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Visual Function Measurements in Eyes With Diabetic Retinopathy: An Expert Opinion on Available Measures

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Clinical Relevance: Visual function impairment from diabetic retinopathy can have a considerable impact on patient's quality of life. Best-corrected visual acuity (BCVA) is most commonly used to assess visual function and guide clinical trials. However, BCVA is affected late in the disease process, is not affected in early disease, and does not capture some of the visual disturbances described by patients with diabetes. The goal of this report is to evaluate the relationship between diabetic retinal disease (DRD) and visual function parameters to determine which if any of them may be used in a future DRD staging system.

Methods: The visual functions working group was 1 of 6 areas of DRD studied as part of the DRD staging system update, a project of the Mary Tyler Moore Vision Initiative. The working group identified 12 variables of possible interest, 7 of which were judged to have sufficient preliminary data to suggest an association with DR to warrant further review: microperimetry, static automated perimetry, electroretinogram (ERG) oscillatory potentials, flicker ERG, low luminance visual acuity (LLVA), contrast sensitivity (CS), and BCVA. The objective field analyzer (OFA) was added after subsequent in-person workshops.

Results: Currently, the only visual function test available for immediate use is BCVA; the remaining tests are either promising (within 5 years) or have potential (>5 years) use. Besides BCVA, most visual function tests had a limited role in current clinical care; however, LLVA, CS, flicker ERG, and OFA demonstrated potential for screening and research purposes.

Conclusions: Although current visual function tests are promising, future prospective studies involving patients with early and more advanced retinopathy are necessary to determine if these tests can be used clinically or as endpoints for clinical studies.

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There are currently >400 million people estimated to be living with diabetes worldwide, with an anticipated 700 million expected by 2045.[1] The increasing global prevalence of diabetes will result in an increasing rate of associated vascular complications including diabetic retinopathy (DR). Currently, in the United States (US), it is estimated that 9.60 million people have diabetic retinal disease (DRD) with an estimated 1.84 million people living with vision-threatening DR.[2] Ocular complications from diabetes continue to be a leading cause of vision loss and new-onset blindness in working-age individuals throughout the US.[3] The Mary Tyler Moore Vision Initiative (MTM Vision) effort seeks to evaluate parameters that can help to better understand DRD, its progression, and its impact on patients.

Visual function impairment from DRD results in a considerable burden on patients' quality of life.[4] Best-corrected visual acuity (BCVA) is the primary method of visual function assessment both in clinical practice and in clinical research for DRD. In clinical practice, visual acuity (VA) is commonly used to monitor disease progression, determine management strategies, and assess the efficacy and safety of treatment, particularly for diabetic macular edema (DME). In clinical research, BCVA is commonly used as a primary or secondary outcome, given its importance to patients and regulatory acceptance. To date, investigators have been driven by regulatory requirements that emphasize VA as the primary functional outcome measure for patients with DR, in addition to the ETDRS Diabetic Retinopathy Severity Score which is a long-term predictor of visual acuity. Given that many patients with DR have

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visual disturbances that may not be fully reflected by BCVA, additional measures of visual function should be considered in clinical care. Furthermore, BCVA is affected late in the disease process and is not affected in early disease. Other visual function measurements, including static automated perimetry (SAP), electroretinogram (ERG), low luminance VA (LLVA), and contrast sensitivity (CS), are associated with certain aspects of DRD but have not been commonly used in clinical care or clinical research.

In this article, we evaluate the relationship between DRD and visual function parameters based on an expert panel's review of the literature and discussions. For each parameter this review provides a description of how the variable is assessed, its association with DRD, its use in prior clinical studies in DRD, gaps in knowledge to guide future research needs, and its potential future use with a DRD staging system.

Methods

The visual functions working group was 1 of 6 areas of DRD studied as part of the DRD staging system update, a project of the MTM Vision. The MTM Vision is a joint effort of JDRF, the Caswell Diabetes Institute, and the Kellogg Eye Center (both at the University of Michigan), and honors Ms. Moore's contributions to diabetes awareness and research. There were 61 participants from 12 countries worldwide included in this initiative (Appendix). Other workgroups included: Vascular Retina, Neural Retina, Systemic Health, Visual Function, and Quality of Life. Appendix 1 provides a listing of initiative leadership and participants.

This article focuses on visual function parameters. The experts who formed the original working group included Adam Glassman (US), Darrell Baskin (US), Mitchell Brigell (US), Victor Chong (United Kingdom), Luis Lesmes (US), Leonard Levin (Canada), Mohamed Ashraf Elmasry (US), and Andreas Wenzel (Switzerland). Subsequently, Laura J Taylor (United Kingdom), Ted Maddess (Australia), and Quentin Davis (US) were invited as coauthors given their particular expertise. The original working group met weekly for approximately 3 months. The objectives of these discussions were to (1) define a full list of potential variables to consider, (2) reduce the full list to parameters of primary interest on which to focus, and (3) discuss how these primary parameters are associated with DRD and their potential predictive and prognostic ability.

The working group identified 12 variables of possible interest. The 12 variables included microperimetry, frequency doubling perimetry, SAP, oscillatory ERG potentials, flicker ERG, LLVA, CS, BCVA, color vision, reading speed, metamorphopsia, and dark adaptation.[5] Of these initial 12 parameters, the working group determined that a detailed review should be completed for the following 7 parameters: microperimetry, SAP, ERG oscillatory potentials, flicker ERG, LLVA, CS, and BCVA. These parameters were reviewed given that they had at least preliminary data suggesting they had an association with DRD. Furthermore, the following parameters, color vision, reading speed, metamorphopsia, dark adaptation, and frequency doubling perimetry were not reviewed in detail given that the expert panel concluded that the tests were difficult to perform, had wide variability, or were unlikely to be significantly related to DRD. It was also determined that given the overlap between the current manuscript and a manuscript by the MTM working group exploring neurodegenerative changes in DR, the sections on microperimetry and ERG oscillatory potentials were not included in this manuscript. In addition, based on subsequent workshops held by MTM Vision both online and in person, the objective field analysis (a form of multifocal pupillometry) was also added as a visual function test of interest.

Each of these parameters was assigned to 1 member of the working group as a primary researcher and 1 as a secondary researcher. For each parameter, a standardized evidence grid based on the US Food and Drug Administration (FDA) Biomarker Qualification guideline (https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/drug-development-tool-ddt-qualification-process) was created by a primary researcher and reviewed by a secondary researcher. Each evidence grid summarized the parameter including how the parameter is assessed, its plausible associations with DRD, clinical evidence of a potential association, statistical considerations, and gap analysis. Each evidence grid was presented by the primary researcher to the full working group for $\geq$2 meetings. After the presentation, based on the full group discussion, the secondary researcher conducted a detailed review of the evidence grid to identify any potential gaps and update as needed.

Based on the evidence grids, the working group categorized each variable as to whether it was ready (within 2 years), promising (within 2−5 years), or had potential (>5 years) for use in a DRD staging system considering the anticipated time frame for its clinical or research use. The categorization was completed within different disease stages.

Results

VA

Visual Function Tested: Central Visual Function (Cones). *Level of Evidence: I.* Visual acuity measures the limits of resolution and clarity of central vision and is the most common and widely adopted method for measuring visual function. The current method of evaluation relies on charts designed to measure VA in terms of the minimum angle of resolution of the eye. Visual acuity charts are widely used to assess visual function in ophthalmology clinics and clinical trials. Best-corrected VA refers to the best possible VA that the person can achieve after correction of refractive error.

The current reference standard for measuring BCVA in a clinical trial setting is the ETDRS chart. The chart, which was adapted from the Bailey-Lovie chart,[6] is designed such that each line has an equal number of letters (5 letters) and similar difficulty scores with consistent spacing between letters and rows to minimize the effect of crowding. There is an equal logarithmic progression of letter sizes between lines, with a doubling of visual angle every 3 lines. The test-retest variability (TRV) is high across multiple studies ranging from ±3 to 10 letters (approximately 2 lines), depending on whether or not the patient had concurrent macular pathology.[7−10] More recently, an electronic version of the ETDRS chart, the electronic VA tester, was developed, and it achieves similar reliability and accuracy as the original physical charts.[11] The electronic VA tester has been adopted in several National Eye Institute studies including all DRCR Retina Network clinical trials. The electronic ETDRS protocol has a high test-retest reliability; with 89% of retests within ±5 letters and 98% within ±10 letters.

The same study reported that VA measured using electronic ETDRS and standard ETDRS was highly correlated ($r = 0.96$) with the possibility of differences >10 letters highly unlikely.

