Validation of a Low Luminance Mobility Test (LLMT) for Retinitis Pigmentosa

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Purpose

The purpose of this study was the validation of a new Low Luminance Mobility Test (LLMT) to support its use as a clinical endpoint in a retinitis pigmentosa (RP) development program.

RP patients are known to have progressive impairment in low light situations. Testing this component of visual impairment in RP has the potential to contribute to the evaluation of patient benefit from RP and other retinal degenerative therapies.

The specific aims of this study included assessing reliability, content validity, and construct validity of the LLMT.

Methods

The LLMT was designed with 13 light levels ranging from 0.12 to 500 lux in even 0.3 log unit increments (a factor of two).

A scoring algorithm analogous to the MNREAD test with use of a Critical Illumination Level (CIL)* and Maximum Step Speed (MSS) was developed.

A prospective, observational test-retest study included 16 visually normal subjects (VN) and a broad range of 20 RP subjects.

- Two visits over two weeks
- Video trials sent to masked graders
- Other testing included BCVA, Contrast Sensitivity (CS), Octopus Kinetic Visual Field (KVF), VA LV VFQ-48 for correlation with the LLMT outcome.

Inter-rater and intra-rater reliability was assessed across 3 studies for larger sample

Results

Subpopulation	RP (n = 20, study eye)		VN (n = 16, study eye)	
Variable	Min and Max	Mean or Median ± SD	Min and Max	Mean or Median ± SD
Age (years)	25, 72	52.20 ±14.2	18, 77	43.13 ± 19.49
BCVA (Log MAR)	0.55, 1.56	1.05 ± 0.35	-0.12, 0.04	-0.07 ± 0.06
Mean Log Visual Field Area*(deg^2)	0.52, 3.96	2.35 ± 1.00	4.02, 4.16	4.11 ± 0.04
CIL (lux)	1000, 0.12	32	0, 0.25	0.12
Mean MSS (steps per minute)	14, 67.5	33.58 ± 14.93	38, 76	61.00 ± 11.01

Table 1 Subject Characteristics

***CIL is defined as the lowest light level at which the subject successfully navigates the course prior to a significant drop in step speed (adjusting for errors).**

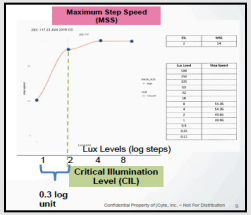


Figure 1 Example of CIL Scoring Curve

LLMT Reliability:

- 15 RP subjects with KVF of at least 12 degrees showed no CIL difference between-visits
- For all 20 RP subjects, the mean variability was 0.35 light levels (<0.2 log units).
- Only the 5 subjects with KVF<12 degree diameter contributed to the total mean test variability

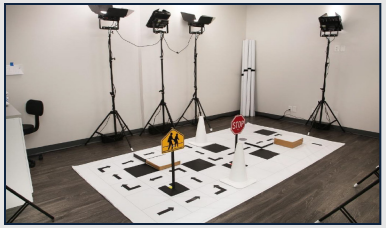


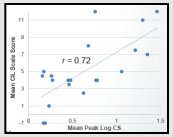
Image 1 LLMT set-up

Correlation of CIL with other outcome measures:

CIL and MSS correlates with other visual function assessments and patient reported outcomes.

- CS, BCVA and logVF were the greatest contributors to CIL variance (R^2=0.75, p=0.004), with CS had the strongest relationship

Figure 2
Relationship of CS and CIL
CS strongly correlated with CIL (r=0.72, p<0.001)



Inter-rater Performance:

Three masked graders were consistent in repeat grading and consistent with other graders, with bias near zero on all Bland-Altman plots and with non-significant differences between graders.

Inter-Rater	# Videos Graded 2x	p-value*	Bias (LOA) Seconds
G1 & G2	388	0.98	-0.032 (-6.9, 6.9)
G2 & G4	634	0.60	0.498 (-5.9, 6.9)

Table 2 Inter-rater Reliability

Conclusions

The novel attributes of the LLMT design and scoring algorithm enable the **reliable** detection of a wide range of performance at various light levels in RP subjects; increased variability is only observed in subjects with advanced constriction.

LLMT scoring utilizes the **CIL** or suprathreshold light level below which functional performance rapidly declines (in contrast to scoring with a binomial pass/fail level in sub-threshold lighting).

Consistent with prior mobility studies, the LLMT is significantly related to several other aspects of visual function and patient reported outcomes supporting its **content validity**.

The LLMT has strong inter-rater and intra-rater reliability

- As a result, the scoring process can be **consistently applied and repeated** by independent, trained raters.

Altogether, these findings support the use of the LLMT as a **robust clinical endpoint** in RP natural history studies, interventional trials, and potentially in studies in other retinal degenerative conditions.

References & Disclosures

1. Chung DC, McCague S, Yu ZF, Thill S, DiStefano-Pappas J, Bennett J, Cross D, Marshall K, Wellman J, High KA. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clin Exp Ophthalmol. 2018;46(3):247-259

RK: jCyte: C
AB: jCyte: C
BM: jCyte: C
JY; jCyte: I, R, S
HK: jCyte: I, R, S

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