1   **Functional Evaluation in Inherited Retinal Disease**

2

3   Malena Daich Varela,[1,2] Michalis Georgiou,[1,2,3] Shaima A. Hashem,[1,2] Richard G. Weleber, [4] Michel Michaelides[1,2]

4

5   [1] UCL Institute of Ophthalmology, University College London, London, United Kingdom.

6   [2] Moorfields Eye Hospital, London, United Kingdom.

7   [3] Department of Ophthalmology, Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

8   [4] Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA

9

10

11 **Corresponding author:**

12 Professor Michel Michaelides,

13 UCL Institute of Ophthalmology,

14 11-43 Bath St, EC1V 9EL.

15 London, United Kingdom.

16 michel.michaelides@ucl.ac.uk

17

18 **Word count: XXXX** words

Abstract

Functional assessments are a fundamental part of the clinical evaluation of patients with inherited retinal diseases (IRD). Their importance and impact have become increasingly notable given the significant breadth and number of clinical trials and studies investigating multiple avenues of intervention across a wide range of IRD, including gene, pharmacological and cellular therapies. Moreover, the fact that many clinical trials are reporting *improvements* in vision, rather than the previously anticipated structural stability/slowing of degeneration, makes functional evaluation of primary relevance. In this review, we will describe a range of methods employed to characterise retinal function and functional vision, beginning with tests variably included in the clinic, such as visual acuity (VA), electrophysiological assessment and colour discrimination; and then discuss assessments often reserved for clinical trials / research studies such as photoaversion testing, full-field static perimetry and microperimetry, and vision-guided mobility testing; discussing perimetry in greatest detail given it is commonly a primary outcome metric. We will focus on how these tests can help diagnose and monitor particular genotypes - also noting their limitations/challenges, exploring analytical methodologies for better exploiting the functional measurements, as well as how they facilitate patient inclusion and stratification in clinical trials and serve as outcome measures.

Introduction

Inherited retinal diseases (IRD) are a complex group of conditions with a wide genotypic and phenotypic spectrum.[1–4] Detailed functional assessment is valuable in the diagnosis and monitoring of IRD, in both clinical and research settings. A wide range of tests and devices have been developed to record and quantify retinal function and functional vision, which vary in their degree of objective measurement and subjective patient response, all having significant benefits and limitations. In these regards, functional characterisation is similar to structural characterisation, in that for both a 'multi-modal' evaluation is most informative. The degree of change in any of these measurements that is universally agreed to be clinically meaningful remains to be established; although for inexorably progressive IRD, any change that is greater than test-retest variability for the metric may be clinically meaningful. Functional testing, whilst subject to concomitant ocular disorders such as media opacity, myopic retinopathy and aging, significantly contributes to our understanding of disease pathophysiology, informs advice on prognosis, assists monitoring the impact of interventions, and increasingly underpins clinical trial endpoints. An overview of the functional assessments included in this review is shown in Tables 1 and 2.

Best Corrected Visual Acuity (BCVA)

Visual acuity (VA) represents the ocular spatial resolving capacity.[5] Quantification of VA is usually the first assessment in clinic, and by far the most commonly performed. Knowing the VA and the BCVA of an individual is essential in the evaluation of the function and integrity of the visual system. The first and most widespread chart was developed by Snellen in 1862.[5] However, it has an imprecise scoring method that uses lines instead of letters and lacks standardization, leading to difficulties in statistical analysis.[6] Hence the current gold standard is the retro-illuminated logarithm of the minimum angle of resolution (LogMAR) chart, following the Early Treatment Diabetic Retinopathy Study (ETDRS) optotype,[7] which has high repeatability, and is therefore the method of choice in clinical trials.[8] Other commonly used methods to assess VA include

54 the Tumbling E-chart, Landolt C optotypes (both for illiterate or non-Latin language speaking patients and children), and

55 those specifically tailored for children such as Kay Pictures, Lea Symbols and Allen Figures.[9]

56   BCVA is typically reduced early in cone dysfunction syndromes (e.g. achromatopsia (ACHM)), cone and cone-rod

57 dystrophies (COD/CORD), macular dystrophies (MD) and early-onset severe retinal dystrophy/Leber congenital amaurosis

58 (EOSRD/LCA), but is often preserved until late stages in rod-cone dystrophies (RCD).[4,10–12] BCVA has been shown to

59 significantly correlate with the width and integrity of the ellipsoid zone (EZ) on optical coherence tomography (OCT),[13] as

60 well as with visual field (VF).[14,15] However, BCVA can show notable disconnect with structural measures (both better or

61 worse respectively, than predicted from anatomy alone), including in certain genotypes such as *RDH12* and *CEP290*, and

62 also in cone density measured with adaptive optics (AO) imaging can be up to 60% decreased and yet acuity remains

63 normal – highlighting the redundancy in the visual system and potentially boding well for cell replacement strategies.[16]

64 BCVA is an outcome measure included in all IRD trials.

65

66 **Low Luminance VA (LLVA)**

67 LLVA can be measured by placing a 2.0 log unit neutral density filter over the patient's best correction or over the ETDRS

68 chart, while the latter is read.[17] Other options include using a U23 NoIR 4% transmission filter to simulate mesopic

69 conditions.[18] Patients with RCD have difficulties in dim environments and have reduced LLVA from the earliest stages of

70 disease.[19] Consequently, changes in LLVA are secondary outcome measures in gene therapy trials for the following RCDs:

71 *USH2A* (NCT03780257), *RHO* (NCT04123626), CHM (NCT03496012) and *RPGR* (NCT03252847). The measurement of

72 LLVA is an inexpensive and simple procedure, although more data regarding its correlation with other parameters are

73 needed.

74

75

Contrast Sensitivity

Reduced contrast sensitivity (CS) is a frequent symptom in IRD – significantly impairing central vision; even in those with normal or near-normal BCVA.[20,21] Multiple methods have been used to assess CS, but Pelli-Robson (PR) charts[20] are currently the most frequently used, both in clinical and research settings.[21,22] However, the PR chart has relatively sparse spatial frequencies and stimulus contrast, which may lead to imprecision. Newer computer-based methods to evaluate CS (e.g. the Quick Contrast Sensitivity Function test and photoreceptor-specific temporal contrast sensitivity) are continuously evolving, with early evidence suggesting higher resolution assessments and thereby more capability to detect change over time.[23–26]

A decrease in CS has been documented in patients with RCD,[27] ACHM,[4,10,22] and CORD.[28] Higher spatial frequencies (6.0 to 18.0) are usually more severely affected, as reported in individuals with *USH2A*-RCD, *ABCA4* retinopathy and *BEST1* maculopathy.[21,29,30] An association between mean retinal sensitivity (MS) and CS has been reported in patients with RCD and ACHM.[22,31] Moreover, CS was significantly associated with reading speed in patients with *ABCA4* retinopathy and RCD.[27,28] CS assessment is an easy and clinically important method to monitor visual function, being currently a secondary outcome measure in many gene therapy trials for the following RCDs: *PDE6A* (NCT04611503), *RLBP1* (NCT03374657) and *RPGR* (NCT04671433); as well as in multiple pharmacological trials for Stargardt disease (STGD; *ABCA4*).[1]

Colour Vision

Colour vision (CV) defects are typically observed at an early stage with CORD, ACHM and cone dysfunction syndromes.[3,10] Individuals with RCD may also report early issues with CV;[32,33] and certainly at later stages of disease as cone function becomes compromised. CV can be assessed by a wide range of tests. The most commonly used in the clinic is one of the oldest: the Ishihara pseudoisochromatic plates.[34] However, whilst easy to use, it lacks evaluation of the tritan axis.[34] Hardy-Rand-Rittler pseudoisochromatic plates are as easy to administer and assess discrimination along all 3 colour axes.[35]

98   Another option are the Farnsworth-Munsell tests, where the patient sorts coloured caps according to their chromaticity. The

99   100-Hue version consists of 85 caps and now also exists as a computer-based test; while the D15 has only 15 caps (with

100   the PV-16 being a low vision version with enlarged caps).[36] These tests are more challenging to administer and more time

101   consuming, but especially useful when assessing and monitoring acquired CV defects.[36] Computerised systems are

102   primarily employed in research and offer a quantitative and more comprehensive characterisation of colour discrimination.

103   The Cambridge Colour Test (CCT) is the first popular computer-based test.[37] It consists of pseudoisochromatic plates at

104   decreasing luminance levels and also has a low vision version (lvvCCT), suitable for visually impaired individuals.[38] Other

105   computerized tests available are the Rabin Cone Contrast Test and the Universal Colour Discrimination Test (UCDT), the

106   latter being suitable for individuals with low vision.[18,38]

107   CV testing helps to discriminate between cone dysfunction syndromes, including between complete and incomplete

108   ACHM - one of the features of the latter being residual colour perception.[4] In addition, tests probing the tritan axis, including

109   that created by Berson et al. are valuable in helping to identify males with blue cone monochromacy.[39] By detailed testing

110   of colour discrimination in individuals with IRD, we can infer how different cone classes are affected and this can help with

111   the differential diagnosis and suggest a genetic basis.[40,41] CV is a secondary outcome measure in on-going ACHM gene

112   therapy trials, including NCT03001310 and NCT02599922 (both *CNGB3*), and also NCT03758404 and NCT02935517 (both

113   *CNGA3*).

