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Diabetic retinal disease cure accelerator: Modernizing staging and endpoints

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ABSTRACT

The "Diabetic Retinal Disease (DRD) Cure Accelerator," a joint initiative by the Mary Tyler Moore Vision Initiative and the Collaborative Community on Ophthalmic Innovation, aims to modernize clinically meaningful staging systems and endpoints for DRD. During a June 2025 workshop involving over 100 international experts, participants emphasized the urgent need for validated structural and functional endpoints grounded in the retinal neurovascular unit. Current DRD staging limitations were highlighted alongside the importance of early biomarkers, including retinal nonperfusion, inner retinal thinning, and disorganization of retinal layers. Functional priorities included contrast sensitivity, electrophysiology, and performance-based mobility parameters that reflect real-world visual impairment. Beyond clinical staging, this approach facilitates precision phenotyping to isolate specific molecular pathogenic pathways driving disease in individual patients. Mechanistic granularity provides a foundation for discovery science, enabling targeted drug re-purposing and the development of curative therapeutics. Key next steps include prospective multicenter studies, harmonized protocols, and reference standards and endpoints for AI based on patient relevant outcomes. By integrating scientific, clinical, and patient-centered perspectives, this Accelerator seeks to establish an international consensus on robust endpoints. Ultimately, this precision-based approach aims to transform DRD diagnosis and treatment, accelerating the access of patients worldwide to therapies that reduce diabetes-related vision loss.

1. Introduction

Diabetic retinal disease (DRD) is a common complication of diabetes and remains the leading cause of blindness among working-age adults in the United States and many high-income countries worldwide (Fong et al., 2003; Hendricks et al., 1998; Solomon et al., 2017; Kropp et al., 2023; Owens et al., 2025). DRD encompasses the vascular abnormalities of diabetic retinopathy, diabetic macular edema (DME), and the

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neurodegenerative changes affecting the retina in diabetes (diabetic retinal neurodegeneration, DRN). The combined compromise of vascular and neural integrity can lead to progressive and potentially irreversible visual impairment. According to the American Academy of Ophthalmology, DRD affects millions of Americans and continues to pose a major public health challenge, with vision-threatening forms impacting nearly 2 million individuals annually, and over 25,000 people with diabetes losing vision every year (Lim et al., 2025).

While effective treatments for advanced stages of DRD are available, there remains a critical gap in the ability to detect, monitor, and intervene during earlier stages of disease, when vision may still be preserved. Current clinical trial endpoints and risk stratification tools are often outdated and insensitive to the full spectrum of DRD pathology, particularly its neuronal components. Current DRD staging and clinical trial paradigms rely heavily on ETDRS severity grading, best-corrected visual acuity (BCVA), central retinal thickness, and progression to proliferative diabetic retinopathy or vision threatening retinopathy or diabetic macular edema. While these measures have enabled major therapeutic advances, they incompletely capture early neurovascular dysfunction, patient-reported visual impairment, and disease heterogeneity. This is the gap the DRD Cure Accelerator seeks to address: by modernizing the clinical research landscape, validating novel surrogate markers and primary endpoints, and accelerating the development of precision treatments, the initiative aims to eliminate vision loss from diabetes through collaborative, mission-driven science.

The Mary Tyler Moore Vision Initiative (MTM Vision) was founded by Dr. S. Robert Levine to honor the legacy of his wife, Mary Tyler Moore, a pioneering actress, producer, and passionate advocate for diabetes research who experienced vision loss due to DRD. Her story continues to shape a mission rooted in urgency, hope, and patient-centered innovation, to eliminate diabetes-related vision loss by addressing three persistent barriers: the absence of a clear disease definition, limited understanding of the human biology of DRD, and the lack of validated surrogate outcomes and primary endpoints, in particular for early-stage disease. Through expert working groups, a research-driven ocular biorepository, and the design of targeted clinical studies, MTM Vision is advancing a multidimensional staging framework for DRD and supporting the validation of both functional and structural measures (Fickweiler et al., 2025; Domalpally et al., 2024).

The Collaborative Community on Ophthalmic Innovation (CCOI) is dedicated to accelerating the development and adoption of ophthalmic medical products worldwide. As a dynamic forum, CCOI unites public and private sector stakeholders to proactively identify and address key barriers to innovation in this field. Its membership includes regulatory agencies, patient advocacy organizations, physicians, healthcare providers and their professional societies, the medical industry, academia, payors, public-private partnerships, research organizations, bioethicists, and foundations. By integrating a broad spectrum of perspectives, expertise, and resources, CCOI fosters a collaborative environment where unilateral efforts would otherwise fall short. This inclusive approach helps eliminate redundancies, streamline initiatives, and maximize impact. The goal is to drive forward solutions that ensure groundbreaking ophthalmic medical products reach the patients who need them most, ultimately improving global eye health.

On June 11, 2025 the newly launched Diabetic Retinal Disease Cure Accelerator, a joint initiative led by MTM Vision in partnership with the CCOI, convened clinicians, researchers, industry representatives, and regulatory officials as the start of a formal consensus-building process around the identification and validation of novel surrogate, clinical and primary endpoints for DRD. Experts in subjects ranging from ophthalmology, biomedical engineering, regulatory science, and patient advocacy provided talks on the latest developments in this field (Tables 1–5). A summary of the principal emerging DRD endpoints and biomarkers, including their strengths, limitations, and current clinical/regulatory readiness, is provided in Supplementary Table S1. The primary goal of the workshop was to work collaboratively to accelerate efforts to improve the regulatory science for evaluating DRD diagnostics and treatments, and thereby accelerate the development and regulatory

Table 1
Clinical assessment of retinal structure.

Speaker Name	Title/Affiliation	Presentation Topic
Paolo Silva, MD	Associate Professor of Ophthalmology, Joslin Diabetes Center, Harvard Medical School	Retinal nonperfusion and future risk of vision-threatening complications
Yali Jia, PhD	Professor of Ophthalmology and Biomedical Engineering, OHSU	AI-driven assessment of nonperfusion on optical coherence tomography angiography (OCTA)
Elliott Sohn, MD	Professor, Ophthalmology and Visual Sciences, University of Iowa	Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinal disease
Stela Vujosevic, MD, PhD	Professor and Head, Medical Retina Unit, University Eye Clinic, San Giuseppe Hospital, Milano	Disorganization of retinal inner and outer layers (DRIL/DROL) and visual function in diabetic retinal disease

Panel Discussion (Q&A): Jennifer K Sun, MD, MPH; Paolo Silva, MD; Michael D Abramoff, MD, PhD; Stela Vujosevic, MD, PhD; Thomas W Gardner, MD, MS.

