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CLINICAL CONSORTIUM

Considerations for Clinical Trial Population for FST

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Disclosures and Funding

- **Presenter Disclosures**
  - Consultant: BlueRock Therapeutics, Janssen, Octant, Sanofi, Sepul Bio, SpliceBio, Sunovion
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Objective

- **In what patient populations could FST be an appropriate clinical trial endpoint?**
  - Which specific retinal dystrophies?
  - What disease severity?

Desirable Properties of Candidate Endpoints

Properties of assessment procedure	
Accurate	Measures the intended quantity
Reproducible	Test-retest, inter-grader, intra-grader
Range	Floor or ceiling effects within the range of interest
Objectively measured	Regulatory preference over subjective measures, reduces bias
Association with the disease	
Clinically meaningful	Directly measures (or is predictive of) how a person feels, functions, or survives
Correlation	Correlates with other measures of disease stage, duration, or rate of progression
Sensitive	Ability to detect changes early, and high “signal to noise” ratio (mean change is large relative to standard deviation)
Ability to detect “real” changes	For discrete events, change is greater than measurement error
Feasibility	
Low cost	Equipment, training, independent expert assessments
Availability	Equipment available at clinical sites
Ease of test administration	Level of study personnel training needed
Ability to perform	Study population considerations (e.g., very young age, poor ocular media clarity)
Goals of future trial	
Phase of trial	Early (exploratory) or late (must demonstrate clinically significant change)
Expected benefit of treatment	Reverse (improve) or stop/slow disease progression
Biological considerations	Mechanism or site of action

Ayala et al., The Importance of Natural History Studies in Inherited Retinal Diseases, Cold Spring Harbor Laboratory Press, 2023

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Example #1: *CEP290*-associated retinal dystrophy

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Twelve-month Natural History Study of Centrosomal Protein 290 (CEP290)-associated Inherited Retinal Degeneration

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Purpose: To define the clinical characteristics of centrosomal protein 290 (*CEP290*)-associated inherited retinal degeneration (IRD) and determine which assessments may provide reliable endpoints in future interventional trials.

Design: Participants in this natural history study were enrolled into 2 best-corrected visual acuity (BCVA) cohorts: light perception to $>$ 1.0 logarithm of the minimum angle of resolution (logMAR) and 1.0 logMAR to 0.4 logMAR. Each comprised 4 age cohorts (3–5, 6–11, 12–17, and $\geq$ 18 years).

Participants: Patients with *CEP290*-associated IRD caused by the intron 26 c.2991+1655A>G mutation and BCVA ranging from light perception to 0.4 logMAR.

Methods: Best-corrected visual acuity, full-field stimulus threshold (FST) sensitivity, Ora–Visual Navigation Challenge (Ora–VNC) composite score, and OCT–outer nuclear layer (OCT–ONL) average thickness were assessed at screening, baseline, 3 months, 6 months, and 12 months.

Main Outcome Measures: Best-corrected visual acuity, FST sensitivity, Ora–VNC composite score, and OCT–ONL average thickness.

Results: Twenty-six participants were included in this analysis. Nineteen were female. All participants were White and 4 reported Hispanic ethnicity. At screening, 13 of 16 adult and 9 of 10 pediatric participants had BCVA $>$ 1.0 logMAR. Baseline BCVA was variable (median [range] = 2.0 [0.5, 3.9] logMAR) and was uncorrelated with age, as were VNC composite score, FST sensitivity, and OCT–ONL average thickness. Mean (95% confidence interval [CI]) test-retest variability was −0.04 (−0.09, 0.01) logMAR for BCVA (n = 25); 0.6 (−0.1, 1.3) for VNC composite score (n = 18); and 0.10 (−0.07, 0.27) log cd.s/m^2 for red FST (n = 14). A greater than expected test-retest variability (5 [0, 10] µm, n = 14) was observed for OCT–ONL average thickness as nystagmus impacted ability to repeat measures at the same retinal location. Functional assessments were stable over 12 months. Mean (95% CI) change from baseline was 0.06 (−0.17, 0.29) logMAR for BCVA (n = 23); −0.1 (−1.2, 1.0) for VNC composite score (n = 21); and −0.15 (−0.43, 0.14) log cd.s/m^2 for red FST (n = 16).

