

Modified Multi-Luminance Mobility Test (modMLMT) to Evaluate Therapeutic Benefit to Night Vision Mediated by Rod Photoreceptors

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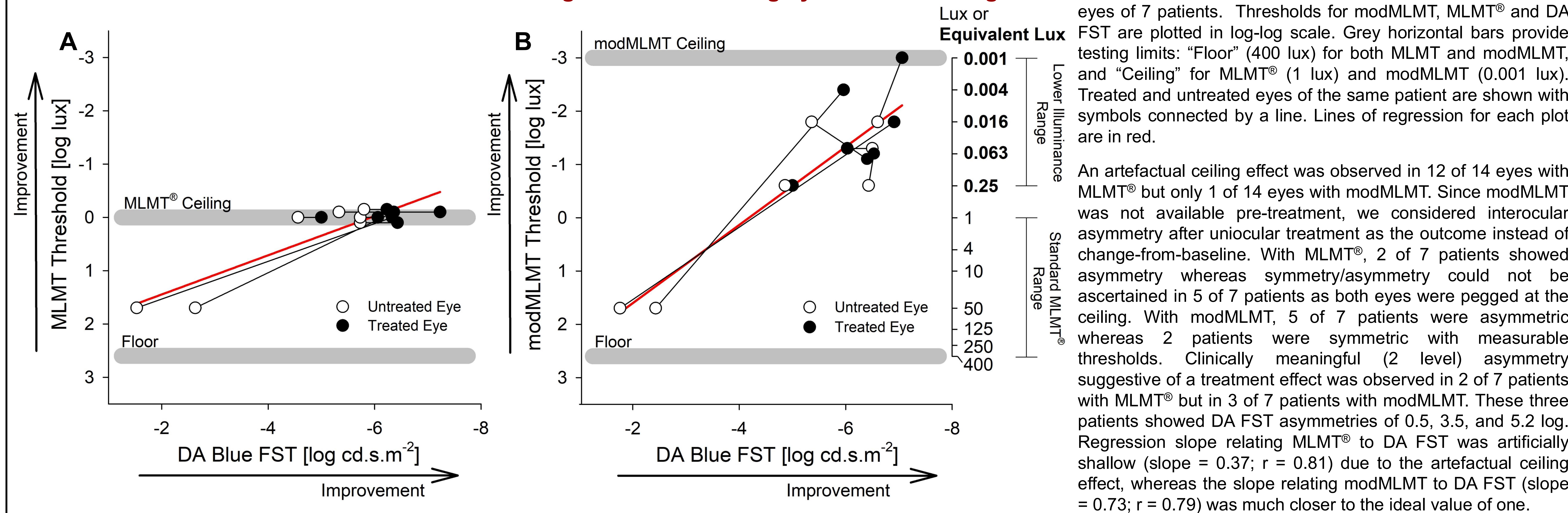
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Introduction

The Multi-Luminance Mobility Test (MLMT[®]) was designed to demonstrate therapeutic benefit of gene therapy in *RPE65-LCA2* patients who tend to have extremely reduced rod-mediated night vision pretreatment (Chung et al., 2018). In contrast, other retinal diseases such as *GUCY2D-LCA1* can retain substantial rod function pretreatment which limits measurable benefit due to a ceiling effect in MLMT[®]. Recognizing this unmet need, the FDA has suggested including illuminance levels below 1 lux in mobility courses. We previously used a custom-built mobility test to measure dark-adapted functional vision (Jacobson et al., 2022; Roman et al., 2022). As an alternative approach, here we present a mobility test that is based on the widely-used MLMT[®], the Modified Multi-Luminance Mobility Test (modMLMT) recorded in *LCA1* patients enrolled in the ATSN-101 gene therapy trial (NCT03920007).

Seven of 15 patients who had been treated with a unioocular subretinal injection of ATSN-101 (Jacobson et al., 2021; Jacobson et al., 2022; Yang et al., 2024) performed modMLMT. Results from modMLMT were quantitatively compared with MLMT[®] and full-field stimulus test (FST).

modMLMT Quantifies Functional Vision at Low Light Levels and Largely Avoids a Ceiling Effect



MLMT[®] and DA FST results from Year 2 (**A**) are compared to modMLMT and DA FST results from Years 3-5 (**B**) for the 14 eyes of 7 patients. Thresholds for modMLMT, MLMT[®] and DA FST are plotted in log-log scale. Grey horizontal bars provide testing limits: "Floor" (400 lux) for both MLMT and modMLMT, and "Ceiling" for MLMT[®] (1 lux) and modMLMT (0.001 lux). Treated and untreated eyes of the same patient are shown with symbols connected by a line. Lines of regression for each plot are in red.