114

115   **Visual Field (VF) and Retinal Sensitivity**

116   In 1927, Traquair first described the VF as "an island of vision in a sea of darkness".[42] Loss of peripheral VF as occurs in

117   early forms of RCD results in symptoms such as tripping, bumping into people/obstacles, struggling to find objects, or

118   difficulty navigating in dim or crowded/unfamiliar environments. In contrast, loss of central VF in COD/CORD, MD and

119   EOSRD/LCA, usually leads to difficulties in recognizing faces, reading signs and identifying objects.

120   VF evaluation, as performed using kinetic and static perimetry, has evolved significantly over the last two decades.

121   Kinetic VF testing has been used to monitor progression in patients with RCD and Usher syndrome - with semi-automated

122   kinetic perimetry (SKP) being more frequently employed.[43–48] However, there is no consensus or standard method of

123   conducting KP, making it challenging to compare results from one centre to another.[49] It requires a higher level of skill,

124   greater training, knowledge about expected field defects in specific diseases, and experience. KP has a higher test-retest

125   variability (up to 20-30%) and its quality and efficiency can vary substantially even within the same clinical centre, from one

126   examination to another, as well as due to patient cooperation.[45,49] Whilst test-retest variability is less for SKP, the major

127   drawback of all KP remains that, because the shape and height of the hill of vision depends upon the existing pathology for

128   the individual patient, it is not possible to fully automate it for all clinical situations.[49] KP is a valuable tool to define sharp

129   borders of blind areas, however it is less able to detect mild slopes or transitions between seeing and unseeing parts, or to

130   distinguish shallow islands of remaining sensitivity.

131   Semi-automated static perimetry (SP) by Octopus 900 is a robust method to comprehensively evaluate retinal

132   sensitivity/visual field integrity and has been applied in a broad range of genotypes in both adults and children, including

133   *RPE65*, *ABCA4*, *RPGR* and *USH2A*.[50–53] It also has lesser dependency than kinetic testing on the technician's expertise,

134   and less inherent test-retest variability. A major advantage of static over KP is the availability of parameters that evaluate

135   the reliability and validity of patient test responses, such as the frequency of false positive and false negative responses,

136   and the quantification of a reliability factor (RF). Variability and inconsistencies between test sessions and among test

137   subjects can be reduced and validity of testing increased by specific instructions read to the patient by the perimetrist before

138   each test as to how to respond to the test stimulus presentations.[54] Static testing is better than kinetic testing at detecting

139   and defining gradual changes of either lesser or greater sensitivity and isolated regions of residual sensitivity in advanced

140   disease.[49] The Humphrey perimetry has been extensively used for clinical studies and trials for glaucoma and to a lesser

141   extent, mostly in the past, for IRD. The fast integrated SITA Standard thresholding algorithm available on the Humphrey

142 perimeter is based on frequency of seeing curves for glaucoma and is, thus, sub-optimal for retinal diseases.[55] The normal

143 4-2-1 strategy on the Humphrey takes much longer and is, therefore not suited for full-field static testing.

144 The Octopus 900 perimeter, using the fast German Adaptive Thresholding Estimation (GATE) algorithm,[56,57] is

145 currently the most robust and optimal system for static testing the entire visual field of patients with IRD. The GATE algorithm

146 is as fast as the SITA Standard and has a validity and precision comparable to the normal 4-2-1 strategy. Octopus 900

147 perimetry using the GATE strategy has become the most commonly used device for clinical studies and treatment trials for

148 IRD.[15,55,58,59] The Octopus system allows (i) use of custom color test targets, (ii) a validated, retina-specific optimized testing

149 strategy to be employed, i.e., GATE, and arguably most importantly (iii) exportation of all raw retinal sensitivity data, which

150 can then be comprehensively and robustly analyzed, using Visual Field Modelling and Analysis (VFMA) methodology

151 (Figure 1),[60] from which topographic displays and hill-of-vision volumetric outputs can be derived; including the total hill-of-

152 vision (V_{TOT}) or any subset e.g. the central 30 degree field of vision (V_{30}).[52] These volumetric analyses afforded by VFMA

153 can be applied equally as well to VF data obtained from microperimetry,[22,61,62] potentially allowing game-changing state-of-

154 the-art retinal function evaluation in IRD and other retinal diseases,[63] and enabling incorporation of all data in a non-biased

155 fashion, truly representing the full impact of disease natural history or treatment effect. Assessment of retinal sensitivity

156 using VFMA with creation of volumetric endpoints, such as V_{TOT}, V_{30}, V_{10}, and V_3, allow direct comparison of values between

157 subjects, at different regions with a given test, and between baseline and follow-up testing.[57] Octopus perimetry is thereby

158 increasingly the static perimeter of choice, both in clinic and in studies/trials - and is being applied as a primary or secondary

159 endpoint in multiple studies and trials including *RPGR* (NCT04671433), *USH2A* (NCT03780257) and *RPE65*

160 (NCT02781480).

161 Fundus-guided perimetry/microperimetry (MP) consists of a static perimetry device with eye tracking and fixation

162 stabilization features, that allows measurement of the sensitivity threshold of individual macular loci under direct retinal

163 visualization, facilitating correlation between structure (especially OCT) and function, and allowing quantification of fixation

164 stability and topographical localization of retinal loci. However, the presence of unstable/poor fixation, which is commonplace

165 in IRD, can lead to registration difficulties. Furthermore, despite their popularity, there is no consensus on the type of retinal

166 sensitivity parameters that should be used to monitor progression and responses to therapeutic intervention.[64] For these

167 reasons, it is arguably less reliable than SP; also, it only tests macular function. MP devices with a broad range of testing

168 abilities (mesopic, photopic and dual-colour scotopic testing) and dynamic ranges are available, including the most

169 commonly used Macular Integrity Assessment (MAIA; CenterVue, Padova, Italy) and Nidek microperimeters (Nidek

170 Technologies Srl, Padova, Italy). MP has been used to characterize and monitor the progression of multiple IRDs, including

171 - STGD,[61,65] ACHM,[22] and both syndromic and non-syndromic *USH2A*-retinopathy;[53] as well as in clinical trials of gene

172 therapy for *RPE65*-LCA (NCT00643747)[66] and *RPGR*-RCD (NCT03252847), pharmacological trials for STGD

173 (NCT03735810, NCT03033108, NCT02402660, NCT03364153), and transplantation of human embryonic stem cell-derived

174 (hESC-) retinal pigment epithelial (RPE) cells in STGD (NCT01469832).[67]

175

176 **Dark Adaptometry**

177 Measuring dark adaptation (DA) provides insight into photoreceptor thresholds and kinetics. Canonical and rapid

178 adaptometers exist, with Goldmann-Weekers being the most commonly employed.[68] DA curves show how retinal sensitivity

179 changes at set locations, after switching from photopic to scotopic conditions.[69] DA is typically biphasic, with an initially

180 cone-mediated phase, followed by a cone-rod breakpoint, and a final, longer phase representing rod function.[70] Elevated

181 thresholds of DA have been reported in a broad range of conditions, including RCD,[71–73] CORD,[74] ACHM,[69] congenital

182 stationary night blindness,[75] and STGD.[76]

183 Newer devices have been developed; portable, LED-based dark adaptometers such as the Scotopic Sensitivity

184 Tester (SST-1) from LKC Technologies Inc. (Gaithersburg, MD, USA),[77] and instruments with increased testing efficiency.

185 Among the latter, the AdaptDx (MacuLogix, Hummelstown, PA) has been used to study delayed DA mainly in age related

186 macular degeneration (AMD).[78] Higgins et al. have recently proposed a novel 'time-to-event' analysis method that can be

187 applied to this data, providing better statistical power.[79]

188 **Assessment of Photoaversion**

189 Testing of light discomfort threshold has been implemented in several conditions such as migraine, blepharospasm, LCA

190 and ACHM.[80–84] The technique used for the first three entities was similar: increasing luminance stimuli were presented to

191 the subject until he/she pressed a button, indicating that the stimulus was uncomfortable and ending the test.[80] For ACHM,

192 an arguably more objective and precise approach has been proposed.[85] This involves video-recording the subject's reaction

193 to different light exposures and capturing various metrics such as average distance between the eyelids (palpebral fissure

194 aperture).[81,83] This method has been included to monitor efficacy in two on-going ACHM gene therapy trials: *CNGB3*-

195 NCT03001310 and *CNGA3*- NCT03758404. Other gene therapy trials, such as *CNGA3*- NCT02935517 and *CNGB3*-

196 NCT02599922, have implemented a device called the Ocular Photosensitivity Analyser (OPA) as a secondary outcome

197 measure. The OPA uses a concave LED and measures patient indication of pain threshold, along with several further

198 metrics such as inter-blink interval and pupil diameter.[85,86]

199   Identifying the most sensitive way to measure and compare photoaversion is certainly challenging. Different groups

200 have proposed their own method, with different approaches regarding adaptation to light levels (Verriotto et al. adapt at 100

201 lux, while Aboshiha et al. use total darkness),[84,85] stimuli intensity and colour, and outcome metrics. A consensus is yet to

202 be established. Qualitative assessments of photoaversion are also being explored and will no doubt be complimentary to

203 the aforementioned objective assessments; these include the questionnaire developed for the *CNGA3*- NCT02610582 trial,

204 'A3-PRO',[87,88] and the Visual Light Sensitivity Questionnaire-8, designed by Verriotto et al.[85]

