

# Advances in diagnosing and treating diabetic retinopathy

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## Abstract

Diabetic retinopathy has traditionally been defined as a microvascular complication of diabetes mellitus; however, advances in retinal imaging, digital technologies and mechanistic insights have challenged this narrow view. Increasing evidence indicates that neuronal and glial dysfunction and degeneration, neuroinflammation, capillary non-perfusion and metabolic dysregulation can occur early in the disease process and can precede or coexist with clinically apparent vascular abnormalities. These insights support the emerging concept of diabetic retinal disease (DRD), which encompasses the full spectrum of diabetes mellitus-related retinal pathology, with or without visible microvascular lesions. In this Review, we summarize the evolution of disease classification and advances made within the past 10 years in diagnostic imaging that enable more precise phenotyping and risk stratification of DRD. We also present a framework for a digitally enabled care pathway spanning screening, diagnosis, treatment and post-treatment follow-up. Finally, we discuss current therapies alongside emerging preventive and personalized treatment strategies that target both vascular and neuroretinal components across the full DRD disease continuum.

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## Key points

- Diabetic retinopathy involves neurovascular dysfunction beyond visible microvascular lesions.
- Multimodal imaging enables refined phenotyping and risk stratification so that patients can be classified on the basis of more precise disease subtypes, improving prediction of disease progression, treatment response and clinical outcomes.
- Digital technologies support scalable, patient-centred care pathways that focus on earlier intervention, more personalized management and better allocation of health-care resources.
- Emerging therapies target vascular and neurovascular mechanisms, aiming to reduce retinal damage, preserve vision, slow disease progression and improve long-term outcomes.
- Preventive strategies such as early screening, glycaemic and blood pressure control, timely treatment, patient education and regular monitoring remain central to reducing vision loss.

## Introduction

Diabetic retinopathy is a leading cause of preventable vision impairment and blindness among the working-age population<sup>1</sup>. By 2045, the number of individuals affected by diabetic retinopathy is projected to reach about 161 million worldwide, including 45 million with vision-threatening diabetic retinopathy (VTDR) and 29 million with clinically significant diabetic macular oedema (DMO)<sup>2</sup>. Beyond visual loss and substantial emotional and psychological burden for patients and their families, the long-term health-care costs are escalating<sup>3</sup>. These trends underscore the urgent need for scalable strategies to identify individuals at risk, enable early diagnosis, prevent progression to VTDR and deliver timely treatment to preserve vision<sup>4,5</sup>. In parallel, there is a critical need to develop affordable and durable therapies to mitigate the growing global burden of diabetes mellitus-related visual impairment<sup>4</sup>.

Historically, the diagnosis and staging of diabetic retinopathy have been based on the presence and progression of visible microvascular abnormalities<sup>6,7</sup>. The diabetic retinopathy severity score remains the reference standard, with well-established prognostic value and validation in natural history studies and clinical trials<sup>8,9</sup>. However, accumulating evidence indicates that diabetes mellitus affects all components of the retinal neurovascular unit (NVU), resulting in functional impairment that can precede overt microvascular disease and range from subclinical changes to irreversible vision loss<sup>10,11</sup>. These observations are supported by structural and functional assessments using advanced retinal imaging modalities<sup>12,13</sup>. The NVU comprises retinal vascular cells, macroglia, microglia and neurons, and has a central role in maintaining the integrity of the inner blood–retina barrier<sup>10,14</sup>.

Recognition of this multilevel retinal involvement has led to the emerging concept of diabetic retinal disease (DRD), which encompasses microvascular dysfunction, neurodegeneration and neuroinflammation<sup>15</sup>. As the term DRD is not yet universally adopted, this Review focuses on diabetic retinopathy while incorporating insights that extend beyond a purely vascular framework. Others in the field have also acknowledged the need to approach diabetic retinopathy in a way that takes the entire NVU into account<sup>16</sup>. Although screening

and diagnosis continue to rely largely on colour fundus photography, management of VTDR in resource-rich settings has increasingly transitioned to multimodal retinal imaging<sup>17</sup>. Key technological advances include the shift from invasive dye-based diagnostics to non-invasive imaging, layer-specific assessment of retinal structure, evaluation of the far retinal periphery and integration of artificial intelligence (AI) to enable automated analysis for screening and management of DMO<sup>17–21</sup>.