Table 2
Cellular and molecular markers of DRD.

Speaker Name	Title/Affiliation	Presentation Topic
Chandra Balaratnasingam, MD, PhD	Clinical Professor, University of Western Australia Medical School, Lions Eye Institute	The pathophysiology of DRD and its relation to visual function
Patrice Fort, PhD	Director, MTM Vision Ocular Biorepository & Resource Center	Changes in the retinal neurovascular unit at the cellular level in DRD

Panel Discussion (Q&A): Machelle T Pardue, PhD; Patrice Fort, PhD.

Table 3
Assessment of the function of retinal neurovascular unit.

Speaker Name	Title/Affiliation	Presentation Topic
José-Alain Sahel, MD	Distinguished Professor and Chair, Department of Ophthalmology, University of Pittsburgh	Measuring functional vision through mobility testing and virtual reality (learning from IRD)
Jason McAnany, PhD	Professor; Director, Clinical Psychophysics and Electrophysiology Lab, University of Illinois	Mechanistic insights from visual function testing in DRD
Luis Lesmes, PhD	CEO, Adaptive Sensory Technology	Contrast sensitivity in DRD

Panel Discussion (Q&A): Thomas W Gardner, MD, MS; José-Alain Sahel, MD; Jason McAnany, PhD; Luis Lesmes, PhD.

Table 4
Validating novel clinical outcome assessments.

Speaker Name	Title/Affiliation	Presentation Topic
Olivia Meyerhofer	Global Value Lead, Boehringer-Ingelheim Pharmaceuticals	Priorities and concerns from patients with diabetes
Amanda Bicket, MD	Assistant Professor, Ophthalmology and Visual Sciences, University of Michigan	Gait assessment as an outcome to assess functional vision

Panel Discussion (Q&A): S. Robert Levine, MD; Olivia Meyerhofer; Amanda Bicket, MD.

Table 5
Translation to action.

Speaker Name	Title/Affiliation	Presentation Topic
Malvina Eydelman, MD	CEO, Collaborative Community on Ophthalmic Innovation (CCOI)	Role of CCOI in building consensus on endpoints for DRD
Michael Abramoff, MD, PhD	Professor of Ophthalmology and Visual Sciences, University of Iowa	Practical matters in identifying/validating endpoints and biomarkers for medical product development
Katie Capanna, MBA	Associate Office Director, Strategic Development, FDA CDRH	FDA Home as a Healthcare Hub: CDRH Initiative to Enable Healthier Living

Panel Discussion (Q&A): Malvina Eydelman, MD; Michael D Abramoff, MD, PhD; Katie Capanna, MBA

approval of medical products that can prevent or reverse vision loss in people with diabetes by refining how DRD is defined, staged, and measured (Levine et al., 2022, 2023). During this one day workshop, the following leading issues were discussed and addressed:

2. Clinical assessment of retinal structure

The importance of retinal nonperfusion as a clinically meaningful surrogate marker for predicting vision-threatening complications (VTC) in DRD was emphasized. Nonperfusion is present even in eyes with subclinical or mild disease and increases with disease severity. DRCR Retina Network Protocol AA established that greater baseline retinal nonperfusion, particularly in the posterior pole and mid-periphery, is significantly associated with increased risk of DRD worsening, onset of proliferative diabetic retinopathy (PDR), and vitreous hemorrhage (Silva et al., 2022). Typically non-perfusion begins in the mid-periphery and progresses toward the posterior pole as disease severity increases, with posterior pole involvement showing the strongest association with PDR onset within two years (Silva et al., 2022). In exploratory analyses, eyes with higher baseline nonperfusion are significantly more likely to develop VTC such as PDR within one to two years (Silva et al., 2025). Clearly, establishing standardized methods for quantifying retinal nonperfusion and integrating these metrics into DRD severity scales is key, so that we can better identify patients at high risk and improve clinical outcomes.

With the rapid advancement of non-invasive, high-resolution retinal imaging technologies, there is broad consensus on the urgent need to develop and validate AI-driven methods to quantify retinal nonperfusion area (NPA) and nonperfusion index (NPI), particularly using noninvasive modalities such as optical coherence tomography angiography (OCTA). OCTA offers distinct advantages over traditional fluorescein angiography (FA), including its ability to provide high-resolution, layer-specific images without the need for dye injection, and its sensitivity to early microvascular changes in DRD. While vessel density is commonly used to assess perfusion, it is highly sensitive to OCTA scan quality, whereas NPA is more stable and reliable across variable imaging conditions (Guo et al., 2018, 2019; Xiong et al., 2023). Collaborative findings from the DRCR Retina Network underscore the superior performance of machine learning-based segmentation techniques over traditional rule-based approaches in detecting NPA, especially in low-quality scans affected by shadowing, defocus, or signal attenuation (Hormel et al., 2025). A prototype widefield OCTA system utilizing 500 kHz swept-source laser has an expanded field of view, enabling improved detection of peripheral lesions, critical for assessing DRD severity and progression (Liang et al., 2023). Collectively, these advancements support AI-determined NPA as a promising quantitative imaging biomarker for DRD, with potential for application in multi-center clinical trials and longitudinal disease monitoring.

Diabetic retinal neurodegeneration (DRN) is increasingly recognized as an early and potentially independent manifestation of DRD, gaining broader clinical attention as a potential biomarker and therapeutic target. In fact, some authors have proposed that DRD is initially a neurodegenerative disease, rather than a purely vascular or combined neurovascular disease (Lynch et al., 2017). Histological comparisons of donor eyes have revealed that patients with diabetes and no clinical sings of retinopathy exhibit thinning of the nerve fiber layer (NFL) and ganglion cell layer (GCL), and in some cases photoreceptor loss, despite the absence of detectable changes in capillary density (Bloodworth, 1962; Barber et al., 1998; Tang et al., 2025; Albertos-Arranz et al., 2025). Longitudinal optical coherence tomography (OCT) data from patients with type 1 diabetes and minimal or no retinopathy have demonstrated progressive thinning of the NFL and GCL/IPL layers over four years, independent of age and glycemic control, at rates comparable to those seen in moderate to severe glaucoma over one to two decades (Sohn et al., 2016). In parallel, animal model studies have revealed inner retinal thinning as early as six weeks after diabetes onset, preceding any observable microvascular changes, suggesting that DRN may not only precede but also contribute to the vascular pathology traditionally associated with DRD (Sohn et al., 2016). Additional evidence from eyes with no to minimal DRD, including peripapillary NFL/GCL thinning and electrophysiologic evidence of inner retinal dysfunction, further supports the potential role of DRN in disease onset and progression (Simo et al., 2014; Carrasco et al., 2007). However, emerging evidence also suggests that early DRD manifestations may be heterogeneous across patients. Findings from the EUROCONDOR studies demonstrated that a substantial proportion of individuals with type 2 diabetes exhibited early microvascular abnormalities without detectable neurodysfunction on mfERG testing, supporting the presence of distinct early DRD phenotypes (Santos et al., 2017; Simo et al., 2019). Collectively, these findings underscore the importance of recognizing DRN as a fundamental component of DRD and highlight the need to explore neurovascular unit (NVU)-preserving interventions aimed at preventing vision loss in people with diabetes.