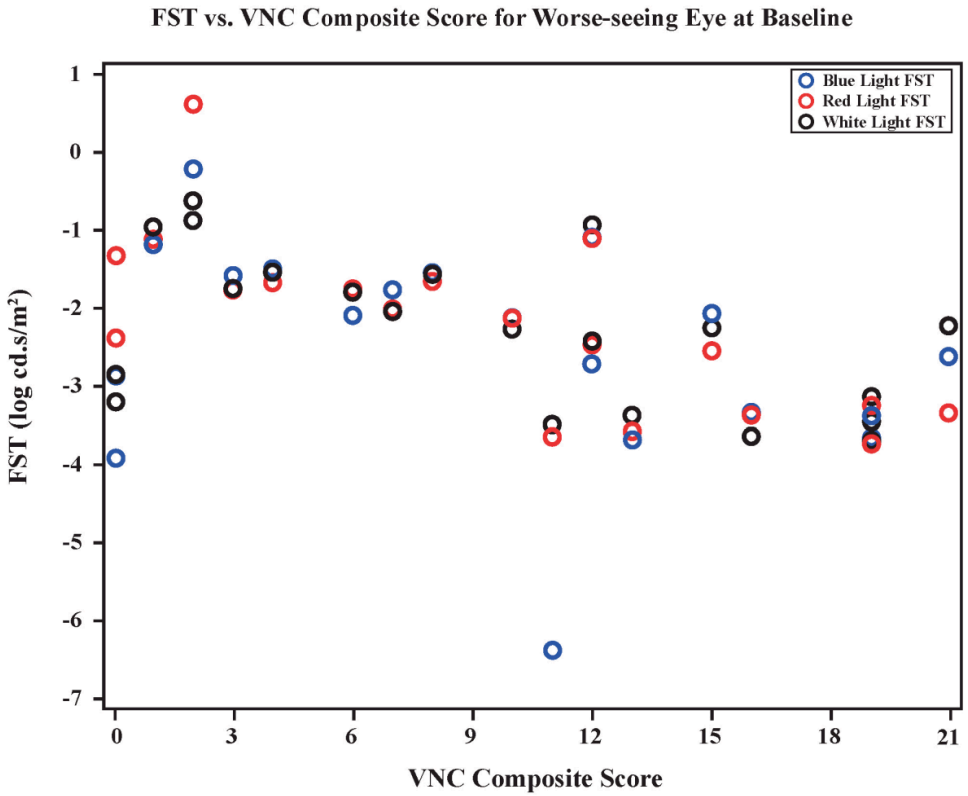
Conclusions: Vision was stable over 12 months. Best-corrected visual acuity, FST, and VNC composite score are potentially viable endpoints for future studies in CEP290-associated IRD. Repeatability of OCT measures poses challenges for quantifying anatomical changes in this population.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2024;4:100483*

- N = 16 adults and 10 children
- Majority of adults and children had BCVA worse than 1.0 logMAR
- FST (red, white, blue) presented twice at baseline and then every 3 months for one year