205

206

Visual Electrophysiology

The electroretinogram (ERG) can be a valuable tool in the diagnosis and characterisation of IRD, especially those with pathognomonic ERG features such as IRD associated with *NR2E3* and *KCNV2*,[89] being able to probe the extent, degree and cellular nature of dysfunction objectively.[90] Electrophysiological assessment is also helpful in providing better informed advice on prognosis (particularly in STGD),[91] in the differential diagnosis of childhood nystagmus/poor vision from birth/early infancy,[92] and helping to distinguish between late-onset IRD and autoimmune retinopathy.[93,94] However, the test-retest variability of ERG is high (20-30%), making it insensitive to measuring change overtime clinically or in clinical trials; with patients also often reporting reluctance to have serial electrophysiological testing.[95–97]

Full-field (ff) ERG measures the global retinal electrical potential changes provoked by light stimuli, under light- and dark-adapted conditions, to provide information on generalized retinal function of both rod and cone systems.[98] The International Society for Clinical Electrophysiology of Vision (ISCEV) recommends a minimum of six stimuli for a complete clinical ERG assessment.[90] Two of the most important components of the ERG are the a and b waveforms. The a wave corresponds to the initial negative deflection and originates from the light-induced hyperpolarization of rod and cone outer segments.[98] The b wave is the positive deflection following the a wave, and represents bipolar cell depolarization. Photoreceptor disorders (e.g. RCD, CORD, ACHM) affect both the a and b wave, whereas conditions involving the post-photoreceptor signal transduction (e.g. X-linked retinoschisis) selectively reduce the b wave, causing an 'electronegative waveform' (b/a ratio <1.0).[99] Macular function can be explored with a range of electrophysiological assessments, including multifocal (mf) ERG, focal ERG, and pattern ERG (PERG). Such testing may be helpful in the diagnosis of e.g. *RP1L1*-occult macular dystrophy,[100] and structure-function correlations including between PERG/mfERG and the high intensity autofluorescence perimacular ring often seen in RCD and CORD.[12]

The electrooculogram (EOG) evaluates the RPE and the photoreceptor-RPE complex, measuring photopic and scotopic changes in the resting potential between the cornea and the retina.[101] It is expressed as a ratio of the peak light-

229   adapted amplitude to the minimum dark-adapted amplitude (Arden ratio, ≥1.8 in normal eyes). The EOG ratio is often

230   reduced when the ffERG is abnormal, and is generally abnormal in autosomal dominant Best disease, where a decreased

231   Arden ratio with normal ffERG is characteristic.[102]

232   Visual Evoked Potentials (VEP) are used to evaluate the integrity of the complete visual pathway, and depend highly

233   on central visual function. ISCEV recommends three basic stimuli: flash (useful for media opacity), pattern reversal (for both

234   pre- and post-chiasmal lesions), and pattern on/off (provides estimates of potential VA).[103]

235   Lastly, full-field light sensitivity threshold (FST) testing is a dark-adapted assessment with white, blue, green and red

236   full-field stimuli, providing a psychophysical assessment of luminance thresholds; which unlike the aforementioned

237   electrophysiological assessments lacks international standardisation.[104] By comparing the responses to stimuli of different

238   wavelengths, inference can be made about which mechanisms are primarily mediating the response.[104] FST has been

239   correlated with dark-adapted perimetry derived retinal sensitivity in a cohort of subjects with a range of IRD.[105] FST has also

240   been correlated with OCT parameters and BCVA in patients with STGD,[106] with disease duration in individuals with *USH2A*-

241   associated retinopathy (both syndromic and isolated),[107] and with ffERG amplitude in patients with RCD.[108] FST has a test-

242   retest variability of around 0.3 log cd/m^2 and has been used as a secondary outcome measure in gene therapy clinical trials

243   for IRD, including the pivotal trial leading to approved treatment for *RPE65*-associated retinal dystrophy.[109,110]

244

245   **Patient-Reported Outcome Measures**

246   Comprehensively understanding the patient experience while living with an IRD is key to fully measuring the impact of IRD

247   including emotionally, psychologically, socially and financially, and is critical to the provision of appropriate management

248   and the development and approval of treatments. Several standardised questionnaires have shown significant reliability

249   and validity and are included in research settings as patient-reported outcome measures (PROs).[111–113]

250   The National Eye Institute Visual Function Questionnaire (NEI-VFQ) is one of the most commonly applied instruments

251 to evaluate vision-related quality of life in visually impaired individuals. A version consisting of 25 items (VFQ25) has been

252 validated and used in the CHM gene therapy clinical trial (NCT01461213) and pivotal *RPE65*-RCD trial, among others.[114–

253 116] The Impact of Vision Impairment (IVI) questionnaire is another option and is available in adult (IVI-A) and child-friendly

254 (IVI-C) versions, and is being used as a secondary outcome measure in *RPGR*-RCD and ACHM gene therapy trials

255 (NCT04671433, NCT03001310 and NCT03758404).[117] Particularly for RCD, Szlyk et al. have developed questionnaires

256 that showed strong correlation with BCVA, CS and VF.[118,119] The Vision Function Scale-plus (19 items) survey, initially

257 developed for cataract, has also provided promising results in RCD.[120] Recently, the Michigan Retinal Degeneration

258 Questionnaire was also validated as a PRO for patients with IRD, employing 59 items in 7 domains.[121]

259   Whilst there remains no consensus on the most appropriate PRO tools in IRD and whether they need to be

260 disease/genotype specific given the extreme clinical heterogeneity of IRD, they provide clinically meaningful information for

261 both patients and researchers and are an integral assessment to fully evaluate treatment efficacy and calculate cost-

262 effectiveness.

263

264 **Functional Magnetic Resonance Imaging (fMRI)**

265 MRI can provide anatomical, physiological and functional information in a single, non-interventional setting. Functional MRI

266 commonly uses the blood oxygenation level-dependent (BOLD) technique, which shows increased signal as

267 deoxyhemoglobin concentration decreases, and vice versa.[122] fMRI has allowed the delineation of retinotopic and

268 population-receptive field maps, which connect visually stimulated retinal regions with a corresponding visual cortex area

269 that responds to this stimulation with an increased BOLD signal.[123] BOLD fMRI has been used to assess how the visual

270 cortex responded to retinal gene therapy in patients with *RPE65*-LCA,[124] and has also recently identified new cone-driven

271 signals in visual cortical areas in a child with ACHM, following gene therapy (NCT03758404 and NCT03001310), with plans
272 for fMRI to be incorporated into other ACHM gene therapy trials.[125]

273

274 **Vision-guided mobility**

275 Orientation and Mobility testing (MT) is a way of assessing functional vision, and can be defined as the physical ability to
276 move efficiently and safely in an environment. Assessments of vision-guided mobility can be helpful in exploring the impact
277 of vision on everyday function, with impaired mobility having been associated with reduced wellbeing. Constricted VF, as
278 well as nyctalopia, seen in RCD and other IRD, are known to markedly impair mobility.[126–128]

279 Increasingly IRD trials, including the pivotal trial for *RPE65*-LCA (where mobility was the primary outcome), employ
280 assessments to quantify vision-guided mobility before and after intervention; with multiple mobility assessments developed
281 to date, including with or without obstacles, with or without visual acuity dependent prompts, performed under a range of
282 different lighting conditions, and of varying sizes and complexities.[110,129,130] One of the most important MT assessments was
283 the one custom designed for the *RPE65* gene therapy pivotal trial (NCT00999609), which was named multi-luminance
284 mobility testing (MLMT) and had a dimension of 7 × 12 ft (equivalent to 2.1 x 3.6 m);[131] for which patients were dark adapted
285 and asked to navigate a path, making turns and avoiding obstacles, with one and/or both eyes open. Other groups have
286 employed a mixed indoors and outdoors setting,[132] while others have directly utilized true real-life scenarios such as
287 shopping malls[128] and sections of hospitals.[133] *RPE65*- NCT02781480 and *RPGR*- NCT03252847 have chosen a different
288 type of MT, with a dimension of 7.2 × 10.8 m, and an adjustable modular platform at decreasing, standardised lighting levels
289 (Figure 2). This test can also include obstacles and has been validated for use in subjects with *RPE65*-LCA.[134]

290 The metrics used to quantify performance on these mobility assessments have varied, however the most commonly
291 employed are the time taken to navigate the course and/or the errors made during navigation, at a given illumination level.
292 These have been used as either continuous variables or incorporated into a pass/fail criterion; and have been included as

293 both inclusion criteria and primary outcome measures in several clinical trials and validation studies.[129,131,134,135] An

294 association between MT parameters and VF has been most strongly established,[134,136] with a correlation with BCVA[135] and

295 CS also reported.[132] Of note, central field loss has not appeared to be as limiting for mobility as peripheral loss.[51] It remains

296 likely that these correlations will be partly disease dependent and/or severity related.

297   The capability to navigate independently in dim environments contributes to quality of life and productivity.[137]

298 Decreased mobility has also been associated with depression.[138] Innovative MT assessments provide an accurate way of

299 understanding how patients perform on a daily basis and how treatments can help improve their quality of life and increase

300 their independence.

301

302 **Virtual Reality and New Methodologies**

303 Virtual reality (VR) represents an additional opportunity to capture aspects of functional vision under real-life-like conditions.