This Review summarizes advances made within the past 10 years in retinal imaging, including optical coherence tomography (OCT), OCT angiography (OCT-A), ultrawide-field imaging (UWFI) and adaptive optics. These technologies have refined our understanding of pre-clinical retinal changes, diabetic macular ischaemia and the interplay between neurodegeneration, neuroinflammation and impaired retinal fluid dynamics. They have also facilitated development of imaging biomarkers to predict treatment response and support personalized care. Collectively, these advances highlight the need to update existing diabetic retinopathy classification and staging systems<sup>22</sup>.

## Multimodal imaging for evaluation of diabetic retinopathy

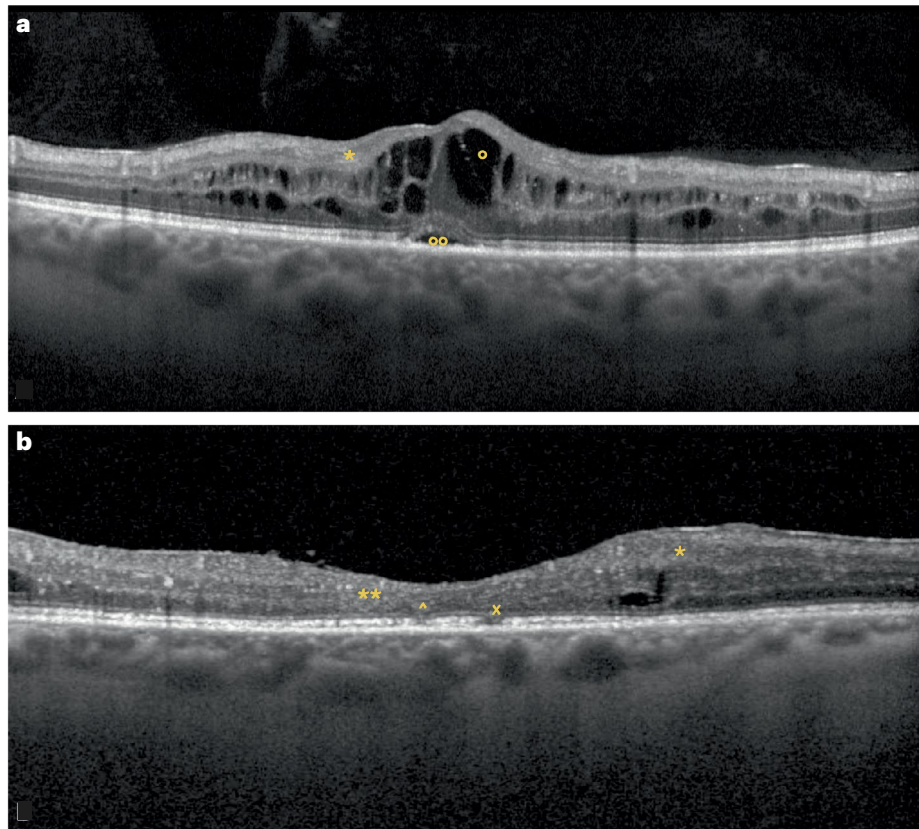
### OCT

Multimodal imaging has largely replaced colour fundus photography and fluorescein angiography as the foundation for diagnosis and management of diabetic retinopathy<sup>20</sup>. While OCT is now indispensable, OCT-A is emerging as a complementary non-invasive modality<sup>23,24</sup>. Together, these techniques facilitate assessment of both neuronal and vascular integrity in patients with diabetes mellitus. OCT provides high-resolution cross-sectional and three-dimensional images of retinal structure, allowing simultaneous qualitative and quantitative evaluation, whereas OCT-A maps retinal microvascular blood flow without the need for contrast agents. OCT-A enables three-dimensional delineation of the superficial and deep retinal capillary networks supplying the inner retinal neurons, as well as the choriocapillaris and deeper choroidal vessels that provide metabolic support to the outer retina and photoreceptors.