The Snellen chart is widely used in nonclinical trial settings for measuring VA but has several disadvantages. Snellen charts have a variable number of letters per line with worse acuity lines having fewer letters compared with better acuity lines. There is also a lack of standardized progression between the lines and variable distances between individual letters within a row and between distinct rows. In addition, there are no clear manufacturing standards for Snellen charts with different manufacturers using different fonts, letters, and spacing ratios. Snellen charts also have a large TRV reaching up to 3 lines, with 13% of patients having a 10-letter (2-line) discrepancy in VA on repeat testing.[12,13] Studies comparing measured VA between ETDRS and Snellen charts have reported that ETDRS BCVA was significantly better than Snellen acuity, particularly in those with poor acuity.[14,15] Despite these limitations, most ophthalmologists use Snellen charts to measure VA in clinical practice (44%−74%).[16,17]

Association With Retinal Function and DRD

Visual acuity is a measure of central visual function and represents the structural and functional integrity of the foveal visual pathway. In eyes with DRD, poor VA is not typically observed until late-stage disease. Some patients with center-involved DME may still have good BCVA. Patients with proliferative DR-related complications such as vitreous hemorrhage or tractional retinal detachment, moderate/severe DME, or extensive macular ischemia may present with decreased VA. However, patients with earlier levels of retinopathy (mild, moderate, or severe nonproliferative DR [NPDR]) without DME typically do not have any alteration to their VA despite changes on fundus imaging. Patients with no DR or early diabetic retinal neurodegeneration, who may have vascular alterations on OCT angiography (OCTA) or changes in other visual function tests, may also have normal VA testing.[18−20]

Prior Clinical Studies in DRD

Best-corrected VA outcomes in clinical studies may be measured as a continuous variable or categorized as a categorical binary outcome.[21] A binary outcome of a ≥15 letter change is frequently used and per the FDA represents a clinically significant change.[22] In the DRCR Retina Network Protocol V, a decrease from the baseline letter score of 5-letters was used as the primary outcome considering eyes at study entry had good VA (20/25 or better).[23] Some drawbacks of using categorical rather than continuous outcomes include the loss of power with the need for a larger sample size, potential misclassification of the outcome if it is too close to the cut-off point, and the potential for a ceiling or floor effect if the VA is too high or too low, respectively.[21] Therefore, it has been suggested that, in general, comparing mean change in the number of letters read or logarithm minimum angle of resolution might be more appropriate since it maximizes the information gained from the data and incorporates both visual improvement and loss.[21] In the landmark DRCR Retina Network Protocols T and I, the mean change in BCVA was used, whereas in the more recent Protocol AB, which compared anti-VEGF to surgery for patients with vitreous hemorrhage, the area under the curve of the average VA over a prespecified period was used instead.[24,25]

Knowledge Gaps

The association between structural changes in the macula detected by current imaging modalities and BCVA is not clearly established. In eyes with DME, VA is only moderately correlated with central subfield thickness.[26] In a post hoc analysis for Protocol T, change in OCT was poorly correlated with change in BCVA with an R^2 value of 12% to 14%.[26] Furthermore, in a subset of patients, there was a paradoxical change with increased central subfield thickness associated with improved vision (5%) and worsening of vision with improvement in OCT (7%−9%).[26] In addition, although Protocol V recruited patients with center-involved DME and excellent VA (20/25 or better), only a third of participants who were in the observation group needed any treatment over 2 years.[23] There have been many structural changes in OCT (intraretinal cysts, subretinal fluid, hyper-reflective foci, disruption of the inner retinal layers, and disruption of the photoreceptor layers) that have been suggested to be associated with VA and predict treatment outcomes.[27,28] However, many of these associations have not been reproduced or as yet evaluated in large prospective clinical studies. OCT angiography has allowed the noninvasive visualization of the different vascular plexuses in the macular area. However, current OCTA studies have reported only a weak correlation between BCVA and the size of the foveal avascular zone as well as other vascular density metrics.[18]

Future Use with DRD Staging System

A new DRD classification should incorporate BCVA given that it is currently the gold standard for central visual function testing. Best-corrected VA can be an excellent tool to follow patients with established vision-threatening disease and monitor treatment response. It can also be used to detect change from baseline which can be used to determine when a patient may require additional testing such as OCT or start treatment. However, there are several limitations to using BCVA as a measure of visual function. It only measures central function and is not a measure of peripheral vision or paracentral macular vision. It is also affected late in the course of the disease and tends to lag other visual function parameters. Furthermore, the association between VA and other visual function parameters, particularly in DR, has not been clearly established. Given the low sensitivity of BCVA in detecting DME, several studies have suggested the incorporation of OCT in DR screening programs.[29−32] Best-corrected VA can also be affected by other ocular pathologies such as age-related macular degeneration (AMD), retinal vein occlusions, cataracts, or refractive

errors. Therefore, it is not specific to DRD. Furthermore, BCVA is measured using ETDRS charts in clinical trials, but in real-world practice, Snellen charts are typically used. Any new classification incorporating BCVA will have to consider using a more user-friendly, rapid, universally applicable test that can be incorporated in all settings and socioeconomic conditions.

LLVA

Visual Function Tested: Central (Cone Primarily—Possible Central Rods). *Level of Evidence: II.* Considering that BCVA is typically unaffected in DRD until later disease stages, the identification and validation of alternative visual function measures such as LLVA is imperative to enable detection and staging of more subtle functional and physiological changes in milder DR. Low luminance VA is a modified version of the BCVA test, performed in low light (mesopic) conditions.[33] Typically, the test is performed using the ETDRS chart with the use of a 2.0 log unit neutral density filter to reduce the chart luminance 100-fold, from 160 cd/m^2 to 1.6 cd/m^2. Low luminance deficit (LLD) is defined as the difference between BCVA and LLVA (LLD = BCVA − LLVA).[33]

Low luminance VA and LLD have been used as outcome measures in clinical studies for both exudative and nonexudative forms of AMD, central serous retinopathy, macular telangiectasia type 2, and specific subtypes of inherited retinal disease, such as choroideremia and RPGR-associated retinitis pigmentosa. There appears to be limited reported use of LLVA and LLD in DRD disease studies. In exudative AMD, LLVA can accurately predict response to anti-VEGF, where those with preserved baseline LLVA (small LLD) responded better to anti-VEGF therapy than those with reduced baseline LLVA (larger LLD).[34] Similarly, in nonexudative AMD, the baseline LLD can predict future VA loss.[33] In a study involving patients with choroideremia and *RPGR*-associated retinitis pigmentosa, LLVA was shown to be representative of a larger extent of central macular function than BCVA, but became unmeasurable when standard BCVA fell below 50 ETDRS letters in choroideremia and 35 ETDRS letters in *RPGR*-associated retinitis pigmentosa.[35] The cut-off point in DRD is unknown.

A review, using healthy control participant data, suggested that those with good VA but with reduced LLVA, such that their LLD is >13, should warrant further investigation of central macular structure and function. Considering this cut-off was obtained for an older population (mean age 64 years), it is possible that a lower cut-off would be more appropriate in younger individuals. Further investigation of this is required to determine whether this LLD cut-off of 13 applies to the broad age range of patients with DRD.

Association With Retinal Function and DRD

Low luminance VA is most likely a marker of cone mediated central macular pathway function.[36] It is currently unknown whether LLVA reflects central macular cone sampling density, contributions from surrounding rod photoreceptors via rod-cone networks in the parafoveal region, or cone-to-cone networks with the aid of cells in the plexiform retinal layers, including horizontal and amacrine cells.[37] Low luminance VA testing is a more sensitive marker of outer neuroretinal changes in DRD than BCVA.[38] In LLVA, as the background luminance levels are reduced, there is a reduction in contrast level. The LLVA reflects a reduction in Weber's contrast (changes in background luminance) as opposed to a reduction in Michaelson contrast (changes due to altered stimuli luminance), which is typically used in classic CS testing. Therefore, the results may reflect different retinal and neuroretinal visual function mechanisms with possible differing outcomes.[39]

Prior Clinical Studies in DRD

Despite the potential usefulness of LLVA, there has been limited research and application of LLVA and LLD in DRD. Low luminance VA results were collected during the CLARITY trial, a randomized controlled trial comparing panretinal photocoagulation (PRP) and anti-VEGF therapy in eyes with proliferative DR (PDR) without DME.[40] In the anti-VEGF group the mean LLD increased from a 10.8 letter score at baseline to 12.5 during follow-up (based on 2 ETDRS letter gain and 0.4 LLVA letter gain). In the PRP group the mean LLD decreased from 12.8 letter score at baseline to 12.1 during follow-up (based on 2.5 ETDRS letter loss and 1.9 LLVA letter loss). These differences are unlikely to be clinically significant.[41,42] The CLARITY trial results suggest there was no overall change in central macular function in either treatment group that could be detected with either VA measure and thus it was concluded that at least in eyes with PDR, LLVA, and LLD are likely to be inappropriate for use as a clinical outcome endpoint in clinical trials.

Further analyses from the CLARITY trial showed that LLVA became more variable and the LLD increased, even as BCVA worsened. This adds further evidence that with increasing macular involvement LLVA (and subsequently LLD) deteriorates at a greater rate than BCVA. Interestingly, this trend has also been reported in other conditions including choroideremia and *RPGR*-associated retinitis pigmentosa with centripetal progression and increasing central macular dysfunction.[35] This suggests LLVA and LLD could be earlier markers of central macular visual dysfunction than BCVA alone in DRD.

