FOUNDATION FIGHTING BLINDNESS
CLINICAL CONSORTIUM

REDI Working Group: FST Data Review

Ocular Disease Forum - Sept 28, 2024

David Birch, PhD

Presented on behalf of the Foundation Fighting Blindness Clinical Consortium Investigator Group & REDI Working Group

Disclosures and Funding

Speaker	Disclosures
David Birch	AGTC/Beacon (F), 4D MT (F), PYC Therapeutics (F), Ocugen (F), Scientific Advisory Board for Nacuity Pharma (S), Editas (C), 4D MT(C), PYC Therapeutics (C), ONL Therapeutics (C), Bluerock Therapeutics (C), Aldyra (C).

Funding provided by Foundation Fighting Blindness

Full Field Stimulus Threshold (FST)

- **A test of vision that is:**
  Subjective (requiring patient responses)
  Non-subjective in its interpretation (automatically calculates threshold and quality score)
- **Patient burden and subjectivity comparable to ETDRS visual acuity**
- **Measures the lowest luminance of a flash that can be detected by the patient**
- **Reflects the response of photoreceptors with the greatest dark-adapted sensitivity and best function**
- **Does not identify retinal location of highest sensitivity**
- **Predicts performance on multi-luminance mobility testing**

Measurement of FST in RUSH2A

- **Full-field stimulus threshold (FST) performed on the Espion E3 (Diagnosys)**
- **White, blue and red stimuli**
- **The value of 0 dB was set to -1 log cd.s/m²**
- **FST thresholds reported in log cd.s/m² were converted from dB:**

$$\log \text{cd.s/m}^2 = \text{dB}/10 - 1.0$$

- **% Change in FST sensitivity can be calculated from estimated change in – dB:**

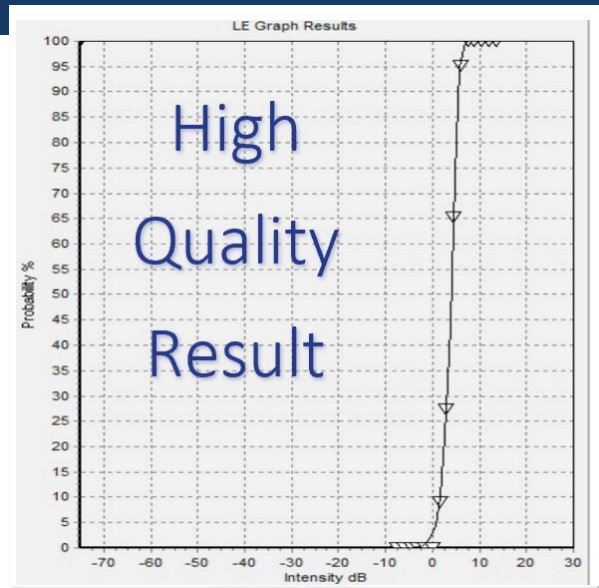
$$\%change\ in\ sensitivity = 100 \times (10^{\Delta/10} - 1)$$

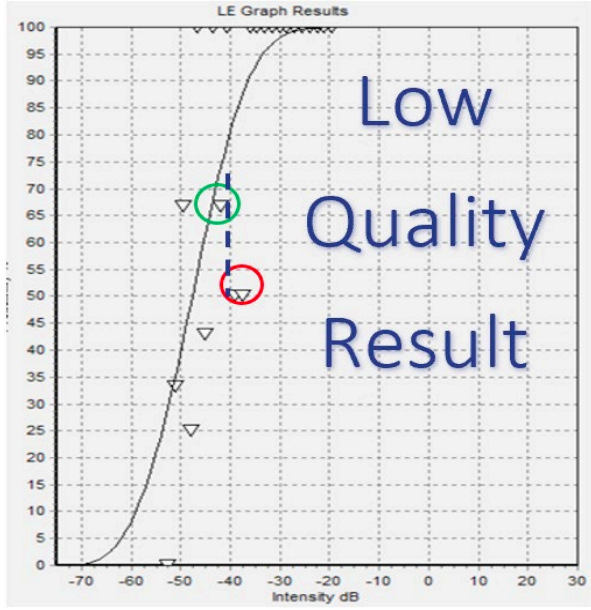
Where Δ = estimated annual change in – dB