Advances include high-resolution OCT systems that achieve axial (depth) resolutions of  $\sim 1\text{--}3\ \mu\text{m}$  and lateral (transverse) resolutions of  $\sim 5\text{--}10\ \mu\text{m}$ , enabling near-cellular visualization of retinal neurons and microvasculature<sup>25</sup>. In parallel, AI, particularly deep learning, has been integrated into OCT analysis to allow automated segmentation of retinal layers, quantification of tissue thickness and detection of structural abnormalities such as fluid and layer disorganization<sup>26</sup>. Several AI-enabled OCT tools now demonstrate performance similar to that of expert graders while reducing analysis time and inter-observer variability<sup>21,27</sup>.

Clinically, changes in the 1-mm central subfield thickness (CST) of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid on OCT scans remain widely used for diagnosing and monitoring DMO and assessing treatment response, as CST is more sensitive than slit-lamp biomicroscopy or colour fundus photography<sup>18</sup>. However, CST correlates only moderately with visual acuity because it reflects retinal thickness alone and does not capture photoreceptor integrity, retinal ischaemia or neuroglial dysfunction<sup>28,29</sup>.

Consequently, OCT-derived biomarkers beyond retinal thickness have been proposed to better link structure with function (Fig. 1). Layer-specific markers, including disorganization of the inner retinal layers (DRIL), photoreceptor integrity and fluid compartmentalization, provide more biologically meaningful correlates of visual acuity and treatment outcomes than CST alone<sup>23</sup>. DRIL, which is defined as loss



**Fig. 1 | Optical coherence tomography scans showing key biomarkers of diabetic retinopathy.**  
**a**, Optical coherence tomography (OCT) scan showing centre-involving diabetic macular oedema and associated biomarkers: intraretinal fluid (°); subfoveal neuroretinal detachment (°°) and disorganization of retinal inner layers (\*). **b**, OCT scan showing neurodegenerative biomarkers: disorganization of retinal outer layers (\*\*); ellipsoid zone loss (x), external limiting membrane loss (△) and disorganization of retinal inner layers (\*).

of clear boundaries between inner retinal layers up to the outer plexiform layer, is among the most robust OCT predictors of visual acuity in diabetic retinopathy with or without DMO<sup>30,31</sup>. It probably reflects neuronal and synaptic dysfunction and predicts poor visual recovery even when CST normalizes. Enlargement of DRIL has therefore been proposed as a prognostic and predictive biomarker following DMO resolution<sup>32</sup>. DRIL is closely associated with diabetic macular ischaemia, implicating retinal hypoxia in its pathogenesis, and correlates with functional impairment measured by microperimetry and best corrected visual acuity<sup>33,34</sup>.

Outer retinal integrity is also strongly associated with visual outcomes. Preservation of the ellipsoid zone, which reflects photoreceptor health, and integrity of the external limiting membrane, which represents Müller cell–photoreceptor interactions, predict better visual acuity and treatment response<sup>23,29</sup>. As a result, a novel concept of disorganization of outer retinal layers has been introduced as a prognostic indicator of poor vision. More eyes have DRIL than disorganization of the outer retinal layers, which substantiates the claim that inner retinal disorganization precedes outer retinal changes<sup>32</sup>. Histological and imaging studies have suggested a hierarchy of neurodegenerative changes, whereby inner retinal thinning can precede overt microvascular pathology and occur before measurable visual acuity loss<sup>10</sup>.