In an abstract describing a large cohort of patients with diabetes (n = 209, 82.2% type 2 diabetics) and healthy control participants (n = 344), LLVA was significantly impaired in those with diabetes. However, there was no significant difference found between those at mild and moderate stages of DRD.[43] In another abstract that studied a small cohort of patients with diabetes (n = 34), increased LLD was associated with increased disease severity and was significantly associated with HbA1c blood glucose levels and mean arterial pressure.[44] However, the level of DRD involvement and diabetic macular disease in this cohort is unknown.

Knowledge Gaps

Currently, there is little information on the correlation of LLVA and LLD with high resolution OCT and OCTA. It is unclear when ischemia with enlarging foveal avascular zone and reduced vessel density is present and at what point LLVA and LLD will begin to deteriorate. It is also unclear whether the functional loss will occur before any noticeable OCT changes. Understanding these longitudinal relationships could allow therapeutic intervention at the appropriate time and with the appropriate therapies when they become available.

Future Use With DRD Staging System

The LLVA test is easy to perform. It is thought that LLVA is affected earlier than BCVA in macular pathology and is more sensitive to neuroretinal changes. As a result, LLVA may act as a predictor of foveal dysfunction and a drop in LLVA may indicate disease progression, impending foveal involvement, and a risk of subsequent BCVA loss. Low luminance deficit provides information about the disparity between LLVA and BCVA;[35,36,39] however, it suffers from the combined variability of BCVA and LLVA measures, somewhat limiting its usefulness as an outcome measure.

In early DRD, neuronal and ischemic changes occur before visible vascular changes. Since LLVA is potentially more sensitive to changes in macular cell-to-cell or neuronal networks, it could be hypothesized that LLVA may be a more sensitive marker of neuroretinal dysfunction in patients with DRD than standard BCVA. Low luminance VA and LLD appear to be insensitive to vascular changes in the peripheral retina and are possibly more dependent on the location of DRD (such as macular involvement), as opposed to overall DRD severity. Specifically, LLVA and LLD may be useful for the detection of early-stage diabetic macular disease. Low luminance VA could provide an inexpensive and simple screening test for the detection and monitoring of diabetic macular disease patients at risk of progressive BCVA loss.

CS

Visual Function Tested: Central Visual Function (Cones). *Level of Evidence: II.* The CS function (CSF) is a 2-dimensional threshold contour that describes how much contrast is needed to see visual details at different sizes (spatial frequencies).[45] The peak of the CSF— which represents an observer's highest sensitivity and lowest threshold—is typically observed at intermediate spatial frequencies of 1.5 to 6 cycles per degree (cpd), with more contrast needed to perceive larger or smaller visual details.[46–48] Despite compelling evidence for CSF testing revealing vision loss in early DRD stages,[22,49–52] and providing better correlations to real-world functional vision than BCVA,[53–55] it remains a clinical research tool without established standards or analytic validation.[22,52,56]

The historical challenge to CSF testing in the clinic is the need for a broad range and fine resolution of required contrasts and spatial frequencies. A broad sampling range for contrast (from 0.5% to 100%) is needed to measure thresholds across spatial frequencies and populations with and without retinal disease. In turn, a fine sampling resolution is needed to measure individual changes over time. As a practical compromise, the Pelli-Robson chart[57] uses a wide contrast range (from 1% to 100%), coarse contrast resolution (0.15 logCS step-size), and severely restricted spatial frequency range (a single optotype size). Underwhelming effects of ranibizumab treatment on CS measured with Pelli-Robson charts have been reported, with mean changes of 0.15 to 0.20 logCS (relative to sham), which barely exceeded the single step-size resolution.[57,58]

Despite its use in research, the Pelli-Robson test does not meet FDA's requirements for demonstrating treatment effects at multiple spatial frequencies.[22] Paper-based and computerized tests that sample more than a single spatial frequency must typically sacrifice the range and resolution for sampling contrast thresholds, thereby reducing test precision.[47] The evaluation of CS at multiple frequencies in DRD has been accomplished using a variety of stimuli, tasks, and decision structures: letters versus gratings, detection versus identification, and yes/no versus forced choice. The lack of standard test conditions has prevented CSF endpoint validation and the definition of clinically meaningful change in CSF in DRD or other retinal diseases. Given that VA and CS are both evaluated on logarithmic scales, a proposed criterion of 0.30 logCS for meaningful change would represent a natural analog to the 3-line change of BCVA. However, if the step-size resolution of many CSF tests is greater than that of VA standards (0.15−0.30 logarithm CS vs. 0.10 logarithm minimum angle of resolution),[59] then it could be posited that the criterion for change using those tests should be larger.

Association With Retinal Function and DRD

Intelligent systems applications to evaluate the retina in DRD have focused almost exclusively on retrospective analyses of ocular images. A complementary approach to visual function in DRD applies Bayesian active learning to optimize the prospective data collected and analyzed during vision testing.[60–64] On digital displays, active learning improves on current practice using intelligent sampling with a broad contrast range (>2.5 logCS) and fine step-size resolution (<0.02 logCS), across a greater number of spatial frequencies. In brief, the test usually begins with presenting a series of letters at a single spatial frequency and varying levels of contrast. Based on the patient's response the active learning algorithm will select the next combination of letters while varying the spatial frequencies and contrast. This quantitative CSF (qCSF) testing will continue until a 2-dimensional individualized curve can be generated that displays CS as a function of spatial frequencies. Metrics provided by the qCSF include the area under the logarithm of CS function and contrast thresholds measured at 1, 1.5, 3, 6, 12, and 18 cpd. In DRD and other retinal disease, this is particularly important given that the active learning provided by the qCSF (Manifold Platform, Adaptive Sensory Technology) reveals notable CSF deficits (0.30−0.60 logCS) with

intermediate contrasts and spatial frequencies that are out-of-range for ETDRS acuity and Pelli-Robson.[61,64–68]

Prior Clinical Studies in DRD

Cross-sectional studies have demonstrated CSF loss in diabetes before clinical signs of retinopathy, and better relation to disease severity in DRD and DME than VA.[49–52] However, there are limited studies that have explored the association of CSF with DR with most studies exploring different questions. Furthermore, it is unclear if these results will be reproducible across different populations and larger cohorts. Using the qCSF, Joltikov et al[69] reported that CSF at low frequencies (1.5 cpd or Snellen equivalent of 20/400) was sensitive in early DR, differentiating eyes without DR from controls and those with mild NPDR from moderate NPDR. A recent study exploring the association of qCSF in DME noted that while central subfield thickness was not well associated with BCVA it was associated with CS thresholds at 6 and 12 cpd but not at 1, 1.5, 3, or 18.[41] Furthermore, there seems to be some evidence of an association between macular (3 × 3 mm and 6 × 6 mm) OCTA vascular metrics with CS suggesting a structure-function relationship.[42]

The demonstration of vision changes to disease state also supports potential for DRD staging. In addition to treatment effects demonstrated with anti-VEGF or photocoagulation, acute CSF deficits induced by hypoxia or hyperglycemia in patients with diabetes can be rapidly reversed.[70–72] These patterns are confirmed by animal models that show reversible CSF deficits measured by optomotor behavior and ERG.[73–78]

Knowledge Gaps

Knowledge gaps include the lack of longitudinal data for disease progression and compelling evidence for treatment effects. Two ongoing studies, CANBERRA (NCT0426526) and DRCR Retina Network Protocol AF (NCT04661358), will provide the longitudinal data in DRD needed to evaluate CSF for potential prognostic value in DRD staging. Another important issue will be the consideration of visual comorbidities. For example, given the incidence of cataracts in diabetes,[79] it will be important to consider other potential contributions to vision loss as part of a potential multidimensional assay of neurodegeneration.

Future Use With DRD Staging System

Because CSF deficits cannot provide a unique assay of neurodegeneration in DRD, it will be critical to combine them with multimodal anatomical endpoints for DRD staging. One important benefit of visual function testing is the potential for testing outside of the retinal clinic, with home-monitoring or real-world testing in general practitioner or community health setting.

Perimetry

Visual Function Tested: Central and Peripheral Visual Function (Cones/Rods). *Level of Evidence: II.* This section will only cover SAP. Microperimetry is covered by another working group.[80] Static automated perimetry measures and records the minimum intensity of light (against a standardized background luminance) needed to elicit a subjective visual response at various predefined points in the subject's field of vision.[81] Static automated perimetry can be subdivided into SAP, in which a white stimulus is projected onto a white background under photopic, light-adapted conditions, and short-wavelength automated perimetry (SWAP) in which a blue stimulus is projected onto a yellow background.[82] The Humphrey Matrix Perimeter, which is produced by Carl Zeiss Meditec, includes SWAP testing capabilities alongside SAP. Static automated perimetry can assess retinal sensitivity with 5 different stimulus sizes as well as luminance that can vary over 4 to 5 orders of magnitude. Static automated perimetry has lower TRV than SWAP. [83] In both SAP and SWAP, local TRV was more pronounced in regions with diminished sensitivity and greater eccentricity from the fovea. Locations beyond 10 degrees showed increased variability in comparison to paracentral test points within the central 10 degrees for both SAP and SWAP.[83] Currently, perimetry is not used in the diagnosis, staging, or management of DRD, and thus there is no generally accepted perimetric approach for those functions. However, perimetric threshold sensitivities in patients with DRD clearly deviate from the normal, healthy population.[81] Perimeters are frequently used in general ophthalmology practices and even in retina subspecialty practices, where they are used in screening for and the management of glaucoma, detection of hydroxychloroquine maculopathy, and other uses. Despite the subjectivity inherent in perimetry which includes reliance upon patient's alertness and timely responses and the effects of possible confounders such as cataracts, perimetry may represent a noninvasive method to ascertain functional damage from DRD.