- **Thresholds measured in triplicate for each color and averaged for analyses of each eye**
- **Analysis Cohort: Study eyes that have test results at 2 or more time points (N=77)** *(Only performed at subset of sites with Espion E3)*

Testing and Quality Assessment

- Each test takes about 1.5 minutes to conduct
- During each test 30-40 flashes are presented to the subject, and 30-40 responses are recorded
- A Weibull function is used to do a best fit of the responses
- The quality algorithm assesses the consistency of all responses, and reports a score on a scale of 0 to 3 (3 being highest)
- The graph enables evaluation by the tester during the test for quality assessment and subject feedback



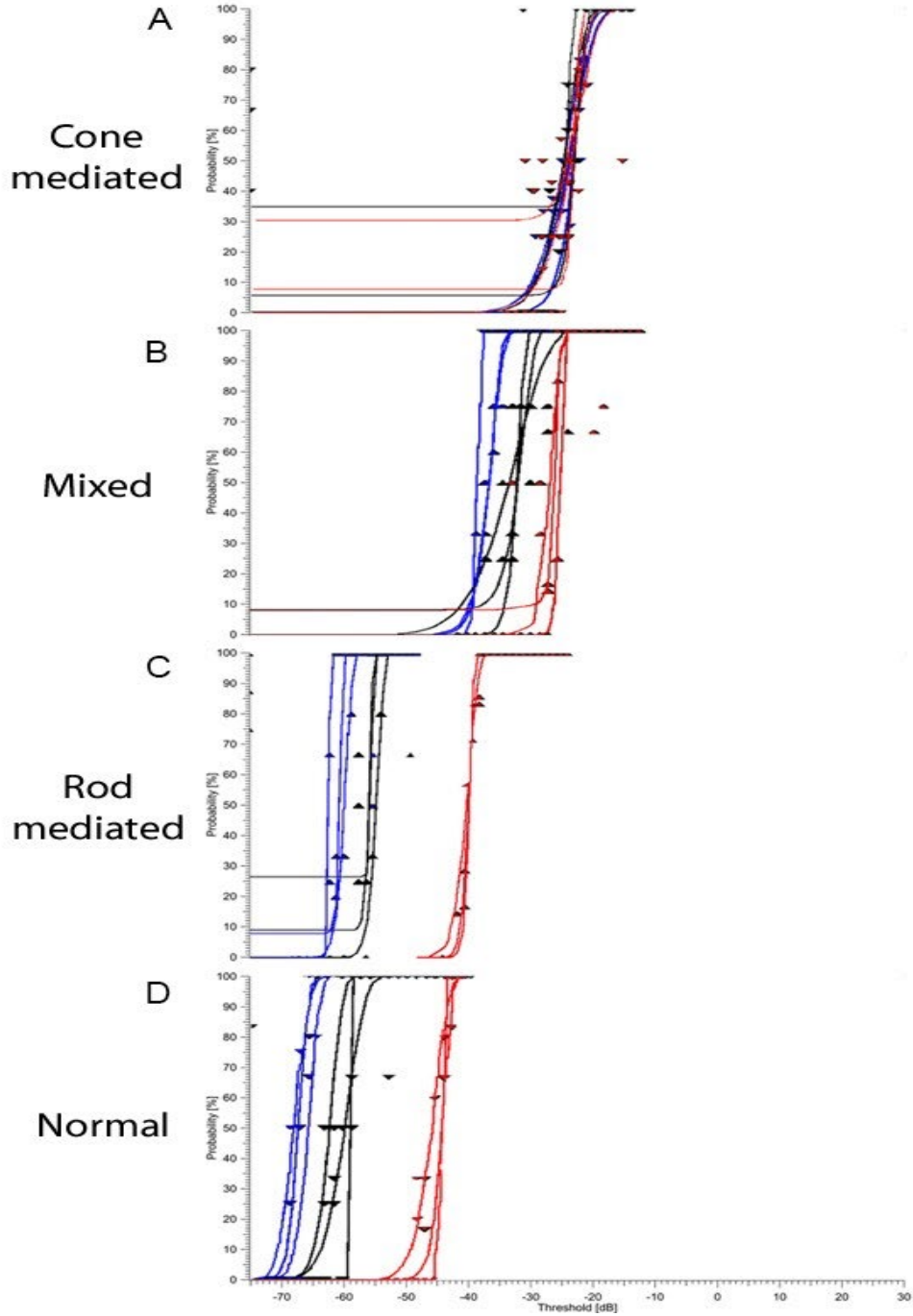


Baseline Examples

FST Results from Three RUSH2A Participants and One Normal Subject

Black, blue and red colors represent responses from white, blue and red stimuli respectively

A) Cone-mediated (USH2, age 55 years)
B) Mixed (USH2, age 19 years)
C) Rod-mediated (USH2, age 61)
D) Normal (age 25)



