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Review Article

Clinical applications of microperimetry in *RPGR*-related retinitis pigmentosa: a review

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ABSTRACT.

Microperimetry, or fundus-tracked perimetry, is a precise static-automated perimetric technique to assess central retinal function. As visual acuity only deteriorates at a late disease stage in *RPGR*-related retinitis pigmentosa (RP), alternative markers for disease progression are of great utility. Microperimetry assessment has been of critical value as an outcome measure in a recently reported phase I/II gene therapy trial for *RPGR*-related RP, both in terms of detecting safety and efficacy signals. Here, we performed a review of the literature. We describe the principles of microperimetry before outlining specific parameters that may be useful as outcome measures in clinical trial settings. The current state of structure–function correlations between short-wavelength autofluorescence, optical coherence tomography and adaptive optics in *RPGR*-related retinitis pigmentosa are also summarized.

Key words: RPGR – retinitis pigmentosa – microperimetry – fundus-tracked perimetry

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Introduction

Mutations in *RPGR* account for up to 70% of X-linked retinitis pigmentosa (RP). The most common phenotype is of a rod–cone dystrophy, characterized by early-onset nyctalopia. Progressive constriction of visual field eventually results in the devastating loss of central vision, with the onset of legal blindness typically occurring in the 4th decade of life (Sandberg et al., 2007). As visual acuity is dependent on the function of the very central fovea, this is usually relatively preserved despite evidence of centripetal degeneration encroaching the macula. Consequently, visual acuity is limited in its ability to monitor disease progression in earlier stages and therefore detect benefits of novel interventions targeted to the macula. Perimetric measures may detect functional deficits at a much earlier disease stage and demonstrate a more predictable graded decline with age. Both these qualities present advantages as trial outcome measures over visual acuity. However, the reliability and precision of conventional static and kinetic perimetry techniques may be reduced by fixation losses, inter- and intra-examiner variability, as well as the inability to ensure projection of testing stimuli onto consistent retinal locations both within and between examinations. Microperimetry, or fundus-tracked perimetry, has been a key step in accurately characterizing central retinal function in *RPGR*-related retinitis pigmentosa (RP), owing to its ability to automatically track the retina as well as overlay functional measurements onto corresponding structural images. There are now several FDA-approved devices and their use in clinical trials is expanding. Here, we focus on two commercially available devices – the CenterVue MAIA and the Nidek MP-1. We review the general principles of microperimetry; specific microperimetry parameters and their potential as clinical trial outcome measures; and structure–function correlations observed by microperimetry studies in *RPGR*-related RP patients.

Methods

The literature review was undertaken via a database search (EMBASE) with the term *RPGR* in conjunction with *microperimetry; fundus + tracked + perimetry;* or *fundus + controlled + perimetry* (using a Boolean operator), which yielded 100 results. Results were manually reviewed for relevance to the review topic. The Clinicaltrials.gov database was queried using:

microperimetry; fundus + tracked + perimetry; and *fundus + controlled + perimetry* as search terms; after manual review trials were excluded if they did not pertain to inherited retinal dystrophies.

Principles of microperimetry

Microperimetry combines the static-automated perimetry techniques with real-time fundus tracking. In this way, point stimuli of varying light intensities are projected to a specific, dynamically tracked retinal location. In contrast, static-automated perimetry does not provide tracking in the same manner and the results are assumed to be less precise due to uncompensated fixation errors throughout testing. This key difference may permit more accurate assessment of macular function and central retinal sensitivity.

The point stimuli are presented in a testing grid in much the same manner as static perimetry, with default grids – for example the 10-2 grid – or application of custom grids to features of interest. If the stimulus is seen, the subject responds by use of a clicker. Each location is examined via a pre-selected testing strategy and then ascribed a threshold sensitivity, given in decibels (dB), which is calculated from the inverse logarithm of the lowest intensity stimulus detected by the individual at that specific retinal location. As this decibel logarithmic scale is set within the maximum and minimum luminance capabilities of each specific microperimetry device, retinal sensitivities are not directly comparable between devices without significant recalculation (Wong et al., 2016; Balasubramanian et al., 2017). The most common examination protocol for rod–cone dystrophies in a clinical trial setting is the use of a 10-2 grid (a 68-point equally spaced grid spanning a radius of approximately ten degrees with a two-degree separation between presented stimuli) (Fig. 1 (A4)), achromatic Goldmann size III stimuli and a stimulus duration of 200 ms, with stimuli presented in a 4-2 staircase strategy. Test reliability is quantified by fixation losses, which are false-positive responses to stimuli presented at the blind spot (Heijl & Krakau, 1975). False positives of 25–30% are generally considered the threshold for reliability (Wu et al., 2015). There are no false-negative catch trials in the devices at present, despite these being known to contribute to significant errors in the recorded sensitivities in static automated perimetry (Wall et al., 2004).

