Primary Endpoint Development for a Phase 3 Inherited Retinal Dystrophy Gene Therapy Trial:

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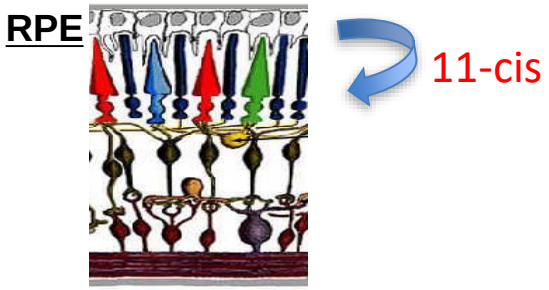
Disclosures:

Spark Therapeutics: Grantee and Consultant

Patent application-Penn docket 14-6790 (MLMT)

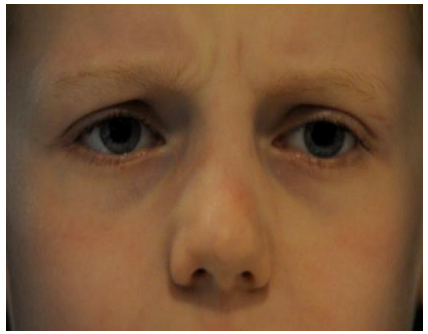
Hereditary Blindness:
Disorders for which there was no Treatment

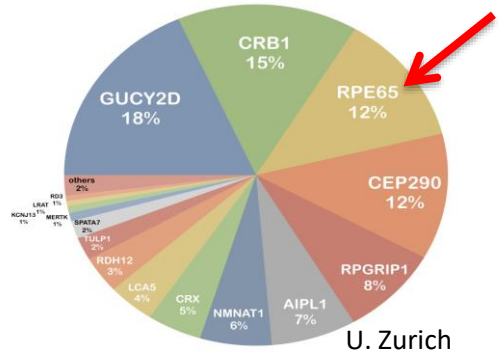
Bi-allelic *RPE65** Mutations



- Rare autosomal recessive disease:
  - Leber congenital amaurosis
  - Retinitis pigmentosa
- Early onset retinal degeneration; night blindness an early symptom
- Progressive: significant impairment by second decade
- No treatment
- Naturally occurring dog models of disease

*RPE65: Retinal Pigmented Epithelium 65kDa Protein





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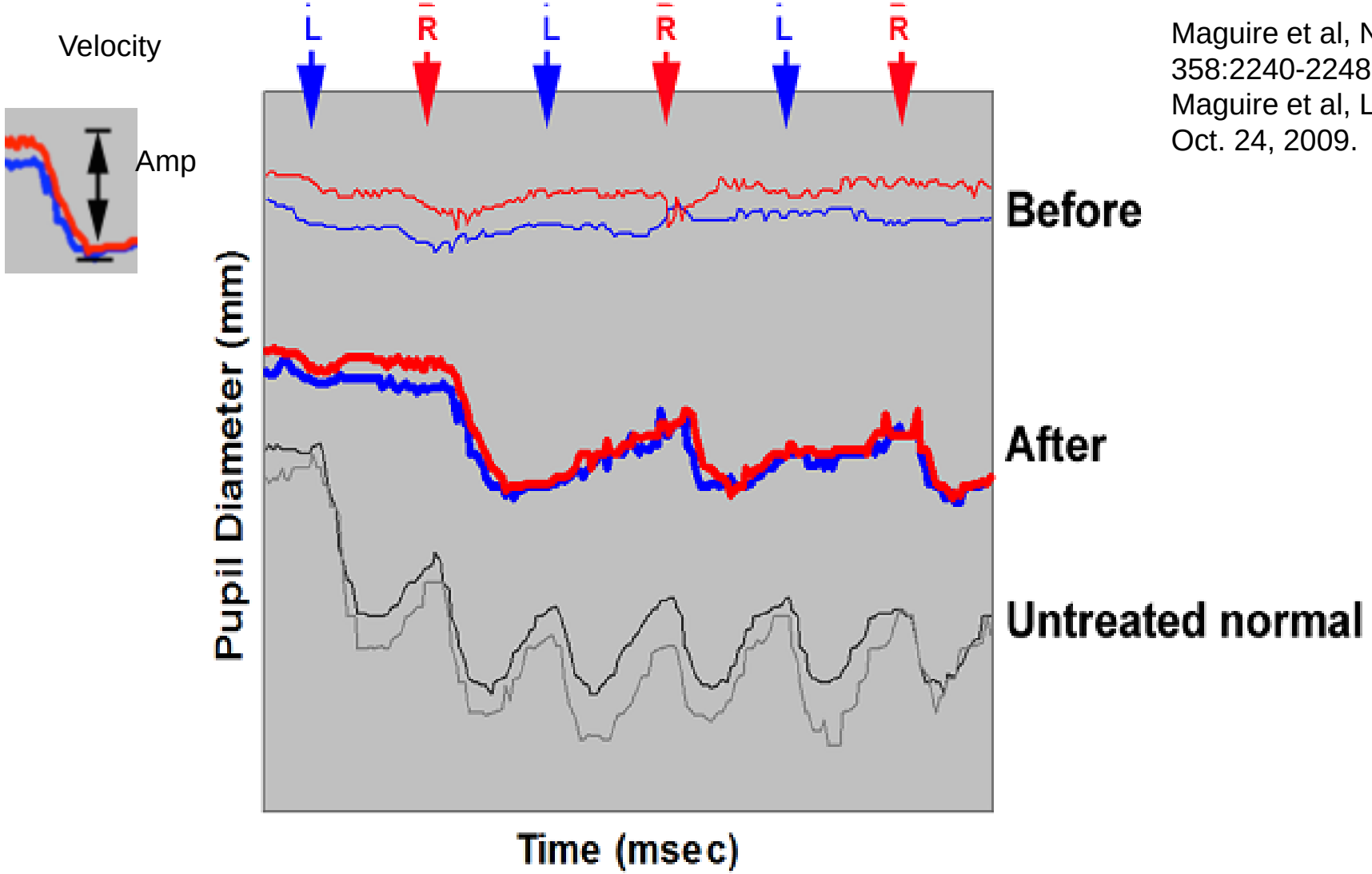
Objective Data: Pupillary Light Reflex (PLR)