FOUNDATION FIGHTING BLINDNESS
CLINICAL CONSORTIUM

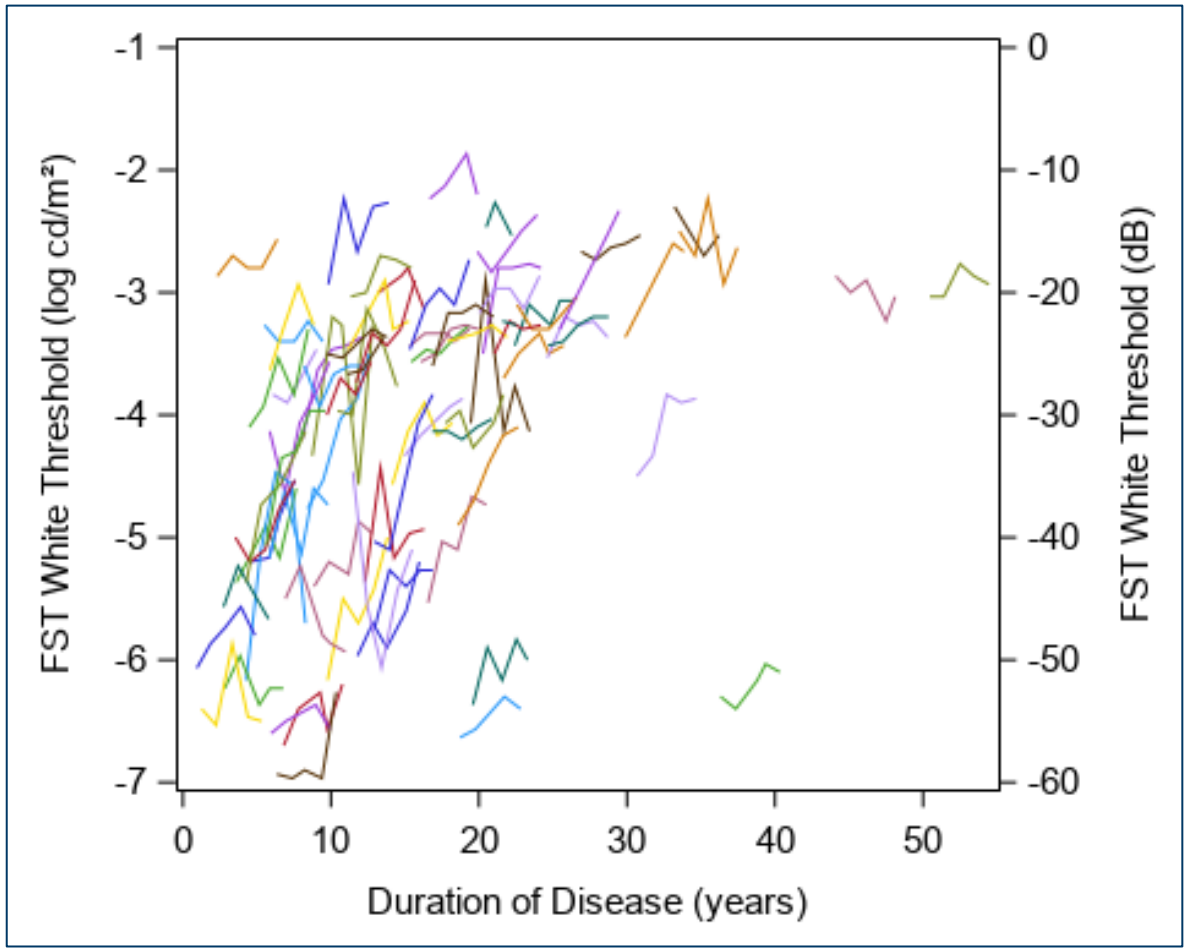
Review of Endpoint Properties

FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

RUSH2A FST Data Over 4 Years

☑ Minimal floor effect (worsening occurred for majority of patients)

Full-field stimulus threshold (FST) for white stimulus



The left y-axis presents the values in log cd/m^2; the right y-axis is in dB

FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

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

FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

Highest % of Eyes Exceeding 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	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%

