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Chapter 8
Restoring Vision to the Blind: Evaluating Visual Function, Endpoints

The Lasker/IRRF Initiative for Innovation in Vision Science

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Introduction

One of the areas of greatest need in visual assessment is for tests to measure the degree of visual function that has been restored to a blind or low vision patient. Visual function and endpoint measures include a wide range of techniques for determining the structural integrity of the eye and visual pathways (e.g., electrophysiology and ocular imaging), for assessing its functional capability (e.g., visual acuity and contrast sensitivity) and for evaluating the impact of vision loss on the person's ability to do everyday visual tasks (performance-based tests, such as reading and self-reported visual ability).

Despite numerous advances in structural, functional, and performance-related endpoints, clinicians are limited to a very restricted range of tests that have received regulatory approval – color fundus photographs, high contrast visual acuity, and a limited set of patient questionnaires. The main goal of this chapter is to promote novel visual function measures that will be useful for evaluating new therapeutic modalities, such as stem cells, gene therapy, and ocular prostheses. For these endpoints to be useful, we must establish that the measures are valid, reliable, and sensitive to change. Throughout this process we must not lose sight of the overriding requirement that our endpoints demonstrate how the new therapies benefit the patient. It is not sufficient merely to establish that a new treatment leads to a statistically significant difference; we also must show that the change is clinically significant, that the difference makes a difference to the patient.

A Focus on Rods (Broadening Our Clinical Assessment)

Some of the new endpoints we will consider have come to our attention because they promise greater sensitivity to early or preclinical disease than conventional measures. Other endpoints are promoted because they measure functional outcomes that are of particular importance to patients. An assessment of rod function does both (Owsley et al., 2007).

Measurements of cone function can be insensitive to change in some forms of retinal disease. As an alternative, measurement of rod function has been underutilized. We believe that the measurement of rod function reflects aspects of visual function of importance to the patient and often can show changes before conventional measures of cone function. It could be that rods are so susceptible to disease and physiologic stress that they show much higher sensitivity to changes due to the varying underlying pathologies and, therefore, are a more sensitive indicator of decline as well as benefit from treatment. Furthermore, with regard to transplantation as a potential therapy, rods are the most likely candidates to be transplanted since, to date, rod transplantation has been more successful than cone transplantation. Therefore, we must be able to adequately and reproducibly measure rod function. In animal model experiments, functional transplantation for rods is far ahead of that for cones in terms of efficiency (Homma et al., 2013; Lakowski et al., 2010; Pearson 2014). The

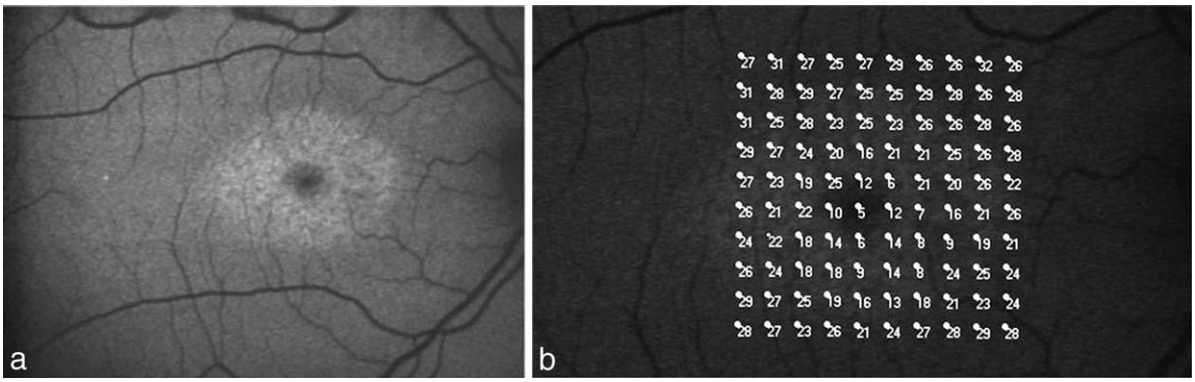

Figure 8.1. *Left*: Increased parafoveal autofluorescence in an asymptomatic 17-year-old patient with codon 172 RDS macular dystrophy *Right*: Fine matrix mapping within the region of abnormally-high autofluorescence reveals that rod sensitivity is reduced on the average of 10 dB relative to normal. Numbers are sensitivity values from scotopic perimetry superimposed on fundus image. The higher the number, the lower the sensitivity; image on right is magnified as compared to left image. (Image reprinted with permission from Downes, S.M., Fitzke, F.W., Holder, G.E., Payne, A.M., Bessant, D.A., Bhattacharya, S.S., & Bird, A.C. (1999). Clinical features of codon 172 RDS macular dystrophy: similar phenotype in 12 families. *Archives of Ophthalmology, 117*(10), 1373–1383. Copyright © 1999 American Medical Association. All rights reserved.)

idea of rods supporting cone survival also should be assessed, and it is important to measure rod and cone function following rod transplantation to determine any subsequent effect on cone function.