There is growing consensus that disorganization of retinal inner and outer layers (DRIL and DROL, respectively) represents a clinically meaningful structural correlate of functional impairment in DRD. Diabetes induces vascular and neuronal changes in the retina, which disrupt the integrity of the neurovascular unit, a complex structure composed of retinal vasculature, glial cells, and neurons that maintains the inner blood-retinal barrier (Solomon et al., 2017; Eleftheriou et al., 2020; Usui, 2020; Gardner et al., 2017). Functional deficits in the retina often precede the clinical signs of DRD and traditional metrics such as best-corrected visual acuity (BCVA) may fail to detect early dysfunction (Rai et al., 2025). More sensitive assessments, including contrast sensitivity, color vision, and microperimetry may be better suited to capture early retinal changes in patients with diabetes. DRIL, defined on OCT as the absence of clear boundaries between the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer (Sun et al., 2014, 2015; Das et al., 2018; Midena et al., 2023; Singh et al., 2023) has been consistently associated with worse visual acuity, increased disease severity, and poor treatment response, particularly in DME (Vujosevic et al., 2020; Zur et al., 2020; Szeto et al., 2024). DROL, involving disruption of the outer retinal layers, especially the inner-segment/outer -segment junction or ellipsoid zone (EZ) (Jonnal et al., 2014), further predicts visual dysfunction (Scarinci et al., 2015; Muftuoglu et al., 2017). The concept of "DROL Plus", which includes combined inner and outer layer disorganization and IS-OS junction/EZ loss, has been linked to more severe functional impairment and reduced retinal sensitivity (Kessler et al., 2021; Munk et al., 2022; Vujosevic et al., 2024). Imaging studies show that DRIL and DROL severity correlate with reduced vessel density in the intermediate and deep capillary plexuses in the retina, increased choriocapillaris flow voids, and greater ischemic burden on OCTA (Vujosevic et al., 2024; Stino et al., 2024). These findings support DRIL and DROL as potentially valuable structural surrogate markers for functional impairment and disease progression in DRD, with emerging AI-based tools offering new

opportunities for quantification and integration into clinical trials and personalized care strategies. Additional studies are needed to understand the cellular and molecular mechanisms that underlie DRIL and DROL. Additional emerging OCT biomarkers include hyperreflective retinal and choroidal foci, which may reflect inflammatory activity, lipid extravasation, or cholesterol crystal deposition in DRD. Recent studies have suggested that changes in hyperreflective retinal and choroidal foci may correlate with diabetic macular edema treatment response and disease activity (Chakravarthy et al., 2025; Yamaguchi et al., 2022; Midena et al., 2024).

A multidisciplinary panel discussed and reached consensus on the need to redefine and expand clinical endpoints for DRD to better reflect its complex pathophysiology and progression. Early detection of peripheral retinal nonperfusion was identified as a critical strategy for preventing irreversible vision loss, with support for integrating UWF-FA and OCTA into dynamic staging frameworks. There was broad agreement that DRD may originate as a neurodegenerative condition, underscoring the importance of accessible, early-stage functional endpoints, such as electrophysiologic measures, that can capture subtle retinal dysfunction. Objective functional tests, including those emerging from new clinical protocols, were proposed as tools to provide more sensitive indicators of disease onset and progression. Structural biomarkers such as DRIL and DROL were recognized as more robustly correlated with visual impairment than central retinal thickness, and AI-enhanced OCTA was highlighted as a promising modality for tracking neurovascular disruption across the disease continuum. Bringing these novel metrics to patients will require outcome studies and an integrated approach to regulation and reimbursement by industry that involves Accelerator participants. Together, these perspectives support a shift toward multidimensional, patient-relevant endpoints that integrate structural, functional, and metabolic markers to guide clinical research and therapeutic innovation in DRD.

3. Cellular and molecular markers of DRD

Emerging histologic evidence has revealed mechanisms of DRD that remain invisible to current clinical imaging. High-resolution techniques such as isolated ocular perfusion and confocal microscopy enable detailed stratification of the macular vasculature and the identification of early retinal injury markers. Among these, inter-pericyte tunneling nanotubules (IP-TNTs) may play a role in compromising NVU integrity by cell-to-cell communication through selective transfer of vesicle, calcium and mitochondria. Recent data have demonstrated that IP-TNTs are reduced in pre-clinical DRD stage suggesting their potential as early biomarkers of disease onset (Hein et al., 2024). Although current evaluation of IP-TNTs relies on advanced imaging techniques that are not yet clinically translatable, these findings may provide mechanistic insights into early neurovascular unit dysfunction. Endothelial dysfunction has been identified as a precursor to vascular occlusion and a promising therapeutic target. Additionally, retinal glial remodeling around microaneurysms may serve as a protective mechanism against leakage, offering potential opportunities for intervention. These findings underscore the importance of human donor tissue in discovering early biomarkers, exploring complications like ischemia, and revealing cellular interactions in the retina critical to disease progression.