304 VR technology has become readily available, providing flexibility, reproducibility, participant engagement, safety, and the

305 ability to tailor countless scenarios with excellent ecological validity (highly accurate designs, displaying the relevant features

306 of the environment).[139] A recent study has tested a VR MT in patients with *RPE65*-LCA, providing proof-of-concept of the

307 utility of this approach and encouraging further broader application to IRD, and potentially resulting in mobility assessments

308 being more accessible and varied.[140]

309   Another interesting field has been the development of tools and applications (apps) that can assess aspects of vision

310 while we use our own digital devices.[141] Information about VF, tracking, CV, CS and VA can be estimated through the use

311 of apps, again potentially providing a more accessible (and arguably more directly functionally relevant) way of

312 characterizing and monitoring vision[141,142] Standardization and validation of such approaches will be necessary.

313

314

Conclusions

Functional testing in IRD has gained increasing relevance over the last decade, superseding structural assessments in providing evidence of efficacy in clinical trials of treatments,[143] given that improvement in function is generally being recorded, thereby shifting the emphasis away from slowing/halting retinal degeneration which is often focused on structure.[115,131] Although some of the assessments provide unique, novel information such as real-life mobility performance, most clinically meaningful features can be assessed through a range of modalities e.g. macular function can be evaluated through static perimetry, microperimetry, CV, BCVA, CS, etc. Ideally, following a genetic diagnosis, patients with IRD should have both a structural and functional multimodal evaluation, to fully characterize their disorder, help to provide better informed advice on prognosis, as well as facilitate determination of eligibility and end-points for interventional clinical trials.

Legends

325 **Legends**

326 Figure 1: Example of semi-automated static Octopus perimetry and corresponding Visual Field Modelling and Analysis

327 (VFMA), displaying the total hill-of-vision volumetric output (V_{TOT}). A) Baseline assessment of an individual with *RPGR*-

328 RCD, with a V_{TOT} of 35.68 decibel-steradians (dB-sr). The latter combines the magnitude and extent of the sensitivity

329 across the test grid. B) Four-year follow up of the same patient, demonstrating a decreased V_{TOT} of 17.28 dB-sr. C)

330 Subtraction analysis of VFMA at baseline (A) and follow-up (B), allowing direct comparison. The 3D image enables us to

331 visualize the representation from above, below, and different angles, to also qualitatively assess the areas where

332 sensitivity has changed, while quantitative analysis reveals a ΔV_{TOT} of -17.07 dB-sr between both time-points.

333

334 Figure 2: Example of mobility assessment. "Fisheye" view from overhead camera showing the Visual Mobility Assessment

335 configuration used in NCT02781480 and NCT02714816 to evaluate individuals affected by *RPE65*-associated retinal

336 dystrophy.

337

References

1. Georgiou M, Fujinami K, Michaelides M. Inherited retinal diseases: Therapeutics, clinical trials and end-points - A review. *Clin Experiment Ophthalmol*. Published online March 2021. doi:10.1111/ceo.13917

2. Kumaran N, Georgiou M, Bainbridge JWB, et al. Retinal Structure in RPE65-Associated Retinal Dystrophy. *Invest Ophthalmol Vis Sci*. 2020;61(4):47. doi:10.1167/iovs.61.4.47

3. Gill JS, Georgiou M, Kalitzeos A, Moore AT, Michaelides M. Progressive cone and cone-rod dystrophies: clinical features, molecular genetics and prospects for therapy. *Br J Ophthalmol*. 2019;103(5):711-720. doi:10.1136/bjophthalmol-2018-313278

4. Aboshiha J, Dubis AM, Carroll J, Hardcastle AJ, Michaelides M. The cone dysfunction syndromes. *Br J Ophthalmol*. 2016;100(1):115-121. doi:10.1136/bjophthalmol-2014-306505

5. Kaiser PK. Prospective evaluation of visual acuity assessment: a comparison of snellen versus ETDRS charts in clinical practice (An AOS Thesis). *Trans Am Ophthalmol Soc*. 2009;107:311-324.

6. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. *Am J Optom Physiol Opt*. 1976;53(11):740-745. doi:10.1097/00006324-197611000-00006

7. Ferris FL 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol*. 1982;94(1):91-96.

8. Raasch TW, Bailey IL, Bullimore MA. Repeatability of visual acuity measurement. *Optom Vis Sci Off Publ Am Acad Optom*. 1998;75(5):342-348. doi:10.1097/00006324-199805000-00024

9. Chaplin PKN, Bradford GE. A historical review of distance vision screening eye charts: what to toss, what to keep, and what to replace. *NASN Sch Nurse*. 2011;26(4):221-228. doi:10.1177/1942602x11411094

10. Hirji N, Aboshiha J, Georgiou M, Bainbridge J, Michaelides M. Achromatopsia: clinical features, molecular genetics, animal models and therapeutic options. *Ophthalmic Genet*. 2018;39(2):149-157.

370   doi:10.1080/13816810.2017.1418389

371 11.   Kumaran N, Moore AT, Weleber RG, Michaelides M. Leber congenital amaurosis/early-onset severe retinal

372   dystrophy: clinical features, molecular genetics and therapeutic interventions. *Br J Ophthalmol*. 2017;101(9):1147-

373   1154. doi:10.1136/bjophthalmol-2016-309975

374 12.   Robson AG, Michaelides M, Saihan Z, et al. Functional characteristics of patients with retinal dystrophy that

375   manifest abnormal parafoveal annuli of high density fundus autofluorescence; a review and update. *Doc*

376   *Ophthalmol*. 2008;116(2):79-89. doi:10.1007/s10633-007-9087-4

377 13.   Hara A, Nakazawa M, Saito M, Suzuki Y. The qualitative assessment of optical coherence tomography and the

378   central retinal sensitivity in patients with retinitis pigmentosa. *PLoS One*. 2020;15(5):e0232700.

379   doi:10.1371/journal.pone.0232700

380 14.   Abe K, Iijima H, Hirakawa H, Tsukahara Y, Toda Y. Visual acuity and 10 degrees automated static perimetry in eyes

381   with retinitis pigmentosa. *Jpn J Ophthalmol*. 2002;46(5):581-585. doi:10.1016/s0021-5155(02)00548-8

382 15.   Iijima H. Visual loss and perimetric sensitivity in eyes with retinitis pigmentosa. *Jpn J Ophthalmol*. 2013;57(6):563-

383   567. doi:10.1007/s10384-013-0271-7

384 16.   Ratnam K, Carroll J, Porco TC, Duncan JL, Roorda A. Relationship between foveal cone structure and clinical

385   measures of visual function in patients with inherited retinal degenerations. *Invest Ophthalmol Vis Sci*.

386   2013;54(8):5836-5847. doi:10.1167/iovs.13-12557

387 17.   Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as

388   a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration.

389   *Ophthalmology*. 2008;115(9):1480-1488, 1488.e1-2. doi:10.1016/j.ophtha.2008.03.009

390 18.   Bittner AK, Ferraz MC. Reliability of Mesopic Measures of Visual Acuity and Contrast Sensitivity and Their

391   Correlation with Rod and Cone Function in Retinitis Pigmentosa. *Ophthalmic Res*. 2020;63(2):133-140.

392   doi:10.1159/000503931

393   19.   Alexander KR, Derlacki DJ, Fishman GA, Peachey NS. Acuity-luminance and foveal increment threshold functions

394   in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1991;32(5):1446-1454.

395   20.   Lindberg CR, Fishman GA, Anderson RJ, Vasquez V. Contrast sensitivity in retinitis pigmentosa. *Br J Ophthalmol*.

396   1981;65(12):855-858. doi:10.1136/bjo.65.12.855

397   21.   Alahmadi BO, Omari AA, Abalem MF, et al. Contrast sensitivity deficits in patients with mutation-proven inherited

398   retinal degenerations. *BMC Ophthalmol*. 2018;18(1):313. doi:10.1186/s12886-018-0982-0

399   22.   Georgiou M, Singh N, Kane T, et al. Long-Term Investigation of Retinal Function in Patients with Achromatopsia.

400   *Invest Ophthalmol Vis Sci*. 2020;61(11):38. doi:10.1167/iovs.61.11.38

401   23.   Hou F, Lesmes LA, Kim W, et al. Evaluating the performance of the quick CSF method in detecting contrast

402   sensitivity function changes. *J Vis*. 2016;16(6):18. doi:10.1167/16.6.18

403   24.   Huchzermeyer C, Fars J, Kremers J. Photoreceptor-Specific Loss of Perifoveal Temporal Contrast Sensitivity in

404   Retinitis Pigmentosa. *Transl Vis Sci Technol*. 2020;9(6):27. doi:10.1167/tvst.9.6.27

405   25.   Huchzermeyer C, Fars J, Stöhr H, Kremers J. [New techniques for quantification of color vision in disorders of cone

406   function : Cambridge color test and photoreceptor-specific temporal contrast sensitivity in patients with

407   heterozygous RP1L1 and RPGR mutations]. *Ophthalmologe*. 2021;118(2):144-153. doi:10.1007/s00347-020-

408   01119-0

409   26.   Burton E, Wattam-Bell J, S Rubin G, et al. Dissociations in Coherence Sensitivity Reveal Atypical Development of

410   Cortical Visual Processing in Congenital Achromatopsia. *Invest Ophthalmol Vis Sci*. 2016;57(4):2251-2259.

411   doi:10.1167/iovs.15-18414

412   27.   Virgili G, Pierrottet C, Parmeggiani F, et al. Reading performance in patients with retinitis pigmentosa: a study using