For assessing rod function, dark-adapted visual fields can be used to establish a good baseline for each patient. Longitudinal measures are useful for detecting regional changes correlated with the site of disease. Alternately, in the case of therapy, rod fields can be used to detect changes correlated to the site of treatment. Progressively fewer photons of light are absorbed as outer segments become shorter or are lost. By the same logic, the shorter outer segments of the cones result in fewer photons being absorbed by the retina compared to rods, thus, partially explaining the lower sensitivity of cones to measurement. Rod photoreceptors measured in dark-adapted conditions can show losses of sensitivity by a factor of 100 even when conventional photopic measurements show minimal or no loss of sensitivity. In this regard, it could be highly beneficial to the patient for us to place equal focus on rods as well as cones in our functional measurements.

One limitation to the assessment of rod function in clinical trials has been the lack of specific equipment. The old standard, the Goldmann-Weekers dark adaptometer, is no longer available and, as yet, nothing has replaced it. Candidate devices include the Nidek MP1S (Birch, Wen, Locke, & Hood, 2011; Crossland, Luong, Rubin, & Fitzke, 2010), which is a fundus perimeter modified for two-color scotopic testing, and modified static perimeters (Jacobson et al., 1986). The limitations of these devices are that they have either limited dynamic ranges (fundus perimeters) or require extensive user modifications (static perimeters). It is expected, however, that an LED perimeter optimized for two-color perimetry will soon be available to facilitate perimetric assessment of rod function.

In terms of detecting changes in visual function before they are noticed by the patient, it has been demonstrated that the RPE of patients with macular dystrophy show an early increase in autofluorescence and that the function of the rod photoreceptors corresponding to this region shows reductions in sensitivity (Downes et al., 1999).

We believe that this may be particularly important in age-related macular degeneration (AMD) where areas of increased parafoveal autofluorescence may be detected despite normal cone function. Therefore, in developing follow-up assessments for AMD patients it would be critical to evaluate the function and integrity of these parafoveal rods. It is well known that in retinitis pigmentosa (RP) rod photoreceptor loss is the primary defect. However, in AMD, a growing body of evidence seems to support the idea that parafoveal rod death actually precedes the geographic macular atrophy (Curcio, Medeiros, & Millican, 1996). In recent years new technology has become available that would allow us to evaluate parafoveal rod integrity; specifically, fundus autofluorescence imaging (FAF) can be used to assess region variations in the health of rods. FAF was shown to detect increased parafoveal autofluorescence in a young 17-year-old patient with no symptoms of vision loss and with a family history of codon 172 RDS macular dystrophy (Downes et al., 1999). This study (Fig. 8.1) showed that abnormally high autofluorescence predated loss of visual acuity or visual field changes in these patients with a high level of reliability, making FAF an extremely powerful tool in evaluating rod function and even predicting the geographic location of rod degeneration before it actually leads to any subjective deficit.