Maguire et al, NEJM 358:2240-2248 (2008); Maguire et al, Lancet, Oct. 24, 2009.

PLR is restored in the (right) retina exposed to AAV2.hRPE65v2 and not in the uninjected (contralateral) retina

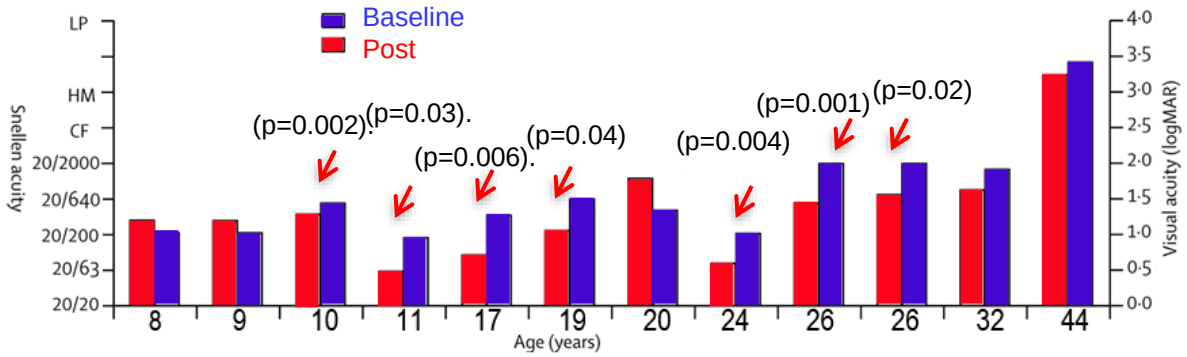
The Law Says…

- A marketing application will be rejected if there is “a lack of substantial evidence that the drug will have the effect it purports or is represented to have … in the proposed labeling..”
- So why doesn‘t the FDA approve any drug, as long as the labeling truthfully states what effect has been demonstrated?

Answer: The effect must be clinically meaningful.

