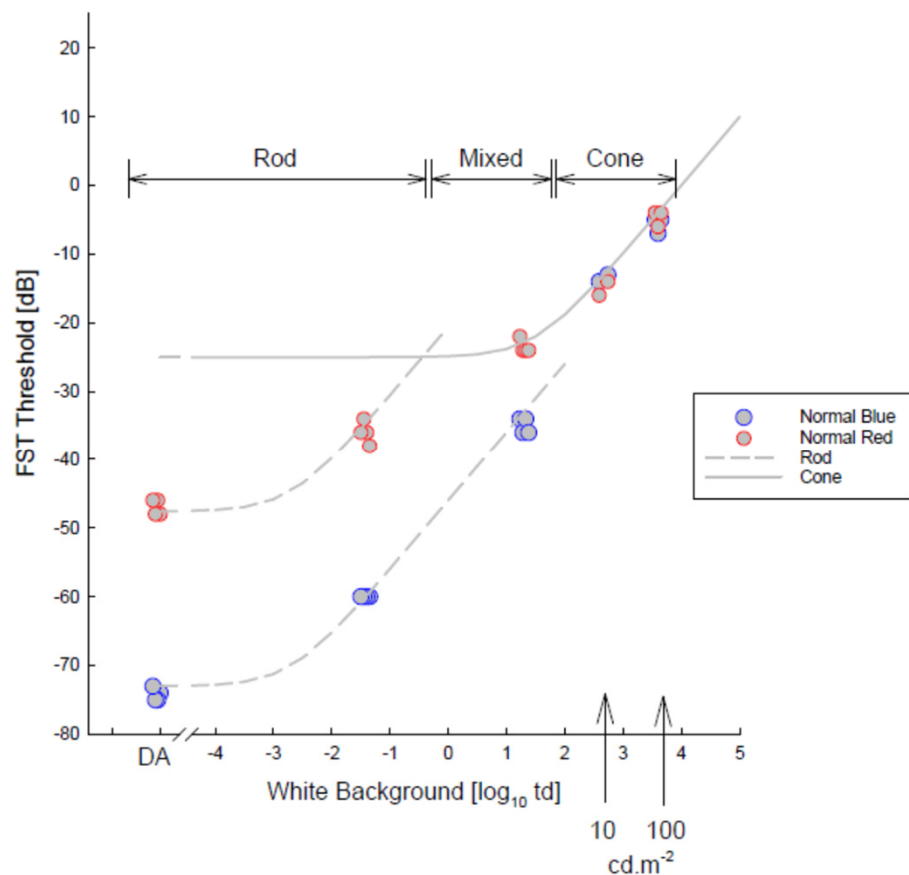
From webvision.med.utah.edu

Use of two colors to determine the dominant photoreceptor type mediating the response under dark-adapted conditions

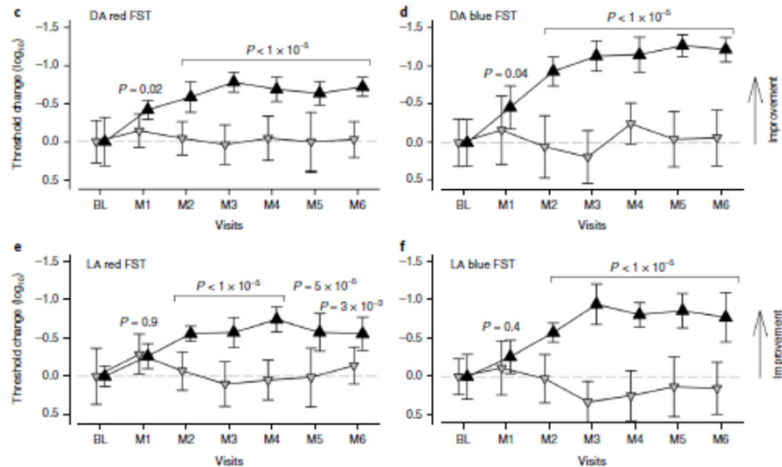
7 examples of photoreceptor mediation in severe vision loss



Evaluating cone function in retinas with retained rod function: Light-adaptation to white background