413   the MNREAD charts. *Invest Ophthalmol Vis Sci*. 2004;45(10):3418-3424. doi:10.1167/iovs.04-0390

414 28. Murro V, Sodi A, Giacomelli G, et al. Reading Ability and Quality of Life in Stargardt Disease. *Eur J Ophthalmol*.
415   2017;27(6):740-745. doi:10.5301/ejo.5000972
416 29. Alexander KR, Derlacki DJ, Fishman GA. Visual acuity vs letter contrast sensitivity in retinitis pigmentosa. *Vision*
417   *Res*. 1995;35(10):1495-1499. doi:10.1016/0042-6989(95)98729-s
418 30. Akeo K, Hiida Y, Saga M, Inoue R, Oguchi Y. Correlation between contrast sensitivity and visual acuity in retinitis
419   pigmentosa patients. *Ophthalmol J Int d'ophtalmologie Int J Ophthalmol Zeitschrift fur Augenheilkd*.
420   2002;216(3):185-191. doi:10.1159/000059627
421 31. Oishi M, Nakamura H, Hangai M, Oishi A, Otani A, Yoshimura N. Contrast visual acuity in patients with retinitis
422   pigmentosa assessed by a contrast sensitivity tester. *Indian J Ophthalmol*. 2012;60(6):545-549. doi:10.4103/0301-
423   4738.103793
424 32. Talib M, van Schooneveld MJ, van Duuren RJG, et al. Long-Term Follow-Up of Retinal Degenerations Associated
425   With LRAT Mutations and Their Comparability to Phenotypes Associated With RPE65 Mutations. *Transl Vis Sci*
426   *Technol*. 2019;8(4):24. doi:10.1167/tvst.8.4.24
427 33. Jolly JK, Groppe M, Birks J, Downes SM, MacLaren RE. Functional Defects in Color Vision in Patients With
428   Choroideremia. *Am J Ophthalmol*. 2015;160(4):822-31.e3. doi:10.1016/j.ajo.2015.06.018
429 34. Fanlo Zarazaga A, Gutiérrez Vásquez J, Pueyo Royo V. Review of the main colour vision clinical assessment tests.
430   *Arch Soc Esp Oftalmol*. 2019;94(1):25-32. doi:10.1016/j.oftal.2018.08.006
431 35. Cole BL, Lian K-Y, Lakkis C. The new Richmond HRR pseudoisochromatic test for colour vision is better than the
432   Ishihara test. *Clin Exp Optom*. 2006;89(2):73-80. doi:10.1111/j.1444-0938.2006.00015.x
433 36. Dain SJ. Clinical colour vision tests. *Clin Exp Optom*. 2004;87(4-5):276-293. doi:10.1111/j.1444-
434   0938.2004.tb05057.x
435 37. Kumaran N, Ripamonti C, Kalitzeos A, Rubin GS, Bainbridge JWB, Michaelides M. Severe Loss of Tritan Color

436 Discrimination in RPE65 Associated Leber Congenital Amaurosis. *Invest Ophthalmol Vis Sci*. 2018;59(1):85-93.

437 doi:10.1167/iovs.17-22905

438 38. Ripamonti C, Kalwarowsky S, Nardini M. A Universal Colour Discrimination Test suitable for observers with low

439 vision. *Invest Ophthalmol Vis Sci*. 2014;55(13):3536.

440 39. Berson EL, Sandberg MA, Rosner B, Sullivan PL. Color plates to help identify patients with blue cone

441 monochromatism. *Am J Ophthalmol*. 1983;95(6):741-747. doi:10.1016/0002-9394(83)90058-2

442 40. McClements M, Davies WIL, Michaelides M, et al. X-linked cone dystrophy and colour vision deficiency arising from

443 a missense mutation in a hybrid L/M cone opsin gene. *Vision Res*. 2013;80:41-50. doi:10.1016/j.visres.2012.12.012

444 41. Patterson EJ, Wilk M, Langlo CS, et al. Cone Photoreceptor Structure in Patients With X-Linked Cone Dysfunction

445 and Red-Green Color Vision Deficiency. *Invest Ophthalmol Vis Sci*. 2016;57(8):3853-3863. doi:10.1167/iovs.16-

446 19608

447 42. Traquair HM. An introduction to clinical perimetry, 1st edn, Vol. *VIII London Henry Kimpt*. 1927;254.

448 43. Grover S, Fishman GA, Brown JJ. Patterns of visual field progression in patients with retinitis pigmentosa.

449 *Ophthalmology*. 1998;105(6):1069-1075. doi:10.1016/S0161-6420(98)96009-2

450 44. Fishman GA, Bozbeyoglu S, Massof RW, Kimberling W. Natural course of visual field loss in patients with Type 2

451 Usher syndrome. *Retina*. 2007;27(5):601-608. doi:10.1097/01.iae.0000246675.88911.2c

452 45. Bittner AK, Iftikhar MH, Dagnelie G. Test-retest, within-visit variability of Goldmann visual fields in retinitis

453 pigmentosa. *Invest Ophthalmol Vis Sci*. 2011;52(11):8042-8046. doi:10.1167/iovs.11-8321

454 46. Birch DG, Locke KG, Felius J, et al. Rates of decline in regions of the visual field defined by frequency-domain

455 optical coherence tomography in patients with RPGR-mediated X-linked retinitis pigmentosa. *Ophthalmology*.

456 2015;122(4):833-839. doi:10.1016/j.ophtha.2014.11.005

457 47. Birch DG, Weleber RG, Duncan JL, Jaffe GJ, Tao W. Randomized trial of ciliary neurotrophic factor delivered by

encapsulated cell intraocular implants for retinitis pigmentosa. *Am J Ophthalmol*. 2013;156(2):283-292.e1. doi:10.1016/j.ajo.2013.03.021

48. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol (Chicago, Ill 1960)*. 2010;128(4):403-411. doi:10.1001/archophthalmol.2010.32

49. Racette L, Fischer M, Bebie H, Holló G, Johnson CA, Matsumoto C. Visual field digest: A guide to perimetry and the Octopus perimeter. *Köniz, Switz Haag-Streit AG*. 2016;289.

50. Strauss RW, Ho A, Muñoz B, et al. The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Studies: Design and Baseline Characteristics: ProgStar Report No. 1. *Ophthalmology*. 2016;123(4):817-828. doi:10.1016/j.ophtha.2015.12.009

51. Kumaran N, Rubin GS, Kalitzeos A, et al. A Cross-Sectional and Longitudinal Study of Retinal Sensitivity in RPE65-Associated Leber Congenital Amaurosis. *Invest Ophthalmol Vis Sci*. 2018;59(8):3330-3339. doi:10.1167/iovs.18-23873

52. Tee JJL, Yang Y, Kalitzeos A, et al. Characterization of Visual Function, Interocular Variability and Progression Using Static Perimetry-Derived Metrics in RPGR-Associated Retinopathy. *Invest Ophthalmol Vis Sci*. 2018;59(6):2422-2436. doi:10.1167/iovs.17-23739

53. Duncan JL, Liang W, Maguire MG, et al. Baseline Visual Field Findings in the RUSH2A Study: Associated Factors and Correlation With Other Measures of Disease Severity. *Am J Ophthalmol*. 2020;219:87-100. doi:10.1016/j.ajo.2020.05.024

54. Kutzko KE, Brito CF, Wall M. Effect of instructions on conventional automated perimetry. *Invest Ophthalmol Vis Sci*. 2000;41(7):2006-2013.

55. Hoffman DR, Hughbanks-Wheaton DK, Spencer R, et al. Docosahexaenoic Acid Slows Visual Field Progression in X-Linked Retinitis Pigmentosa: Ancillary Outcomes of the DHAX Trial. *Invest Ophthalmol Vis Sci*.

480   2015;56(11):6646-6653. doi:10.1167/iovs.15-17786

481   56.   Murata H, Asaoka R, Fujino Y, et al. Comparing the usefulness of a new algorithm to measure visual field using the

482   variational Bayes linear regression in glaucoma patients, in comparison to the Swedish interactive thresholding

483   algorithm. *Br J Ophthalmol*. Published online January 2021. doi:10.1136/bjophthalmol-2020-318304

484   57.   Schiefer U, Pascual JP, Edmunds B, et al. Comparison of the new perimetric GATE strategy with conventional full-

485   threshold and SITA standard strategies. *Invest Ophthalmol Vis Sci*. 2009;50(1):488-494. doi:10.1167/iovs.08-2229

486   58.   Birch DG, Bennett LD, Duncan JL, Weleber RG, Pennesi ME. Long-term Follow-up of Patients With Retinitis

487   Pigmentosa Receiving Intraocular Ciliary Neurotrophic Factor Implants. *Am J Ophthalmol*. 2016;170:10-14.

488   doi:10.1016/j.ajo.2016.07.013

489   59.   Nakazawa M, Ohguro H, Takeuchi K, Miyagawa Y, Ito T, Metoki T. Effect of nilvadipine on central visual field in

490   retinitis pigmentosa: a 30-month clinical trial. *Ophthalmol J Int d'ophtalmologie Int J Ophthalmol Zeitschrift fur*

491   *Augenheilkd*. 2011;225(2):120-126. doi:10.1159/000320500

492   60.   Weleber RG, Smith TB, Peters D, et al. VFMA: Topographic Analysis of Sensitivity Data From Full-Field Static