Visual Function vs. Age

ETDRS Acuity (Cone –mediated)



Maguire *et al,* Lancet 374(9701):1597 (2009)

Increasing age

Summary

- For marketing approval, there must be *substantial evidence* (consisting of adequate and well-controlled investigations) *of something that matters*

RESULTS- Exploratory Endpoint

Pre Injection 3 Months Post Injection

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Need for novel primary endpoint

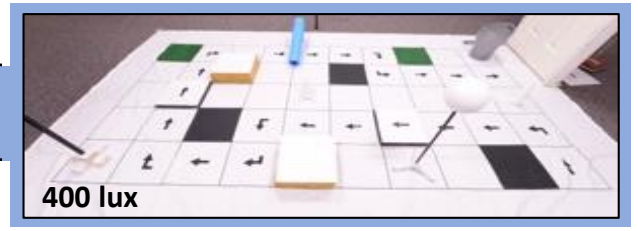
- Endpoint developed in discussion with FDA
  - Goal was to develop a clinically relevant measure of functional vision
  - Task is to navigate a course independently and accurately within a time limit
  - Integrates input from VA, VF and light sensitivity
  - Traditional mobility metrics do not incorporate effects of level of environmental illumination on speed and accuracy
  - Allows for use in a pediatric population
- Conducted at 7 different light levels ranging from 1 lux to 400 lux

Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Russell S, et al. Lancet 2017; 390(10097):849-60.

MLMT: Designed to detect changes in functional vision across a range of light levels

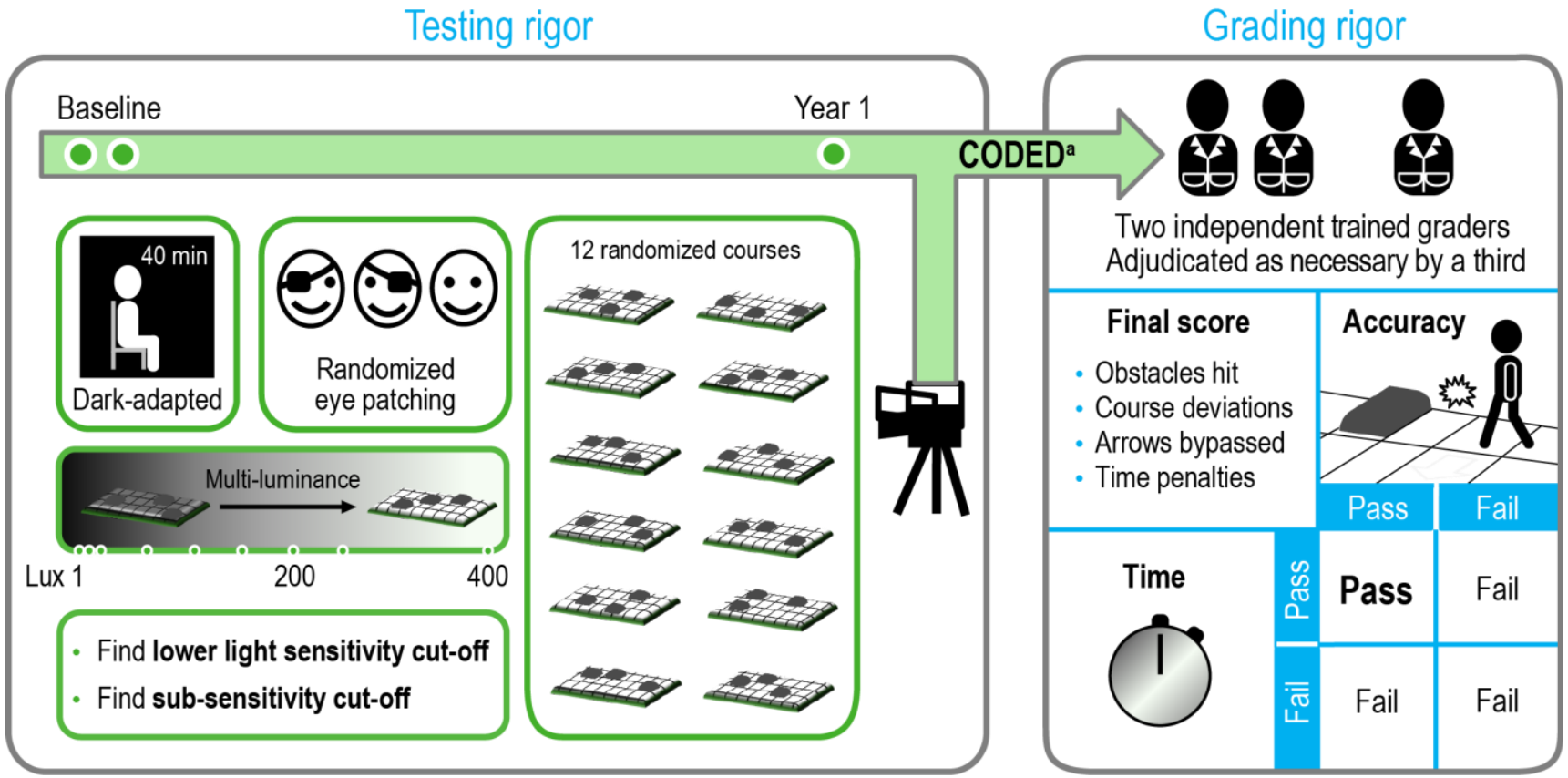
Light Levels	Examples
1 lux	Moonless summer night; Indoor nightlight
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / bus at night
250 lux	Interior of elevator or office hallway
400 lux	Office environment or food court