Assessment Test-Retest Variability and Stability in the Worse Eye

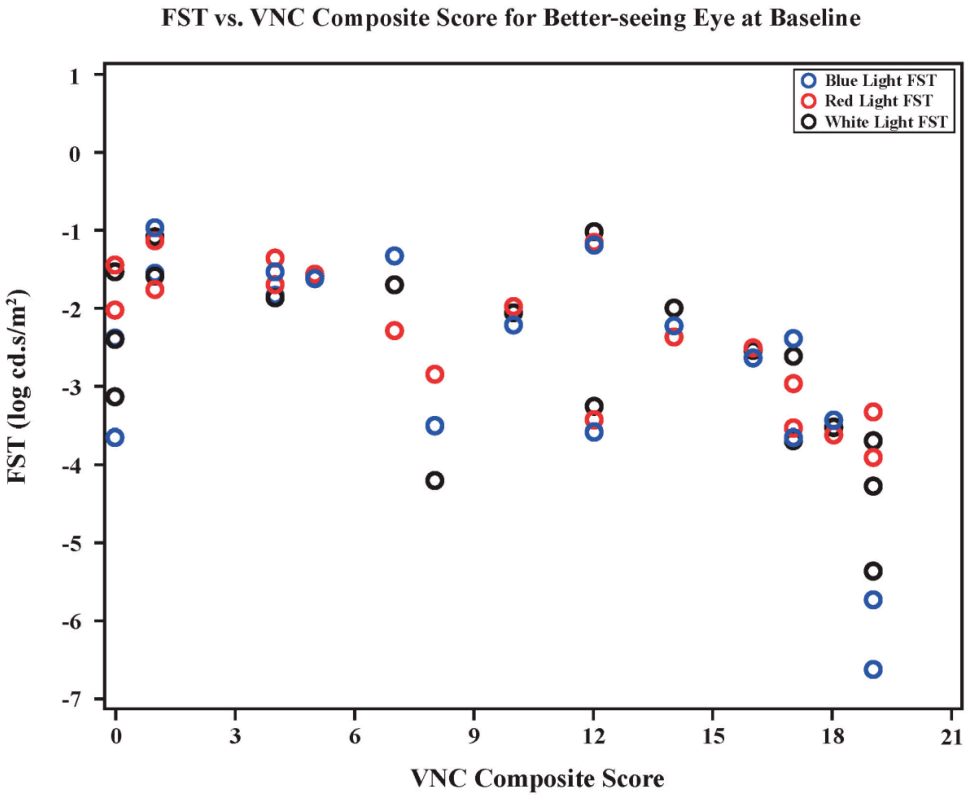
Assessment	Mean (SD) [n] of Worse Eye at Baseline	Test-Retest	Mean (95% CI) [n] Change from Baseline in Worse Eye		
			M3	M6	M12
BCVA (logMAR)	2.18 (1.17) [26]	−0.04 (−0.09, 0.01) [25]	0.09 (−0.02, 0.20) [24]	0.04 (−0.08, 0.15) [20]	0.06 (−0.17, 0.29) [23]
Blue light FST (log cd.s/m^2)	−2.41 (1.42) [20]	0.17 (−0.38, 0.73) [16]	−0.43 (−1.00, 0.13) [14]	−0.05 (−0.23, 0.13) [14]	−0.33 (−0.88, 0.21) [17]
Red light FST (log cd.s/m^2)	−2.15 (1.13) [20]	0.10 (−0.07, 0.27) [14]	−0.15 (−0.37, 0.07) [13]	−0.10 (−0.30, 0.10) [13]	−0.15 (−0.43, 0.14) [16]
White light FST (log cd.s/m^2)	−2.22 (1.03) [22]	0.16 (−0.24, 0.56) [18]	−0.32 (−0.91, 0.27) [15]	−0.16 (−0.48, 0.15) [16]	−0.39 (−1.02, 0.24) [19]