493   Perimetry. *Transl Vis Sci Technol*. 2015;4(2):14. doi:10.1167/tvst.4.2.14

494   61.   Tanna P, Georgiou M, Aboshiha J, et al. Cross-Sectional and Longitudinal Assessment of Retinal Sensitivity in

495   Patients With Childhood-Onset Stargardt Disease. *Transl Vis Sci Technol*. 2018;7(6):10. doi:10.1167/tvst.7.6.10

496   62.   Josan AS, Buckley TMW, Wood LJ, Jolly JK, Cehajic-Kapetanovic J, MacLaren RE. Microperimetry Hill of Vision

497   and Volumetric Measures of Retinal Sensitivity. *Transl Vis Sci Technol*. 2021;10(7):12. doi:10.1167/tvst.10.7.12

498   63.   Subash M, Comyn O, Samy A, et al. The Effect of Multispot Laser Panretinal Photocoagulation on Retinal

499   Sensitivity and Driving Eligibility in Patients With Diabetic Retinopathy. *JAMA Ophthalmol*. 2016;134(6):666-672.

500   doi:10.1001/jamaophthalmol.2016.0629

501   64.   Wong EN, Mackey DA, Morgan WH, Chen FK. Intersession test-retest variability of conventional and novel

502   parameters using the MP-1 microperimeter. *Clin Ophthalmol*. 2016;10:29-42. doi:10.2147/OPTH.S92018

503 65. Schönbach EM, Janeschitz-Kriegl L, Strauss RW, et al. The Progression of Stargardt Disease using Volumetric Hill

504   of Vision Analyses Over 24 Months: ProgStar Report No.15. *Am J Ophthalmol*. Published online May 2021.

505   doi:10.1016/j.ajo.2021.04.015

506 66. Bainbridge JWB, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital

507   amaurosis. *N Engl J Med*. 2008;358(21):2231-2239. doi:10.1056/NEJMoa0802268

508 67. Mehat MS, Sundaram V, Ripamonti C, et al. Transplantation of Human Embryonic Stem Cell-Derived Retinal

509   Pigment Epithelial Cells in Macular Degeneration. *Ophthalmology*. 2018;125(11):1765-1775.

510   doi:10.1016/j.ophtha.2018.04.037

511 68. Yang G-Q, Chen T, Tao Y, Zhang Z-M. Recent advances in the dark adaptation investigations. *Int J Ophthalmol*.

512   2015;8(6):1245-1252. doi:10.3980/j.issn.2222-3959.2015.06.31

513 69. Aboshiha J, Luong V, Cowing J, et al. Dark-adaptation functions in molecularly confirmed achromatopsia and the

514   implications for assessment in retinal therapy trials. *Invest Ophthalmol Vis Sci*. 2014;55(10):6340-6349.

515   doi:10.1167/iovs.14-14910

516 70. RUSHTON WA. Dark-adaptation and the regeneration of rhodopsin. *J Physiol*. 1961;156(1):166-178.

517   doi:10.1113/jphysiol.1961.sp006666

518 71. Burstedt MS, Forsman-Semb K, Golovleva I, Janunger T, Wachtmeister L, Sandgren O. Ocular phenotype of

519   bothnia dystrophy, an autosomal recessive retinitis pigmentosa associated with an R234W mutation in the RLBP1

520   gene. *Arch Ophthalmol (Chicago, Ill 1960)*. 2001;119(2):260-267.

521 72. Alexander KR, Fishman GA. Prolonged rod dark adaptation in retinitis pigmentosa. *Br J Ophthalmol*.

522   1984;68(8):561-569. doi:10.1136/bjo.68.8.561

523 73. Moore AT, Fitzke FW, Kemp CM, et al. Abnormal dark adaptation kinetics in autosomal dominant sector retinitis

pigmentosa due to rod opsin mutation. *Br J Ophthalmol*. 1992;76(8):465-469. doi:10.1136/bjo.76.8.465

74. Michaelides M, Holder GE, Hunt DM, Fitzke FW, Bird AC, Moore AT. A detailed study of the phenotype of an autosomal dominant cone-rod dystrophy (CORD7) associated with mutation in the gene for RIM1. *Br J Ophthalmol*. 2005;89(2):198-206. doi:10.1136/bjo.2004.050773

75. Kabanarou SA, Holder GE, Fitzke FW, Bird AC, Webster AR. Congenital stationary night blindness and a "Schubert-Bornschein" type electrophysiology in a family with dominant inheritance. *Br J Ophthalmol*. 2004;88(8):1018-1022. doi:10.1136/bjo.2003.033555

76. Fishman GA, Farbman JS, Alexander KR. Delayed rod dark adaptation in patients with Stargardt's disease. *Ophthalmology*. 1991;98(6):957-962. doi:10.1016/s0161-6420(91)32196-1

77. Peters AY, Locke KG, Birch DG. Comparison of the Goldmann-Weekers dark adaptometer and LKC Technologies Scotopic Sensitivity tester-1. *Doc Ophthalmol*. 2000;101(1):1-9. doi:10.1023/a:1002765024774

78. Jackson GR, Edwards JG. A short-duration dark adaptation protocol for assessment of age-related maculopathy. *J Ocul Biol Dis Infor*. 2008;1(1):7-11. doi:10.1007/s12177-008-9002-6

79. Higgins BE, Montesano G, Binns AM, Crabb DP. Optimising assessment of dark adaptation data using time to event analysis. *Sci Rep*. 2021;11(1):8323. doi:10.1038/s41598-021-86193-3

80. Collison FT, Park JC, Fishman GA, McAnany JJ, Stone EM. Full-Field Pupillary Light Responses, Luminance Thresholds, and Light Discomfort Thresholds in CEP290 Leber Congenital Amaurosis Patients. *Invest Ophthalmol Vis Sci*. 2015;56(12):7130-7136. doi:10.1167/iovs.15-17467

81. Vanagaite J, Pareja JA, Støren O, White LR, Sand T, Stovner LJ. Light-induced discomfort and pain in migraine. *Cephalalgia*. 1997;17(7):733-741. doi:10.1046/j.1468-2982.1997.1707733.x

82. Adams WH, Digre KB, Patel BCK, Anderson RL, Warner JEA, Katz BJ. The evaluation of light sensitivity in benign essential blepharospasm. *Am J Ophthalmol*. 2006;142(1):82-87. doi:10.1016/j.ajo.2006.02.020

546   83.   Zelinger L, Cideciyan A V, Kohl S, et al. Genetics and Disease Expression in the CNGA3 Form of Achromatopsia:
547   Steps on the Path to Gene Therapy. *Ophthalmology*. 2015;122(5):997-1007. doi:10.1016/j.ophtha.2014.11.025

548   84.   Aboshiha J, Kumaran N, Kalitzeos A, Hogg C, Rubin G, Michaelides M. A Quantitative and Qualitative Exploration
549   of Photoaversion in Achromatopsia. *Invest Ophthalmol Vis Sci*. 2017;58(9):3537-3546. doi:10.1167/iovs.17-21935

550   85.   Verriotto JD, Gonzalez A, Aguilar MC, et al. New Methods for Quantification of Visual Photosensitivity Threshold
551   and Symptoms. *Transl Vis Sci Technol*. 2017;6(4):18. doi:10.1167/tvst.6.4.18

552   86.   Aguilar MC, Gonzalez A, Rowaan C, et al. Automated instrument designed to determine visual photosensitivity
553   thresholds. *Biomed Opt Express*. 2018;9(11):5583-5596. doi:10.1364/BOE.9.005583

554   87.   Wilhelm B, Koegel A, Kahle N, et al. How do patients rate their subjective symptoms after CNGA3 gene therapy:
555   first application of the instrument A3-PRO. *Invest Ophthalmol Vis Sci*. 2017;58(8):4678.

556   88.   Fischer MD, Michalakis S, Wilhelm B, et al. Safety and Vision Outcomes of Subretinal Gene Therapy Targeting
557   Cone Photoreceptors in Achromatopsia: A Nonrandomized Controlled Trial. *JAMA Ophthalmol*. 2020;138(6):643-
558   651. doi:10.1001/jamaophthalmol.2020.1032

559   89.   Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs. A review and update. *Retina*. 2013;33(1):5-
560   12. doi:10.1097/IAE.0b013e31827e2306

561   90.   McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015
562   update). *Doc Ophthalmol*. 2015;130(1):1-12. doi:10.1007/s10633-014-9473-7

563   91.   Fujinami K, Lois N, Davidson AE, et al. A longitudinal study of stargardt disease: clinical and electrophysiologic
564   assessment, progression, and genotype correlations. *Am J Ophthalmol*. 2013;155(6):1075-1088.e13.
565   doi:10.1016/j.ajo.2013.01.018

566   92.   Suppiej A, Ceccato C, Maritan V, Cermakova I, Colavito D, Leon A. Exome sequencing and electro-clinical features
567   in pediatric patients with very early-onset retinal dystrophies: A cohort study. *Eur J Paediatr Neurol EJPN Off J*

568   *Eur Paediatr Neurol Soc*. 2021;31:1-9. doi:10.1016/j.ejpn.2021.01.003

569   93.   Soumplis V, Sergouniotis PI, Robson AG, et al. Phenotypic findings in C1QTNF5 retinopathy (late-onset retinal

570   degeneration). *Acta Ophthalmol*. 2013;91(3):e191-5. doi:10.1111/aos.12010

571   94.   Canamary AMJ, Takahashi WY, Sallum JMF. Autoimmune retinopathy: A Review. *Int J Retin Vitr*. 2018;4:1.