Light meter: National Institute of Standards and Technology-calibrated,
Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Introducing rigor into MLMT



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MLMT scoring

- At baseline, determine lowest light level at which subject can achieve a passing score, and the highest level at which they failed
  - Penalty points for colliding with obstacles; wandering off course; bypassing arrows
  - Both time and penalty points assessed in final score

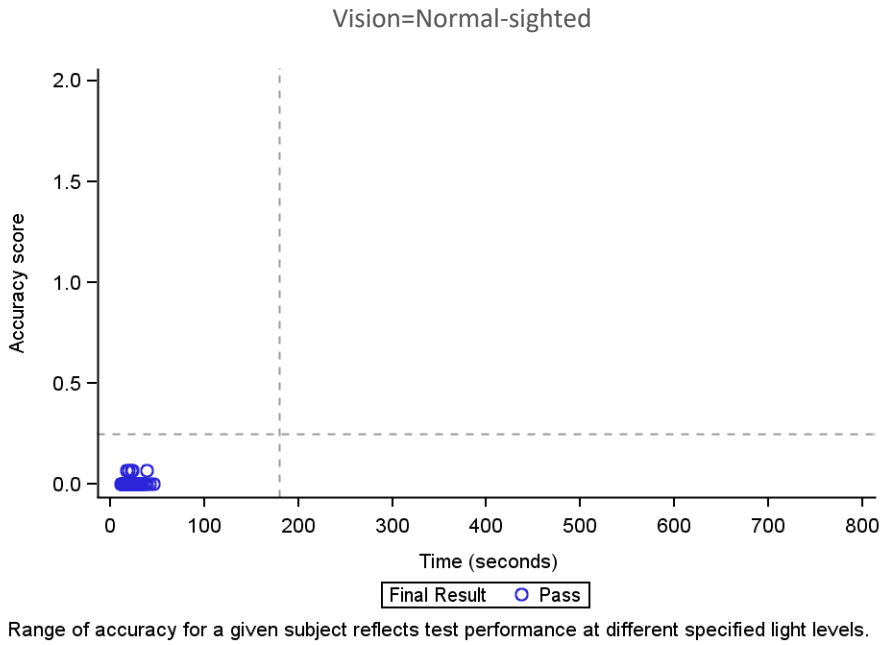
Multi-luminance mobility test (MLMT) validation study

- Evaluated performance of both normal-sighted and inherited retinal disease (IRD) subjects
- Correlated with measures of visual function: VA and VF
- Normal-sighted subjects
  - No change in testing
  - All passed at lowest level (1 Lux)
- IRD subjects
  - None improved from baseline to 1 year
  - 8 (28.5%) subjects declined in performance over 1 year
- High reliability: concordance between baseline visits 1 month apart – correlations for accuracy were 94% and 98% between lowest and highest light levels tested