Mesopic, scotopic and photopic conditions

It is known that the relative contribution of rod and cones vary across different light intensities, with rods becoming increasingly important in low-light conditions (Zele & Cao, 2015). This property may be applied in microperimetry to isolate rod versus cone function by selection of background luminances within the photopic (cone function), mesopic (primarily cone function (Crossland et al., 2012)) and scotopic (rod function) ranges. Some devices offer the ability to select between multiple background luminances, for example the Nidek MP-1 (Nidek Technologies, Padova, Italy) and the Macular Integrity Assessment (MAIA) (CenterVue, Padova, Italy). Most published studies in *RPGR*-related retinitis pigmentosa have utilized mesopic microperimetry. Whilst scotopic function in RPGR-related RP has been studied using two-colour static-automated perimetric techniques (Roman et al., 2005; Huang et al., 2012; Charng et al., 2016; Cideciyan et al., 2018; Bennett et al., 2019), this is yet to be examined with scotopic microperimetry. Comparisons between retinal function in scotopic and mesopic conditions may be highly informative to determine patterns of rod and cone degeneration in the natural history of the disease and potentially rod-driven response to novel therapies (Cehajic-Kapetanovic et al., 2020).

Microperimetry parameters as clinical trial outcome measures

There has been a rapid adoption of microperimetry as primary and secondary outcome measures in clinical trials for inherited retinal dystrophies (IRD) (Fig. 2). There are currently three separate ongoing clinical trials for *RPGR*-related RP investigating the safety and efficacy of subretinal delivery of an adenovirus-associated vector (AAV) encoding a codon-optimized (NCT03116113 and NCT03316560) or truncated (NCT03252847) *RPGR* transgene (Kapetanovic et al., 2019). The results from a phase I/II clinical trial (NCT03116113) were recently reported with microperimetry forming a key outcome measure (Cehajic-Kapetanovic et al., 2020). Here, we discuss specific microperimetry parameters across the different devices and their potential as trial outcome measures.