572   doi:10.1186/s40942-017-0104-9

573   95.   Marcus M, Cabael L, Marmor MF. Are circadian variations in the electroretinogram evident on routine testing? *Doc*

574   *Ophthalmol*. 2004;108(2):165-169. doi:10.1023/b:doop.0000036844.67273.1b

575   96.   Fishman GA, Chappelow A V, Anderson RJ, Rotenstreich Y, Derlacki DJ. Short-term inter-visit variability of erg

576   amplitudes in normal subjects and patients with retinitis pigmentosa. *Retina*. 2005;25(8):1014-1021.

577   doi:10.1097/00006982-200512000-00010

578   97.   Grover S, Fishman GA, Birch DG, Locke KG, Rosner B. Variability of full-field electroretinogram responses in

579   subjects without diffuse photoreceptor cell disease. *Ophthalmology*. 2003;110(6):1159-1163. doi:10.1016/S0161-

580   6420(03)00253-7

581   98.   Stevens T. Electrophysiologic Testing in Disorders of the Retina, Optic Nerve, and Visual Pathway, (Ophthalmology

582   Monographs, No. 2). *Arch Ophthalmol*. 2001;119(11):1734.

583   99.   Ba-Abbad R, Robson AG, Yap YC, Moore AT, Webster AR, Holder GE. Prph2 mutations as a cause of

584   electronegative ERG. *Retina*. 2014;34(6):1235-1243. doi:10.1097/IAE.0000000000000052

585   100.   Davidson AE, Sergouniotis PI, Mackay DS, et al. RP1L1 variants are associated with a spectrum of inherited retinal

586   diseases including retinitis pigmentosa and occult macular dystrophy. *Hum Mutat*. 2013;34(3):506-514.

587   doi:10.1002/humu.22264

588   101.   Ryan SJ, Sadda SR. *Ryan's Retinal Imaging and Diagnostics E-Book*. Elsevier Health Sciences; 2013.

589   102.   Khan KN, Islam F, Holder GE, et al. NORMAL ELECTROOCULOGRAPHY IN BEST DISEASE AND AUTOSOMAL

590   RECESSIVE BESTROPHINOPATHY. *Retina*. 2018;38(2):379-386. doi:10.1097/IAE.0000000000001523

591   103.   Odom JV, Bach M, Brigell M, et al. ISCEV standard for clinical visual evoked potentials: (2016 update). *Doc*

592   *Ophthalmol*. 2016;133(1):1-9. doi:10.1007/s10633-016-9553-y

593   104.   Roman AJ, Cideciyan A V, Aleman TS, Jacobson SG. Full-field stimulus testing (FST) to quantify visual perception

594   in severely blind candidates for treatment trials. *Physiol Meas*. 2007;28(8):N51-6. doi:10.1088/0967-3334/28/8/N02

595   105.   Roman AJ, Schwartz SB, Aleman TS, et al. Quantifying rod photoreceptor-mediated vision in retinal degenerations:

596   dark-adapted thresholds as outcome measures. *Exp Eye Res*. 2005;80(2):259-272. doi:10.1016/j.exer.2004.09.008

597   106.   Collison FT, Fishman GA, McAnany JJ, Zernant J, Allikmets R. Psychophysical measurement of rod and cone

598   thresholds in stargardt disease with full-field stimuli. *Retina*. 2014;34(9):1888-1895.

599   doi:10.1097/IAE.0000000000000144

600   107.   Birch DG, Cheng P, Duncan JL, et al. The RUSH2A Study: Best-Corrected Visual Acuity, Full-Field

601   Electroretinography Amplitudes, and Full-Field Stimulus Thresholds at Baseline. *Transl Vis Sci Technol*.

602   2020;9(11):9. doi:10.1167/tvst.9.11.9

603   108.   Messias K, Jägle H, Saran R, et al. Psychophysically determined full-field stimulus thresholds (FST) in retinitis

604   pigmentosa: relationships with electroretinography and visual field outcomes. *Doc Ophthalmol*. 2013;127(2):123-

605   129. doi:10.1007/s10633-013-9393-y

606   109.   Klein M, Birch DG. Psychophysical assessment of low visual function in patients with retinal degenerative diseases

607   (RDDs) with the Diagnosys full-field stimulus threshold (D-FST). *Doc Ophthalmol*. 2009;119(3):217-224.

608   doi:10.1007/s10633-009-9204-7

609   110.   Maguire AM, Russell S, Wellman JA, et al. Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65

610   Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. *Ophthalmology*.

611   2019;126(9):1273-1285. doi:10.1016/j.ophtha.2019.06.017

612 111. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute
613   Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. *Arch Ophthalmol (Chicago, Ill 1960)*.
614   1998;116(11):1496-1504. doi:10.1001/archopht.116.11.1496

615 112. Lacy GD, Abalem MF, Musch DC, Jayasundera KT. Patient-reported outcome measures in inherited retinal
616   degeneration gene therapy trials. *Ophthalmic Genet*. 2020;41(1):1-6. doi:10.1080/13816810.2020.1731836

617 113. Clemons TE, Chew EY, Bressler SB, McBee W. National Eye Institute visual function questionnaire in the age-
618   related eye disease study (AREDS): AREDS report no. 10. *Arch Ophthalmol*. 2003;121(2):211-217.

619 114. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye
620   Institute Visual Function Questionnaire. *Arch Ophthalmol (Chicago, Ill 1960)*. 2001;119(7):1050-1058.
621   doi:10.1001/archopht.119.7.1050

622 115. Bainbridge JWB, Mehat MS, Sundaram V, et al. Long-term effect of gene therapy on Leber's congenital amaurosis.
623   *N Engl J Med*. 2015;372(20):1887-1897. doi:10.1056/NEJMoa1414221

624 116. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: initial findings
625   from a phase 1/2 clinical trial. *Lancet (London, England)*. 2014;383(9923):1129-1137. doi:10.1016/S0140-
626   6736(13)62117-0

627 117. Lamoureux EL, Pallant JF, Pesudovs K, Hassell JB, Keeffe JE. The Impact of Vision Impairment Questionnaire: an
628   evaluation of its measurement properties using Rasch analysis. *Invest Ophthalmol Vis Sci*. 2006;47(11):4732-4741.
629   doi:10.1167/iovs.06-0220

630 118. Szlyk JP, Fishman GA, Alexander KR, Revelins BI, Derlacki DJ, Anderson RJ. Relationship between difficulty in
631   performing daily activities and clinical measures of visual function in patients with retinitis pigmentosa. *Arch
632   Ophthalmol (Chicago, Ill 1960)*. 1997;115(1):53-59. doi:10.1001/archopht.1997.01100150055009

633 119. Lodha N, Westall CA, Brent M, Abdolell M, Héon E. A modified protocol for the assessment of visual function in

634   patients with retinitis pigmentosa. *Adv Exp Med Biol*. 2003;533:49-57. doi:10.1007/978-1-4615-0067-4_7

635 120. Costela FM, Pesudovs K, Sandberg MA, Weigel-DiFranco C, Woods RL. Validation of a vision-related activity scale

636   for patients with retinitis pigmentosa. *Health Qual Life Outcomes*. 2020;18(1):196. doi:10.1186/s12955-020-01427-

637   8

638 121. Lacy GD, Abalem MF, Andrews CA, et al. The Michigan Retinal Degeneration Questionnaire: A Patient-Reported

639   Outcome Instrument for Inherited Retinal Degenerations. *Am J Ophthalmol*. 2021;222:60-68.

640   doi:10.1016/j.ajo.2020.08.032

641 122. Duong TQ, Muir ER. Magnetic resonance imaging of the retina. *Jpn J Ophthalmol*. 2009;53(4):352-367.

642   doi:10.1007/s10384-009-0688-1

643 123. Ritter M, Hummer A, Ledolter AA, Holder GE, Windischberger C, Schmidt-Erfurth UM. Correspondence between

644   retinotopic cortical mapping and conventional functional and morphological assessment of retinal disease. *Br J*

645   *Ophthalmol*. 2019;103(2):208-215. doi:10.1136/bjophthalmol-2017-311443

646 124. Ashtari M, Cyckowski LL, Monroe JF, et al. The human visual cortex responds to gene therapy-mediated recovery

647   of retinal function. *J Clin Invest*. 2011;121(6):2160-2168. doi:10.1172/JCI57377

648 125. Farahbakhsh M, Anderson EJ, Rider A, et al. A demonstration of cone function plasticity after gene therapy in

649   achromatopsia. *medRxiv*. Published online 2020.

650 126. Soong GP, Lovie-Kitchin JE, Brown B. Does mobility performance of visually impaired adults improve immediately

651   after orientation and mobility training? *Optom Vis Sci Off Publ Am Acad Optom*. 2001;78(9):657-666.

652   doi:10.1097/00006324-200109000-00011

653 127. Long RG, Rieser JJ, Hill EW. Mobility in individuals with moderate visual impairments. *J Vis Impair Blind*.

654   1990;84(3):111-118.

