Current and Emerging Endpoints for IRDs

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Demonstrating Efficacy of Therapeutic Interventions in IRD Clinical Trials Presents a Unique Challenge

- **Conventional outcome measures may lack adequate sensitivity** due to phenotypic heterogeneity, slow progression, preferential peripheral vision loss, and small recruitment pools with advanced vision loss
- **IRD trials require novel, specialized endpoints** tailored to the clinical characteristics of each disease
- **In 2017, the FDA approved the first and only ocular gene therapy, voretigene,** for patients with genetic variants in both copies *RPE65* gene, typically diagnosed as LCA2 or severe early-onset RP
  - Primary endpoint was binocular performance on the MLMT®, and a key secondary endpoint was FST
  - Established a precedent for utilizing endpoints other than change in VA for IRD clinical studies

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FDA, Food and Drug Administration; FST, full-field stimulus test; IRD, inherited retinal disease; MLMT, Multi-Luminance Mobility Test®.
1. Igoe JM, et al. *J Clin Med*. 2024;13(18):5512.

Primary Efficacy Outcomes in Published IRD Trials Have Been Based on BCVA, Microperimetry, and/or Mobility Tests

Endpoints in Published IRD Clinical Trials Have Included:

Functional

- **Best-corrected visual acuity (BCVA)**
- **Perimetry and microperimetry**
- Pupillometry
- Full-threshold stimulus test (FST)
- Electroretinogram (ERG)
- Contrast sensitivity
- Color vision testing
- Photosensitivity

Structural

- Optical coherence tomography (OCT)
- OCT Angiography (OCTA)
- Fundus autofluorescence (FAF)
- Adaptive optics (AO)

Patient-Focused

- **Performance-based mobility tests**
  - MLMT
  - Ora Visual Navigation Course
  - LDNA
  - MLoMT
- Patient reported outcomes

While BCVA has been used in many late-stage IRD trials, it loses sufficient sensitivity with a basement effect at the threshold of CF and a ceiling effect due to foveal sparing in IRDs, such as RP

BCVA, best-corrected visual acuity; CF, counting fingers; ERG, electroretinogram; FST, full-field stimulus threshold; IRD, inherited retinal disease; LDNA, luminance dependent navigation assessment; LLVA, low-luminance visual acuity; MLMT, Multi-Luminance Mobility Test; MLoMT, MLoMT, multi-luminance orientation and mobility test; QoL, quality of life; RP retinitis pigmentosa.

1. Igoe JM, et al. *J Clin Med*. 2024;13:5512.

Microperimetry Can Evaluate Retinal Sensitivity when Central Vision and Fixation are Poor Due to Macular Pathology

- Tests up to 30 degrees from the fovea in mesopic, scotopic, and photopic conditions
- FDA criterion for significant change on MP is proportion with a mean change of ≥7 dB, with improvement from baseline at ≥5 pre-selected loci
- Limitations as an endpoint:
  - Methods vary across trials, with variation in devices, testing strategies, and reporting metrics
  - MP testing can be lengthy and challenging for both patients and operators

- MP has been used as an endpoint in clinical trials for XLRP, choroideremia, LCA, STDG1, X-linked retinoschisis, and achromatopsia
- MP was used as a primary endpoint in the XLRP Phase 2/3 XIRIUS trial*

*NCT03116113. The trial did not achieve its primary endpoint and Biogen discontinued the program.
FDA, Food and Drug Administration; LCA, Leber Congenital Amaurosis; MP, microperimetry; STDG1, Stargardt disease type 1; XLRP; X-linked retinitis pigmentosa.
1. Igoe JM, et al. *J Clin Med*. 2024;13:5512.