Blue: r= -0.3473, p=0.1451

Red: r= -0.7214, p=0.0005

White: r= -0.5398, p=0.0115



Blue: r= -0.5868, p=0.0083

Red: r= -0.7900, p<0.0001

White: r= -0.6048, p=0.0047

Ophthalmology Science 2024;4:100483

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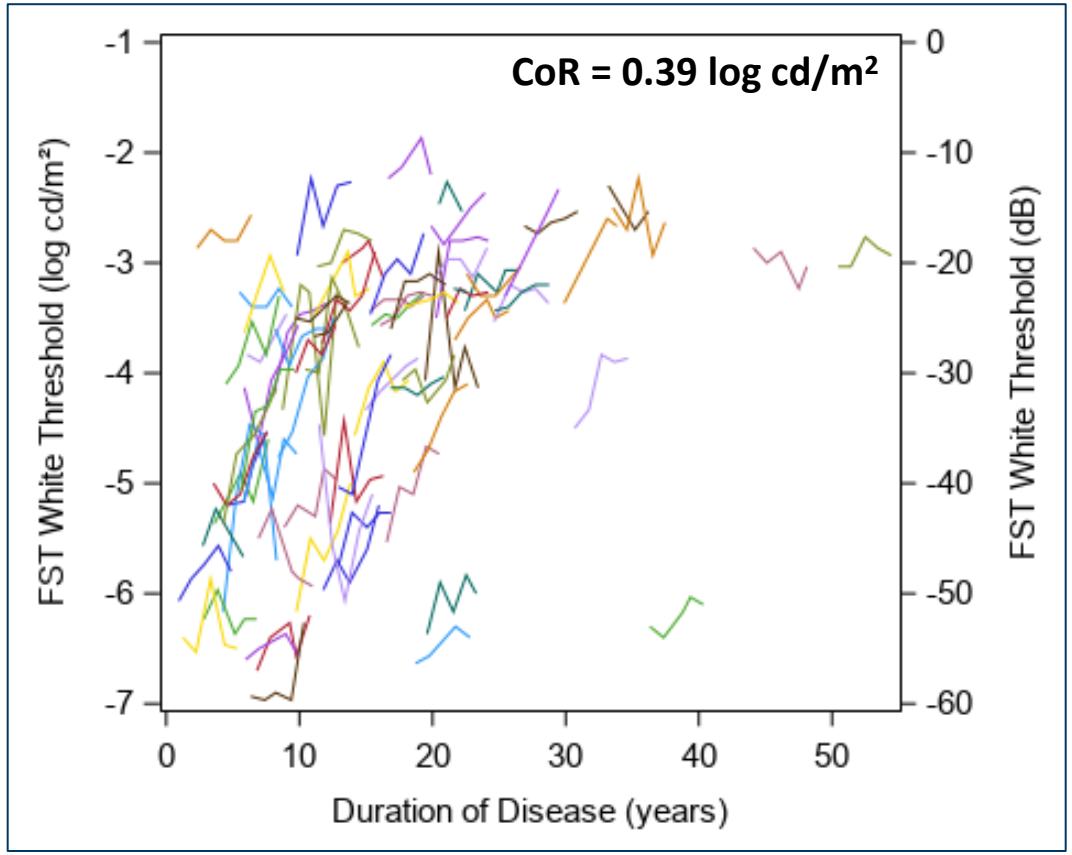
Example #2: *USH2A*-associated retinal degeneration & the RUSH2A study

RUSH2A FST Data Over 4 Years

Full-field stimulus threshold (FST) for white stimulus



- N = 103 participants
- BCVA ≥ 20/50
- Correlated with baseline EZ area (r=-0.73) and disease duration (r=0.51)
- Negligible floor effect
- Low test-retest variability
- High standardized rate of change

Estimated Annual Rates of Change

☑ Sensitive measure of disease progression

Slope Estimate	Change in log cd/m²		% Change in log cd/m²	
	Equally weighted model	Outliers down-weighted	Equally weighted model	Outliers down-weighted
	N=77	N=77	N=77	N=77
White Stimulus	0.09	0.09	22.6	22.3
Blue Stimulus	0.10	0.09	26.0	24.3
Red Stimulus	0.05	0.05	12.3	11.6

Comparison with other endpoints

	BCVA	EZ area*	SP MS_{CW}*	MP MS*	FST
Standardized rate of change	-0.89	-0.95	-1.58	-1.01	1.09

* Preserved cohort

Birch et al, Ophthalmology Science 2025;5(2)

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Highest % of Eyes Exceeding Coefficient of Repeatability (CoR)

- ☑ Low test-retest variability
- ☑ Ability to detect "real" changes
- ☑ Significant changes are evident quickly

FST Range of measurement is -7 to -2 log cd.s/m2 (so CoR value of 0.39 is comparatively low)

	SP V_{TOT} dB-sr	SP V_{30} dB-sr	SP V_{PERIPH} dB-sr	SP MS dB	MP MS dB	BCVA Letters	FST log cd.s/m²
CoR – i.e. "real" change	14.0	3.4	11.4	3.5	2.2	8.8	0.39
N at 2 Years	77	78	68	78	70	88	69
% Worsening at 2 Years	8%	8%	9%	12%	14%	5%	30%
% Improving at 2 years	1%	1%	1%	1%	1%	1%	3%
N at 4 Years	78	80	67	79	72	95	66
% Worsening at 4 Years	21%	24%	27%	19%	33%	12%	47%
% Improving at 4 years	0%	0%	1%	0%	3%	0%	3%