655 128. Haymes S, Guest D, Heyes A, Johnston A. Mobility of people with retinitis pigmentosa as a function of vision and

psychological variables. *Optom Vis Sci Off Publ Am Acad Optom*. 1996;73(10):621-637. doi:10.1097/00006324-199610000-00001

129. Chung DC, McCague S, Yu Z-F, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. *Clin Experiment Ophthalmol*. 2018;46(3):247-259. doi:10.1111/ceo.13022

130. Jacobson SG, Cideciyan A V, Ratnakaram R, et al. Gene therapy for leber congenital amaurosis caused by RPE65 mutations: safety and efficacy in 15 children and adults followed up to 3 years. *Arch Ophthalmol (Chicago, Ill 1960)*. 2012;130(1):9-24. doi:10.1001/archophthalmol.2011.298

131. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet (London, England)*. 2017;390(10097):849-860. doi:10.1016/S0140-6736(17)31868-8

132. Marron JA, Bailey IL. Visual factors and orientation-mobility performance. *Am J Optom Physiol Opt*. 1982;59(5):413-426. doi:10.1097/00006324-198205000-00009

133. Geruschat DR, Bittner AK, Dagnelie G. Orientation and mobility assessment in retinal prosthetic clinical trials. *Optom Vis Sci Off Publ Am Acad Optom*. 2012;89(9):1308-1315. doi:10.1097/OPX.0b013e3182686251

134. Kumaran N, Ali RR, Tyler NA, Bainbridge JWB, Michaelides M, Rubin GS. Validation of a Vision-Guided Mobility Assessment for RPE65-Associated Retinal Dystrophy. *Transl Vis Sci Technol*. 2020;9(10):5. doi:10.1167/tvst.9.10.5

135. Velikay-Parel M, Ivastinovic D, Koch M, et al. Repeated mobility testing for later artificial visual function evaluation. *J Neural Eng*. 2007;4(1):S102-7. doi:10.1088/1741-2560/4/1/S12

136. Turano KA, Broman AT, Bandeen-Roche K, Munoz B, Rubin GS, West S. Association of visual field loss and mobility performance in older adults: Salisbury Eye Evaluation Study. *Optom Vis Sci Off Publ Am Acad Optom*. 2004;81(5):298-307. doi:10.1097/01.opx.0000134903.13651.8e

678   137. Miraldi Utz V, Coussa RG, Antaki F, Traboulsi EI. Gene therapy for RPE65-related retinal disease. *Ophthalmic*

679   *Genet*. 2018;39(6):671-677. doi:10.1080/13816810.2018.1533027

680   138. Milaneschi Y, Penninx BWJH. Depression in older persons with mobility limitations. *Curr Pharm Des*.

681   2014;20(19):3114-3118. doi:10.2174/13816128113196660060

682   139. Bennett CR, Bex PJ, Bauer CM, Merabet LB. The Assessment of Visual Function and Functional Vision. *Semin*

683   *Pediatr Neurol*. 2019;31:30-40. doi:10.1016/j.spen.2019.05.006

684   140. Aleman TS, Miller AJ, Maguire KH, et al. A Virtual Reality Orientation and Mobility Test for Inherited Retinal

685   Degenerations: Testing a Proof-of-Concept After Gene Therapy. *Clin Ophthalmol*. 2021;15:939-952.

686   doi:10.2147/OPTH.S292527

687   141. Ahmed SF, McDermott KC, Burge WK, et al. Visual function, digital behavior and the vision performance index. *Clin*

688   *Ophthalmol*. 2018;12:2553-2561. doi:10.2147/OPTH.S187131

689   142. Scott IU, Feuer WJ, Jacko JA. Impact of visual function on computer task accuracy and reaction time in a cohort of

690   patients with age-related macular degeneration. *Am J Ophthalmol*. 2002;133(3):350-357. doi:10.1016/s0002-

691   9394(01)01406-4

692   143. Daich Varela M, Esener B, Hashem S, Guimaraes T, Georgiou M, Michaelides M. Structural evaluation in inherited

693   retinal diseases. *Br J Ophthalmol*. Published online 2021.

694

Table 1: Summary of the most common methods used in clinic for IRD functional evaluation.

Imaging Modality	Characteristics	Use in Inherited Retinal Disorders (IRD)
Best Corrected Visual Acuity (BCVA)	Usually, the first assessment in clinical practice, and the most commonly performed.	BCVA is a fundamental parameter with significant correlation with Optical Coherence Tomography (OCT) parameters, as well as with visual field (VF). BCVA is an outcome measure in several gene therapy trials.
Contrast Sensitivity (CS)	Multiple methods to assess CS are available, with the Pelli-Robson charts being the most common. Newer methods that test a wide range of spatial frequencies and stimulus contrasts are increasingly being employed.	CS is notably reduced in most IRD and has been correlated with OCT features, retinal sensitivity and reading speed. CS is a secondary outcome measure in many gene therapy trials.
Color Vision (CV)	Colour can be assessed by a wide range of tests, complex and simple, computer and paper-based, and specifically tailored for visually impaired individuals.	Particularly useful in specific differential diagnoses such as discrimination between complete and incomplete achromatopsia (ACHM). Also, helpful to infer how cone systems are affected and potentially measure differences in specific cone response to intervention.
VF and Retinal Sensitivity	• Kinetic VF testing largely superseded by static perimetry. • Octopus to a greater extent than Humphrey automated static perimetry is better suited to the evaluation of retinal sensitivity cross-sectionally and longitudinally in IRD.	Evaluating VF and retinal sensitivity is key to monitoring disease progression, as well as impact of interventions. Recent advances include modelling and Hill-of-Vision analysis software,

	• Microperimetry = fundus-guided perimetry allows assessment of central macular sensitivity and improved correlation between structure and function. Some devices also have a range of testing conditions (photopic, mesopic and scotopic) and dual-colour testing.	from which topographic information and volumetric assessments can be derived. Testing under a range of conditions and 2-colour microperimetry provides differential information on rod, cone and mixed mechanisms, with a high correlation with OCT parameters. Static perimetry and microperimetry are very common outcome measures in a wide range of clinical trials.
Visual Electrophysiology	• Full-field (ff) electroretinogram (ERG): measures the retinal electrical potential changes provoked by light stimuli, under light and dark-adapted conditions. • Multifocal (mf) ERG: measures retinal function in the central macula and paramacula. • Pattern ERG (PERG): typically uses a contrast-reversing checkerboard stimulus to detect macular dysfunction. It reflects the integrity of bipolar cells, retinal ganglion cells, and macular photoreceptors. • Electrooculogram (EOG): evaluates the RPE and the photoreceptor-RPE complex.	• ffERG provides information on generalised retinal function. • mfERG assesses localized macular function. • PERG: assesses macular and optic nerve function. • EOG: valuable in the diagnosis of disorders of the RPE such as Best disease, where a normal ffERG and abnormal EOG are characteristic. • FST: provides information on which cell type is primarily mediating the responses. First

		• Full-field light-sensitivity threshold (FST): provides a psychophysical assessment of luminance thresholds using white, blue, green and red full-field stimuli.	developed for use in patients with profound visual impairment unable to perform perimetry. Has been shown to correlate with perimetry, OCT parameters, BCVA, disease duration and ffERG amplitude. It is a secondary outcome measure in several gene therapy trials.

696

697

698

699

700

701

702

703

704

705

706

707

708

709

710

Table 2: Summary of the current and developing methods for IRD functional evaluation used in research and
clinical trial settings.

Imaging Modality	Characteristics	Use in Inherited Retinal Disorders (IRD)
Low Luminance Visual Acuity (LLVA)	Can be measured by placing a filter over the patient's best correction or over the letter chart, to simulate mesopic conditions.	Changes in LLVA are secondary outcome measures in several IRD gene therapy trials.
Dark adaptometry	Yields insights into photoreceptor function, measuring change in retinal sensitivity during transition from photopic to scotopic conditions.	Provides information on rod and cone kinetics and thresholds - which are variably abnormal in many IRD.
Photoaversion Testing	Both qualitative and quantitative assessment of light discomfort and / or its associated impact on vision e.g. BCVA and CS. Known as photosensitivity, photoaversion and photophobia.	Particularly useful in cone dysfunction syndromes such as ACHM, and COD/CORD. Currently a secondary/exploratory outcome measure in gene therapy trials for ACHM.
Patient Reported Outcome Measures	General and disease-specific questionnaires designed to better evaluate the impact of IRD on patients' lives.	Invaluable instruments to help fully evaluate treatment efficacy and calculate cost-effectiveness.
Functional Magnetic Resonance Imaging (fMRI)	Provides anatomical, physiological and functional information in a single, non-interventional setting.	fMRI has allowed the delineation of retinotopic and population-receptive field maps; providing objective visual function data and being currently used to measure gene therapy outcomes.
Vision-guided Mobility	Mobility testing (MT) is a way of assessing functional vision, which refers to the impact played by vision on	MT is able to differentiate between controls and patients and to capture longitudinal changes. It is

	everyday activities. It gives novel information on real-world navigation.	an important outcome measure in gene therapy trials.
Virtual reality (VR) and new trends	VR represents a cost efficient and readily available opportunity to capture aspects of functional vision under real-life-like conditions. Tools and apps that assess our vision while we use our own digital devices are also under development.	VR assessed-mobility performance has been shown in a proof-of-concept study to be a useful measure of functional vision in individuals with *RPE65*-LCA. Apps potentially allow VF, tracking, CV, CS and VA to be estimated whilst using commonplace digital devices.

713