An artefactual ceiling effect was observed in 12 of 14 eyes with MLMT[®] but only 1 of 14 eyes with modMLMT. Since modMLMT was not available pre-treatment, we considered interocular asymmetry after unioocular treatment as the outcome instead of change-from-baseline. With MLMT[®], 2 of 7 patients showed asymmetry whereas symmetry/asymmetry could not be ascertained in 5 of 7 patients as both eyes were pegged at the ceiling. With modMLMT, 5 of 7 patients were asymmetric whereas 2 patients were symmetric with measurable thresholds. Clinically meaningful (2 level) asymmetry suggestive of a treatment effect was observed in 2 of 7 patients with MLMT[®] but in 3 of 7 patients with modMLMT. These three patients showed DA FST asymmetries of 0.5, 3.5, and 5.2 log. Regression slope relating MLMT[®] to DA FST was artificially shallow (slope = 0.37; r = 0.81) due to the artefactual ceiling effect, whereas the slope relating modMLMT to DA FST (slope = 0.73; r = 0.79) was much closer to the ideal value of one.

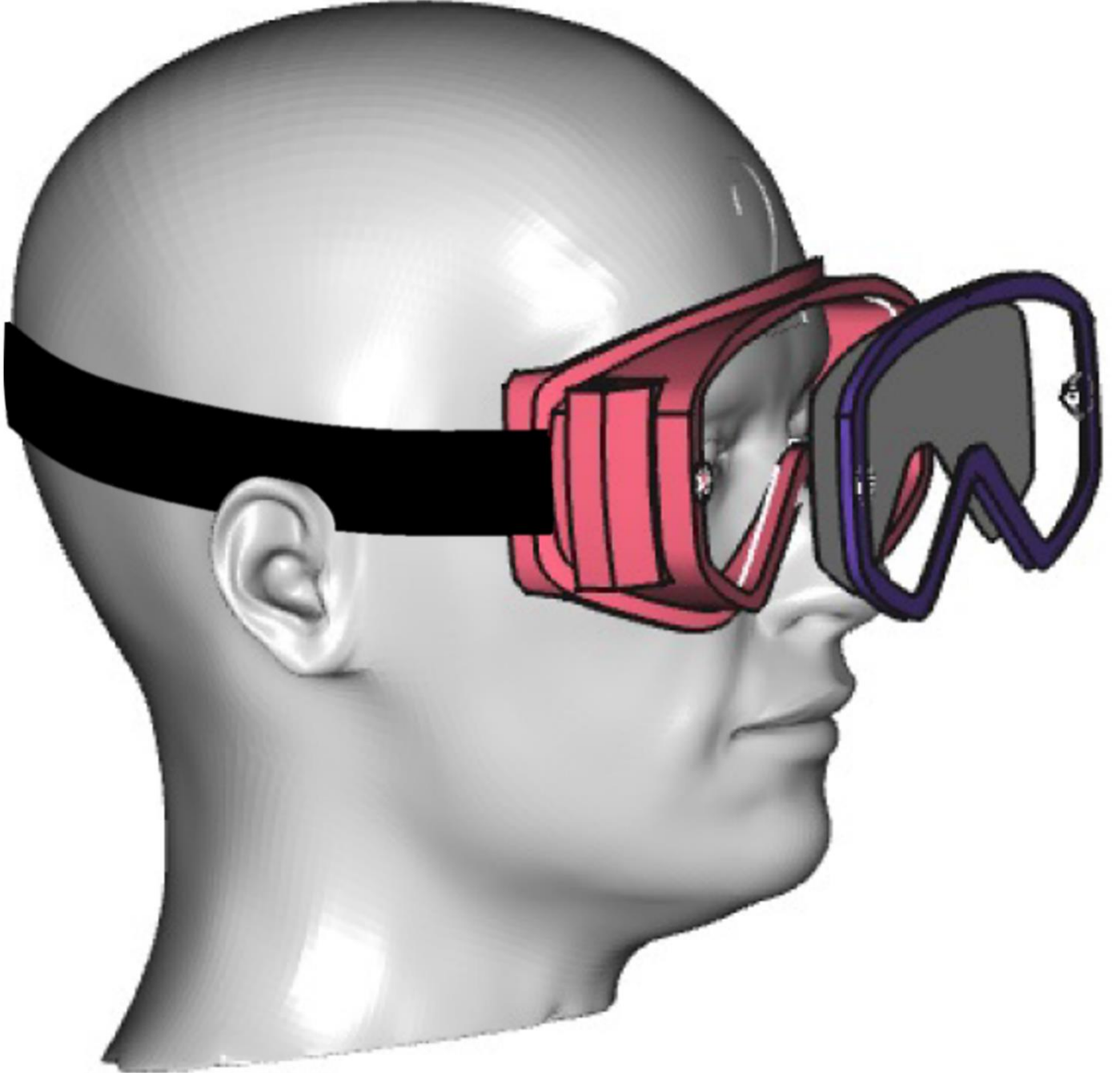
Summary

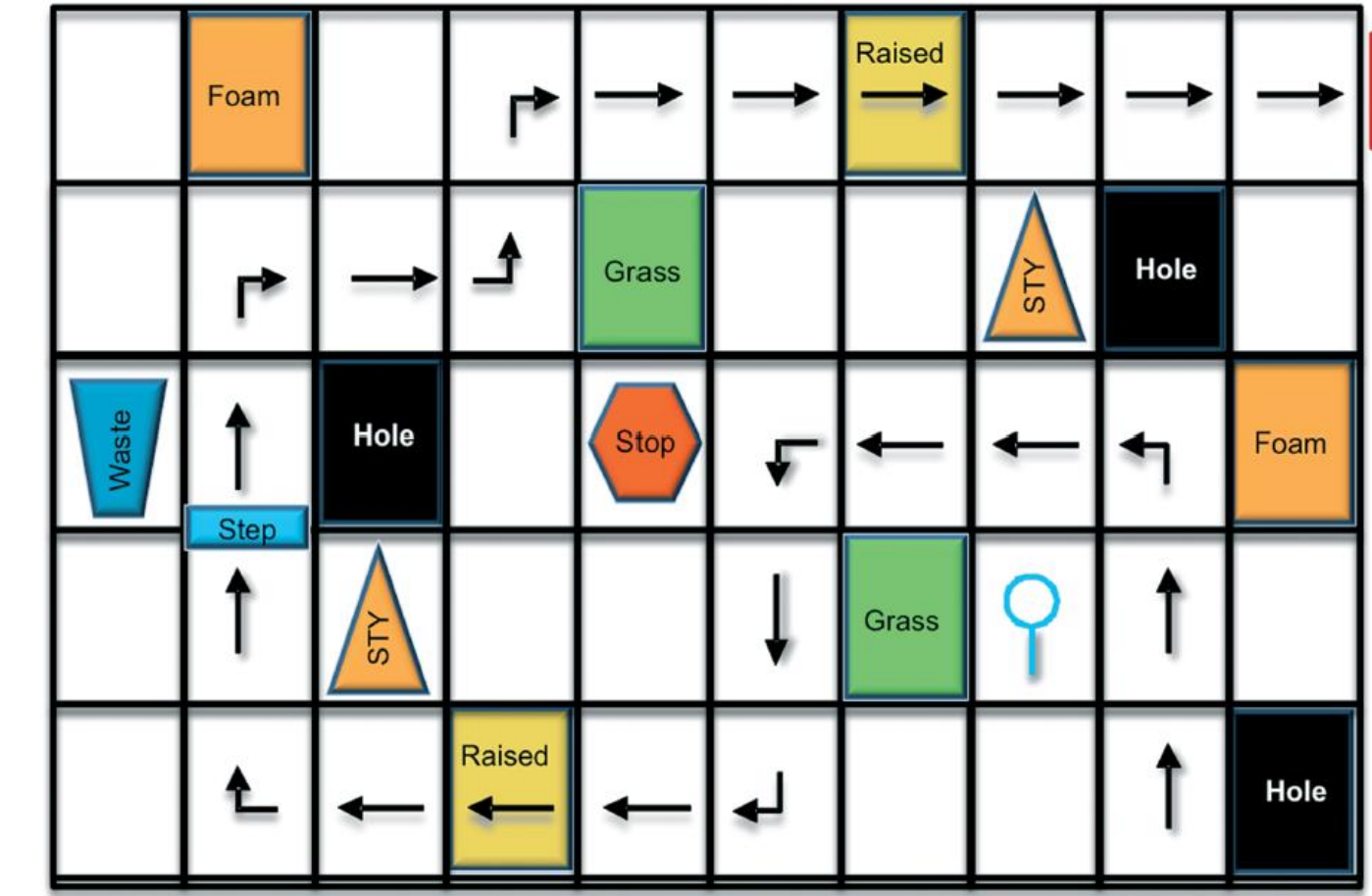
- The FDA has suggested measuring functional vision at low light levels to show meaningful therapeutic benefit in clinical treatment trials for inherited retinal diseases.
- There is an artefactual ceiling effect observed in MLMT[®] for *LCA1* patients treated with ATSN-101 gene therapy due to retained rod vision. As such, there is a need to develop a method to measure functional vision in low light for these patients.
- modMLMT uses light attenuating goggles to add 5 light levels <1 lux to assess functional vision over a large range of 0.001 – 400 lux.
- modMLMT thresholds are predictable from DA FST thresholds.
- modMLMT demonstrates treatment effect of ATSN-101 in more patients compared to MLMT[®].
- modMLMT addresses the ceiling effect observed in MLMT[®] for most patients with retained rod vision and in doing so provides a more informative quantification of functional vision in more patients compared to MLMT[®].