Pupillometry is a Valuable Endpoint in the Setting of Advanced Vision Loss

- PLR remains intact even as vision approaches NLP
- Objectively evaluates photoreceptor function in severe forms of IRDs, including in children who cannot perform psychophysical tasks[1,2]
- Transient PLR is obtained with a sequence of full-field red or blue stimuli of increasing luminance with contralateral eye patched[1,2]
  - **Objective technique to test the visual pathway**, including retina and optic nerve
  - **Convenient, non-invasive, and non-contact**, and can be used to complement other visual function tests

- TPLR has been used as objective outcomes in several clinical trials including LCA caused by GUCY2D, CEP290, and NPHP5 mutations and CNGA3-linked achromatopsia[2]
- TPLR can be used as an inclusion criterion to confirm functional fidelity of the retinopretectal tract

NLP, no light perception; PLR, pupillary light reflex

1. Igoe JM, et al. *J Clin Med*. 2024;13:5512. **2.** Cideciyan AV, et al. *Annu Rev Vis Sci*. 2021;7:747-772.

FST has Become an Important Endpoint for Measuring Residual Vision When Perimetry Cannot be Performed

- Psychophysical measure of whole-field retinal light sensitivity and **can quantify to the level of light perception**
- Variations can preferentially evaluate different subsets of photoreceptors
  - Dark-adapted FST can distinguish between cone and rod deficits
  - Light-adapted FST can distinguish between different cone subpopulations using chromatic stimuli and backgrounds
- Originally developed for patients with LCA, **FST is widely used as a secondary endpoint in IRD trials**
  - Often used in conjunction with mobility tests, which cannot assess visual function below a luminance of 1 lux
  - FST is not currently accepted by the FDA as a primary endpoint

FST was used as the primary endpoint in the 2023 approval of voretigene in Japan

FDA, Food and Drug Administration; FST, full-threshold stimulus test.

1. Igoe JM, et al. *J Clin Med*. 2024;13(18):5512.

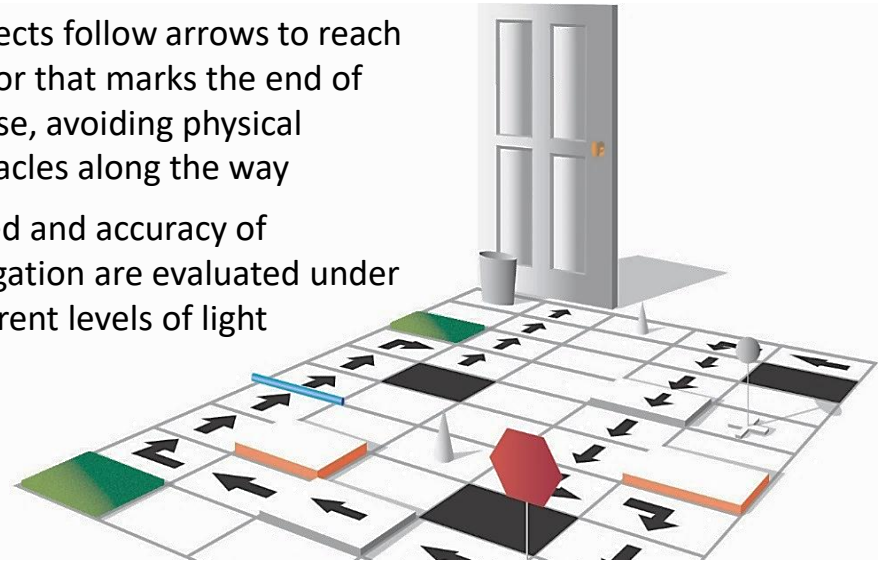
Development of the MLMT® was Groundbreaking and Effective, but Has Several Limitations

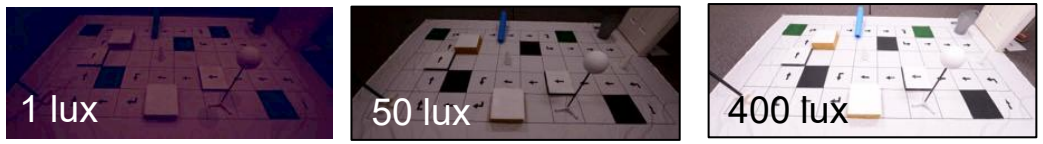
Drawbacks of MLMT

- Tripping hazards for patient
- Requires large designated space
- Time-consuming to set-up and reconfigure
- Difficult to ensure uniform illumination
- Limited number of tests per session
- Potential for echolocation
- Subjects with good visual acuity do well
- Requires a reading center (potential for bias)
- Long wait time for analysis
- Risk of confidentiality breech (videotaped date)

MLMT physical course detects changes in functional vision across a range of light levels