Making the Case for Clinical Relevance

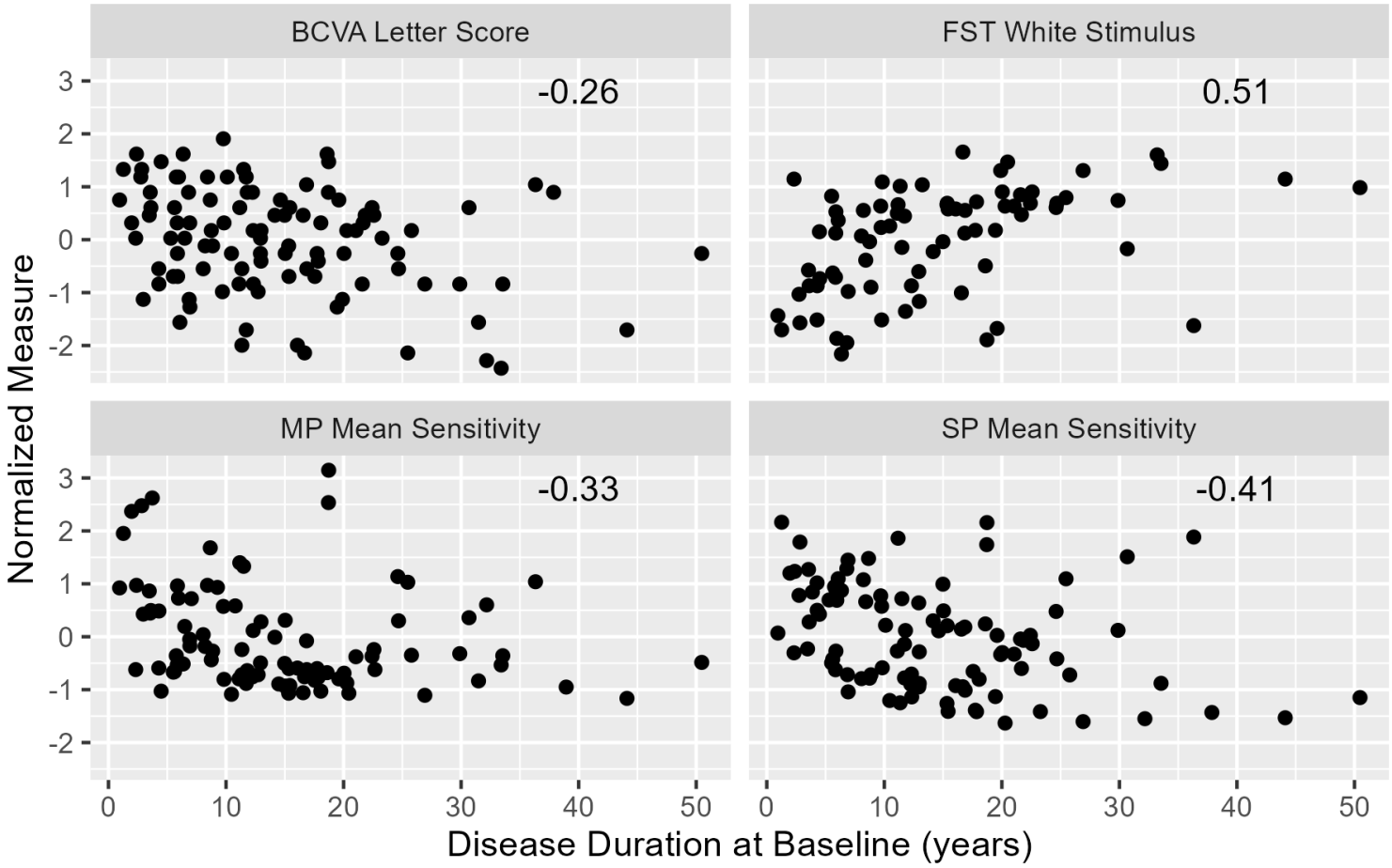
Disease Duration vs FST at Baseline

☑ 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)



Mediation Type

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

Changes are in the direction you would expect –