Association With Retinal Function and DRD

There is a strong scientific rationale for an association between perimetric threshold metrics and DRD. Diabetes leads to microvascular and neurodegenerative changes that result in progressive loss of normal retinal sensitivity to light. Perimeters currently in clinical use are designed to detect decreased retinal sensitivity which can be quantitatively and spatially measured.

Prior Clinical Studies in DRD

There is a moderate expectation that perimetry could perform well in the measurement of DRD. A prospective, cross-sectional study of 59 diabetic patients with varying degrees of DRD tested with SAP and SWAP demonstrated that perimetry results correlated better with ETDRS Diabetic Retinopathy Severity Scale (DRSS) score than did ETDRS VA score.[84] Another prospective, cross-sectional study of 50 diabetic patients with varying degrees of DRD tested with SAP and SWAP also concluded that worse perimetric threshold sensitivities correlated with worse ETDRS DRSS scores.[83] Joltikov et al[69] also conducted a prospective, cross-sectional study of diabetic patients who underwent SAP and SWAP, finding that worse visual field metrics correlated

with worse DRD stage. However, a prospective longitudinal study examining perimetric threshold sensitivities and DRSS scores did not detect this correlation.[85] Only 6 of 74 eyes underwent a 2-step deterioration in DRSS score during the average of 4 years of follow-up, with the chief limitation of the study being the lack of DRSS progression events which prevented them from adequately detecting a correlation between SAP deterioration and DRSS progression.[85]

The DRCR Network Protocol S published 5-year results of its prospective, longitudinal study of patients with PDR who were randomly assigned to treatment with PRP or ranibizumab. Seventy-nine patients completed 5 years of follow-up with both 30-2 and 60-4 perimetry. Eyes with PRP had an early loss of retinal sensitivity measured after their laser procedures; however, from years 2 through 5, the ranibizumab group had a progressive decline in perimetric sensitivity, thus underscoring the progression of DRD despite ostensible DRSS improvements with ranibizumab injections.[86] It should be noted that these eyes on average had visual field deficits at baseline (mean deviation −6.4 (4.6) decibels and −7.0 (5.2) decibels in the PRP and ranibizumab groups, respectively).

Knowledge Gaps

Within the currently available literature, which includes several small prospective cross-sectional and 1 longitudinal study, there appears to be level II evidence supporting perimetry in the measurement of DRD. The ongoing DRCR Retina Protocol AF will include some sites with perimetry, but none of these patients will be enrolling with more advanced diseases, such as PDR. Thus, a large, multicenter, prospective, longitudinal study enrolling patients across the spectrum of DRSS scores that includes perimetry would help determine the utility of perimetry in DR assessment.

Future Use With DRD Staging System

Although the DRSS might exhibit apparent improvement following VEGF inhibition by reducing individual DR lesions, the underlying issue of capillary nonperfusion remains unchanged. These areas of nonperfusion, observed through fluorescein angiography, could align with diminished perimetric threshold sensitivities.[87,88] Given these observations, there is a scientific basis advocating for perimetry as an additional parameter in evaluating the severity of DRD, especially when dealing with pharmaceutical VEGF inhibition. Perimetry offers a less invasive approach compared with fluorescein angiography. However, conducting further longitudinal studies, possibly spanning several years or strategically timed to capture progressive changes akin to the DRCR Network Protocol S timeline, would be necessary to validate these observations.

Flicker ERG

Level of Evidence: Ib. *Area of Function Being Assessed.Cone Function (Peripheral and Macula)* An ERG objectively assesses retinal function by measuring the electrical response to flashes of light. In a flicker ERG test, a rapid sequence of stimulus flashes generates a response dominated by postphotoreceptor components of the cone pathway from the entire retina.[89] The flicker ERG is therefore sensitive to changes affecting the cones and inner retina which may or may not be associated with retinal and choroidal vascular changes that may be affected in DR.[89–91] Unlike BCVA, LLVA, and CS, flicker ERG (and perimetry) measures function throughout the retina and not just the foveal region. Flicker ERG results are not affected by refractive errors, and only modestly affected by cataracts, where timing is not affected and amplitude is reduced by 1.5x when comparing results before and after cataract surgery.[92,93]

As early as 1987, research demonstrated a correlation of the light-adapted flicker ERG with DRD and other ischemic diseases.[94–99] The flicker ERG has also been shown to have predictive and prognostic values in DRD and other diseases. Similarly, pupillary response has been shown to be correlated with the DR severity.[5,100–109]

While traditional uses of ERGs involved an hour-long process of light-adapted and dark-adapted testing to elucidate difficult cases of unexplained vision loss, newer systems have simplified the process for DRD testing.[5] The RETeval device's DR assessment test generates a DR score that combines an ERG flicker time, amplitude, pupillary response, and age into a single number that increases with disease severity. This test is performed on undilated eyes using skin electrodes and requires <5 minutes for both eyes. The technical failure rate is <1% and the test is highly reproducible with an intraclass correlation coefficient of 90.2%. Both cross-sectional studies comparing flicker ERG results with structural DR features found on photography, slit-lamp, indirect ophthalmoscopy, and OCT, as well as longitudinal studies relating ERG results to DR interventions and DR progression, have been performed.[5,100,110–112]

Association with Retinal Function and DRD

There is a strong scientific rationale for an association between ERGs and DRD. Diabetic retinal disease has both vascular and neurodegenerative components;[113] by combining the flicker ERG's sensitivity to ischemia and the pupil response's sensitivity to neuropathy, the RETeval DR score is sensitive to both components.

Although we are not aware of a correlation between the ERG and patient-reported outcomes in DRD,[114] a parallel loss of vision and decline of ERG has been shown in mouse models and a correlation between BCVA and ERG signals can be found in some diseases (e.g., Stargardt, Usher, birdshot chorioretinopathy), but not all (e.g., retinitis pigmentosa).[115–118]

Prior Clinical Studies in DRD

There are several cross-sectional trials showing the correlation between flicker, pupil response, and the DR score with DR severity determined by structural measures.[5,91–94,104,111,112] All 3 of these measures have also been found to differ between subjects without diabetes and subjects with type 2 diabetes mellitus without DR.[119] Thus,

these measures may be useful to monitor early stages of the disease and treatment thereof. The mean DR score for 62 subjects without diabetes was 17.9 while the mean DR score for 25 subjects with PDR was 31.5 and the TRV has been reported to be 1.25.[5,112,119]

In a longitudinal study, medical records were reviewed for patients who had baseline assessments of the RETeval DR score and 7-field ETDRS fundus imaging as part of a cross-sectional study. The review focused on ocular interventions such as pars plana vitrectomy, intravitreal injections, and the requirement for retinal laser treatment. The primary goal of the study was to ascertain whether the RETeval DR score and ETDRS images could predict the need for treatment in subjects with DR.[100] Treatment of DR was chosen as the outcome variable because it is a definitive timepoint and the study was done at a VA hospital where treatment costs would not be a factor and centralized medical records minimized the subjects lost to follow-up. At the time of the chart review, the average follow-up time was 2.4 years for the 279 patients. Eyes with a baseline RETeval DR score of $\geq$ 23.5 (RETeval+) had an 11 times greater risk of progressing. Eyes having a photographic DRSS score $\geq$ 53 (ETDRS+) had a 3.5 times greater risk of progressing; while patients with CSME or a DRSS score $\geq$ 53 at baseline had a relative risk of 4.2. Patients at baseline that were ETDRS+ and RETeval+ had a 15 times higher chance of progressing. The authors concluded that combining structure and function leads to better prediction of subsequent interventions. These results have yet to be replicated in a different population.

Knowledge Gaps

There is strong evidence that flicker ERGs and the RETeval DR score correlate with disease severity even in the absence of clinically detectable lesions and can be used to assess disease stage and progression. The areas of insufficient knowledge encompass optimal utilization of the DR score in clinical management, such as aiding in the establishment of appropriate disease monitoring follow-up schedules and providing valuable insights for treatment decisions. The relation between patient-reported outcomes (current and future) and flicker ERG measures such as the DR score is also unknown.

Future Use With DRD Staging System

The DR score is an objective and easy to perform test with a portable device, using skin electrodes and no dilation in <5 minutes. In many studies, the DR score demonstrated a strong correlation to the disease severity and there is limited data to suggest that DR score can be used to predict disease progression in DR. Flicker ERG—but not the DR score—has been used for treatment monitoring in laser and anti-VEGF treatments to assess toxicity and benefit of treatments. The DR score—as a combination of flicker ERG amplitude, time, and pupillary response—is a measure of cone system function (from the cones through the inner retina) and therefore is sensitive to both vascular and neuroretinal dysfunction.