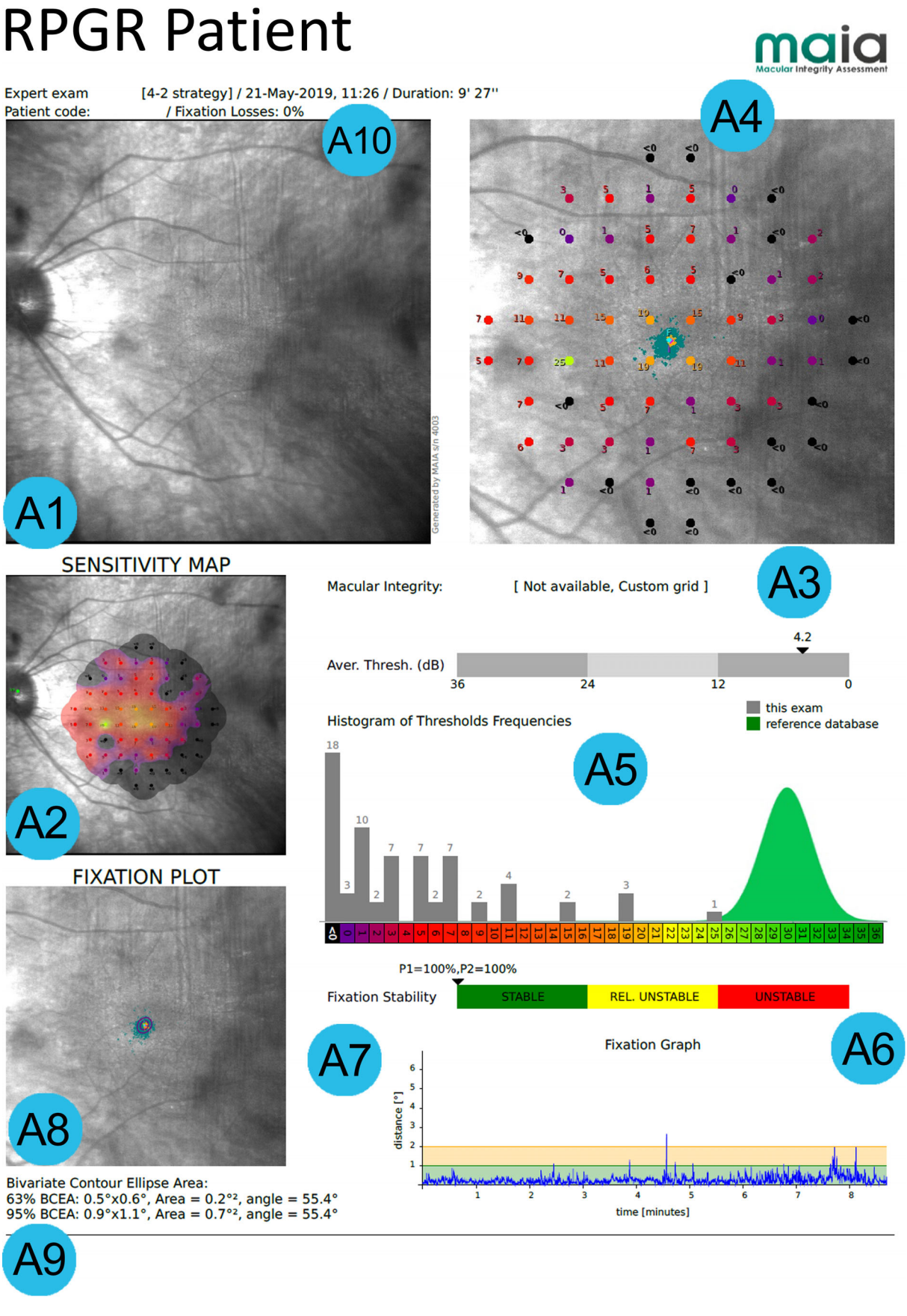
Outcome measures

Mean sensitivity

The most commonly used outcome measure is the mean sensitivity, which represents the average of individual point sensitivities across the testing-grid (Fig. 1 (A3)). In *RPGR*-related RP, this is markedly impaired compared to normal controls and the sensitivity map often demonstrates the presence of a para-central ring scotoma (Fig. 1(A2) and Fig. 3B). In contrast, the best corrected visual acuity (BCVA) can be normal or near-normal at this disease stage (Cehajic-Kapetanovic et al., 2020; Buckley et al., 2020; Menghini et al., 2020). Repeatability for MAIA microperimetry has been established in this cohort (Buckley et al., 2020) – a typical example of test-retest variability is given in Fig. 3.

Advantages to the mean sensitivity include it being a standard output across all devices; it is clinically intuitive, reproducible and demonstrates a high index of interocular symmetry (Buckley et al., 2020). Indeed, recently

Fig. 1. MAIA microperimetry in patient with RPGR-related RP. A1. Fundus photograph taken with a SLO camera. A2. Interpolated heatmap. Black represents deep scotoma, and colours indicate sensitivity. A3. Mean sensitivity (dB). A4. Individual point sensitivities and their presented retinal locations. A5. Histogram of point sensitivities. The number of points given above columns and sensitivity is displayed on the x-axis. The normal distribution is displayed in green. A6. Fixation stability, defined by percentage of fixations within 1 degree (P1) and 2 degrees (P2). A7. Fixation graph, with time on the x-axis and the eccentricities of tracked eye movements in degrees on the y-axis. A8. Map of all recorded fixation points. A9. Bivariate contour ellipse areas returning the area enclosing a given proportion of points about the centre of mass of all recorded fixations. A10. Fixation losses as recorded by false-positive responses to intermittent presentations at the blind spot.



reported results for a phase I/II clinical trial demonstrated the mean sensitivity was a key efficacy and safety signal (Cehajic-Kapetanovic et al., 2020). Gains in microperimetry mean sensitivity were associated with subjective reports of improved visual clarity and visual field, which validates its use as a patient-relevant outcome. However, the