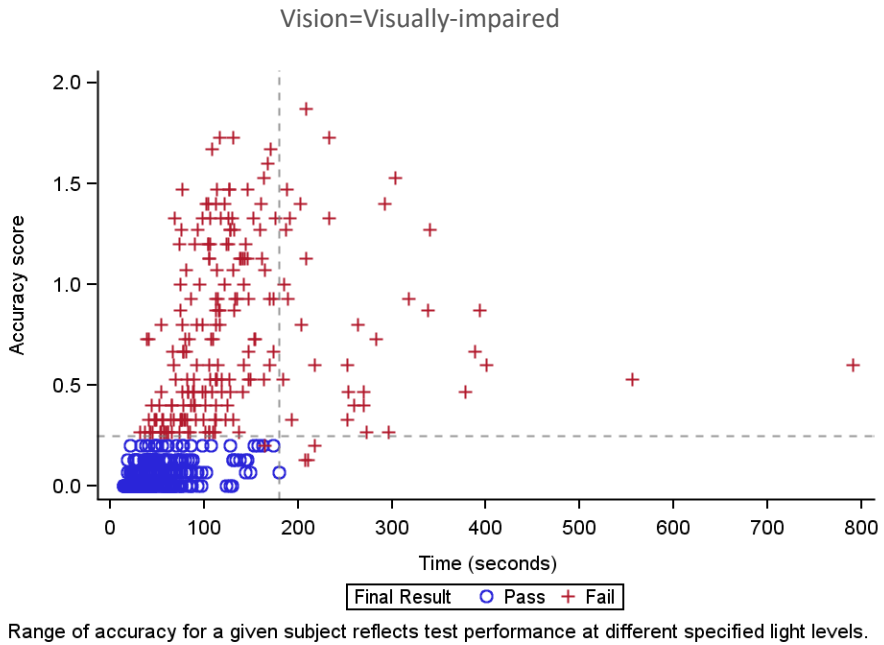
Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Time and accuracy score, by pass/fail status

Test distinguishes between normal-sighted and visually-impaired subjects



Range of accuracy for a given subject reflects test performance at different specified light levels.



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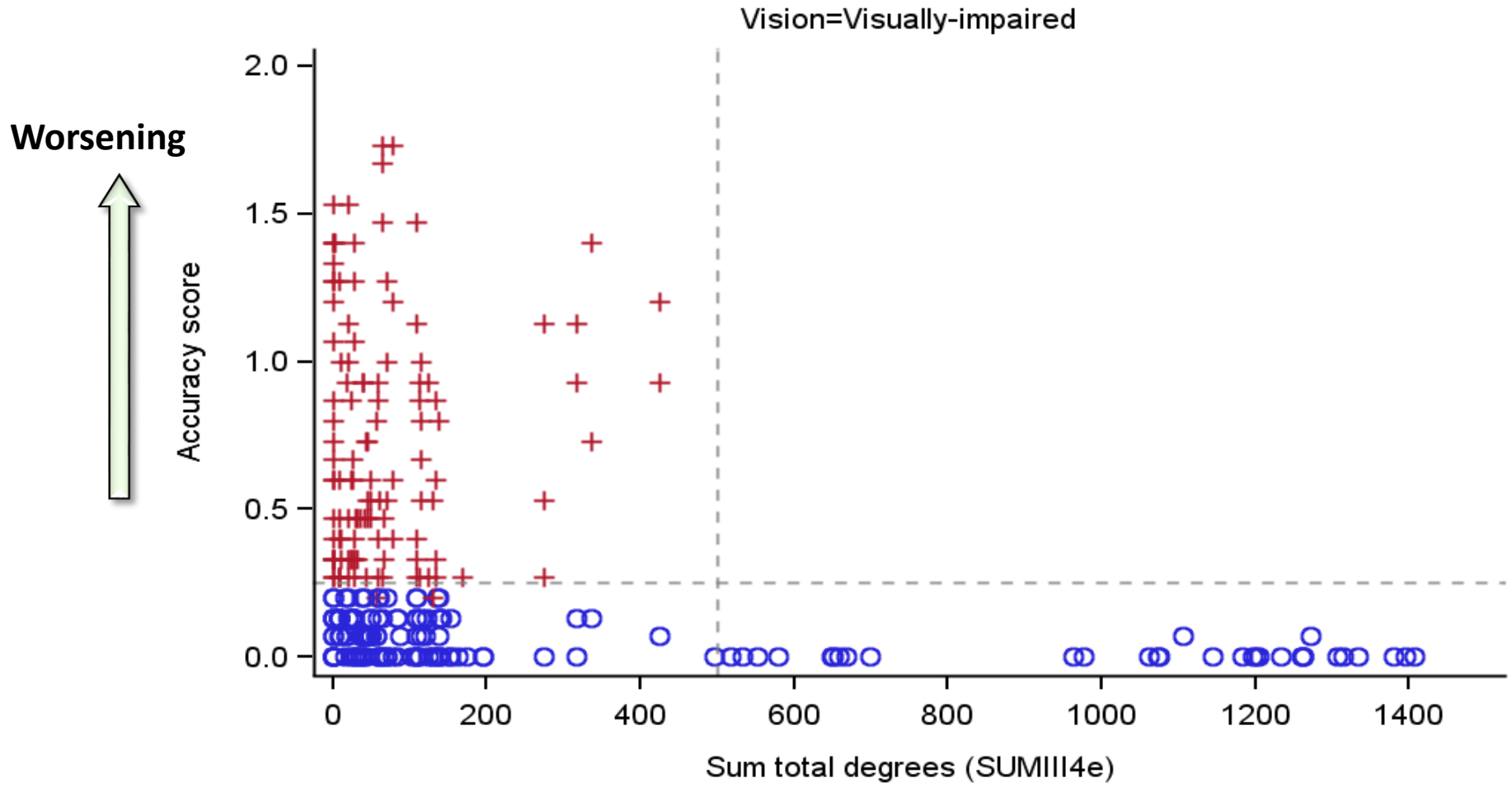
Goldmann Visual Fields and Accuracy Score by Pass / Fail Status