- Subjects follow arrows to reach a door that marks the end of course, avoiding physical obstacles along the way
- Speed and accuracy of navigation are evaluated under different levels of light

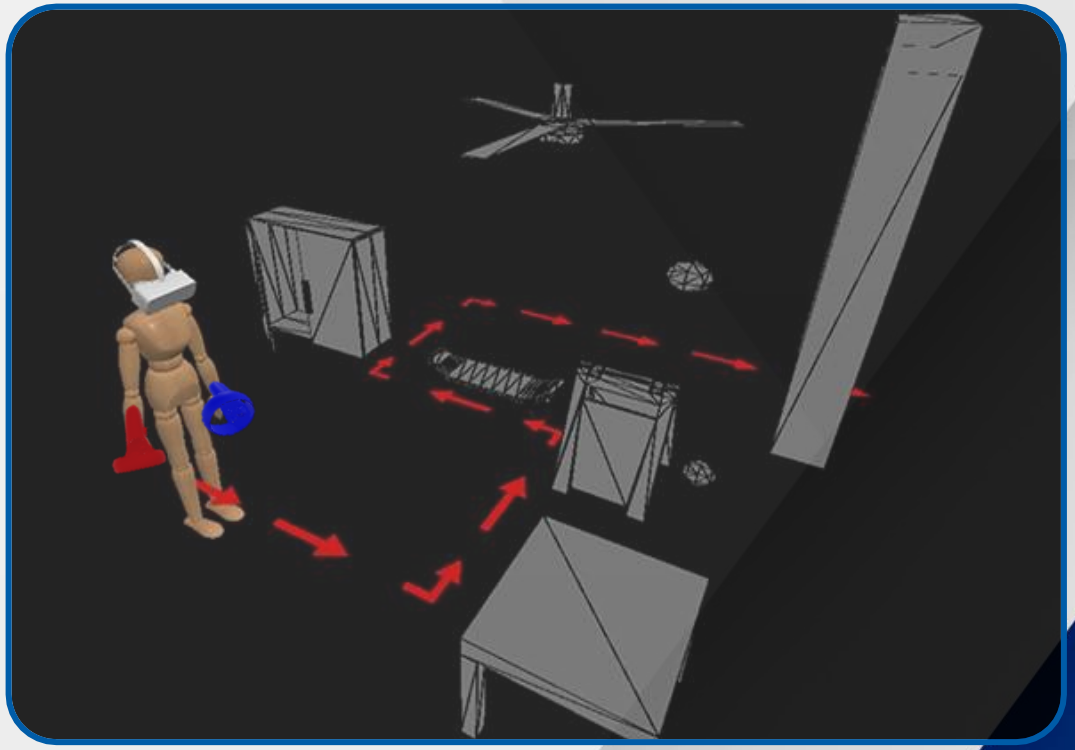




MLMT, Multi-luminance mobility test.

Functional Vision Assessment with a Multi-Luminance Orientation and Mobility Test Overcomes Limitations of Physical Settings