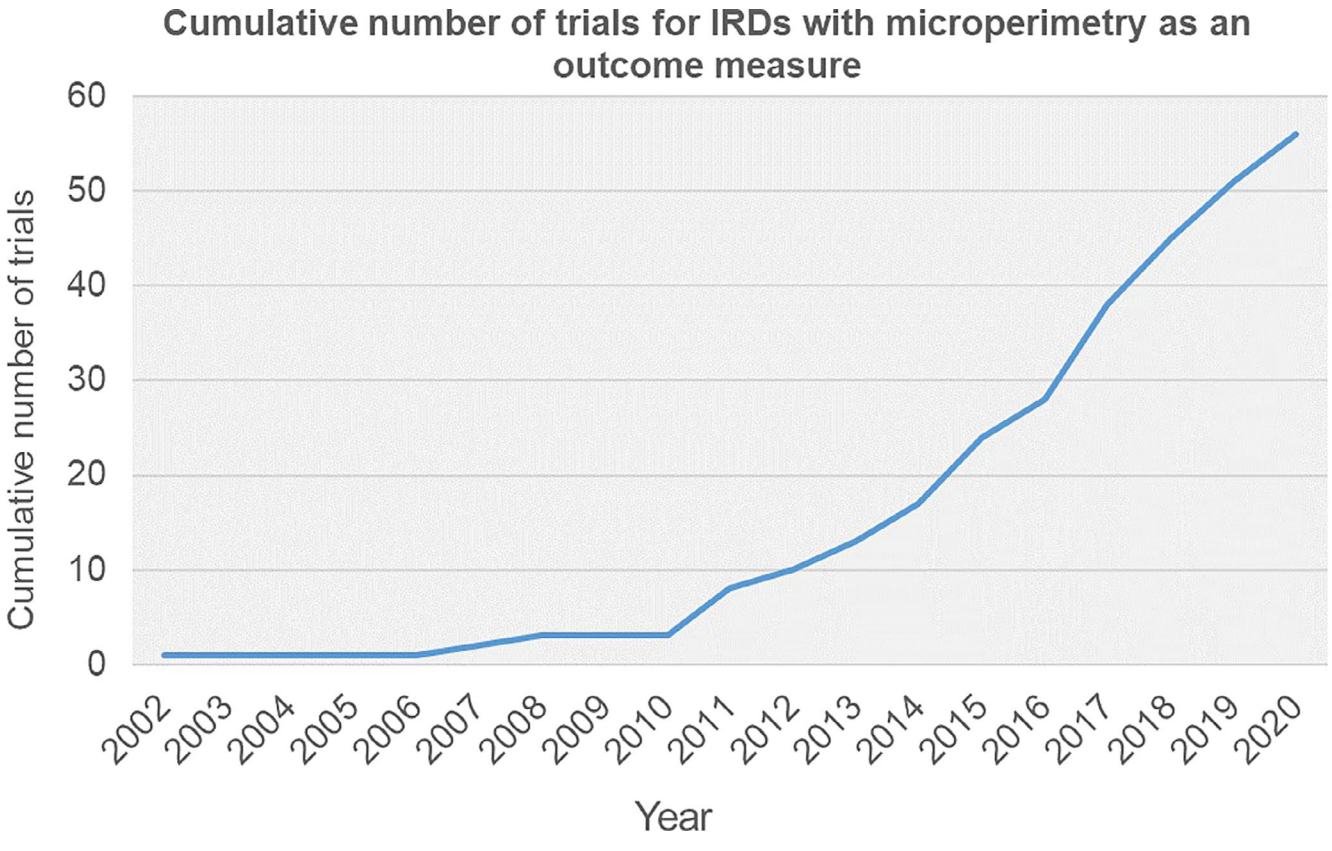


Fig. 2. cumulative number of registrations of observational and interventional studies for inherited retinal dystrophies (IRDs) that list microperimetry as a primary or secondary outcome measure in their publicly accessible trial record (ClinicalTrials.gov – accessed May 2020).

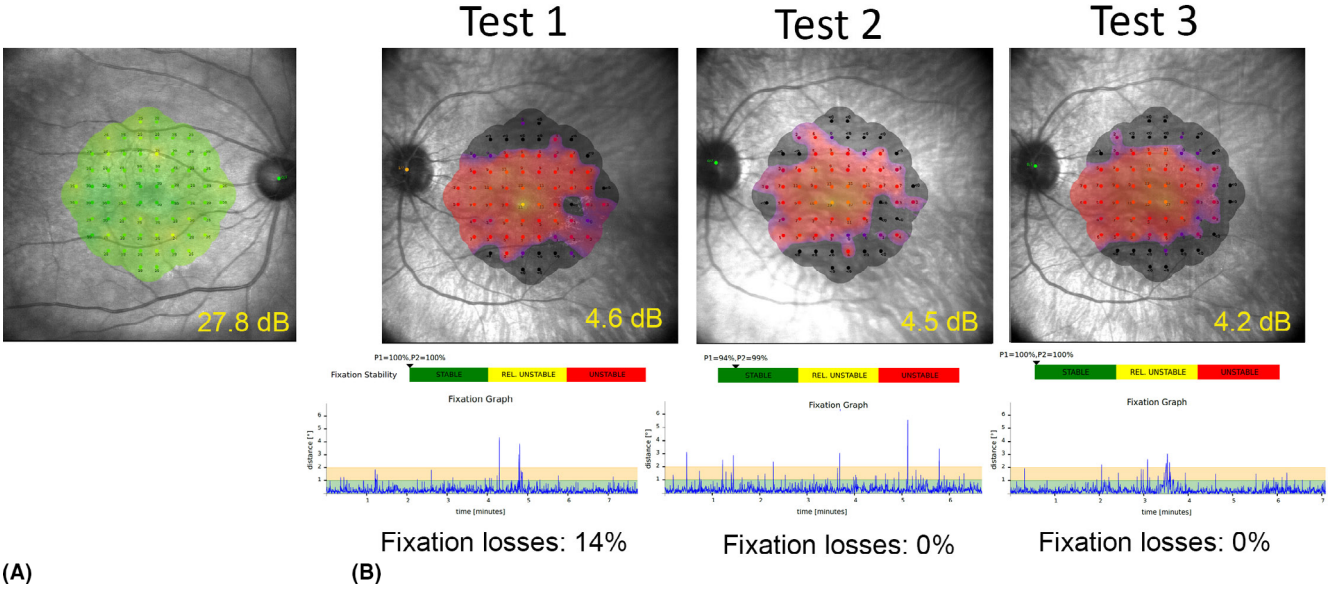


Fig. 3. (A) MAIA microperimetry interpolated heat map from the right eye of a healthy control (mean sensitivity 27.8 dB). (B) Test-retest variability in a typical male RPGR-related RP patient. Interpolated heat maps are shown of the right eye, demonstrating test-retest variability both spatially and numerically in the mean sensitivity. Fixation is plotted over time, and fixation losses are displayed underneath the fixation graphs.

mean sensitivity may reach floor effects in advanced disease, especially with the use of relatively widely spaced grids such as the 10-2 grid; be insensitive to very localized changes; and is a flawed measure in non-uniform testing grids where the measurement is weighted to regions of high sampling density.