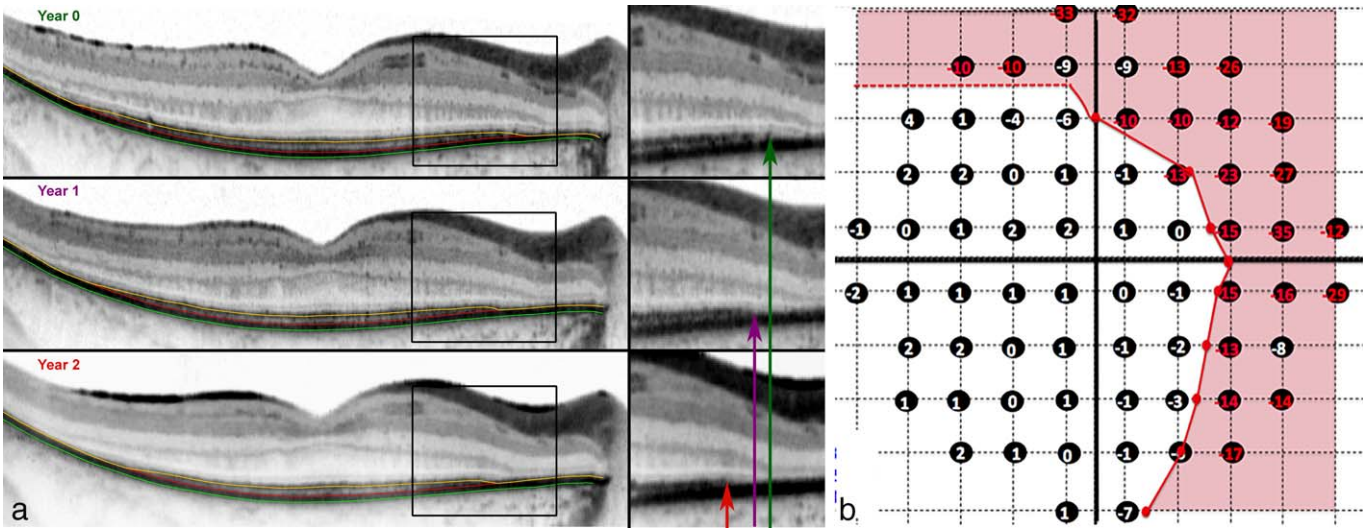

Figure 8.2. *Left*: EZ line is sensitive to progression in x-linked retinitis pigmentosa; constriction over three years in representative patient. The *arrows* in the magnified sections to the *right* show the nasal termination of the EZ on each visit. (Reprinted with permission from Birch, D.G., Locke, K.G., Wen, Y., Locke, K.I., Hoffman, D.R., & Hood, D.C. (2013). Spectral-domain optical coherence tomography measures of outer segment layer progression in patients with X-linked retinitis pigmentosa. *JAMA Ophthalmology, 131*(9), 1143–1150. Copyright © 2013 American Medical Association. All rights reserved.) *Right*: EZ line correlates with visual field loss. The Humphrey 10-2 visual field losses (dB) are shown with the boundary (*red curve*) of the EZ loss for the patient. *White numbers* indicate field locations where sensitivity is within 3 dB of mean normal; *red numbers* indicate loss of at least 10 dB. (From Hood, D.C., Ramachandran, R., Holopigian, K., Lazow, M., Birch, D.G., & Greenstein, V.G. (2011). Method for deriving visual field boundaries from OCT scans of patients with retinitis pigmentosa. *Biomedical Optics Express, 2,* 1106–1114.)

Spectral-domain optical coherence tomography (OCT) is another tool that can reveal structural abnormalities that may be highly correlated to changes in rod and cone function over time. Recent studies have focused on the width of the inner segment ellipsoid zone (EZ; i.e., inner/outer segment border). The general finding is that the edge of the EZ band marks the edge of the patient's "usable" visual field. Once the patient has lost the EZ band entirely, there is a visual field reduction of at least 8 dB (Hood et al., 2011). Birch et al. (2013) showed the validity of this technique as an outcome measure for clinical trials of RP. Of the patients with x-linked RP (XLRP) evaluated, 96% showed a significant decrease in the EZ width after 2 years, with a mean annual decrease of 7%, which would be difficult or even impossible to detect with a standard visual field (Fig. 8.2). Considering the repeat variability was less than the annual rate of change in these patients (95% of the test–retest differences fell within a change of only 3.5%), this method promises to reliably assess changes in retinal function over a relatively short period of time (Birch et al., 2013). EZ width or area is a structural correlate of the visual field. The advantage of EZ width measurements is that they are less variable on a visit-to-visit basis than visual field measurements. It appears that the edge of the EZ band on horizontal or vertical line scans was most effective for detecting progression, and this can be done manually without the aid of an algorithm or segmentation (Ramachandran et al., 2013). This type of evaluation is highly valuable to the patient for its ability to establish their rate of progression/improvement over long periods of time.

The advantage of this technique is that it is a very short test that is easy on the patient and operator with excellent reproducibility in human and animal studies. The disadvantages are that it cannot separate rod versus cone loss, reliability can be reduced in patients with poor fixation, and far peripheral vision is difficult to assess (outside $\pm$ 30°). Because it is limited at present to the central retina, it, therefore, is not the ideal measure for early detection of vision loss in diseases that first show defects in the peripheral retina.