Objective Field Analyzer

Level of Evidence: II. *Area of Retina Being Assessed.M18: Macular Function (Central 20 Degrees)W20: Central 60 Degrees* A recent innovation in perimetric testing is multifocal pupillographic objective perimetry (mfPOP). Multifocal pupillographic objective perimetry assesses visual function by monitoring pupil responses to retinal stimuli presented to multiple locations in the visual field. It shares some features with precursor technologies like multifocal ERGs and multifocal visual evoked potentials. Like those methods, many independent stimuli are concurrently presented to assess multiple parts of the visual field(s), producing sensitivities and response delays for each tested region. Thus, like those methods, mfPOP is objective. Unlike those methods mfPOP is noncontact. The mfPOP method is now available in the form of the FDA-cleared objective field analyzer (OFA) from Konan Medical. Of most interest to testing type 1 diabetes mellitus (T1DM) are 2 OFA methods that only take 82 seconds to assess both eyes at the same time (M18 and W20). This allows young people and children to be tested and followed into adulthood using the same noncontact, easy-to-use tests.[120,121] Unlike multifocal ERGs and multifocal visual evoked potentials, OFA is highly tolerant of blinks. In addition, small pupils in older persons do not negatively impact the testing given that only relative pupil size change is used.

Association with Retinal Function and DRD

Neurodegenerative changes have been shown to occur in the retina prior to clinically evident retinopathy. Multifocal pupillographic objective perimetry is a noncontact method to record responses from many locations in visual field from both eyes concurrently by observing pupillary responses (amplitude and time to peak response delay). The current OFA methods include M18 and W20.

M18 assesses 18 regions within the central 20 degrees (6 mm, i.e., the macula) which is similar to the area tested by microperimetry. Unlike microperimetry, M18's test regions exactly match the size and shape of the ETDRS zones used by all OCT manufacturers to report localized retinal thicknesses (and volumes). This makes it useful to compare function and structure data. A recent cross-sectional study of persons with all stages of AMD using M18 showed that it had superior area under the receiver operator curves compared with ETDRS thickness, or BCVA in early-stage disease (AREDS 1−3).[122] M18 is perhaps most relevant for DME and synergizes well with macular OCT results. The W20 82-second stimulus tests 20 regions within the central 60 degrees of the retina, covering much of the area of interest for DR (9 times greater than M18).

Prior Clinical Studies in DR

Early second and third generation OFA methods had good diagnostic power for discriminating persons with type 2 diabetes, but no DR, from normal controls,[123] Similarly, in patients with T1DM, OFA was able to detect visual field abnormalities in both eyes with no DR and mild NPDR

Table 1. Relevance of Testing Paradigms to Disease Stage

	Ready (For Current Use or within the Next 1–2 Years)	Promising (Unmet, but Defined Research Needs That Can Be Accomplished within the Next 5 Years)	Potential (Unmet Research Needs that Will Need >5 Years to Accomplish)
Preclinical		Flicker ERG OFA	
Early-stage clinical disease*		Contrast sensitivity LLVA Flicker ERG	OFA
Mid-stage clinical disease*	BCVA	Contrast sensitivity LLVA Flicker ERG	OFA
Late-stage clinical disease*	BCVA	Contrast sensitivity LLVA SAP	

BCVA = best-corrected visual acuity; ERG = electroretinogram; LLVA = low luminance visual acuity; OFA = objective field analyzer; SAP = static automated perimetry.
*Stage of disease defined based on the amount of visual acuity loss.

and differentiate them from control subject (area under the curve 90.4 ± 8.9% for no DR vs. controls and 85.9 ± 8.8% for mild NPDR vs. controls)[124] Localized changes to mild off-axis DME are correlated with changes in local OFA per-region sensitivities and delays.[125] Furthermore, in another study, eyes that had DME which showed improvement and reduction in retinal thickness recovered to more normal OFA sensitivities and delays.[126] Persons with type 2 diabetes and no DR could be distinguished from those with NPDR (mild or moderate NPDR).[127]

Knowledge Gaps

While OFA may be a good tool to detect preclinical changes and early neurodegenerative retinal changes, how this will be reflected in clinical care and practice is still lacking. Most of the studies have been conducted on small populations and there is need for larger longitudinal prospective studies looking at these measurements over time. In addition, the device should ideally be tested on a large population data set with both T1DM and type 2 diabetes mellitus. Finally, it is unclear what the association is between OFA measurements at baseline and progression and whether they will have any role in driving or modifying treatment.

Future Use With DRD Staging System

While OFA may not have a significant role in more advanced DR, it may play a role in early stages of the disease. Also, given its ease of use, it may be of particular benefit in children and younger patients with T1DM. Objective field analyzer has demonstrated good diagnostic power in patients with diabetes mellitus and no DR versus control as well as those with no DR and NPDR. Therefore, it may be of significant benefit in a DRD staging earlier in the disease course.

Summary of Visual Function Testing and DRD Staging

There are several different measures of vision, such as minimum legible threshold (the smallest letter that the patient can identify), minimum visible threshold (the minimum contrast of a target at which the patient can distinguish it from the background), minimum separable threshold (the minimum visual angle between 2 separate objects at which the objects can be identified separately), and Vernier acuity (the smallest detectable misalignment of 2 line segments).[128] This review article has focused on the first 2 aspects covering 4 different visual function tests: BCVA, SAP, LLVA, and CS. This review also includes evaluation of visual function, not by

Table 2. Best Categories for Which the Visual Function Test is Expected to Prove Useful Based on Current Data

	Best Categories*						
	Diagnostic	*Monitoring*	*Predictive*	*Prognostic*	*Pharmacodynamic/Response*	*Safety*	*Susceptibility/Risk*
BCVA		X	X	X	X		
LLVA		X			X		X
Contrast sensitivity		X	X	X	X		X
SAP		X					
Flicker ERG	X	X	X	X	X		
OFA	X	X		X			

BCVA = best-corrected visual acuity; ERG = electroretinography; LLVA = low luminance visual acuity; OFA = objective field analyzer; SAP = static automated perimetry.
*Biomarkers, endpoints, and other tools categories.

Table 3. Potential Strength Based on Current Evidence Available of Each of the Visual Function Tests in Screening, Clinical Management, and Research

	Screening	Clinical Management	Research
BCVA	Strong	Strong	Strong
LLVA	Moderate	Weak	Moderate
Contrast sensitivity	Moderate	Weak	Moderate
SAP	Weak	Weak	Moderate
Flicker ERG	Moderate	Weak	Moderate
OFA	Moderate	Weak	Moderate

BCVA = best-corrected visual acuity; ERG = electroretinography; LLVA = low luminance visual acuity; OFA = objective field analyzer; SAP = static automated perimetry.

asking the patient what they see, but by measuring the physiological responses of the retina through ERG and OFA. Given the ease of measurement and wealth of experience with BCVA, it is likely ready for use in a DRD staging system for mid to late-stage clinical disease. Limitations of its use remain its frequent disassociation with retinal disease morphology and other factors that can confound BCVA assessment.

Additional research is needed to determine how CS and LLVA could be used in a DRD staging system. Although their utility in DRD staging is promising, future research may provide insight as to when these measures might have the most utility along the arc of disease progression. Given CS and LLVA deficits in eyes of patients with diabetes, it is possible that these measures could be used in early-stage clinical disease as well as mid to late-stage disease, while flicker ERG and OFA could have most utility in early to mid-stage disease. Although SAP is more challenging to measure, current research suggests it might be promising for future DRD staging, particularly for late-stage clinical disease. Table 1 summarizes the anticipated timeframe and at what disease stage each visual function measurement might contribute to DRD staging. Table 2 classifies how each visual function measure might be used in the diagnosis, evaluation, prediction, and monitoring of DRD. Given that few clinical trials used CS, LLVA, SAP, flicker ERG, and OFA, DRD staging using these measurements should only be considered possible but not probable with more research being needed. Table 3 provides the relevance of each variable as it relates to screening, clinical management, and research in DRD.

Discussion

Visual function deficits in patients with DRD can impact quality of life, particularly in the more advanced stages of DR. However, the current DRD staging scales do not directly take visual function into account. In general, the more severe DR or DME, the worse the visual function. However, there is a broad distribution of visual function outcomes within different severity levels of DR. Best-corrected VA is the most common, accessible, and well-documented visual function parameter. Even within different stages of DR, differences in VA could influence prognosis and clinical management of disease. More specifically, current staging systems ignore DME and neuronal retinal dysfunction which can have a profound impact on VA. Future staging systems should include not only DME, given potential differences in the impact on patients and how they are managed.

Although BCVA is important, its utility is primarily in mid- to later-stage disease. Other visual function measurements have the potential to help monitor early disease and predict progression to more advanced disease. However, large longitudinal studies are needed to evaluate their benefit.