Point sensitivity

The sensitivity at an individual test point, termed point sensitivity, permits local structure–function correlation. Both Nidek and MAIA devices output the sensitivity in decibels, with a colour coding dependent on underlying sensitivity (Fig. 1, (A4)). In the MAIA, a histogram of point sensitivities, with a

normal distribution for healthy controls is displayed. Both the Nidek and MAIA devices display the testing grid as an interpolated heat map. Point sensitivities may be of interest to detect localized treatment effects, for exampple a subretinal bleb, or detection of disease progression. Sensitivity of the central four points on the 10-2 testing grid is of potential interest, as these correlate strongly with BCVA (Menghini et al., 2020). The sensitivity of these points, which lie approximately 1.4 degrees from the centre of fixation, is likely most similar to that of the foveal centre, whose sensitivity is not determined directly in the 10-2 testing grid. A central point may be presented, however, the true foveal threshold may still be masked by the presence of a fixation target (Balasubramanian et al., 2017; Nizawa et al., 2017). As expected, test-retest variability of individual point sensitivity is greater than that for the mean sensitivity (Buckley et al., 2020). Regional averages in clusters of points may demonstrate intermediate values of coefficients of repeatability between those of pointwise and of mean sensitivity (Wong et al., 2015). Cluster analysis and their associated mean sensitivities may be considered as an alternative or additional outcome measure to the overall mean sensitivity (Cideciyan et al., 2018).

Normative comparisons

In the MAIA device, the proprietary *macular integrity index* gives a score of how likely the examination result is likely to be abnormal compared to a proprietary normative database. The equivalent measure in the Nidek MP-1 is the *mean defect*, which is analogous to the mean deviation in static-automated perimetry. The Nidek device also outputs a second display of individual point sensitivity differences from normal controls, as well as colour-coded points according to a local defect classification (analogous to pattern deviation maps).

Scotoma size and borders

Scotoma points are those in which no response is registered and are given a threshold value of <0 dB (0 dB being a response to the brightest stimulus). Stabilization of, or reduction, in the size of the scotoma may constitute a suitable trial endpoint. Indeed, reduction in the size of the scotoma was observed in a recently reported gene-therapy trial (Cehajic-Kapetanovic et al., 2020). It is important to note however that a scotoma may not be absolute and merely have reached the lower end of the dynamic range of the microperimeter – described as a floor effect. This floor effect will vary between devices depending on the brightest intensity stimulus that can be achieved (Parodi et al., 2015). It can also be appreciated that the exact spatial pattern and extent of the scotoma demonstrates some test-retest variability (see Fig. 3B), which has been defined in *RPGR*-related RP with the MAIA device (Buckley et al., 2020). There are multiple possibilities underlying this: inherent variability in psychophysical testing; a property of diseased retina; patient behavioural factors; fixational tracking errors; or landmark registration errors. Distinguishing between these remains empirically difficult. It has been suggested that the fundus tracking frequency, for example 25 Hz in the MAIA device, may be a limitation, especially as false-positive response to blind-spot testing may be detected without evidence of concurrent saccades on the fixation graph (Fig. 3B, test 1). In support of this, Wu et al. have previously demonstrated significant variability exists at the border of the optic nerve in healthy controls, representing a deep physiological scotoma with no underlying retinal disease (Wu et al., 2015). However, this phenomenon may also be explained due to the presence of a small head tilt in the participant when placed on the chin rest, which is not detected by current microperimetry systems as it presents with a clear image.

Fixation stability

A key feature of microperimetry is fixation tracking. As fixation is recorded, this presents a unique opportunity to qualify and quantify fixation stability. One measure of fixation stability is the bivariate contour ellipse area (BCEA), representing an elliptical area in which either 63% (1 standard deviation) or 95% (2 standard deviations) of fixation points were recorded during the examination (Fig. 1 (A8 and A9)). A categorical classification of stability is also in use (P1 and P2) (Fig. 1, (A6)), with fixation being termed stable when 75% or more of fixations throughout the test occur within a one-degree circle (P1 > 75%) (Fujii et al., 2002; Morales et al., 2016). In a cross-sectional study using the MAIA device, we previously reported a mean threshold of 66 ETDRS letters in *RPGR*-related RP patients before fixation stability deteriorated to an unstable level (Davies et al., 2019). Both fixation and visual acuity reflect foveal function, which is preserved until the late stage of the centripetal degeneration. Importantly, however, prolonged fixation stability over the course of several minutes is also a property of patient cognition and attention (Wall et al., 2004), which adds a caveat to the use of fixation stability as an outcome marker.

The effect of lens status

It is appreciated that patients with *RPGR*-related RP develop cataract at an earlier age than normally sighted controls (Liew et al., 2019), the majority of which are posterior subcapsular cataracts (PSC) (Pruett, 1983). The absolute effect of media opacity on microperimetry thresholds in *RPGR*-related RP is yet to be empirically established. One study in normally sighted controls with symptomatic cataract calculated a 1 dB decrease in mean sensitivity on the MP-1 device for each additional grade of posterior subcapsular cataract (PSC) on the LOCS grading system (Richter-Mueksch et al., 2011). Taking the difference between the incident and received illumination, a grade 3 PSC would be the equivalent of a 0.30 log-unit neutral density filter. On the MAIA machine (Wong et al., 2016), a grade 1 PSC might theoretically interfere to the extent that a point sensitivity of 25 dB might be reduced to 22 dB. These sensitivities are frequently encountered in the central 4 points in RPGR-RP patients. Whilst the lens status is difficult to quantify objectively, it should be borne in mind in interpretation of microperimetry results, especially in longitudinal studies and determining the long-term effectiveness of novel therapies.