Adaptive Optics Microperimetry is a novel, yet extremely powerful tool in that it enables the operator to measure psychophysical function from individual cone photoreceptors or assess visual function in regions with visible retinal pigment epithelial cells, while simultaneously imaging them using an adaptive optics scanning laser ophthalmoscope (AOSLO) (Figure 8.3) (Poonja et al., 2005; Tuten et al., 2012). This technique may be particularly useful to assess visual function with cellular resolution in diseases with intraretinal variability such as age-related macular degeneration and Stargardt disease, where it may be useful to assess function in regions of lipofuscin accumulation or at the margins of

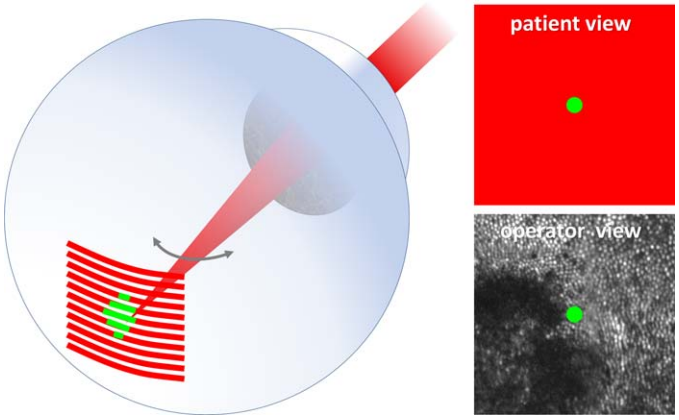

Figure 8.3. Imaging and stimulating photoreceptors through adaptive optics scanning laser ophthalmoscope (AOSLO). By modulating the scanning beam, test stimuli can be delivered to one or a small number of cones. The subject sees the green stimulus against a red background. The operator sees the green test light stabilized on the cone mosaic. With eye tracking and image stabilization it is possible to test the same cones on subsequent visits. (Image courtesy of Austin Roorda, PhD, University of California, Berkeley.)

atrophy, and in macular telangiectasia type 2, in which very focal regions of abnormality can exist adjacent to nearly normal or normal retinal structures. Adaptive optics microperimetry could be used in conjunction with other measurement endpoints to assess improvement following targeted neuroprotective therapies including sub-retinal injection or even photoreceptor transplantation to evaluate the structure and function of those specifically treated or transplanted cells as they integrate into the retina (Menghini & Duncan, 2014). Evaluation of rods and cones in regions where the new cells can be identified following transplantation will be essential to determine their functional efficacy.

Session participants also discussed the evidence that preservation of rods would generate long-term benefit to cone function. From the patient's point of view, preservation of cone function is extremely important, but investigations of rod function may provide an earlier indicator of therapeutic benefit, but for the quality of life of patients, cone function in may cases takes priority, although standard measures of cone function such as visual acuity are often preserved until late stages of the disease, making them insensitive measures of disease progression. Some of this technology is not widely used yet; however, it could provide the means to detect impending cone death before it actually happens. It will be important to encourage the standardization and widespread use of these techniques if we are to develop a new clinical standard that allows for the evaluation of endpoints based on rod functional measurements.

Additional Structural and Functional Outcome Measures

Additional potential outcome measures that should be considered are listed below:

1. Reflectometry is a method not currently used; however, it allows for the measurement of rhodopsin concentration. This method will allow us to identify subtypes of disease potentially, prior to going into clinical trials. In some forms of retinal disease, patients can lose rod function, but still have plenty of rhodopsin, and in other diseases, the loss of function is due to rod cell death specifically; therefore, these patients would have lower rhodopsin levels (Kilbride & Keehan, 1990).
2. Electrophysiology measurements have an important role in the clinic for safety measurements as well as for localized measurements of function by using multifocal ERG as well as localized ERG. However, these techniques are subject to high variability, which must be taken into account as we look toward standardized outcomes (Fishman, Chappelow, Anderson, Rotenstreich, & Derlacki, 2005). Combining these outcome measurements with data from visual fields and optical coherence tomography (OCT) could serve to lower this inherent variability.
3. Dark adaptation kinetics may be particularly important for assessment of early AMD (Owsley, Jackson, White, Feist, & Edwards, 2001). However, it may be most useful as a screening test to analyze several different locations on the retina. Depending on disease course and progression, some patients will have a perfectly normal acuity, but severe dysfunction in the far periphery. Unfortunately, this outcome measure is limited by the number of locations that can be accurately and reproducibly measured and by the time consumed for the patient and the operator.