Advances in multi-scale analysis have reinforced the understanding that DRD affects not only vascular structures but also neuronal and glial components (Albertos-Arranz et al., 2025; Sohn et al., 2016; Llorian-Salvador et al., 2024). A dual investigative approach, combining region-specific multi-omics analysis of retinal tissue and ocular fluids with spatially resolved imaging coupled with donor phenotyping, has enabled detailed characterization of the NVU across disease stages (Grimes et al., 2025). Single-cell and nuclear transcriptomics, proteomics, and lipidomics across foveal, macular, and peripheral retinal zones, have revealed differential molecular signatures that vary by disease stage and region (Zhang et al., 2023). High-resolution imaging, including OCT, optical coherence microscopy (OCM), and fundus photography, further enables detailed mapping of structural and cellular changes around DRD features. Co-staining techniques with markers like collagen IV (for the matrix of the vasculature) and Ulex Europaeus Agglutinin (UEA) for endothelial cells help identify perfusion loss and retinal vascular remodeling, while preliminary analyses of spatial transcriptomics and lipid distribution offer insights into localized NVU disruption. These integrative methods support the development of phenotype-based stratification strategies and the identification of novel therapeutic targets, advancing the capacity to understand and intervene in DRD at the cellular level. Emerging evidence also supports a role for bone marrow-derived inflammatory and progenitor cells in retinal vascular injury and repair processes, further highlighting the complex multicellular nature of DRD progression and its potential implications for prognosis and therapeutic stratification (Bhatwadekar et al., 2017; Li Calzi et al., 2010; Park et al., 2017).

A panel highlighted a growing consensus around NVU as a central feature in retinal dysfunction, with emphasis on the interconnected roles of vascular, glial, and neuronal components in DRD. Functional hyperemia testing and glial behavior in diabetic mouse models were presented as promising tools to assess neurovascular dynamics, while early molecular changes in the vitreous of diabetic donors, detected even before clinical signs of retinopathy, suggested a potential window for preclinical intervention. The panel underscored the need for accessible, quantifiable biomarkers that capture regional retinal alterations and support individualized risk assessment and therapeutic strategies. While early detection remains a key priority, advancing the availability of treatments for patients at later stages was also recognized as critical to improving visual outcomes for patients with diabetes.

4. Assessment of the function of retinal neurovascular unit

Advances in functional vision testing are reshaping how therapeutic impact is measured in retinal degeneration, with growing relevance for DRD. A comprehensive framework has emerged that spans gene therapy targeting the underling genetic defects, neuroprotective strategies to preserve retinal cells, and vision restoration using prosthetics, optogenetics, or stem cells (Roska et al., 2018; Sahel et al., 2019). Central to this evolution is the recognition that clinical visual acuity usually does not reflect a patient's ability to navigate real-world environments. This limitation has led to a strong emphasis on performance-based endpoints, particularly mobility testing, as more meaningful indicators of therapeutic benefit. One illustrative case study involved a young patient treated with the first FDA- and EMA-approved gene therapy (AAV2-CBA-RPE65 aka Luxturna) for Leber congenital amaurosis (RPE65 mutation), whose mobility dramatically improved post-treatment (Russell et al., 2017). Such examples underscore the value of outcome measures that capture real-life functionality. However, regulatory progress remains challenged by the need for robust natural history data, optimized trial design, and more agile engagement with regulatory agencies. To address these gaps, reproducible, patient-centered performance tests have been developed, including virtual reality-based mobility assessments validated across multiple cohorts. These tests, such as the multi-luminance mobility maze and the (virtual reality - visual search assessment (VR-VISA)) object detection task, have demonstrated strong correlation with traditional measures like visual fields and contrast sensitivity, and are now being adopted in natural history studies and clinical trials (Authie et al., 2024).

Mechanistic insights into neural dysfunction in DRD have been explored using non-invasive visual function testing. Neural impairment often precedes clinically apparent vascular changes, highlighting the need for tools that assess the neurovascular unit beyond traditional imaging. Current work focuses on three categories of functional assessment: electrophysiological measures (including full-field and multifocal ERG, and visually evoked potentials), pupillometry, and psychophysical tests such as contrast sensitivity and dark adaptation.

Two modalities, full-field ERG and psychophysical flicker sensitivity, illustrate how cone-mediated dysfunction can be detected in patients with minimal or no retinopathy. High-frequency flicker ERG has demonstrated a significant reduction in response amplitude among diabetic patients, even those without visible retinal pathology (McAnany et al., 2018, 2019). This selective loss of high-frequency sensitivity suggests early cone dysfunction and offers a potential stratification axis for DRD staging. To complement ERG findings, a novel flicker-based visual field perimeter has been developed to quantify psychophysical flicker thresholds. Results showed strong correlation with ERG data and revealed a consistent 28% loss in flicker sensitivity among patients with diabetes (McAnany et al., 2019). These measures provide valuable insights into retinal neural integrity and may serve as early functional biomarkers for DRD progression, with potential utility in refining disease classification and trial endpoints.

A detailed overview of contrast sensitivity function (CSF) was presented, including its potential as a visual primary endpoint in DRD. DRD progression was framed as a multidimensional trajectory involving neural, vascular, and biochemical deterioration, emphasizing the need for staging systems that reflect this complexity. Drawing parallels to efforts in age-related macular degeneration (Miller et al., 2025), longitudinal tracking of phenotypic data clouds was proposed to better inform drug development. Within MTM Vision's visual function working group, CSF emerged as a candidate endpoint capable of capturing vision loss across all stages of DRD, unlike BCVA, which typically declines only in advanced disease. The CSF test is described as a two-dimensional map of visual pattern visibility, measured using active machine learning algorithms that adaptively present letter triplets varying in size and contrast. Metrics such as area under the log CSF and low-contrast visual acuity demonstrated strong signal-to-noise ratios and minimal patient burden, with most tests completed in under 7 min. The conserved shape of the CSF curve across species, neural stages, and even deep learning models, underscores its biological relevance (Akbarinia et al., 2023; Goulet et al., 2025). Validation studies have shown CSF correlates with quality of life, OCTA-derived vascular metrics, and patient-reported outcomes, with additional longitudinal trials underway, including the MAGIC, and CANBERRA studies, and DRCR Retina Network protocols AF, AFA, AQ, AR and AS, to further determine its utility (Ha et al., 2025; Choi et al., 2024; Kerwin et al., 2025). CSF is a multidimensional, scalable endpoint with strong potential for inclusion in future DRD registration trials.

A panel discussion explored the convergence of structural and functional deficits in DRD, emphasizing the need for multidimensional endpoints that reflect real-world patient experience. A holistic view of vision was proposed, noting that patients prioritize mobility, daylight vision, and contrast sensitivity over isolated photoreceptor metrics. The importance of correlating patient-reported outcomes with functional measures was highlighted to better capture quality-of-life impacts. Cone-mediated flicker sensitivity loss was discussed as a marker of neural dysfunction that may vary independently from vascular changes even among patients with similar phenotypes. Strong correlations between ERG and psychophysical flicker sensitivity reinforced the potential of these tools for early DRD staging. Contrast sensitivity testing, particularly under low luminance conditions, reveals subtle deficits not captured by high-contrast visual acuity. Together, the panel underscored the value of integrating electrophysiology, psychophysics, and contrast sensitivity into a multi-scale framework for endpoint development. They agreed that the DRCR Protocols AR and AS offer a promising platform to validate these approaches and move toward regulatory acceptance of novel biomarkers that reflect both disease progression and functional impairment.