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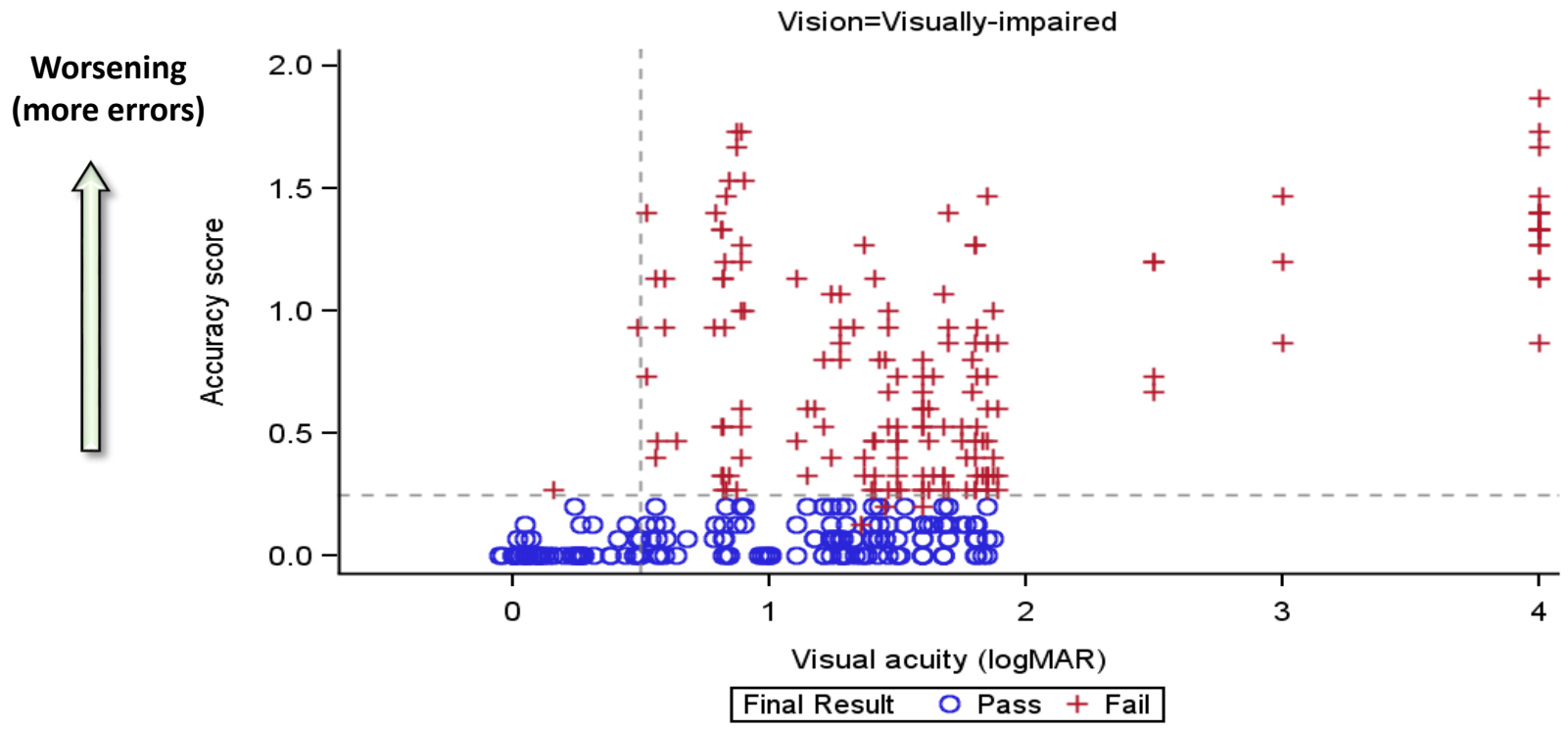
Visual acuity (LogMAR) and accuracy score by pass / fail status