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

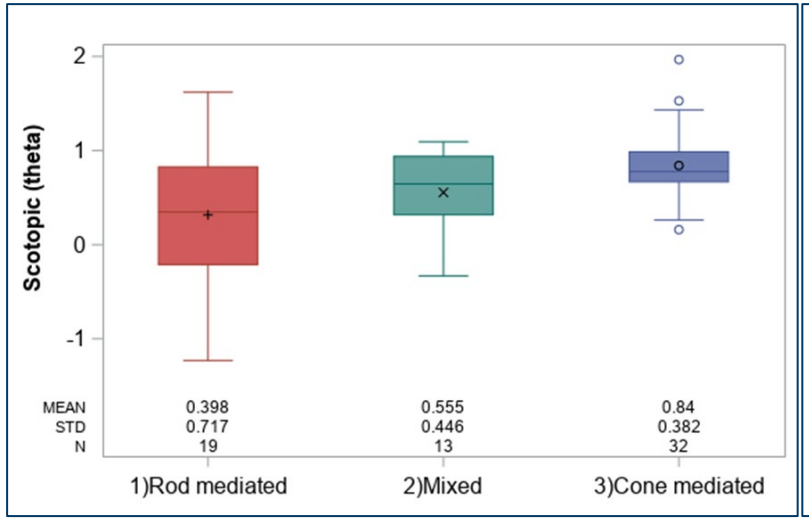
Cone mediated: < -1.0 log cd/m^2

PRO Results at Year 4 (MRDQ)

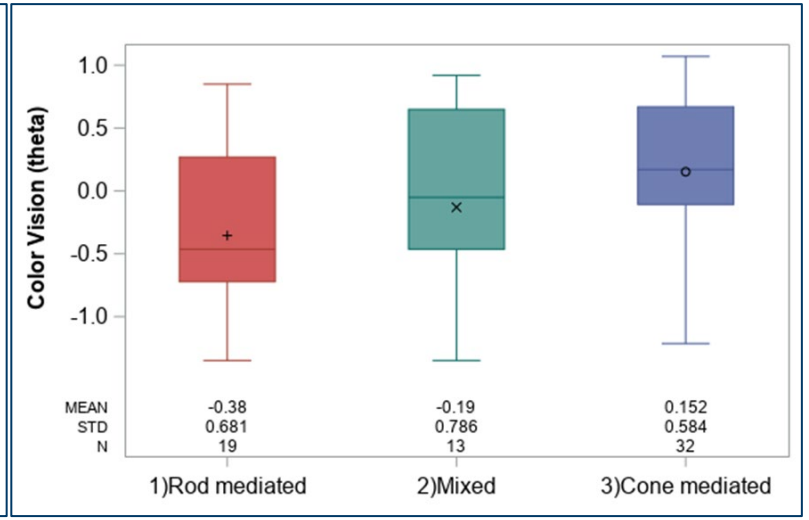
☑ Correlates with how patients report feeling and functioning

