

# Macular Disease: Current and Future Needs for Outcomes Analysis Review with Perspective

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## Abstract

The increasing life span of the populations worldwide along with the severe rise in the prevalence of diabetes has promoted macular disease to now become the major cause of mild, moderate, and severe vision loss, not only in the elderly (glaucoma and macular degeneration) but also in the working age group (diabetic retinopathy). Currently there are severe limitations of current, clinically available methods to detect disease, monitor progression, and define treatment outcomes until the severe end stages with neuronal death and atrophy with severe functional loss that is not retrievable.

This article reviews the limitations of current retinal imaging techniques and vision measurements and identifies potential new methods that appear necessary to adopt in order to detect the neuronal and microvascular disease process during the stages when reversible, not just slowing the disease progression but potentially providing vision improvement. It is only when such systems are made available for routine screening and monitoring that such prevalent macular diseases can be detected and intervention methods and periods assigned to treat sufficiently early that excellent functional vision is maintained. However, for multiple reasons, patients may miss such potential evaluations and present at later stages, requiring that interventions throughout the disease course must be adequately evaluated and rehabilitation methods, improved with a better understanding of the functional deficits, applied.

**Keywords:** macular imaging; vision testing

## Summary

The increasing life span of the populations worldwide along with the severe rise in the prevalence of diabetes has promoted macular disease to now become the major cause of mild, moderate, and severe vision loss, not only in the elderly (glaucoma and macular degeneration) but also in the working age group (diabetic retinopathy). This has demanded significant change in the implementation of programs to screen for retinal disease as well as to monitor the progression that will determine when to intervene as well as the chronologic efficacy of the promoted interventions.

Until just recently the methods used to define and monitor the progressive retinal disease process have been primarily via fundus examination through a dilated pupil (or via fundus color photography and more recently OCT sectional imaging through an un-dilated pupil) together with functional evaluation by chart acuity (or contrast sensitivity) [Dunbar, et al 2022] and Humphrey photopic, spot contrast perimetry, predominantly with the 20-2 in which few spots are obtained within the macula. However, it is now well recognized that these fail to detect the diseases early in the course or to adequately define progression until moderately late in the injury process when there is significant functional vision loss due to multiple level and wide-spread retinal neuronal apoptotic injury, death and atrophy.

It must be remembered that all three diseases are focal in their onset and progression, very often initially involving the parafoveal retinal structures, thereby creating para-fixation defects in the field of functional vision. Screening for structural abnormalities, usually performed by fundus

examination or color fundus photography, detects the disease only when there is sufficient, color-defined atrophy or with the occurrence of secondary lesions (e.g. microaneurysms, hemorrhages, IRMA or NV) that are currently the focus of AI image evaluation and disease staging. In addition, images acquired over time are not registered for overlay to define progression of local abnormalities. Because of this, the interventions have been primarily oriented toward the later detected stages, and clinical trials, while demonstrating a slowing of the disease progression, demonstrate minimal improvement in function. For example in multiple studies of diabetic retinopathy, only 25– 34% demonstrate improvement of  $\geq 3$  ETDRS lines visual acuity, and primarily only among the eyes with severe retinopathy and poor initial vision, and with 23% considered non-responders and 27% having only a “moderate” response [Bressler, et al., 2012][Brown, et al., 2013][Zhang, et al., 2014][DRCR Network, 2015][Bressler, et al., 2019][McAnany, et al, 2022]. Clinical treatments of severe atrophic AMD or glaucoma demonstrate the same failure of significant vision recovery [Fleckenstein, et al 2018][Heier, 2020][Thiele, et al 2022]. Even when OCT is performed to define the neuronal injury, the process is detected only when there is sufficient neuronal layer atrophy occurring over a sufficient area that the structural injury can be identified, or progression defined. The use of charts to define foveal function is not reliable as the patient moves fixation to overlay the best functioning retinal area over the chart letters, and most commonly testing is done under photopic conditions, whereas repeated

studies have shown that vision tasks performed under mesopic conditions with lowered contrast decline first and are most severely affected. Furthermore, chart measurements have been repeatedly shown to fail to correlate with real world visual task management that requires integration of the central visual field perceived elements and motion (eg, reading, driving, catching or hitting a ball, recognizing faces) [West,CG, 2002][West, SK, 2002][Slakter, 2005][Conlin, 2022]. For example, reading speed and comprehension fall off severely with right, para-fixation, visual field defects (in the western world), even with good chart acuity, because of the failure to integrate letter and word form and to manage saccades[Sunness, 1996]. Unfortunately, Humphrey visual fields, which measure only threshold sensitivity for contrasted spot detection, do not detect paraxial defects of identified structures with presentations mimicking real world fixation times and with poor management of monocular or binocular fixation. Rarely are they performed under mesopic luminance conditions and with adequate density in the central (macular) field of view.