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MLMT scoring system is highly reproducible

High inter-grader and intra-grader agreement

		Inter-grader	Grade-regrade			
			Consensus	Grader #1	Grader #2	Grader #3
		n=4158	n=425	n=383	n=100	n=118
Intraclass Correlation	# Obstacles hit	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)	0.99 (0.99 - 0.99)
	# Times off-course	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.98 (0.97 - 0.99)	0.99 (0.99 - 0.99)
	# Times re-guided	0.99 (0.99 - 0.99)	1.00 (1.00 - 1.00)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	1.00 (1.00 - 1.00)
	# Tiles bypassed	0.91 (0.91 - 0.92)	0.93 (0.91 - 0.94)	0.92 (0.91 - 0.94)	0.90 (0.86 - 0.93)	0.95 (0.92 - 0.96)
	Obstacles plus Penalties	0.98 (0.98 - 0.98)	0.98 (0.98 - 0.98)	0.97 (0.97 - 0.98)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)
	Accuracy score	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)	0.99 (0.99 - 0.99)
	Course time	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
	Time score	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Kappa	Course completed	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	0.67 (0.05 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
	Accuracy Pass/Fail	0.95 (0.94 - 0.96)	0.94 (0.90 - 0.97)	0.91 (0.87 - 0.95)	0.96 (0.90 - 1.00)	0.91 (0.84 - 0.99)
	Time Pass/Fail	0.98 (0.98 - 0.99)	0.98 (0.96 - 1.00)	0.99 (0.98 - 1.00)	0.97 (0.91 - 1.00)	0.98 (0.94 - 1.00)
	Final Pass/Fail	0.95 (0.94 - 0.96)	0.94 (0.91 - 0.97)	0.92 (0.88 - 0.96)	0.96 (0.90 - 1.00)	0.93 (0.86 - 1.00)
n (%) Agree	Course completed	4158 (100.0%)	425 (100.0%)	382 (99.7%)	100 (100.0%)	118 (100.0%)
	Accuracy Pass/Fail	4059 (97.6%)	412 (96.9%)	366 (95.6%)	98 (98.0%)	113 (95.8%)
	Time Pass/Fail	4133 (99.4%)	422 (99.3%)	382 (99.7%)	99 (99.0%)	117 (99.2%)
	Final Pass/Fail	4070 (97.9%)	413 (97.2%)	368 (96.1%)	98 (98.0%)	114 (96.6%)

Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Phase 3: Efficacy endpoints (ITT) and results

Assessment	Measurement	Difference (95% CI) (Intervention-Control)	p value
Primary Endpoint			
MLMT performance	Bilateral, score change	1.6 (0.72, 2.41)	**p = 0.0013**
Secondary Endpoints			
FST testing	Averaged over both eyes, log10(cd.s/m^2)	-2.11 (-3.19, -1.04)	**p = 0.0004**
MLMT performance	Assigned first eye, score change	1.7 (0.89, 2.52)	**p = 0.0005**
Visual acuity	Averaged over both eyes, LogMAR (Holladay)	-0.16 (-0.41, 0.08)	**p = 0.17**
Additional Endpoint			
Visual field	Goldmann III4e sum total degrees, averaged over both eyes	378.7 (145.5, 612.0)	**Nominal p = 0.0059**
	Humphrey macula threshold, dB, averaged over both eyes	7.9 (3.5, 12.2)	**Nominal p = 0.0005**

Russell S, et al. Lancet 2017; 390(10097):849-60.