MP – Microperimetry; MS – mean sensitivity; SP – static perimetry

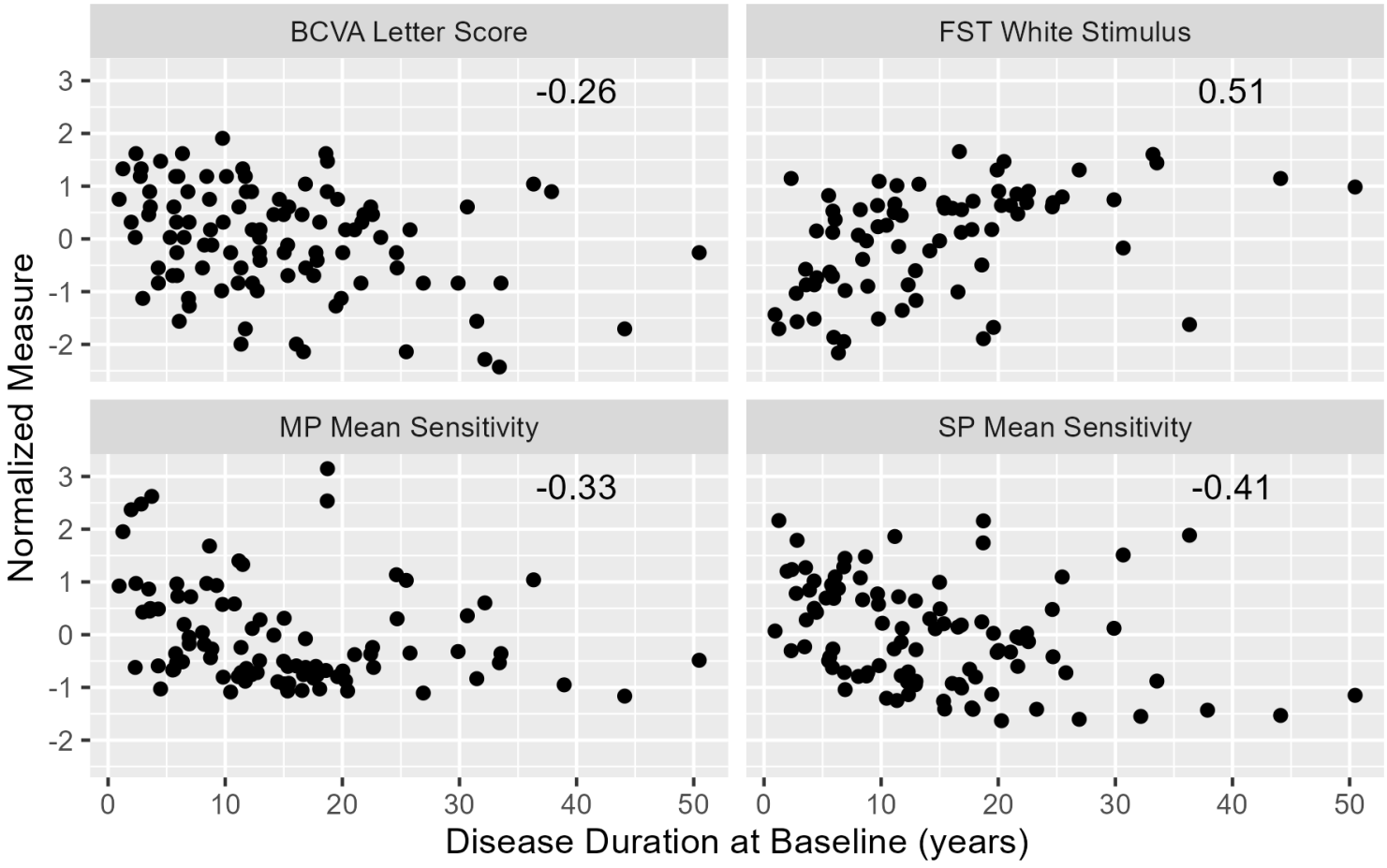
Disease Duration vs Baseline FST

☑ Correlates with disease duration

Disease Duration	N	FST White (log cd/m²) Mean ± SD
<10 yrs	23	-4.70 ± 1.26
10-<20 yrs	27	-4.00 ± 1.03
≥20 yrs	16	-3.14 ± 0.89