5. Validating novel clinical outcome assessments

A multi-phase international market research study examined treatment patterns, patient experiences, and unmet needs in DRD (Vujosevic et al., 2025). The study included qualitative and quantitative interviews with 79 physicians across five countries, as well as 1300 documented patient records, followed by in-depth interviews with 17 patients spanning moderate to proliferative stages of disease. Among healthcare professionals, the prevailing theme was a lack of proactive treatment options for patients without DME, with "watch and wait" remaining the standard of care in moderate and even severe NPDR. Physicians expressed frustration over their limited ability to alter prognosis, citing a need for therapies that could halt disease progression and serve as alternatives to laser treatment. Notably, patients with moderate NPDR reported symptoms such as reading difficulty, light sensitivity, and visual field deficits, challenging the assumption that this population is asymptomatic. Interviews revealed a pervasive sense of fear and uncertainty, with individuals expressing anxiety over both long-term vision loss and short-term invasive treatments. Despite limited understanding of disease progression, patients were generally receptive to the idea of preventative intravitreal therapy, provided the benefits were clearly communicated. The findings underscore the importance of patient education, early symptom recognition, and the development of non-invasive, progression-halting therapies.

There is additional potential for using wearable and smartphone derived biomarkers as novel endpoints for trials. A compelling case was presented for incorporating real-world gait assessment as a functional endpoint in DRD. Building on earlier presentations that emphasized structural and cellular biomarkers, the session emphasized the limitations of traditional in-clinic measures and patient-reported outcomes, which often fail to capture real world experience of patients, requiring a long path from real world visual function loss, to clinically valid metrics, to therapies that improve these clinical metrics back to real world vision improvements. Such (passively generated) biomarkers allow bypassing this side path and go directly from real world dysfunction to real world visual function outcome improvements. There is an important role for industry for creating access to such biomarkers through validation and integration with other outcome related biomarkers. Wearable devices, particularly inertial measurement units, were identified as promising tools to quantify daily function by tracking sleep, activity, and walking patterns outside the clinic. Evidence from glaucoma research has demonstrated that visual field loss and contrast sensitivity impair gait in measurable ways, especially under changing lighting conditions (Bicket et al., 2020). These deficits appear even in early disease and are not always reflected in patient self-assessments. Recent studies comparing in-clinic and at-home gait metrics have revealed greater variability in real-world settings, underscoring the need for context-aware endpoints. Applying this model to DRD, gait, often referred to as the "sixth vital sign", could serve as a sensitive, patient-centered measure of functional impairment, although further validation in DRD populations is needed. A new study supported by the Michigan Diabetes Research Center, is underway to evaluate gait responses in patients with diabetes, accounting for peripheral and autonomic neuropathy. The session concluded by emphasizing the regulatory relevance of such endpoints, noting that real-world functional measures may be key to demonstrating meaningful therapeutic benefit in future DRD trials.

A panel discussion reached consensus on the growing importance of functional endpoints in DRD, with a particular focus on gait assessment as a sensitive and patient-centered measure. Gait changes, especially those influenced by lighting conditions and contrast sensitivity, were recognized as early indicators of neurovascular dysfunction, often preceding more overt structural damage. The panel agreed that wearable technologies, including commercially available devices such as smart watches and rings, hold promise for capturing real-world mobility data, though further research is needed to determine which gait metrics are most clinically meaningful. There was broad alignment on the need to adapt clinical development strategies to incorporate emerging functional endpoints into later-stage protocols. These efforts reflect a shift toward more holistic trial designs, which aim to validate endpoints that better capture therapeutic impact from the patient's perspective. The

panel emphasized that integrating such measures is critical for demonstrating meaningful benefit beyond anatomical improvements. In closing, patient advocates reinforced the consensus around early detection and prevention, expressing optimism that functional endpoints - particularly those grounded in real-world experience - could reshape care pathways and improve outcomes for individuals living with DRD.

6. Translation to action

A strategic overview of the "DRD Cure Accelerator" highlighted its mission to transform DRD care through global consensus and regulatory alignment. The discussion emphasized the importance of centering the patient voice in every decision, noting that restoring vision and preserving independence must remain the core goals of innovation. While scientific breakthroughs are essential, they must be paired with regulatory approval and market adoption to achieve meaningful real-world impact. Key gaps in DRD medical product development were identified, including the absence of FDA-cleared tools for diagnosis, progression tracking, and treatment beyond laser photocoagulation. The lack of standardized endpoints and biomarkers has hindered trial design and slowed innovation. To address this limitation, the "DRD Cure Accelerator" will build consensus on clinically meaningful, scientifically sound surrogate and primary endpoints that can be translated into international standards and adopted by regulators worldwide. As a first step, CCOI is partnering with Natter, an AI-powered platform that enables large-scale, anonymous stakeholder engagement. Through rapid digital focus groups, Natter will gather insights from patients, clinicians, and innovators to identify highly relevant outcomes and stakeholder concerns. These findings were synthesized and presented at the MTM Vision Symposium on Curing Vision Loss from Diabetes in November, 2025, forming the foundation for structured consensus-building. The initiative reaffirms its commitment to eradicating DRD-related vision loss through collaboration, standardization, and patient-centered innovation.

In developing endpoints for DRD, key practical and ethical considerations were outlined, emphasizing that patient-centered outcomes must guide both scientific and regulatory efforts. Effective endpoints must meet core requirements; they must be verifiable, demonstrate patient benefit in some form, and directly reflect patient outcomes. However, in chronic diseases like DRD, primary endpoints often take years to validate, resulting in unacceptable delays and costs for innovation. Surrogate endpoints, which predict or correlate with clinical outcomes, offer a pathway to expedite trials. Currently FDA-accepted functional primary endpoints for retinal trials include visual acuity, perimetry, contrast sensitivity, and full-field stimulus threshold, while patient-focused measures such as the multi-luminance mobility test are gaining recognition. Patient-reported outcomes, though not yet accepted as primary metrics, are increasingly valued. Functional surrogate endpoints under evaluation include blood flow via laser speckle flowgraphy, electrophysiology (ERG), pupillometry, and color vision testing, while structural surrogates include fundus photograph biomarkers such as autofluorescence, and OCT-derived metrics such as central thickness and layer volume. Composite endpoints are also being explored to better capture disease complexity. A multidimensional framework has been proposed to stratify DRD into ischemic (ETDRS progression, electrophysiology), neurodegenerative (OCT RNFL, perimetry), and diabetic macular edema (visual acuity, OCT biomarkers) components. For advanced disease stages, composite measures such as MLMT and FST may offer more holistic assessment. An increased role of real world, wearable derived biomarkers and endpoints can be expected. By integrating such accepted and emerging endpoints, this approach aims to shorten trial timelines, improve therapeutic relevance, and accelerate access to effective treatments, reinforcing the imperative to align innovation with meaningful patient impact.