4. Full-field sensitivity test (FST) is a quick test that is easy for the patient and operator alike. However, it has very low spatial resolution, making it a poor outcome measure for evaluating decline or even long-term improvement. Nonetheless, for patients who have lost enough of their photoreceptors to justify photoreceptor transplantation this would be an ideal test, as it will pick up the response of the most sensitive cells remaining in the retina and could be used to confirm functional integration of transplanted photoreceptors (Jacobson et al., 2009; Klein & Birch, 2009).

Importance of Standardization

One obstacle at this point has been the lack of suitable and standardized equipment. Possible approaches utilizing new equipment that can be widely used and standardized were discussed. Unfortunately, there is not an agreed-upon standard, and the outcome measures that are slightly more standardized, such as dark-adapted visual fields, are very time consuming and still do not generate a complete picture of disease progression or improvement. It will be important to develop a new clinical standard that allows endpoints that can be widely accepted by the community, and that are comprehensive and easy to perform for the patient and operator.

Patient-Reported Outcome Measures (PROMs) and Performance-Based Tests

PROMs have seized the attention of clinicians and regulators. Along with this increased interest there has been a deluge of new questionnaires – over 100 for eyes and vision alone. There is not space here to even begin a description of relevant questionnaires, but it is important to note that, along with the newfound interest in questionnaires, there has been a shift in the psychometric methods used to validate the questionnaires. So-called "Classical Test Theory" that uses techniques like factor analysis to develop scoring algorithms and subscales has been supplanted by "Item Response Theory," especially Rasch analysis (Bond & Fox, 2007). Rasch analysis purports to convert ordinal rating scales that are used with most questionnaires into interval scales, making the questionnaire better suited for computer-aided testing and parametric statistics.

Performance-based tests (PBTs) measure subjects' speed and accuracy while performing laboratory-based simulations of everyday visual tasks. These include mobility tasks, reading, and face and object recognition. The tests can be simple – reading sentences presented in a graduated series of letter sizes—or complex—navigating through a virtual obstacle course in a virtual reality lab. One of the challenges raised by these PBTs is standardization versus relevance to real-world tasks. Take reading, for example. There are highly standardized reading tests that use sequences of unrelated words, all with the same word length and frequency, versus tests based on passages of meaningful text with uncontrolled syntactic and semantic complexity. The former removes cognitive and linguistic factors that may be unrelated to vision.

Standardization increases reliability, but does this come at the price of reducing the relevance of the test to real-world activities? The answer seems to be "no." Measured performance on a highly standardized reading test still is closely correlated with reading speed measured at home under natural conditions (West, Rubin, Munoz, Abraham, & Fried, 1997). A second challenge is to develop performance-based tests that can be used by people in different cultures and who speak different languages. This is hardly a problem for structural outcome measures (e.g., OCT) or visual function tests (e.g., visual field), but it is far more difficult when one wants to measure reading speed in a multicenter clinical trial. It is not enough merely to translate the text into the local language; the texts may have to be linguistically equated for differences in complexity (Hahn et al., 2006).

Finally, there is the problem of the speed/accuracy tradeoff. This is particularly evident for timed tasks like reading and mobility where patients may differ in how they prioritize speed versus accuracy in performing the task.

As we move toward the standardization of novel outcome measures, an example we may wish to follow is that set by the Core Outcome Measures in Effectiveness Trials Initiative (COMET) trials, where people come together and agree in advance which outcome measures need to be done or established. This requires a level of cooperation that we as a community do not always exhibit. Our goal is to achieve a standard similar to the International Society for the Clinical Electrophysiology of Vision (ISCEV) where the main objectives are to promote and extend the knowledge of certain agreed-upon clinical endpoints as well as to promote cooperation and communication among workers in the field. This would involve the generation and publication of thoroughly validated and accepted measures that could be set in place for the greater goal of accurately and reproducibly measuring the patient endpoint.

Consensus Recommendations

1. Develop new methods of measuring visual function, especially for those undergoing treatments for restoring vision.
2. Develop standardized outcome measures that are accepted by the field. This requires cooperation in generating these measures.
3. Place renewed focus on measuring rod function and defects.
4. Recognize that certain endpoints may not be ideal for a specific level of vision loss. Encourage the identification of measurements specific for various levels of vision loss.

This chapter is part of the Restoring Vision to the Blind report by the Lasker/IRRF Initiative for Innovation in Vision Science. The full report, Restoring Vision to the Blind, including a complete list of contributors, is available in the Supplementary Material.

Correspondence: See Appendix 2 in the Supplementary Material.

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