Phase 3: MLMT time to completion, averaged over lux levels, (mITT) Intervention vs. Control

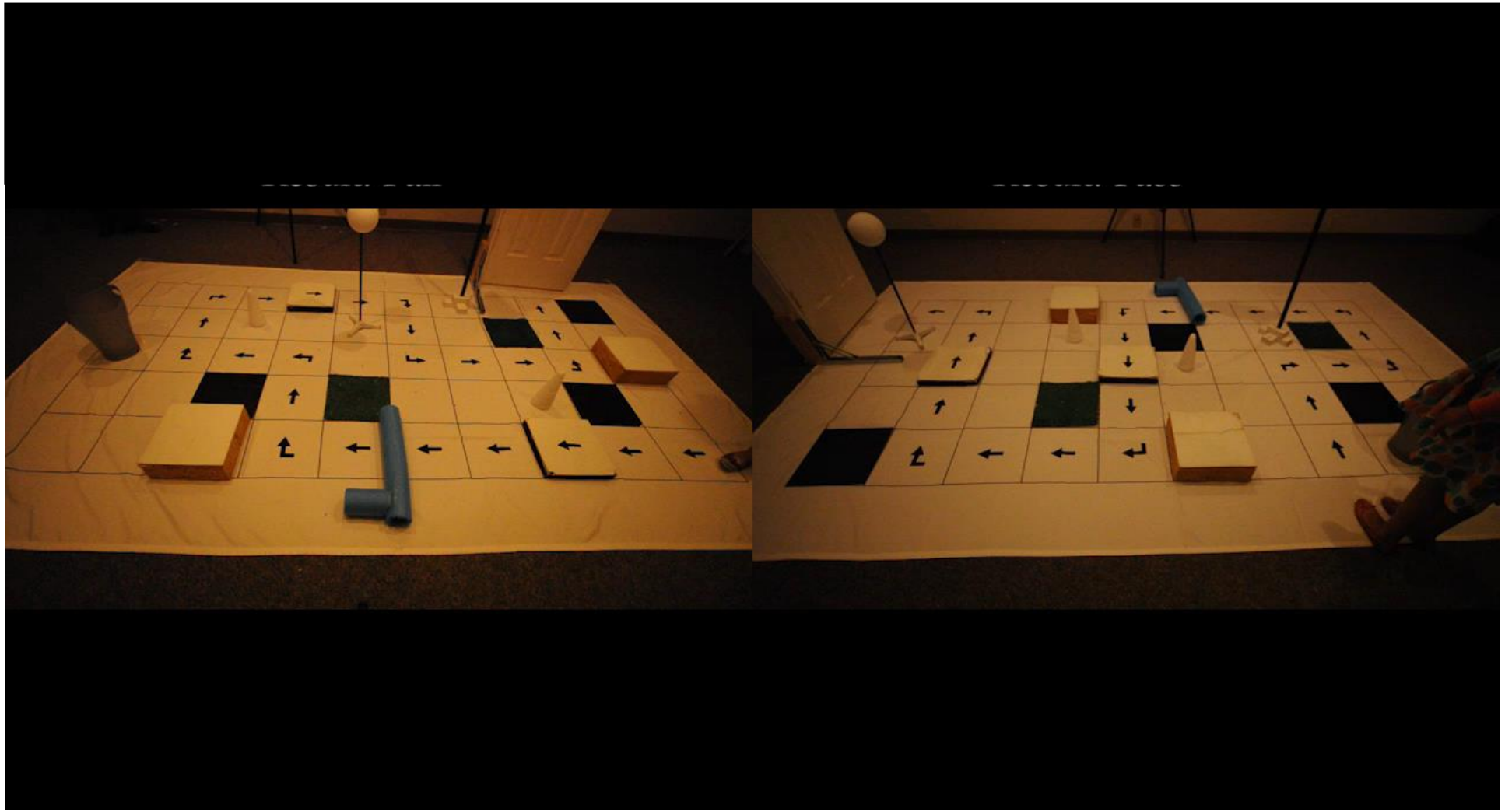
Bilateral Time to Complete (sec)	Intervention (N=20)			Control (N=9)		
	Baseline	Year 1	Change	Baseline	Year 1	Change
Mean (SD)	101.1 (41.7)	49.0 (35.6)	-52.1 (38.1)	81.8 (20.8)	79.3 (20.3)	-2.6 (23.5)

Data on File. Study 301 Core Efficacy:CO25. Oct 2017. Spark Therapeutics, Inc. Philadelphia, PA.

Phase 3 Trial : Mobility Test Videos

FAIL

PASS



Maguire, AAO, Nov 2015

Mobility test study results support use of MLMT to measure functional vision in patients with IRDs

- Differentiate low vision from normal controls
- Detect changes in performance over time
- Identify wide range of performance among visually impaired
- High reproducibility
  - > 4000 videos evaluated
- Demonstrated construct and content validity
- Generates a quantifiable measure of functional vision

Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Data on File. MLMT Video Library. Spark Therapeutics, Inc. Philadelphia, PA.

Acknowledgements

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