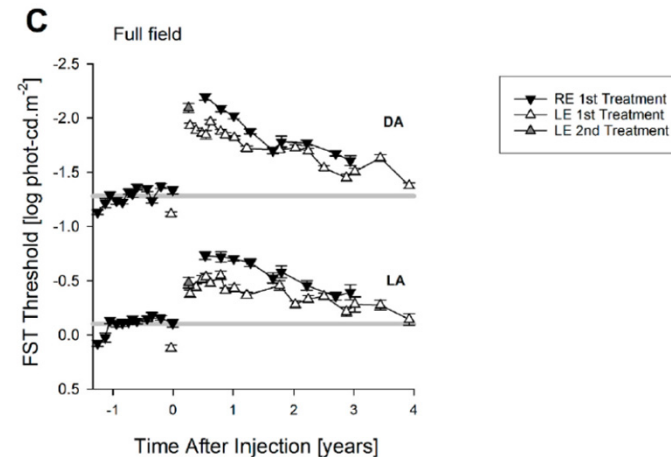


DA vs LA FST



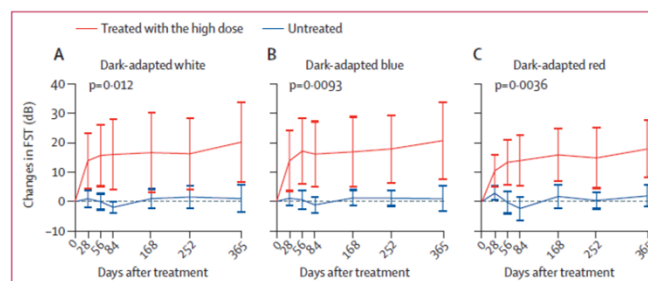
Effect of an intravitreal antisense oligonucleotide on vision in Leber congenital amaurosis due to a photoreceptor cilium defect

Artur V. Cideciyan^{1,2}, Samuel G. Jacobson^{1,2}, Arlene V. Drack¹, Allen C. Ho¹, Jason Chang¹, Alexandra V. Garafalo¹, Alejandro J. Roman¹, Alexander Sumaroka¹, Ian C. Ho¹, Maria D. Hochstetler¹, Wanda L. Pfeiffer¹, Elliott S. Silver¹, Magdalene Taylor¹, Michael R. Schwartz¹, Patricia B. Russell¹, Wilma de Wit¹, Michael E. Cheetham¹, Peter Adamson¹, David M. Rodman¹, Gerard Plonsberg¹, Maria D. Tamer¹, Vinu Balakrishna¹, Tanya Norrick¹, Julie Du Zany¹, Caroline Van Cwesenbergh¹, Bart P. Leroy¹ and Stephen R. Russell¹



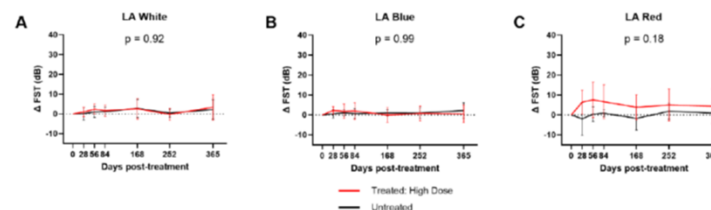
Durable vision improvement after a single intravitreal treatment with antisense oligonucleotide in *CEP290*-LCA: Replication in two eyes

Artur V. Cideciyan^{1,2}, Samuel G. Jacobson^{1,2}, Allen C. Ho¹, Malgorzata Swider¹, Alexander Sumaroka¹, Alejandro J. Roman¹, Vivian Wu¹, Robert C. Russell¹, Iryna Viarbitskaya¹, Alexandra V. Garafalo¹, Michael R. Schwartz¹, Aniz Girach¹



Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in *GUCY2D*: a phase 1/2, multicentre, open-label, unilateral dose escalation study

Paul Yang, Laura P. Pardon, Allen C. Ho, Andreas K. Lauer, Dan Yoon, Shannon E. Boye, Sanford L. Boye, Alejandro J. Roman, Vivian Wu, Alexandra V. Garafalo, Alexander Sumaroka, Malgorzata Swider, Iryna Viarbitskaya, Tomas S. Aleman, Mark E. Pennes, Christine N. Kay, Kenji P. Fujita, Artur V. Cideciyan



Personal opinions based on two decades of FST use:

- Most appropriate for detecting improvement of photoreceptor sensitivity from retina-wide severe vision loss
- Simple and fast to obtain highly quantitative data directly related to the primary function of photoreceptors
- Need to be careful interpreting underlying mediation (e.g. red is not always cones)
- Meaningful change depends on photoreceptor type
 - $>1 \log$ ($>10 \text{ dB}$) for rods
 - $>0.5 \log$ ($>5 \text{ dB}$) for cones
- FST does not localize to retina, but neither does BCVA $< 20/50$

Alejandro J. Roman, Alexander Sumaroka,
Alexandra V. Garafalo, Malgorzata Swider,
Vivian Wu, Robert Russell, Iryna Viarbitskaya,
Mariejel Weber, **and Tomas S. Aleman**



Samuel G. Jacobson