When considering any of these functional measures in the staging of DR it is important to consider factors other than DR that can affect the parameter. Cataract has a high prevalence in the diabetic population and the presence and progression of cataracts can reduce VA measures and CS, particularly at higher spatial frequencies. Senile miosis can preferentially reduce LLVA and can increase the mean deviation of SAP. The flicker ERG measured by the DR score, however, appears unaffected by senile miosis and cataract. Early stages of AMD can affect VA measures, CS at higher spatial frequencies, and central areas of the visual field. Changes in these associated conditions should be considered when using visual function assessments in the staging of DR.

Despite the working group's expertise, there may be a bias in terms of which assessments were selected. One limitation of this process is that it was not a formal systematic review. However, the multistep evaluation approach by multiple experts should have helped identify any gaps in the review. It is quite possible that with future studies and more data, other visual function studies not included in the final manuscript will prove to be relevant. The current work reflects the knowledge and experience of the experts at the current time.

As illustrated in Table 3, each of the visual function parameters has differing strengths. Some work better as screening tools while others are more for clinical care and/or research. It is important to understand what each test can offer in a new DRD system. The needs of a population-based screening classification may differ from clinical care or research. Screening programs have limited staff, equipment, and funds, and most programs can accommodate only 1 or 2 tests. Furthermore, while accurate diagnosis and prognostication are important in clinical care, detecting those requiring referral (while limiting over-referral) is more important for a screening tool. Hence, while evaluating visual function tests it is important to clearly identify what the specific goal of the classification system is expected to achieve and in what setting it will be used.

The ETDRS DRSS is the currently accepted standard for the staging of DR, yet only considers retinal vascular changes that are visible in color fundus photographs.[129] This scale has been validated in the original ETDRS study, which showed increased severity increased the risk of vision loss due to PDR or DME. [130] More recently, the PANORAMA study showed that reduction of DRSS by treatment with aflibercept reduced the risk of subsequent development of vision-threatening complications of DR (i.e., PDR or center-involved DME).[131] With this validation of the DRSS, it has been accepted by regulatory agencies such as the FDA as a registration endpoint for the treatment of DR. However,

an increased understanding of the nature of DR, including its biochemical origins and the independence of neuronal dysfunction from vascular pathology, as well as advances in retinal imaging, have made it clear that sensitivity could be increased by a revision of the staging system.[132] Refined measurements of visual function are a necessary part of a revised staging system not only as components of the scale to increase its prognostic value, but also as outcome measures, particularly in early stages of the disease where VA is preserved.

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Data collection: Glassman, Elmasry, Baskin, Brigell, Chong, Davis, Lesmes, Levin, Maddess, Taylor, Wenzel

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **cpd** = cycles per degree; **CS** = contrast sensitivity; **CSF** = contrast sensitivity function; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRD** = diabetic retinal disease; **DRSS** = Diabetic Retinopathy Severity Scale; **ERG** = electroretinogram; **FDA** = Food and Drug Administration; **LLD** = low luminance deficit; **LLVA** = low luminance visual acuity; **mfPOP** = multifocal pupillographic objective perimetry; **MTM Vision** = Mary Tyler Moore Vision Initiative; **NPDR** = nonproliferative diabetic retinopathy; **OCTA** = OCT angiography; **OFA** = objective field analyzer; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **qCSF** = quantitative contrast sensitivity function; **SAP** = static automated perimetry; **SWAP** = short-wavelength automated perimetry; **T1DM** = type 1 diabetes mellitus; **TRV** = test-retest variability; **US** = United States; **VA** = visual acuity.

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References

1. International Diabetes Federation: facts and figures. http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures. Accessed September 26, 2016.
2. Lundeen EA, Burke-Conte Z, Rein DB, et al. Prevalence of diabetic retinopathy in the US in 2021. *JAMA Ophthalmol*. 2023;141:747–754.
3. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med*. 2012;366:1227–1239.
4. Fenwick EK, Pesudovs K, Rees G, et al. The impact of diabetic retinopathy: understanding the patient's perspective. *Br J Ophthalmol*. 2011;95:774–782.
5. Maa AY, Feuer WJ, Davis CQ, et al. A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy. *J Diabetes Complications*. 2016;30:524–532.
6. Bailey IL, Lovie JE. The design and use of a new near-vision chart. *Am J Optom Physiol Opt*. 1980;57:378–387.
7. Falkenstein IA, Cochran DE, Azen SP, et al. Comparison of visual acuity in macular degeneration patients measured with snellen and early treatment diabetic retinopathy study charts. *Ophthalmology*. 2008;115:319–323.
8. Lovie-Kitchin JE, Brown B. Repeatability and intercorrelations of standard vision tests as a function of age. *Optom Vis Sci*. 2000;77:412–420.
9. Rosser DA, Murdoch IE, Fitzke FW, Laidlaw DA. Improving on ETDRS acuities: design and results for a computerised thresholding device. *Eye (Lond)*. 2003;17:701–706.
10. Ferris 3rd FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol*. 1982;94:91–96.
11. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol*. 2003;135:194–205.
12. Gibson RA, Sanderson HF. Observer variation in ophthalmology. *Br J Ophthalmol*. 1980;64:457–460.
13. Loumann Knudsen L. Visual acuity testing in diabetic subjects: the decimal progression chart versus the Freiburg visual acuity test. *Graefes Arch Clin Exp Ophthalmol*. 2003;241:615–618.
14. Yu HJ, Kaiser PK, Zamora D, et al. Visual acuity variability: comparing discrepancies between Snellen and ETDRS measurements among subjects entering prospective trials. *Ophthalmol Retina*. 2021;5:224–233.
15. 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.
16. Moutray TN, Williams MA, Jackson AJ. Change of visual acuity recording methods in clinical studies across the years. *Ophthalmologica*. 2008;222:173–177.
17. Williams MA, Moutray TN, Jackson AJ. Uniformity of visual acuity measures in published studies. *Invest Ophthalmol Vis Sci*. 2008;49:4321–4327.
18. Ashraf M, Sampani K, Clermont A, et al. Vascular density of deep, intermediate and superficial vascular plexuses are differentially affected by diabetic retinopathy severity. *Invest Ophthalmol Vis Sci*. 2020;61:53.
19. Ashraf M, Nesper PL, Jampol LM, et al. Statistical model of optical coherence tomography angiography parameters that correlate with severity of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2018;59:4292–4298.
20. Sokol S, Moskowitz A, Skarf B, et al. Contrast sensitivity in diabetics with and without background retinopathy. *Arch Ophthalmol*. 1985;103:51–54.
21. Beck RW, Maguire MG, Bressler NM, et al. Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology*. 2007;114:1804–1809.
22. Csaky KG, Richman EA, Ferris 3rd FL. Report from the NEI/FDA ophthalmic clinical trial design and endpoints symposium. *Invest Ophthalmol Vis Sci*. 2008;49:479–489.
23. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321:1880–1894.
24. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the protocol W randomized clinical trial. *JAMA Ophthalmol*. 2021;139:701–712.
25. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123:1351–1359.
26. Bressler NM, Odia I, Maguire M, et al. Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibizumab: a post hoc analysis of the protocol T randomized clinical trial. *JAMA Ophthalmol*. 2019;137:977–985.
27. Ashraf M, Souka A, Adelman R. Predicting outcomes to anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema: a review of the literature. *Br J Ophthalmol*. 2016;100:1596.
28. Bressler SB, Odia I, Maguire MG, et al. Factors associated with visual acuity and central subfield thickness changes when treating diabetic macular edema with anti–vascular endothelial growth factor therapy: an exploratory analysis of the protocol T randomized clinical trial. *JAMA Ophthalmol*. 2019;137:382–389.
29. Wong RL, Tsang CW, Wong DS, et al. Are we making good use of our public resources? The false-positive rate of screening by fundus photography for diabetic macular oedema. *Hong Kong Med J*. 2017;23:356–364.
30. Horton MB, Silva PS, Cavallerano JD, Aiello LP. Operational components of telemedicine programs for diabetic retinopathy. *Curr Diab Rep*. 2016;16:128.
31. Sun JK, Weinstock R, Warren M, et al. Optical coherence tomography (OCT) screening at diabetes visits increases retina referral for patients with diabetic macular edema (DME). *Invest Ophthalmol Vis Sci*. 2017;58:2028.
32. Aiello LP, Jacoba CMP, Sun JK, Silva PS. Integrating macular optical coherence tomography with ultrawide field imaging in a diabetic retinopathy telemedicine program using a single device. *Invest Ophthalmol Vis Sci*. 2021;62:1941.
33. Sunness JS, Rubin GS, Broman A, et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity

loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115:1480−1482.
34. Wu Z, Luu CD, Hodgson LAB, et al. Secondary and exploratory outcomes of the subthreshold nanosecond laser intervention randomized trial in age-related macular degeneration: a LEAD study report. *Ophthalmol Retina*. 2019;3:1026−1034.
35. Wood LJ, Jolly JK, Josan AS, et al. Low luminance visual acuity and low luminance deficit in choroideremia and RPGR-associated retinitis pigmentosa. *Transl Vis Sci Technol*. 2021;10:28.
36. Wood LJ, Jolly JK, Buckley TM, et al. Low luminance visual acuity as a clinical measure and clinical trial outcome measure: a scoping review. *Ophthalmic Physiol Opt*. 2021;41:213−223.
37. Owsley C, McGwin Jr G, Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. *Invest Ophthalmol Vis Sci*. 2006;47:528−535.
38. McAnany JJ, Park JC, Liu K, et al. Contrast sensitivity is associated with outer-retina thickness in early-stage diabetic retinopathy. *Acta Ophthalmol*. 2020;98:e224−e231.
39. Wood LJ, Jolly JK, Andrews CD, et al. Low-contrast visual acuity versus low-luminance visual acuity in choroideremia. *Clin Exp Optom*. 2021;104:90−94.
40. Karatsai E, Sen P, Gurudas S, Sivaprasad S. Low luminance visual acuity and low luminance deficit in proliferative diabetic retinopathy. *J Clin Med*. 2021;10:358.
41. Barrio A, Antona B, Puell MC. Repeatability of mesopic visual acuity measurements using high- and low-contrast ETDRS letter charts. *Graefes Arch Clin Exp Ophthalmol*. 2015;253:791−795.
42. Siderov J, Tiu AL. Variability of measurements of visual acuity in a large eye clinic. *Acta Ophthalmol Scand*. 1999;77:673−676.
43. Das R, Perais J, Graham K, et al. Can visual function tests act as early functional biomarkers of diabetic retinopathy prior to clinical features? *Invest Ophthalmol Vis Sci*. 2019;60:5317, 2019 Annual Meeting Association for Research in Vision and Ophthalmology, ARVO 2019. Vancouver, BC, Canada.
44. Ong RR, Valero SO. The visual function of type 2 diabetics with retinopathy in correlation to low luminance deficit. *Invest Ophthalmol Vis Sci*. 2017;58:5034, 2017 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2017. Baltimore, MD, United States.
45. Campbell FW, Robson JG. Application of Fourier analysis to the visibility of gratings. *J Physiol*. 1968;197:551−566.
46. Chung ST, Legge GE. Comparing the shape of contrast sensitivity functions for normal and low vision. *Invest Ophthalmol Vis Sci*. 2016;57:198−207.
47. Pelli DG, Bex P. Measuring contrast sensitivity. *Vis Res*. 2013;90:10−14.
48. Chung ST, Legge GE, Tjan BS. Spatial-frequency characteristics of letter identification in central and peripheral vision. *Vis Res*. 2002;42:2137−2152.
49. Chen XD, Gardner TW. A critical review: psychophysical assessments of diabetic retinopathy. *Surv Ophthalmol*. 2021;66:213−230.
50. Pescosolido N, Buomprisco G. Psychophysical exams as early indicators of diabetic retinopathy. *Eur Endocrinol*. 2014;10:61−65.
51. Jenkins KS, Steel JC, Layton CJ. Systematic assessment of clinical methods to diagnose and monitor diabetic retinal neuropathy. *J Ophthalmol*. 2018;2018:8479850.
52. Midena E, Vujosevic S. *Visual Psychophysics in Diabetic Retinopathy*. Springer Science+Business Media, LLC; 2012.
53. Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of 'real-world' targets. *Br J Ophthalmol*. 1987;71:791−796.
54. Owsley C. Contrast sensitivity. *Ophthalmol Clin North Am*. 2003;16:171−177.
55. Rohaly AM, Owsley C. Modeling the contrast-sensitivity functions of older adults. *J Opt Soc Am A*. 1993;10:1591−1599.
56. Nair P, Aiello LP, Gardner TW, et al. Report from the NEI/FDA diabetic retinopathy clinical trial design and endpoints workshop. Diabetic retinopathy trial design and endpoints. *Invest Ophthalmol Vis Sci*. 2016;57:5127−5142.
57. Pelli D, Robson J. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci*. 1988;2:187−199.
58. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013−2022.
59. Thurman SM, Davey PG, McCray KL, et al. Predicting individual contrast sensitivity functions from acuity and letter contrast sensitivity measurements. *J Vis*. 2016;16:15.
60. Lesmes LA, Lu Z-L, Baek J, Albright TD. Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method. *J Vis*. 2010;10:17.
61. Vingopoulos F, Wai KM, Katz R, et al. Measuring the contrast sensitivity function in non-neovascular and neovascular age-related macular degeneration: the quantitative contrast sensitivity function test. *J Clin Med*. 2021;10:2768.
62. Traber GL, della Volpe-Waizel M, Maloca P, et al. New technologies for outcome measures in glaucoma: review by the European Vision Institute Special Interest Focus Group. *Ophthalmic Res*. 2020;63:88−96.
63. Hou F, Huang C-B, Lesmes L, et al. qCSF in clinical application: efficient characterization and classification of contrast sensitivity functions in amblyopia. *Invest Ophthalmol Vis Sci*. 2010;51:5365−5377.
64. Lesmes LA, Dorr M. *Active Learning for Visual Acuity Testing*. APPIS '19: Proceedings of the 2nd International Conference on Applications of Intelligent Systems. 2019:1−6. https://doi.org/10.1145/3309772.3309798.
65. Ou WC, Lesmes LA, Christie AH, et al. Normal-and low-luminance automated quantitative contrast sensitivity assessment in eyes with age-related macular degeneration. *Am J Ophthalmol*. 2021;226:148−155.
66. Thomas M, Silverman RF, Vingopoulos F, et al. Active learning of contrast sensitivity to assess visual function in macula-off retinal detachment. *J Vitreoretin Dis*. 2021;5:313−320.
67. Wai KM, Vingopoulos F, Garg I, et al. Contrast sensitivity function in patients with macular disease and good visual acuity. *Br J Ophthalmol*. 2022;106:839−844.
68. Silverman RF, Kasetty M, Vingopoulos F, et al. Measuring contrast sensitivity function with active learning in retinal vein occlusion: a new endpoint of visual function. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:392−400.
69. Joltikov KA, de Castro VM, Davila JR, et al. Multidimensional functional and structural evaluation reveals neuroretinal impairment in early diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2017;58:BIO277−BIO290.
70. Verrotti A, Lobefalo L, Petitti MT, et al. Relationship between contrast sensitivity and metabolic control in