The "Home as a Health Care Hub" initiative launched by the FDA's Center for Devices and Radiological Health, aims to advance person-centered medical device innovation by shifting care delivery closer to patients, particularly in the context of chronic disease, aging populations, and strained healthcare systems (Zhang et al., 2010). The initiative highlights the role of MedTech solutions, such as screening tools, continuous glucose monitors, and automated insulin delivery systems, in supporting early intervention and preventing disease progression. To support innovation in home-based care, the FDA introduced the Idea Lab, a suite of resources designed to help developers visualize how devices integrate into patients' daily lives (van Dijk et al., 2011). These include detailed patient personas, design prompts, and Lilypad™, a virtual reality experience that immerses users in realistic home environments to simulate lived experiences. Usability considerations include varying levels of visual function, including contrast sensitivity deficits common in DRD. By fostering empathy-driven design and leveraging real-world insights, the initiative seeks to accelerate the creation of safe, effective, and accessible devices that meet patients where they are.

A panel discussion explored practical strategies for accelerating endpoint development in DRD, with a focus on patient-centered innovation and real-world usability. Panelists emphasized the adaptability of the Lilypad virtual-reality platform, noting its potential to simulate progressive visual impairment and integrate physical space with virtual environments to better inform device design. Developers were encouraged to use open-source tools to create immersive experiences that reflect the evolving needs of patients with DRD. The importance of remote data acquisition, particularly for underserved populations with limited access to eye care, was also highlighted, along with the need for home-based diagnostics that are both clinically meaningful and reimbursable. Gait analysis was identified as a promising early functional metric that could be captured without modifying existing platforms. The panel discussed the need for validated tools to assess endpoints, and underscored the value of formal patient preference studies in shaping regulatory decisions and accelerating risk-benefit evaluations. The multidisciplinary panel reached consensus on the need for a coordinated, multi-stakeholder approach to endpoint development and validation that integrates clinical relevance, usability, and patient priorities.

7. Bridging precision phenotyping and discovery science

The consensus-building efforts of the MTM Vision Initiative and the CCOI "DRD Cure Accelerator" Working Groups provide a necessary framework for advancing patient-centric discovery science. By tracing the evolution of DRD pathogenesis and standardizing high-resolution imaging metrics, this initiative facilitates the identification of specific molecular pathogenic pathways driving disease in individual patients (Antonetti et al., 2021; Sun et al., 2021). This granular approach recognizes that DRD affects the entire retinal neurovascular unit, allowing the research community to transition from broad clinical staging to exact therapeutic targeting (Gardner et al., 2017; Jampol et al., 2021). Such precision in phenotyping is essential for drug re-purposing and the acceleration of clinical trials, as it enables the matching of existing molecular inhibitors to specific structural and functional phenotypes.

8. Concluding remarks

The virtual workshop's discussions concluded with powerful reflections from Drs. Thomas W. Gardner and S. Robert Levine, who traced MTM Vision's journey from the 2018 Restoring Vision Moonshot to the present launch of the DRD Cure Accelerator. Emphasizing the shift from discovery to action, they celebrated the growing momentum behind patient-centered innovation and collaborative progress. Dr. Gardner called for continued synergy across disciplines and a commitment to confronting the unknowns, while Dr. Levine invoked the spirit of President John J. Kennedy's moonshot, reminding the community that curing vision loss from diabetes is a challenge worth pursuing not because it is easy, but because it is necessary. With passion, discipline, and collaboration, the initiative moves forward with clarity and resolve. This workshop is an important next step on reaching international

consensus by integrating scientific, clinical, and patient-centered perspectives to accelerate the development of robust endpoints that align with regulatory expectations and incorporate patient preferences that can transform DRD diagnosis, monitoring, and treatment to reduce diabetes-related vision loss worldwide.

CRediT authorship contribution statement

Konstantina Sampani: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Ward Fickweiler:** Writing – review & editing. **Dorene S. Markel:** Project administration. **Latrice Faulkner:** Writing – review & editing, Project administration. **Stela Vujosevic:** Writing – review & editing. **Tunde Peto:** Writing – review & editing. **Olivia Meyerhoffer:** Writing – review & editing. **Malvina Eydelman:** Writing – review & editing. **S. Robert Levine:** Writing – review & editing, Supervision, Conceptualization. **Jennifer K. Sun:** Writing – review & editing, Supervision, Conceptualization. **Thomas W. Gardner:** Writing – review & editing, Supervision, Conceptualization. **Michael D. Abramoff:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Competing interests

K.S., W.F., D.S.M., and L.F., T.P. declare no competing interests.

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O.M. employed by Boehringer Ingelheim.

M.E. serves as co-founder of Salution Health; serves as president and CEO of Salution Nexus.

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M.D.A. reports patents and patent applications assigned to the University of Iowa and Digital Diagnostics relevant to the subject. He serves as Director, Consultant, and shareholder of Digital Diagnostics Inc.; Executive Secretary of the Healthcare AI Coalition; Treasurer of the Collaborative Community on Ophthalmic Imaging; and is a member of both the American Academy of Ophthalmology AI Committee and the AMA's AI Workgroup for the Digital Medicine Payment Advisory Group.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preteyeres.2026.101485.

Data availability

No datasets were generated or analyzed during the current study.