Structure–function correlations

Optical coherence tomography (OCT)

Optical coherence tomography (OCT) affords the ability to correlate outer

retinal structure with microperimetry sensitivity, of which there are several key features pertinent to *RPGR*-related RP. Firstly, a 'transition zone' between disrupted and preserved ellipsoid zone (EZ) can be identified on OCT (Hood et al., 2011). Longitudinal studies with static-automated perimetry demonstrate that the highest rates of sensitivity loss localize to this region and identify it as an area of degeneration (Birch et al., 2015). Future studies with microperimetry may be able to define this more precisely. Internal to the transition zone, where the EZ is preserved, the thickness of the EZ is directly correlated with the sensitivity measured by microperimetry (Menghini et al., 2020). It is evident, however, that a significant proportion of *RPGR*-related RP patients do not demonstrate a quantifiable EZ (Tee et al., 2019; Menghini et al., 2020), but yet may still demonstrate measurable microperimetry sensitivity. It is likely that this is due to partially functioning photoreceptors that have lost outer segment structure and thus fall below the limit of detection for cross-sectional OCT-based imaging systems.

Short-wave autofluorescence (AF)

The presence of hyperautofluorescent rings has been documented in *RPGR*-related RP (Tee et al., 2018; Song et al., 2019). Anatomically, there is loss of visible ellipsoid zone (EZ) on OCT at the boundary of the ring and may correspond to photoreceptors that have lost their outer segments (Song et al., 2019). In patients with these characteristic autofluorescence findings, this would correspond to the transition zone identified on OCT. The relative hyperautofluorescence is thought to arise from lipofuscin accumulation within a metabolically-stressed retinal pigment epithelium (RPE) supporting degenerating photoreceptors within this transition zone. This hypothesis is supported by abnormal mesopic microperimetry sensitivities at the ring itself; normal sensitivities internal to the ring; and loss of sensitivity radially external to the ring, which has been observed in a cohort of genetically heterogenous retinitis pigmentosa patients (Popović et al., 2005; Fleckenstein et al., 2009). A similar but inverse pattern of retinal sensitivity has been shown in *RPGR*-related cone-rod dystrophy (CRD), although by static-automated perimetry and electroretingropahy (Robson et al., 2008) and not microperimetry. Microperimetry assessments of *RPGR*-related disease may afford greater accuracy in these structure–function correlations.

Another autofluorescence feature of interest is the characteristic radial streak pattern observed in heterozygous carrier females (Nanda et al., 2018), arising from variable X-chromosome inactivation within individual photoreceptors across the retina. A patchy distribution of impaired sensitivity can be observed in microperimetry in asymptomatic female carriers, with a greater loss of sensitivity correlating with a more severe phenotype (Genead et al., 2010; Acton et al., 2013). Importantly, some female patients are severely affected, with microperimetry assessments indistinguishable from male patients (Salvetti et al., 2020).

Adaptive optics

Reductions in foveal cone density have been observed in a longitudinal study of mixed cohort of RP patients. This study included two patients with mutations in *RPGR* and was associated with progressive loss of central retinal sensitivity determined by an adaptive-optics microperimeter (Foote et al., 2019). In a separate recent study, Duncan et al. characterized sensitivity of foveal cones in *RPGR* patients using adaptive optics microperimetry, drawing informative comparisons between the *RPGR* cohort and patients with autosomal dominant *RHO*-related RP (Foote et al., 2020). A key finding was that retinal sensitivity was directly proportional to cone density in RHO-related RP and healthy controls, whereas in *RPGR*-related RP patients there was a significantly greater loss of sensitivity than expected for their remaining cone density. Another important observation was that the ellipsoid zone was proportionally much thinner with respect to cone density for *RPGR*-related RP than for RHO-related RP. Our observations that the EZ in paediatric RPGR-related RP patients may already be thinned to the same degree as their adult counterparts (Menghini et al., 2020) are in keeping with these findings. Taken together, it is possible that primary structural (i.e. outer segment shortening) and functional (i.e. reduced sensitivity) deficits may be a product of mutant *RPGR* protein in cones, whilst the eventual secondary cone photoreceptor loss may share the same (as yet unexplained) mechanism universal to rod–cone dystrophies. At present, adaptive optics microperimetry remains solely a research tool.

Conclusion

Microperimetry has become an essential tool and appears to be an emerging gold-standard in the assessment of central retinal sensitivity in *RPGR*-related RP. It is a reproducible, well-tolerated test that permits informative structure–function correlations that are highly relevant in the natural history of the disease, as well as monitoring functional responses to novel interventions with respect to both safety and efficacy. Potential limitations of microperimetry include a limited dynamic range of stimulus intensity that can give rise to floor effects in more advanced patients; and that current generation devices lack false-negative trials as a measure of patient reliability. These could be addressed in new-generation devices. Future applications of microperimetry within this condition may include assessment of rod function with scotopic microperimetry; further characterization of female *RPGR*-related RP patients, especially in whom a severe 'male' phenotype may warrant intervention with novel gene-therapy-based treatments; and the anticipated results of ongoing natural history (Menghini et al., 2019) and interventional trials in which microperimetry is a key outcome measure.