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

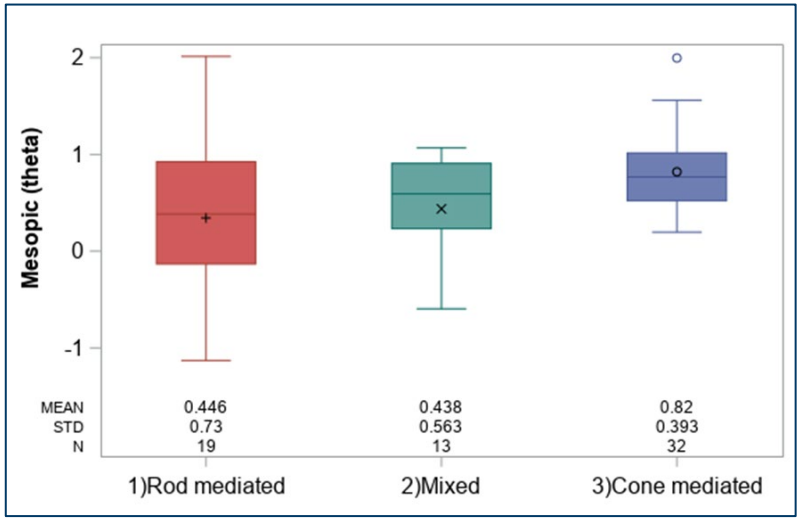
SCOTOPIC
-0.44 (*P*=0.02)



COLOR VISION
-0.54 (*P*=0.007)



MESOPIC
-0.37 (*P*=0.04)



FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

Some Additional Preliminary Data from Pro-EYS

Correlation with PROs at Baseline

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

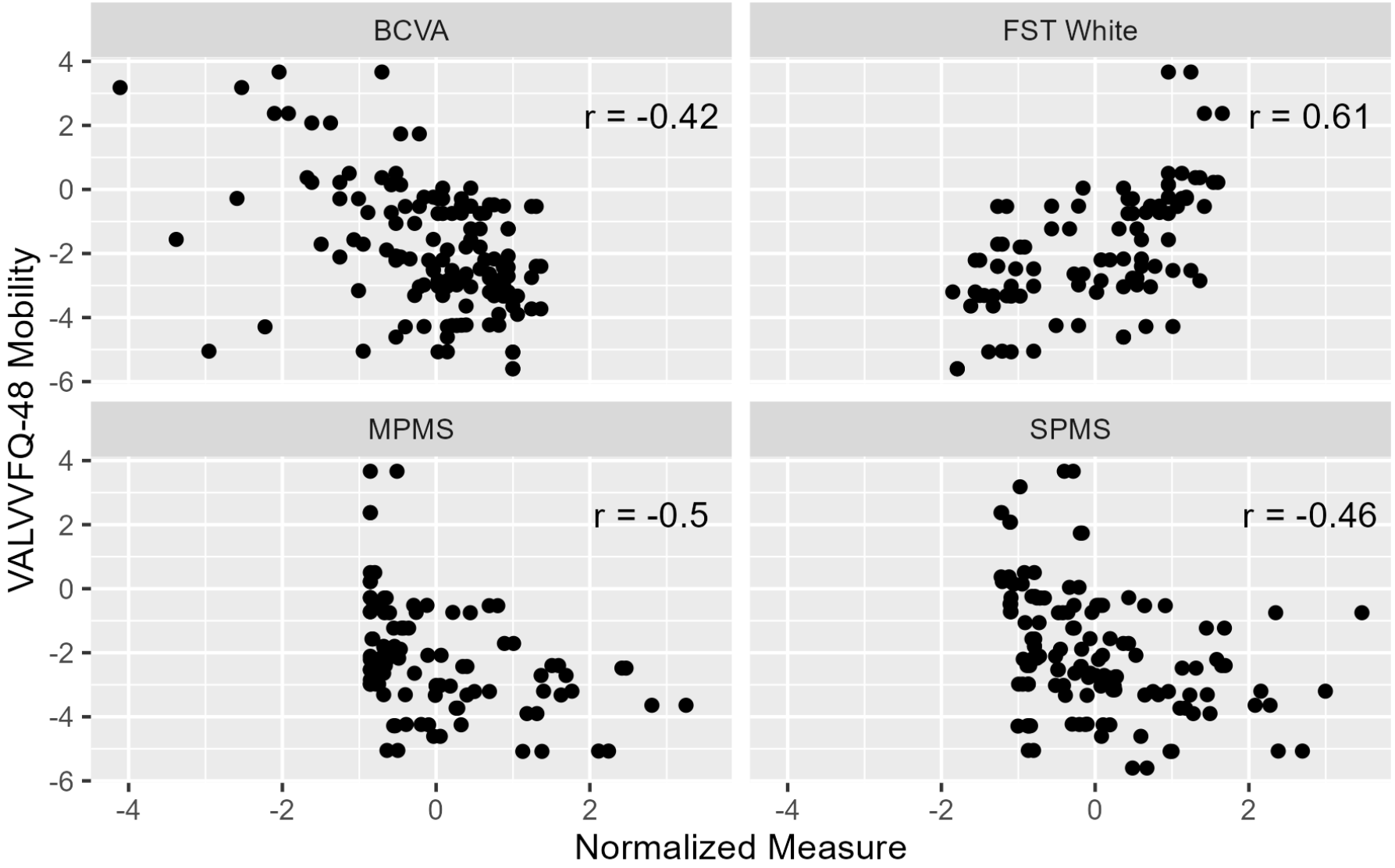
Measure	ViSIO Total	MRDQ Photopic	MRDQ Scotopic	MRDQ Mesopic	VALVVFQ-48 Mobility	PROMIS Physical	PROMIS Anxiety
FST White	**0.57**	**0.65**	**0.59**	**0.57**	**0.61**	**0.55**	**0.54**
MP MS	**0.45**	**0.56**	**0.40**	**0.37**	**0.50**	**0.31**	**0.22**
SP MS	**0.45**	**0.64**	**0.44**	**0.49**	**0.46**	**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

FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

Some Additional Preliminary Data from Pro-EYS

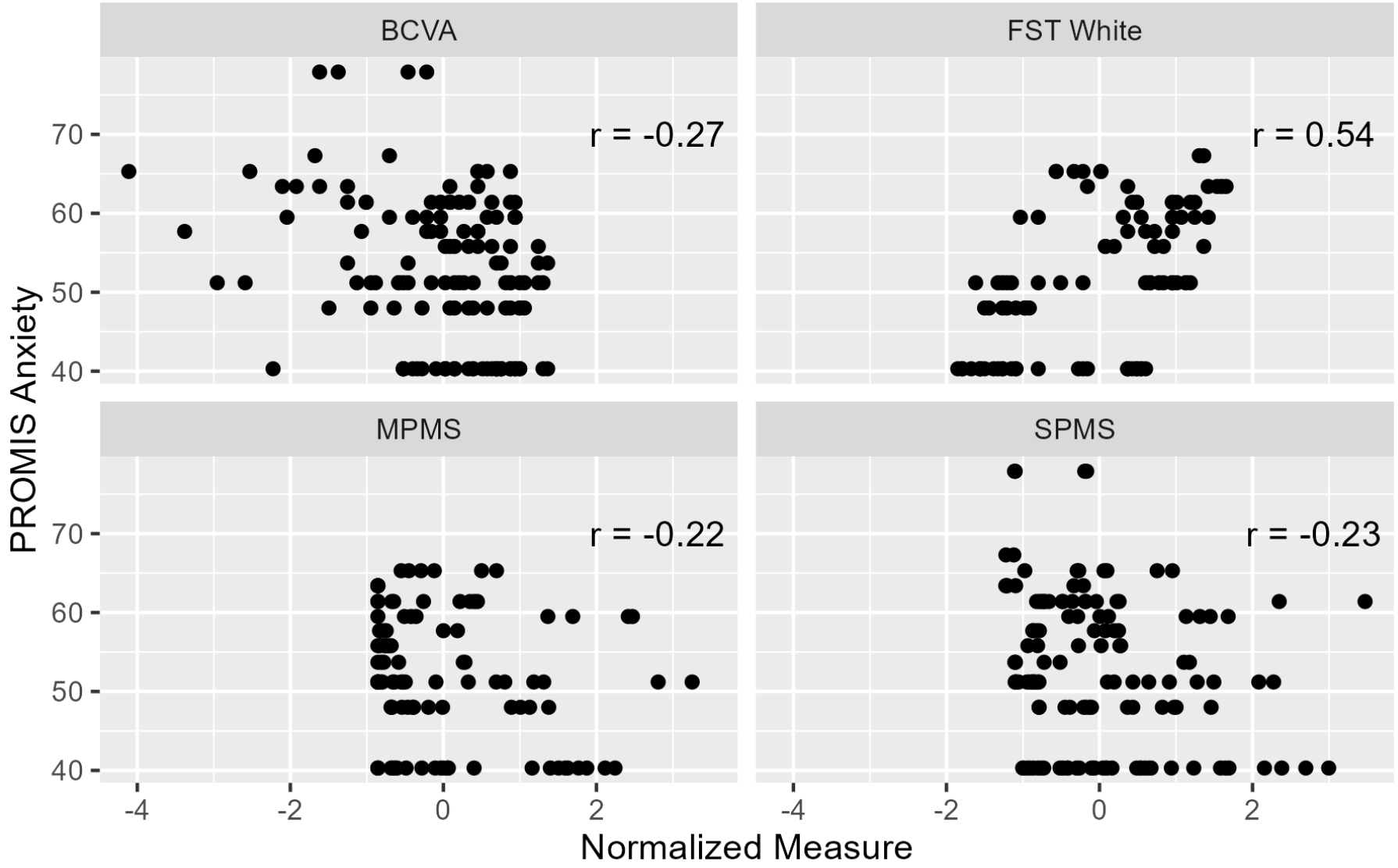
Correlation with Mobility



FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

Some Additional Preliminary Data from Pro-EYS

Correlation with Anxiety



FOUNDATION FIGHTING BLINDNESS
CLINICAL CONSORTIUM

Summary and Discussion

FOUNDATION FIGHTING BLINDNESS CLINICAL CONSORTIUM

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

Limitations

- **May not detect localized improvements from gene and cell therapies that do not affect the area that is most sensitive at baseline**

- **Clinical impact of change in FST among RUSH2A patients with good central vision is not clear**
  - *RPE65*-associated retinal dystrophies: FST highly correlated with performance on the multi-luminance mobility test in this population with reduced central vision

Discussion Questions to Consider

Regulatory guidance on pursuing FST as an endpoint?

- What is a potential roadmap for FST to be an acceptable primary endpoint in a Phase II or Phase III trial?

Would a published FST Data Review Paper be helpful for industry + regulators to reference in making decisions?

- The Consortium/REDI group plans to develop an FST Data Review Paper – including a lit review of FST data and a synopsis of our Consortium analyses of FST data. Would this be helpful? Any suggestions on the ideal approach?

What additional data would be helpful to support FST as an endpoint?

- Currently launching RUSH2A Extension (7- and 9-year visits) + VR mobility course and longitudinal MRDQ.
  - We hope to show early changes in FST predict later changes in PROs and mobility course performance, or vision function measures.
- We have several other ongoing Consortium natural history studies (other IRD genes).
  - We hope to confirm FST endpoint properties are consistent in other genes.
  - These studies also have additional PROs (MRDQ, ViSIO, PROMIS) which will be collected BL, 2yr, 4yr – so we will also have longitudinal PRO data to correlate with changes in FST.
- Suggestions on anything else to consider or pursue?

Questions?