P=0.004 from multivariate model

Spearman Correlation *Ordered by strength of correlation at Baseline*		95% CI
FST White	0.51	(0.32, 0.66)
EZ Area	-0.50	(-0.63, -0.33)
SP V_{30}	-0.43	(-0.58, -0.26)
SP MS	-0.41	(-0.56, -0.24)
SP V_{TOT}	-0.37	(-0.53, -0.19)
SP V_{PERIPH}	-0.34	(-0.50, -0.15)
MP MS	-0.33	(-0.50, -0.14)
BCVA	-0.26	(-0.44, -0.07)



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Mediation Type

☑ Able to capture specific functional changes in disease (can delineate rod vs cone function)

Changes are in the expected direction:

12 eyes changed from **rod-mediated** at Baseline to mixed- or cone-mediated at Year 4

0 eyes changed from **cone-mediated** at Baseline to mixed or rod-mediated at Year 4

Baseline	Year 4		
	Rod Mediated	Mixed	Cone Mediated
Rod Mediated	19	5	1
Mixed	0	8	6
Cone Mediated	0	0	27

Based on Blue - Red

Rod mediated: > -2.0 log cd/m^2

Mixed: -2.0 to -1.0 cd/m^2

Cone mediated: < -1.0 log cd/m^2

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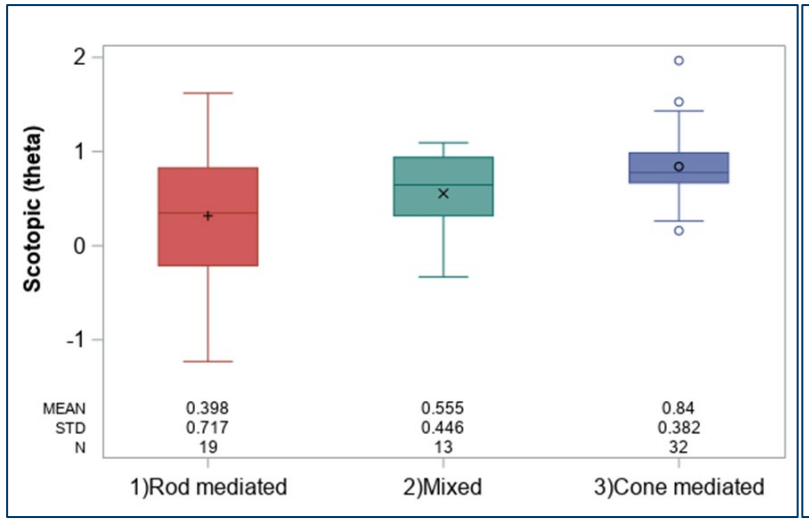
PRO Results at Year 4 (MRDQ)

☑ Correlates with patient reports

Significant difference between rod- vs cone- mediated groups for the following domains

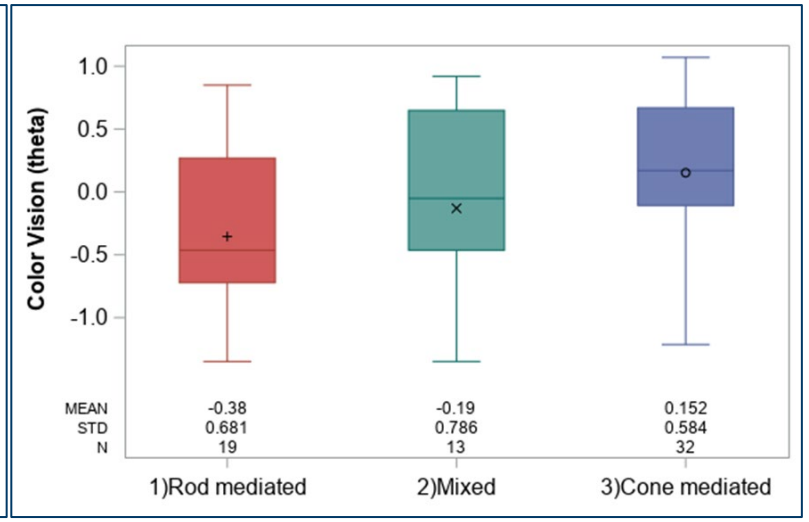
SCOTOPIC

-0.44 (*P*=0.02)