Desperately needed are new measurements of the neurovascular elements that can identify earlier injury from these focal, progressive disease processes at a time when the resultant apoptotic injury is reversible, not when the cells are dead and atrophied. Furthermore, they must be provided in a routine screening mode in general medical as well as ophthalmic/optometric clinics and can be quantitated to define position, severity and area of structure involvement. Furthermore, these must be overlaid to define the focal effect upon visual function as measured by monocular as well as binocular resolution visual fields that are presented under conditions of contrast and luminance as well as with fixation times that mimic real world tasks. Methods to perform such measurements are on the near horizon and must be clinically integrated into routine ocular screening and monitoring, especially in the arena of treatment evaluation and promotion.

Injury to individual neurons that result in apoptosis can now be imaged by fluorescent cell surface tagging at a potentially reversible stage instead of following cell death and structure atrophy as now defined by OCT retinal layer analysis. Bis,zinc-dipicolylamine, currently administered intra-venous, has been demonstrated to pass the blood retinal barrier and stain individual neurons undergoing apoptosis [Kwong, 2014]. It is currently undergoing confirmation studies in animals mimicking human retinal structure and is scheduled to begin human trials via a potential nasal spray delivery and with an imaging capability to define fluorescent cells within multiple retinal neuron layers (e.g. via the trans-scleral optical phase imaging camera [Laforest, 2020] [dos Santos, 2021]). Evaluation of alterations of the internal retinal microvasculature, obtained through OCTAngio imaging, has been limited by the scanning time of current scanners reducing the outcomes to detections only of the microvasculature, interpreted as the generalized microvascular density in the perifovea, hence indicating flow obstruction (or enlargement overall area of the foveal avascular zone). Improvements in the speed of image acquisition (now to less than 100 microseconds) has improved the evaluation of flow characteristics, and with sufficient resolution that now with luminal chip analysis the microvasculature can be analyzed to define focal irregularities of pre-capillary, arteriolar, as well as capillary lumen diameters (indicating endothelial and pericyte early injury), tortuosity, vessel branching angles, microvascular occlusion, and modes of stimulated revascularization versus neovascularization. With repeated measurements, these evaluations of the focal neurovascular structures will allow chronologic evaluations of the progressive injury or improvement with treatment when images, taken over time, are overlaid en-face.

Improvements in central field vision testing are now acquired with resolution visual fields performed under luminance and contrast conditions mimicking common photopic and mesopic tasks and with presentations mimicking common fixation times. The fields provide adequate density analysis within the central 20° diameter “useful field of view” but has been limited by methods to track fixation through spectacles. With adequate fixation measurement and control when testing is conducted in a head-mounted goggle device), it can potentially be aligned with the structural imaging pathology to define the relationship of the pathology to the localized visual dysfunction. However, this has been thwarted by the inability to know the fundus position of fixation, which commonly is altered as pathology progresses to involve the fovea. In addition, such micro-perimetry, when

conducted with an SLO camera, although providing the 1.5 um lateral resolution to project figures as small as 20/20, the application has been restricted to photopic condition measurements because the reduced illumination levels required to measure vision under mesopic conditions prevent simultaneous adequate imaging of the retinal structures. Finally, when achieved, these results must then be compared with outcome real world functional measures derived from the sub-group analysis of visual function questionnaires relating tasks performed under similar luminance and target conditions, not the overall summary score as is now performed with questionnaires such as the VFQ's 14-24, or with measurements of actual task performance under such conditions, (e.g. reading speed, store label shopping, driving simulation, etc).

It is now commonly believed that only with such systems made available for routine screening and monitoring that such prevalent macular diseases can be detected, and intervention periods assigned to treat sufficiently early that excellent functional vision is maintained. However, for multiple reasons, patients may miss such potential evaluations and present at later stages, requiring that interventions though out the disease course must be adequately evaluated and rehabilitation methods, improved with a better understanding of the functional deficits, applied [Isacksson, 2020]. As recently documented in a severe criticism of the current failures of pharmaceutical companies to adequately report the outcomes of trials [Rofagha, 2022], not only must we define earlier interventions, but adequately monitor the risks along with the benefits, as well as patient perceptions toward adherence when treatments are applied at all stages of the disease process. Furthermore, it must be remembered that in systemic diseases, such as diabetes, the retina neurovascular abnormalities mirror similar processes progressing in other organs, such as the brain cortex (diabetes now representing a major cause of small vessel, non-Alzheimer's dementia), peripheral nerves and small vessel disease in the myocardium. As such, the retina offers the optimal opportunity as an outcome measure for clinical trial design of systemic chemotherapy.

## Disclosure:

The author reports no conflicts of interest in this work.

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