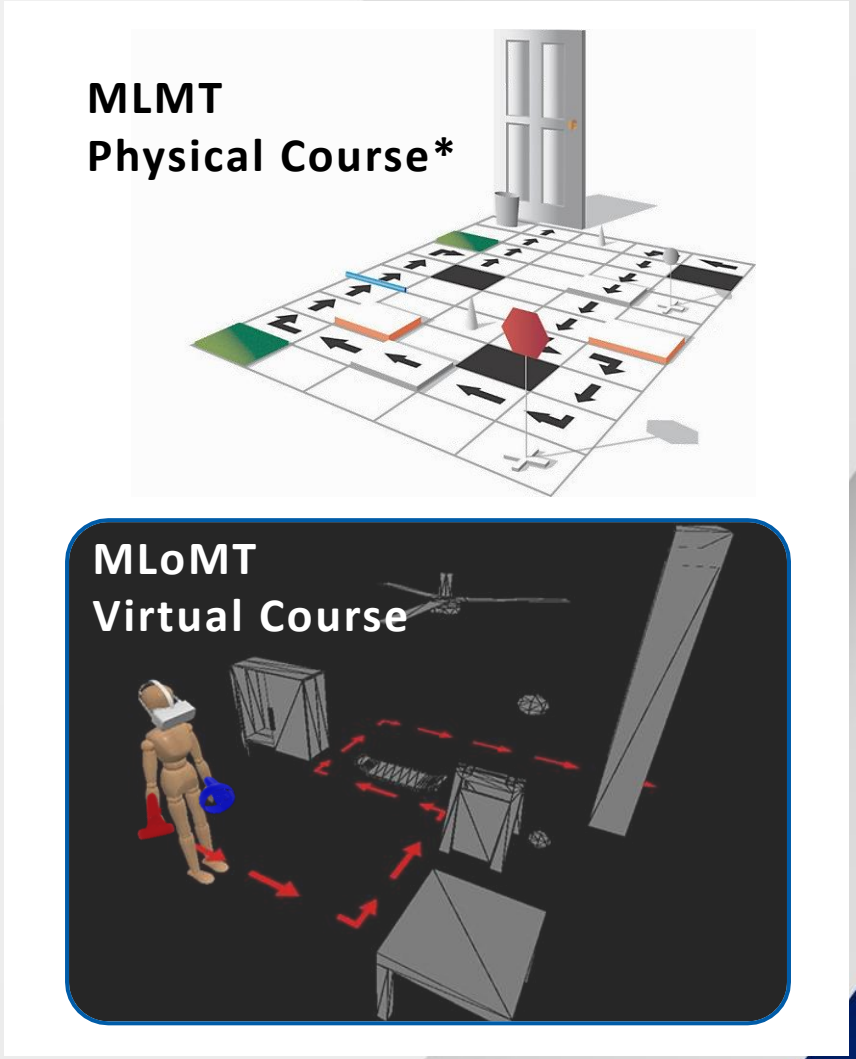
- Utilizes a VR headset with body trackers to navigate a virtual course
- Household objects are presented at increasing illumination while the subject follows a path of red arrows
- Subject identifies and “touches” obstacles while following the path
- Establishes a threshold of functional vision that may be used to assess impact of disease and treatments
- Enormous amount of data automatically collected
- Relates well with clinical readouts (visual acuity, visual fields, and visual sensitivity)



MLoMT, multi-luminance orientation and mobility test.

MLoMT Builds Upon the Success of MLMT

- Endlessly-randomizable; can conduct numerous tests over a broader range of lighting levels and in a quicker timeframe
- Ability to duplicate test across sites
- Minimal equipment and room requirements
- No physical obstacles that could cause harm in a collision
- Ability to test one or both eyes
- Automated capture of quantitative parameters (no requirement of a reading center)
- **FDA deemed MLoMT a "nonsignificant risk" and approved its use in clinical studies in subjects 8 years and older**