References

Akbarinia, A., Morgenstern, Y., Gegenfurtner, K.R., 2023. Contrast sensitivity function in deep networks. Neural Netw. 164, 228–244.
Albertos-Arranz, H., et al., 2025. Neuronal degeneration and glial activation in the absence of vascular changes in human retinas of patients with diabetes. Investig. Ophthalmol. Vis. Sci. 66 (3), 53.
Antonetti, D.A., Silva, P.S., Stitt, A.W., 2021. Current understanding of the molecular and cellular pathology of diabetic retinopathy. Nat. Rev. Endocrinol. 17 (4), 195–206.
Authie, C.N., et al., 2024. Development and validation of a novel mobility test for rod-cone dystrophies: from reality to virtual reality. Am. J. Ophthalmol. 258, 43–54.
Barber, A.J., et al., 1998. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J. Clin. Investig. 102 (4), 783–791.
Bhatwadekar, A.D., et al., 2017. Hematopoietic stem/progenitor involvement in retinal microvascular repair during diabetes: implications for bone marrow rejuvenation. Vis. Res. 139, 211–220.
Bicket, A.K., et al., 2020. Gait in elderly glaucoma: impact of lighting conditions, changes in lighting, and fear of falling. Transl. Vis. Sci. Technol. 9 (13), 23.
Bloodworth Jr., J.M., 1962. Diabetic retinopathy. Diabetes 11, 1–22.
Carrasco, E., et al., 2007. Lower somatostatin expression is an early event in diabetic retinopathy and is associated with retinal neurodegeneration. Diabetes Care 30 (11), 2902–2908.
Chakravarthy, U., et al., 2025. Effect of Faricimab versus aflibercept on hyperreflective foci in patients with diabetic macular edema from the YOSEMITE/RHINE trials. Ophthalmol. Sci. 5 (5), 100798.
Choi, H., et al., 2024. Quantitative contrast sensitivity function and the effect of aging in healthy adult eyes: a normative database. Ophthal. Surg. Laser. Imag. Retina 55 (4), 212–219.
Das, R., et al., 2018. Disorganization of inner retina and outer retinal morphology in diabetic macular edema. JAMA Ophthalmol. 136 (2), 202–208.
Domalpally, A., et al., 2024. Data harmonization, standardization, and collaboration for Diabetic Retinal Disease (DRD) research: report from the 2024 mary Tyler Moore Vision Initiative workshop on data. Transl. Vis. Sci. Technol. 13 (10), 4.
Eleftheriou, C.G., Ivanova, E., Sagdullaev, B.T., 2020. Of neurons and pericytes: the neuro-vascular approach to diabetic retinopathy. Vis. Neurosci. 37, E005.
Fickweiler, W., et al., 2025. Advancing toward a world without vision loss from diabetes: insights from the Mary Tyler Moore vision Initiative symposium 2024 on curing vision loss from diabetes. Transl. Vis. Sci. Technol. 14 (5), 12.
Fong, D.S., et al., 2003. Diabetic retinopathy. Diabetes Care 26 (1), 226–229.
Gardner, T.W., Davila, J.R., 2017. The neurovascular unit and the pathophysiologic basis of diabetic retinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 255 (1), 1–6.
Goulet, L., Farivar, R., 2025. NeuroCSF: an fMRI method to measure contrast sensitivity function in human visual cortex. J. Neurophysiol. 133 (6), 1699–1716.
Grimes, W.N., et al., 2025. Layer-specific anatomical and physiological features of the retina's neurovascular unit. Curr. Biol. 35 (1), 109–120 e4.
Guo, Y., et al., 2018. MEDnet, a neural network for automated detection of avascular area in OCT angiography. Biomed. Opt. Express 9 (11), 5147–5158.
Guo, Y., et al., 2019. Development and validation of a deep learning algorithm for distinguishing the nonperfusion area from signal reduction artifacts on OCT angiography. Biomed. Opt. Express 10 (7), 3257–3268.
Ha, S.K., et al., 2025. Structure-function associations between quantitative contrast sensitivity function and peripapillary optical coherence tomography angiography in diabetic retinopathy. Investig. Ophthalmol. Vis. Sci. 66 (4), 69.
Hein, M., et al., 2024. Interpericyte tunneling nanotubes are nonuniformly distributed in the human macula. Investig. Ophthalmol. Vis. Sci. 65 (13), 28.
Hendricks, L.E., Hendricks, R.T., 1998. Greatest fears of type 1 and type 2 patients about having diabetes: implications for diabetes educators. Diabetes Educat. 24 (2), 168–173.
Hormel, T.T., et al., 2025. Artificial intelligence versus rules-based approach for segmenting NonPerfusion area in a DRCR retina network optical coherence tomography angiography dataset. Investig. Ophthalmol. Vis. Sci. 66 (3), 22.
Jampol, L.M., Tadayoni, R., Ip, M., 2021. Need for a new classification of diabetic retinopathy. Retina 41 (3), 459–460.
Jonnal, R.S., et al., 2014. The cellular origins of the outer retinal bands in optical coherence tomography images. Investig. Ophthalmol. Vis. Sci. 55 (12), 7904–7918.
Kerwin, T., et al., 2025. Mesopic and glare driving performance in a driving simulator. Traffic Inj. Prev. 1–7.
Kessler, L.J., et al., 2021. Ellipsoid zone integrity and visual acuity changes during diabetic macular Edema therapy: a longitudinal study. J. Diabetes Res. 2021, 8117650.
Kropp, M., et al., 2023. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications-risks and mitigation. EPMA J. 14 (1), 21–42.
Levine, S.R., et al., 2022. It is time for a moonshot to find "Cures" for diabetic retinal disease. Prog. Retin. Eye Res. 90, 101051.
Levine, S.R., et al., 2023. Report from the 2022 mary Tyler Moore Vision Initiative diabetic retinal disease clinical endpoints workshop. Transl. Vis. Sci. Technol. 12 (11), 33.
Li Calzi, S., et al., 2010. Endothelial progenitor dysfunction in the pathogenesis of diabetic retinopathy: treatment concept to correct diabetes-associated deficits. EPMA J. 1 (1), 88–100.