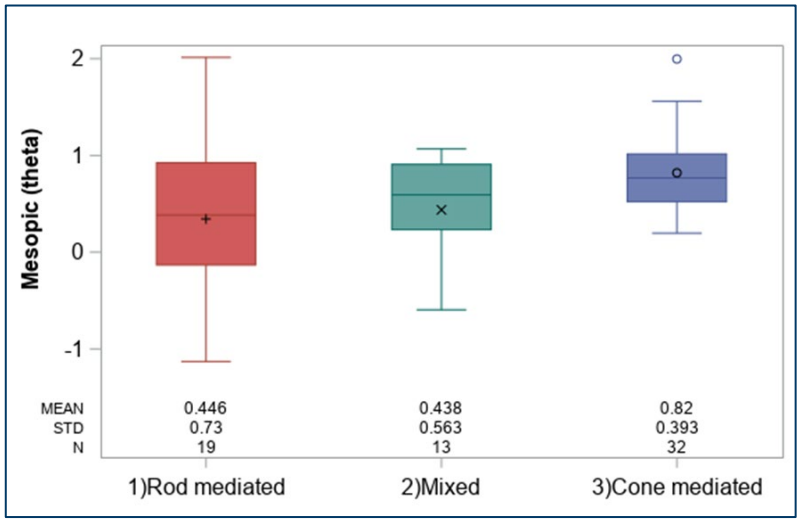
COLOR VISION

-0.54 (*P*=0.007)



MESOPIC

-0.37 (*P*=0.04)



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Preliminary Data from Pro-EYS

Correlation with PROs at Baseline

Further preliminary support that FST correlates with how patients feel/function

Measure	ViSIO Total	MRDQ Photopic	MRDQ Scotopic	MRDQ Mesopic	VALVVFQ-48 Mobility	PROMIS Physical	PROMIS Anxiety
FST White	**0.57**	**0.65**	**0.59**	**0.57**	**0.61**	**0.55**	**0.54**
MP MS	**0.45**	**0.56**	**0.40**	**0.37**	**0.50**	**0.31**	**0.22**
SP MS	**0.45**	**0.64**	**0.44**	**0.49**	**0.46**	**0.43**	**0.23**
SP V_{TOT}	**0.42**	**0.63**	**0.45**	**0.52**	**0.41**	**0.41**	**0.20**
SP V_{30}	**0.43**	**0.62**	**0.44**	**0.48**	**0.43**	**0.39**	**0.26**
SP V_{PERIPH}	**0.35**	**0.56**	**0.43**	**0.48**	**0.33**	**0.34**	**0.12**
BCVA	**0.44**	**0.43**	**0.36**	**0.37**	**0.42**	**0.41**	**0.27**
LLVA	**0.45**	**0.44**	**0.37**	**0.37**	**0.41**	**0.38**	**0.28**

Note: Correlations with FST are positive, all others are negative

MP – Microperimetry; MS – mean sensitivity; SP – static perimetry

Summary

FST has many good candidate endpoint properties

- ✓ Relatively low patient burden and subjectivity, comparable to visual acuity
- ✓ Minimal floor effect (worsening occurred for majority of patients)
- ✓ Sensitive measure of disease progression
- ✓ Good reproducibility (low test-retest variability)
- ✓ High percentage of eyes exceeding threshold for “real” change
- ✓ Significant changes are evident quickly
- ✓ Correlates with disease duration
- ✓ Able to delineate specific functional changes in disease (rod vs cone)
- ✓ Correlates with direct measures of how a patient feels or functions

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Open questions

Open questions

- **How generalizable are these properties and strengths?**
  - Opportunities to answer this question with ongoing Consortium studies
- **Study-specific considerations**
  - Mechanism of action
  - Disease severity targeted
  - Expectation for outcome