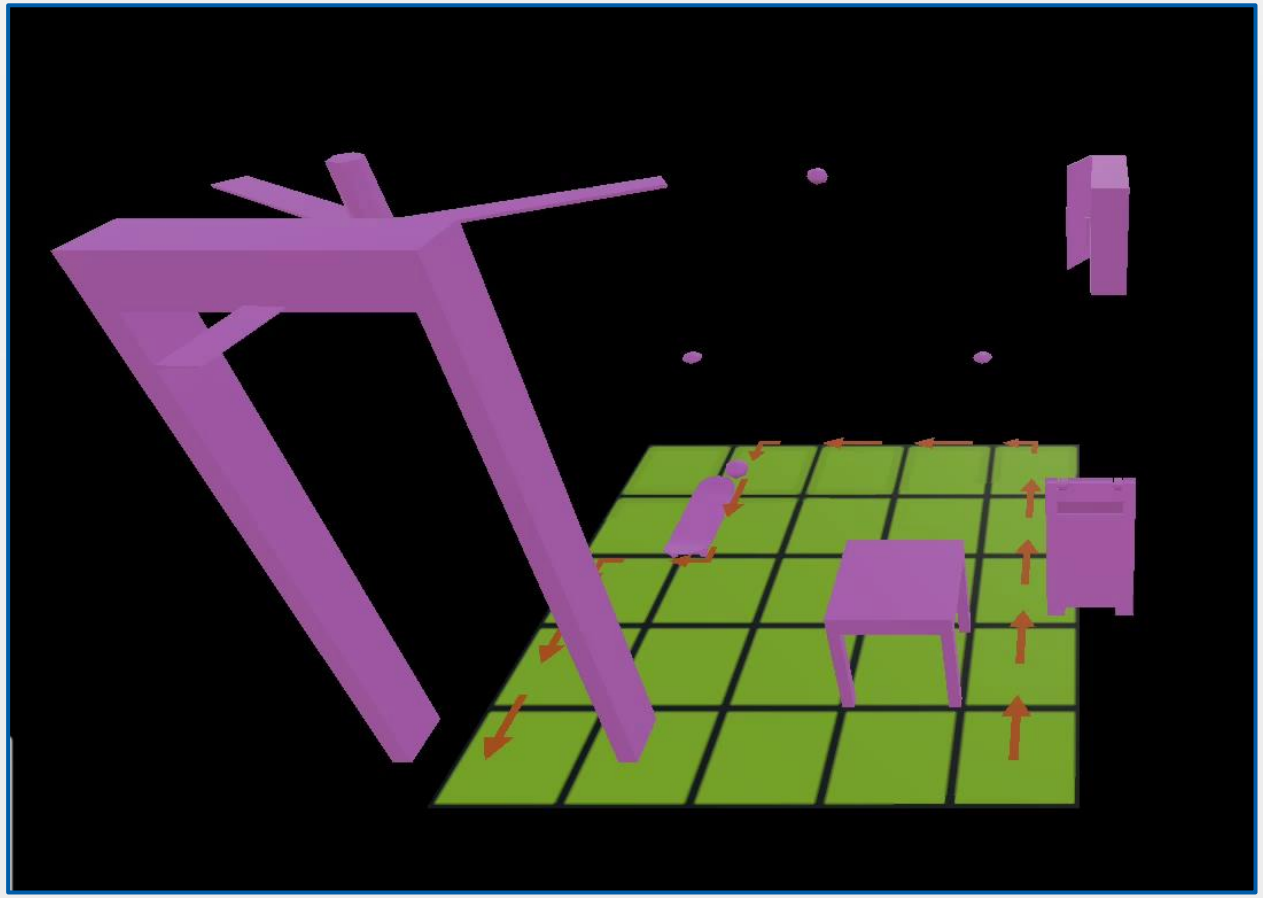


MLoMT, Multi-luminance orientation and Mobility Test; MLMT, Multi-Luminance Mobility Test.

1. Bennett J, et al. *Transl Vis Sci Technol*. 2023;12:28; 2. Aleman et al. *Clin Ophthalmol*. 2021;15:939

Virtual Reality Test Design of MLoMT

No mechano-sensory feedback and no possibility for the subject to echo-locate an object



- Ability to follow a path of red arrows at increasing levels of luminance
- Ability to identify (“tag”) objects at differing heights/sizes (similar to those found in daily living) while following arrows on a path at increasing levels of luminance

Conclusions

- Conventional outcome measures such as BCVA may lack adequate sensitivity for IRD clinical trials
- Primary endpoints utilized in IRD gene therapy trials include microperimetry, pupillometry, FST, and mobility tests
- In the future, there will likely to be an increasing range of validated and FDA-accepted outcome measures for IRD clinical trials
- **Phase 1/2 Study of OPGx-LCA5** in patients with *LCA5* is ongoing; Outcome measures include BCVA, FST, TPLR, microperimetry, and MLoMT[2]
- **OPGx-BEST1** for BEST1-associated disease has plans to initiate a **Phase 1/2 study in Q4 2025;** Outcome measures include BCVA, LLVA, perimetry, and microperimetry

BCVA, best-corrected visual acuity; FST, full-field sensitivity testing; IRD, inherited retinal disease; LCA5, Leber congenital amaurosis 5; LDNA, luminance dependent navigation assessment; LLVA, low-luminance visual acuity; MAIA, macular integrity assessment; MLoMT, multi-luminance orientation and mobility test.

1. NCT06388200. https://clinicaltrials.gov/study/NCT06388200?term=NCT06388200&rank=1 **2.** NCT05616793. https://clinicaltrials.gov/study/NCT05616793?cond=LCA5&rank=1