Liang, G.B., et al., 2023. Single-shot OCT and OCT angiography for slab-specific detection of diabetic retinopathy. Biomed. Opt. Express 14 (11), 5682–5695.
Lim, J.I., et al., 2025. Diabetic retinopathy preferred practice pattern®. Ophthalmology 132 (4), P75–P162.
Llorian-Salvador, M., et al., 2024. Glial cell alterations in diabetes-induced neurodegeneration. Cell. Mol. Life Sci. 81 (1), 47.
Lynch, S.K., Abramoff, M.D., 2017. Diabetic retinopathy is a neurodegenerative disorder. Vis. Res. 139, 101–107.
McAnany, J.J., Park, J.C., 2018. Temporal frequency abnormalities in early-stage diabetic retinopathy assessed by electroretinography. Investig. Ophthalmol. Vis. Sci. 59 (12), 4871–4879.
McAnany, J.J., et al., 2019. Amplitude loss of the high-frequency flicker electroretinogram in early diabetic retinopathy. Retina 39 (10), 2032–2039.
Midena, E., et al., 2023. The disorganization of retinal inner layers is correlated to muller cells impairment in diabetic macular edema: an imaging and omics study. Int. J. Mol. Sci. 24 (11).
Midena, G., et al., 2024. Hyperreflective choroidal foci in diabetic eyes with and without macular edema: novel insights on diabetic choroidopathy. Exp. Eye Res. 247, 110020.
Miller, J.M.L., et al., 2025. Dissecting the biological complexity of age-related macular degeneration: is it one disease, multiple separate diseases, or a spectrum? Exp. Eye Res. 254, 110304.
Muftuoglu, I.K., Unsal, E., Ozturker, Z.K., 2017. Restoration of photoreceptors in eyes with diabetic macular edema. Eur. J. Ophthalmol. 27 (5), 585–590.
Munk, M.R., et al., 2022. The role of intravitreal corticosteroids in the treatment of DME: predictive OCT biomarkers. Int. J. Mol. Sci. 23 (14).
Owens, D.R., et al., 2025. IDF diabetes atlas: a worldwide review of studies utilizing retinal photography to screen for diabetic retinopathy from 2017 to 2024 inclusive. Diabetes Res. Clin. Pract. 226, 112346.
Park, S.S., et al., 2017. Advances in bone marrow stem cell therapy for retinal dysfunction. Prog. Retin. Eye Res. 56, 148–165.
Rai, B.B., Maddess, T., Nolan, C.J., 2025. Functional diabetic retinopathy: a new concept to improve management of diabetic retinal diseases. Surv. Ophthalmol. 70 (2), 232–240.
Roska, B., Sahel, J.A., 2018. Restoring vision. Nature 557 (7705), 359–367.
Russell, S., et al., 2017. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet 390 (10097), 849–860.
Sahel, J.A., Bennett, J., Roska, B., 2019. Depicting brighter possibilities for treating blindness. Sci. Transl. Med. 11 (494).
Santos, A.R., et al., 2017. Functional and structural findings of neurodegeneration in early stages of diabetic retinopathy: cross-sectional analyses of baseline data of the EUROCONDOR project. Diabetes 66 (9), 2503–2510.
Scarinci, F., et al., 2015. Association of diabetic macular nonperfusion with outer retinal disruption on optical coherence tomography. JAMA Ophthalmol. 133 (9), 1036–1044.
Silva, P.S., et al., 2022. Assessment of fluorescein angiography nonperfusion in eyes with diabetic retinopathy using ultrawide field retinal imaging. Retina 42 (7), 1302–1310.
Silva, P.S., et al., 2025. Retinal non-perfusion and incident vision threatening complications: exploratory DRCR protocol AA analyses. Investig. Ophthalmol. Vis. Sci. 66 (8), 331.
Simo, R., Hernandez, C., European, R., 2014. Consortium for the early treatment of diabetic, neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol. Metabol. 25 (1), 23–33.
Simo, R., et al., 2019. Effects of topically administered neuroprotective drugs in early stages of diabetic retinopathy: results of the EUROCONDOR clinical trial. Diabetes 68 (2), 457–463.
Singh, R., et al., 2023. Deep learning algorithm detects presence of disorganization of retinal inner layers (DRIL)-an early imaging biomarker in diabetic retinopathy. Transl. Vis. Sci. Technol. 12 (7), 6.
Sohn, E.H., et al., 2016. Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. Proc. Natl. Acad. Sci. U. S. A. 113 (19), E2655–E2664.
Solomon, S.D., et al., 2017. Diabetic retinopathy: a position statement by the American diabetes association. Diabetes Care 40 (3), 412–418.
Stino, H., et al., 2024. Intereye microvascular differences in patients with same-stage diabetic retinopathy revealed by OCTA. Investig. Ophthalmol. Vis. Sci. 65 (6), 11.
Sun, J.K., et al., 2014. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 132 (11), 1309–1316.
Sun, J.K., et al., 2015. Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes 64 (7), 2560–2570.
Sun, J.K., et al., 2021. Updating the staging system for diabetic retinal disease. Ophthalmology 128 (4), 490–493.
Szeto, S.K., et al., 2024. Optical coherence tomography in the management of diabetic macular oedema. Prog. Retin. Eye Res. 98, 101220.
Tang, Z., et al., 2025. Relationship of OCT-based diabetic retinal neurodegeneration to the development and progression of diabetic retinopathy: a cohort study. Investig. Ophthalmol. Vis. Sci. 66 (2), 32.
Usui, Y., 2020. Elucidation of pathophysiology and novel treatment for diabetic macular edema derived from the concept of neurovascular unit. JMA J. 3 (3), 201–207.
van Dijk, H.W., et al., 2011. Association of visual function and ganglion cell layer thickness in patients with diabetes mellitus type 1 and no or minimal diabetic retinopathy. Vis. Res. 51 (2), 224–228.
Vujosevic, S., et al., 2020. Diabetic macular edema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. Acta Diabetol. 57 (3), 287–296.
Vujosevic, S., et al., 2024. Severity of disorganization of retinal layers and visual function impairment in diabetic retinopathy. Ophthalmol. Retina 8 (9), 880–888.
Vujosevic, S., et al., 2025. Clinical trial simulation in diabetic retinopathy: insights from patients and site staff. Ophthalmol. Ther. 14 (8), 1773–1787.
Xiong, H., et al., 2023. Deep learning-based signal-independent assessment of macular avascular area on 6x6 mm optical coherence tomography angiogram in diabetic retinopathy: a comparison to instrument-embedded software. Br. J. Ophthalmol. 107 (1), 84–89.
Yamaguchi, M., et al., 2022. Identifying hyperreflective foci in diabetic retinopathy via VEGF-induced local self-renewal of CX3CR1+ vitreous resident macrophages. Diabetes 71 (12), 2685–2701.
Zhang, X., et al., 2010. Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA 304 (6), 649–656.
Zhang, Y., et al., 2023. Single-cell transcriptomics-based multidisease analysis revealing the molecular dynamics of retinal neurovascular units under inflammatory and hypoxic conditions. Exp. Neurol. 362, 114345.
Zur, D., et al., 2020. Disorganization of retinal inner layers as a biomarker in patients with diabetic macular oedema treated with dexamethasone implant. Acta Ophthalmol. 98 (2), e217–e223.