References

Acton JH, Greenberg JP, Greenstein VC et al. (2013): Evaluation of multimodal imaging in carriers of X-linked retinitis pigmentosa. Exp Eye Res **113**: 41–48.

Balasubramanian S, Uji A, Lei J, Velaga S, Nittala M & Sadda SV (2017): Interdevice comparison of retinal sensitivity assessments in a healthy population: The CenterVue MAIA and the Nidek MP-3 microperimeters. Br J Ophthalmol **102**(1): 109–113.

Bennett LD, Metz G, Klein M, Locke KG, Khwaja A & Birch DG (2019): Regional variations and intra-/intersession repeatability for scotopic sensitivity in normal controls and patients with inherited retinal degenerations. Investig Ophthalmol Vis Sci **60**(4): 1122–1131.

Birch DG, Locke KG, Felius J et al. (2015): Rates of decline in regions of the visual field defined by frequency-domain optical coherence tomography in patients with RPGR-mediated X-linked retinitis pigmentosa. Ophthalmology **122**(4): 833–839.

Buckley TMW, Jolly JK, Menghini M, Wood L, Nanda A & MacLaren RE (2020): Test-retest repeatability of microperimetry in patients with retinitis pigmentosa caused by mutations in RPGR. Clin Experiment Ophthalmol **48**(5): 714–715.

Cehajic-Kapetanovic J, Xue K, Martinez-Fernandez de la Camara C et al. (2020): Initial results from a first-in-human gene therapy trial on X-linked retinitis pigmentosa caused by mutations in RPGR. Nat Med **26**: 354–359.

Charng J, Cideciyan AV, Jacobson SG et al. (2016): Variegated yet non-random rod and cone photoreceptor disease patterns in RPGR-ORF15-associated retinal degeneration. Hum Mol Genet **25**(24): 5444–5459.

Cideciyan AV, Charng J, Roman AJ et al. (2018). Progression in X-linked retinitis pigmentosa due to ORF15-RPGR mutations: Assessment of localized vision changes over 2 years. Invest Ophthalmol Vis Sci Association for Research in Vision and Ophthalmology Inc.; **59**: 4558–4566.

Crossland MD, Tufail A, Rubin GS & Stockman A (2012): Mesopic Microperimetry Measures Mainly Cones; Dark-adapted Microperimetry Measures Rods And Cones | IOVS | ARVO Journals. Invest Ophthalmol Vis Sci. **53**(14): 4822.

Davies A, Nanda A & MacLaren RE (2019): Effect of reduced visual acuity on microperimetry performance in patients with inherited retinal degenerations. IOVS **60**(9): 1820.

Fleckenstein M, Charbel Issa P, Fuchs HA et al. (2009): Discrete arcs of increased fundus autofluorescence in retinal dystrophies and functional correlate on microperimetry. Eye **23**(3): 567–575.

Foote KG, de la Huerta I, Gustafson K et al. (2019): Cone spacing correlates with retinal thickness and microperimetry in patients with inherited retinal degenerations. Investig Ophthalmol Vis Sci **60**(4): 1234–1243.

Foote KG, Wong JJ, Boehm AE et al. (2020): Comparing cone structure and function in *RHO*- and *RPGR*- associated retinitis pigmentosa. Investig Opthalmology Vis Sci **61**(4): 42.

Fujii G, de Juan EJ, Sunness J, Humayun M, Pieramici D & Chang T (2002): Patient selection for macular translocation surgery using the scanning laser ophthalmoscope. - PubMed - NCBI. Ophthalmology **109**(9): 1737–1744.

Genead MA, Fishman GA & Lindeman M (2010): Structural and functional characteristics in carriers of x-linked retinitis pigmentosa with a tapetal-like reflex. Retina **30**(10): 1726–1733.

Heijl A & Krakau Cet (1975): An automatic static perimeter, design and pilot study. Acta Ophthalmol **53**(3): 293–310.

Hood DC, Lazow MA, Locke KG, Greenstein VC & Birch DG (2011): The transition zone between healthy and diseased retina in patients with retinitis pigmentosa. Investig Ophthalmol Vis Sci **52**(1): 101–108.

Huang WC, Wright AF, Roman AJ et al. (2012): RPGR-associated retinal degeneration in human X-linked RP and a murine model. Investig Ophthalmol Vis Sci **53**(9): 5594–5608.

Kapetanovic JC, McClements ME, Camara C-F & MacLaren RE (2019): Molecular strategies for RPGR gene therapy. Genes (Basel). **10**(9): 674.

Liew G, Strong S, Bradley P et al. (2019): Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol **103**(8): 1163–1166.

Menghini M, Birch DG, Boon C et al. (2019): Natural history of the progression of RPGR-associated X-linked retinitis pigmentosa (XOLARIS) Study. Cross-Sectional Analysis of Baseline Characteristics | IOVS | ARVO Journals. IOVS **60**(9): 5168.