diabetics with and without retinopathy. *Ann Med*. 1998;30:369–374.
71. Harris A, Arend O, Danis RP, et al. Hyperoxia improves contrast sensitivity in early diabetic retinopathy. *Br J Ophthalmol*. 1996;80:209–213.
72. Khan MI, Barlow RB, Weinstock RS. Acute hypoglycemia decreases central retinal function in the human eye. *Vis Res*. 2011;51:1623–1626.
73. Miller WP, Yang C, Mihailescu ML, et al. Deletion of the Akt/mTORC1 repressor REDD1 prevents visual dysfunction in a rodent model of type 1 diabetes. *Diabetes*. 2018;67:110–119.
74. Aung MH, Na Park H, Han MK, et al. Dopamine deficiency contributes to early visual dysfunction in a rodent model of type 1 diabetes. *J Neurosci*. 2014;34:726–736.
75. Berkowitz BA, Kern TS, Bissig D, et al. Systemic retinaldehyde treatment corrects retinal oxidative stress, rod dysfunction, and impaired visual performance in diabetic mice. *Invest Ophthalmol Vis Sci*. 2015;56:6294–6303.
76. Allen RS, Hanif AM, Gogniat MA, et al. TrkB signalling pathway mediates the protective effects of exercise in the diabetic rat retina. *Eur J Neurosci*. 2018;47:1254–1265.
77. Aung MH, Kim MK, Olson DE, et al. Early visual deficits in streptozotocin-induced diabetic long evans rats. *Invest Ophthalmol Vis Sci*. 2013;54:1370–1377.
78. Umino Y, Solessio E. Loss of scotopic contrast sensitivity in the optomotor response of diabetic mice. *Invest Ophthalmol Vis Sci*. 2013;54:1536–1543.
79. Becker C, Schneider C, Aballéa S, et al. Cataract in patients with diabetes mellitus—incidence rates in the UK and risk factors. *Eye*. 2018;32:1028–1035.
80. Channa R, Wolf RM, Simo R, et al. A new approach to staging diabetic eye disease: staging of diabetic retinal neurodegeneration and diabetic macular edema. *Ophthalmol Sci*. 2023;4:100420.
81. Trick GL, Trick LR, Kilo C. Visual field defects in patients with insulin-dependent and noninsulin-dependent diabetes. *Ophthalmology*. 1990;97:475–482.
82. Hudson C, Flanagan J, Turner G, et al. Short-wavelength sensitive visual field loss in patients with clinically significant diabetic macular oedema. *Diabetologia*. 1998;41:918–928.
83. Bengtsson B, Hellgren KJ, Agardh E. Test–retest variability for standard automated perimetry and short-wavelength automated perimetry in diabetic patients. *Acta Ophthalmol*. 2008;86:170–176.
84. Bengtsson B, Heijl A, Agardh E. Visual fields correlate better than visual acuity to severity of diabetic retinopathy. *Diabetologia*. 2005;48:2494–2500.
85. Hellgren KJ, Agardh E, Bengtsson B. Progression of early retinal dysfunction in diabetes over time: results of a long-term prospective clinical study. *Diabetes*. 2014;63:3104–3111.
86. Maguire MG, Liu D, Glassman AR, et al. Visual field changes over 5 years in patients treated with panretinal photocoagulation or ranibizumab for proliferative diabetic retinopathy. *JAMA Ophthalmol*. 2020;138:285–293.
87. Chee C, Flanagan DW. Visual field loss with capillary nonperfusion in preproliferative and early proliferative diabetic retinopathy. *Br J Ophthalmol*. 1993;77:726–730.
88. Federman J, Lloyd J. Automated static perimetry to evaluate diabetic retinopathy. *Trans Am Ophthalmol Soc*. 1984;82:358.
89. Kondo M, Sieving PA. Post-photoreceptoral activity dominates primate photopic 32-Hz ERG for sine-, square-, and pulsed stimuli. *Invest Ophthalmol Vis Sci*. 2002;43:2500–2507.
90. Robson AG, Frishman LJ, Grigg J, et al. ISCEV standard for full-field clinical electroretinography (2022 update). *Doc Ophthalmol*. 2022;144:165–177.
91. Wangsa-Wirawan ND, Linsenmeier RA. Retinal oxygen: fundamental and clinical aspects. *Arch Ophthalmol*. 2003;121:547–557.
92. Kato K, Kondo M, Nagashima R, et al. Factors affecting mydriasis-free flicker ERGs recorded with real-time correction for retinal illuminance: study of 150 young healthy subjects. *Invest Ophthalmol Vis Sci*. 2017;58:5280–5286.
93. Miura G, Sato E, Yamamoto S. Flicker electroretinograms recorded with mydriasis-free RETeval system before and after cataract surgery. *Eye*. 2017;31:1589–1593.
94. Bresnick GH, Palta M. Temporal aspects of the electroretinogram in diabetic retinopathy. *Arch Ophthalmol*. 1987;105:660–664.
95. Hayreh SS. Photocoagulation for retinal vein occlusion. *Prog Retin Eye Res*. 2021;85:100964.
96. Holopigian K, Seiple W, Lorenzo M, Carr R. A comparison of photopic and scotopic electroretinographic changes in early diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1992;33:2773–2780.
97. Kjeka O, Bredrup C, Krohn J. Photopic 30 Hz flicker electroretinography predicts ocular neovascularization in central retinal vein occlusion. *Acta Ophthalmol Scand*. 2007;85:640–643.
98. Satoh S, Iijima H, Imai M, et al. Photopic electroretinogram implicit time in diabetic retinopathy. *Jpn J Ophthalmol*. 1994;38:178–184.
99. Tahara K, Matsuura T, Otori T. Diagnostic evaluation of diabetic retinopathy by 30-Hz flicker electroretinography. *Jpn J Ophthalmol*. 1993;37:204–210.
100. Brigell MG, Chiang B, Maa AY, Davis CQ. Enhancing risk assessment in patients with diabetic retinopathy (DR) by adding retinal function assessment to structural information. *Invest Ophthalmol Vis Sci*. 2019;60:5313.
101. Hiraiwa T, Horio N, Terasaki H, et al. Preoperative electroretinogram and postoperative visual outcome in patients with diabetic vitreous hemorrhage. *Jpn J Ophthalmol*. 2003;47:307–311.
102. Miyata R, Kondo M, Kato K, et al. Supernormal flicker ERGs in eyes with central retinal vein occlusion: clinical characteristics, prognosis, and effects of anti-VEGF agent. *Invest Ophthalmol Vis Sci*. 2018;59:5854–5861.
103. Nakayama M, Nakamura J, Hamada Y, et al. Aldose reductase inhibition ameliorates pupillary light reflex and F-wave latency in patients with mild diabetic neuropathy. *Diabetes Care*. 2001;24:1093–1098.
104. Ortube MC, Kiderman A, Eydelman Y, et al. Comparative regional pupillography as a noninvasive biosensor screening method for diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2013;54:9–18.
105. Smith S, Smith S. Reduced pupillary light reflexes in diabetic autonomic neuropathy. *Diabetologia*. 1983;24:330–332.
106. Straub R, Thies U, Jeron A, et al. Valid parameters for investigation of the pupillary light reflex in normal and diabetic subjects shown by factor analysis and partial correlation. *Diabetologia*. 1994;37:414–419.
107. Straub RH, Jeron A, Kerp L. The pupillary light reflex. 2. Prevalence of pupillary autonomic neuropathy in diabetics using age-dependent and age-independent pupillary parameters. *Ophthalmologica*. 1992;204:143–148.

108. Wang H, Li F, Li J, et al. Electrophysiology as a prognostic indicator of visual recovery in diabetic patients undergoing cataract surgery. *Graefes Arch Clin Exp Ophthalmol*. 2021;259:1879−1887.
109. Wu L, Wu D, Luo T. The significance of preoperative visual electrophysiology for vitrectomy. *Zhonghua Yan Ke Za Zhi*. 1997;33:344−346.
110. Brigell MG, Davis Q, Waheed NK. Predictive value of ERG, OCT-A, and UWF-FA in patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2020;61:4038.
111. Değirmenci MFK, Demirel S, Batıoğlu F, Özmert E. Role of a mydriasis-free, full-field flicker ERG device in the detection of diabetic retinopathy. *Doc Ophthalmol*. 2018;137:131−141.
112. Zeng Y, Cao D, Yang D, et al. Retinal vasculature−function correlation in non-proliferative diabetic retinopathy. *Doc Ophthalmol*. 2020;140:129−138.
113. Lynch SK, Abràmoff MD. Diabetic retinopathy is a neurodegenerative disorder. *Vis Res*. 2017;139:101−107.
114. Jackson GR, Barber AJ. Visual dysfunction associated with diabetic retinopathy. *Curr Diab Rep*. 2010;10:380−384.
115. Birch DG, Cheng P, Duncan JL, et al. The RUSH2A study: best-corrected visual acuity, full-field electroretinography amplitudes, and full-field stimulus thresholds at baseline. *Transl Vis Sci Technol*. 2020;9:9.
116. Koulen P, Edwards G, Johnston TP. Synergism of mechanisms underlying early-stage changes in retina function after experimentally induced dyslipidemia and hyperglycemia. *Invest Ophthalmol Vis Sci*. 2021;62:3130.
117. Sobrin L, Lam BL, Liu M, et al. Electroretinographic monitoring in birdshot chorioretinopathy. *Am J Ophthalmol*. 2005;140:52.e1−52.e18.
118. Zahid S, Jayasundera T, Rhoades W, et al. Clinical phenotypes and prognostic full-field electroretinographic findings in Stargardt disease. *Am J Ophthalmol*. 2013;155:465−473.e3.
119. Zeng Y, Cao D, Yu H, et al. Early retinal neurovascular impairment in patients with diabetes without clinically detectable retinopathy. *Br J Ophthalmol*. 2019;103:1747−1752.
120. Ali EN, Carle CF, Lueck CJ, et al. Assessing migraine patients with multifocal pupillographic objective perimetry. *BMC Neurol*. 2021;21:1−12.
121. Ali EN, Lueck CJ, Carle CF, et al. Response characteristics of objective perimetry in persons living with epilepsy. *J Neurol Sci*. 2022;436:120237.
122. Rai BB, Sabeti F, Carle CF, et al. Rapid objective testing of visual function matched to the ETDRS grid and its diagnostic power in age-related macular degeneration. *Ophthalmol Sci*. 2022;2:100143.
123. Bell A, James AC, Kolic M, et al. Dichoptic multifocal pupillography reveals afferent visual field defects in early type 2 diabetes. *Invest Ophthalmol Vis Sci*. 2010;51:602−608.
124. Sabeti F, Carle CF, Nolan CJ, et al. Multifocal pupillographic objective perimetry for assessment of early diabetic retinopathy and generalised diabetes-related tissue injury in persons with type 1 diabetes. *BMC Ophthalmol*. 2022;22:1−13.
125. Rai BB, Maddess T, Carle CF, et al. Comparing objective perimetry, matrix perimetry, and regional retinal thickness in mild diabetic macular edema. *Transl Vis Sci Technol*. 2021;10:32.
126. Sabeti F, Rai BB, van Kleef JP, et al. Objective perimetry identifies regional functional progression and recovery in mild diabetic macular oedema. *PLoS One*. 2023;18:e0287319.
127. Sabeti F, Nolan CJ, James AC, et al. Multifocal pupillography identifies changes in visual sensitivity according to severity of diabetic retinopathy in type 2 diabetes. *Invest Ophthalmol Vis Sci*. 2015;56:4504−4513.
128. American Academy of Ophthalmology. *Section 3 - Clinical Optics. BCSC Basic and Clinical Science Course (aaoorg)*. The American Academy of Ophthalmology; 2021.
129. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs - an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98:786−806.
130. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology*. 1991;98(5 suppl):766−785.
131. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol*. 2021;139:946−955.
132. Sun JK, Aiello LP, Abramoff MD, et al. Updating the staging system for diabetic retinal disease. *Ophthalmology*. 2021;128:490−493.