Methods

There were two illuminance ranges tested in modMLMT: the standard MLMT[®] range (1-400 lux), and a lower illuminance range (0.001-0.25 lux equivalent). The extension of the illuminance range to lower levels was achieved by using wide-field, light attenuating goggles (Roman et al., 2022) worn by the patient while the room illuminance remained fixed at 1 lux. This method, rather than reducing room illuminance, ensures patient safety since at 1 lux, course administrators could see the patient and the course and intervene as required. The light attenuating goggles allow neutral density (ND) filters to be stacked in the frames to achieve dimmer illuminance conditions for the patient. Each ND filter attenuates the light by 0.6 log units, and 1-5 filters were stacked to test 5 lower illuminance levels. The field of view through the goggles was approximately 60° in extent superior, temporal and nasal, and 45° in extent towards inferior field. Overall, in modMLMT, there were 12 levels covering 5.6 log units of illuminance.

Seven patients unilaterally treated with ATSN-101 gene therapy were evaluated with modMLMT at a single visit 3-5 years post-treatment. Patients were dark adapted and then performed a practice test with both eyes open wearing the goggles at 0.063 equivalent lux to acclimate to visibility of the course. The modMLMT protocol was then performed starting at 0.001 equivalent lux and ending at 400 lux, with eyes tested separately at each level. Performance was recorded and evaluated from videos by independent graders masked to eye and illuminance. The threshold for modMLMT was defined as the lowest light level passed, which is the same definition used for MLMT[®]. Dark-adapted full-field stimulus testing (DA FST) using a blue stimulus was also conducted (Roman et al., 2007) at the modMLMT recording visit. Results from modMLMT and DA FST were compared with the MLMT[®] and DA FST results collected for the same patients at their Year 2 visits.

A  Light Attenuating Goggles. ND filters are stacked into the goggle frames to achieve different levels of light attenuation.

B  Example MLMT[®] or modMLMT course layout. Taken from Chung et al., 2017

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Room Lux	1	1	1	1	1	1	4	10	50	125	250	400
Light Attenuating Goggle Use: Number of filters (log attenuation)	5 (3.0)	4 (2.4)	3 (1.8)	2 (1.2)	1 (0.6)	No Goggles	No Goggles	No Goggles	No Goggles	No Goggles	No Goggles	No Goggles
Equivalent Lux	0.001	0.004	0.016	0.063	0.25	1	4	10	50	125	250	400

 Methodology of using light attenuating goggles with ND filters to achieve a testing illuminance range of 0.001 – 400 lux in the modMLMT.

References

- Chung DC, McCague S, Yu ZF, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. *Clin Exp Ophthalmol.* 2018;46:247-259.
- Jacobson SG, Cideciyan AV, Ho AC, et al. Safety and improved efficacy signals following gene therapy in childhood blindness caused by *GUCY2D* mutations. *iScience.* 2021;24:102409.
- Jacobson SG, Cideciyan AV, Ho AC, et al. Night vision restored in days after decades of congenital blindness. *iScience.* 2022;25:105274.
- Roman AJ, Cideciyan AV, Aleman TS, et al. Full-field stimulus testing (FST) to quantify visual perception in severely blind candidates for treatment trials. *Physiol Meas.* 2007;28:N51-6.
- Roman AJ, Cideciyan AV, Wu V, et al. Mobility test to assess functional vision in dark-adapted patients with Leber congenital amaurosis. *BMC Ophthalmol.* 2022;22:266.
- Yang P, Pardon LP, Ho AC, et al. 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. *Lancet.* 2024;404:962-970.

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