Menghini M, Cehajic-Kapetanovic J & MacLaren RE (2020): Monitoring progression of retinitis pigmentosa: current recommendations and recent advances. Expert Opin Orphan Drugs **8**(2-3): 67–78.

Menghini M, Jolly JK, Nanda A, Wood L, Cehajic-Kapetanovic J & MacLaren RE (2020): Early cone photoreceptor outer segment length shortening in RPGR X-linked retinitis pigmentosa. Ophthalmologica. https://doi.org/10.1159/000507484. [Epub ahead of print].

Morales MU, Saker S, Wilde C et al. (2016): Reference clinical database for fixation stability metrics in normal subjects measured with the MAIA microperimeter. Transl Vis Sci Technol **5** (6): 6.

Nanda A, Salvetti AP, Clouston P, Downes SM & Maclaren RE (2018): Exploring the variable phenotypes of RPGR carrier females in assessing their potential for retinal gene therapy. Genes (Basel) **9**(12): 643.

Nizawa T, Baba T, Kitahashi M, Oshitari T & Yamamoto S (2017): Different fixation targets affect retinal sensitivity obtained by microperimetry in normal individuals. Clin Ophthalmol **11**: 2011–2015.

Parodi MB, Triolo G, Morales M et al. (2015): MP1 and maia fundus perimetry in healthy subjects and patients affected by retinal dystrophies. Retina **35**(8): 1662–1669.

Popović P, Jarc-Vidmar M & Hawlina M. (2005). Abnormal fundus autofluorescence in relation to retinal function in patients with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol. [cited 2020 May 1];**243**(10): 1018–1027.

Pruett RC (1983): Retinitis pigmentosa: Clinical observations and correlations. Trans Am Ophthalmol Soc **81**: 693–735.

Richter-Mueksch S, Sacu S, Weingessel B, Vécsei-Marlovits VP & Schmidt-Erfurth U (2011): The influence of cortical, nuclear, subcortical posterior, and mixed cataract on the results of microperimetry. Eye **25**(10): 1317–1321.

Robson AG, Michaelides M, Saihan Z et al. (2008): Functional characteristics of patients with retinal dystrophy that manifest abnormal parafoveal annuli of high density fundus autofluorescence; a review and update. Documenta Ophthalmol. Springer **116**: 79–89.

Roman AJ, Schwartz SB, Aleman TS et al. (2005): Quantifying rod photoreceptor-mediated vision in retinal degenerations: Dark-adapted thresholds as outcome measures. Exp Eye Res **80**(2): 259–272.

Salvetti AP, Nanda A & MacLaren RE (2020): RPGR-related X-linked retinitis pigmentosa carriers with a severe "Male Pattern". Ophthalmologica **244**: 60–67.

Sandberg MA, Rosner B, Weigel-DiFranco C, Dryja TP & Berson EL (2007): Disease course of patients with X-linked retinitis pigmentosa due to RPGR gene mutations. Investig Ophthalmol Vis Sci **48**(3): 1298–1304.

Song WK, Nanda A, Cehajic-Kapetanovic J & MacLaren RE (2019): Enhanced autofluorescence ring findings in RPGR-associated retinitis pigmentosa | IOVS | ARVO Journals. Investig Ophthalmol Vis Sci **60**(9): 4524.

Tee JJL, Kalitzeos A, Webster AR, Peto T & Michaelides M (2018): Quantitative analysis of hyperautofluorescent rings to characterize the natural history and progression in rpgr -associated retinopathy. Retina **38**(12): 2401–2414.

Tee JJL, Yang Y, Kalitzeos A, Webster A, Bainbridge J & Michaelides M (2019): Natural history study of retinal structure, progression, and symmetry using ellipzoid zone metrics in rpgr-associated retinopathy. Am J Ophthalmol **198**: 111–123.

Wall M, Woodward KR & Brito CF (2004): The effect of attention on conventional automated perimetry and luminance size threshold perimetry. Investig Ophthalmol Vis Sci **45**(1): 342–350.

Wong EN, Mackey DA, Morgan WH & Chen FK (2015): Intersession test–retest variability of conventional and novel parameters using the MP-1 microperimeter. Clin Ophthalmol **10**: 29–42.

Wong EN, Mackey DA, Morgan WH & Chen FK (2016): Inter-device comparison of retinal sensitivity measurements: The CenterVue MAIA and the Nidek MP-1. Clin Exp Ophthalmol **44**(1): 15–23.

Wu Z, Ayton LN, Makeyeva G, Guymer RH & Luu CD (2015): Impact of reticular pseudodrusen on microperimetry and multifocal electroretinography in intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci **56**(3): 2100–2106.

Wu Z, Jung CJ, Ayton LN, Luu CD & Guymer RH (2015): Test—retest repeatability of microperimetry at the border of deep scotomas. Investig Ophthalmol Vis Sci **56**(4): 2606–2611.

Zele AJ & Cao D (2015): Vision under mesopic and scotopic illumination. Front Psychol **5**: 1594.

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