Taking fluid compartment morphology into account further refines our understanding of structure–function relationships. Intraretinal fluid is strongly associated with poor vision and reflects inner blood–retina barrier breakdown and Müller cell dysfunction<sup>23</sup>. Subretinal fluid-dominant DMO might represent a distinct phenotype driven by changes in the vasculature and the retinal pigment epithelium

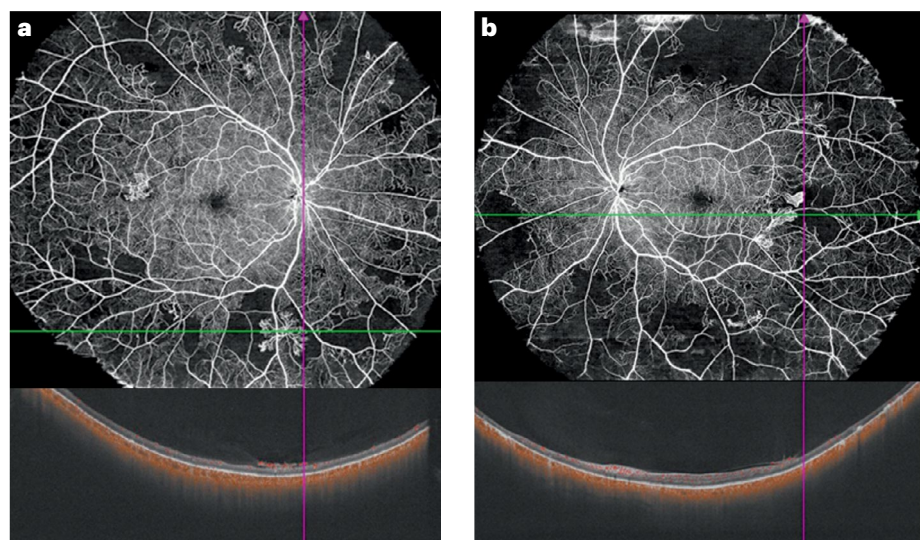
with some preservation of inner retinal neurons<sup>35</sup>. Although some inner retinal neurons are preserved, DMO can also be associated with persistent subretinal neurosensory detachment, which is associated with impaired retinal sensitivity<sup>35</sup>.

Inflammation also contributes to diabetic retinopathy and DMO pathophysiology, as evidenced by vitreous cytokine profiles and retinal histology<sup>36–38</sup>. Hyperreflective foci (HRF) on OCT are seen as small punctate lesions with reflectivity similar to the nerve fibre layer<sup>39,40</sup>. They are thought to represent activated microglia, lipid-laden macrophages or inflammatory debris<sup>39</sup>. HRF might therefore indicate neuroinflammation or neurodegeneration, although reports on their predictive value for treatment response remain inconsistent<sup>41,42</sup>. Supporting an inflammatory phenotype, subretinal detachment is associated with higher vitreous levels of IL-6 and correlates with increased HRF burden<sup>43,44</sup>.

## OCT angiography

The retina has a layered vascular architecture that reflects the metabolic demands of distinct neuronal populations. Traditional angiography collapses this complexity into two dimensions, whereas OCT-A enables non-invasive, depth-resolved visualization of individual capillary plexuses, including superficial, intermediate, deep and peripapillary networks. This technology allows direct assessment of layer-specific neurovascular dysfunction<sup>44</sup>.

In diabetic retinopathy, OCT-A has been applied across disease stages to assess macular and peripapillary microvasculature. It enables detailed characterization of the foveal avascular zone, perifoveal capillary disruption, retinal perfusion and non-perfusion metrics, choriocapillaris flow voids, differentiation between neovascularization



**Fig. 2 | Widefield optical coherence tomography angiography (26 × 21 mm) of the right and left eye of a patient with corresponding OCT scans.** **a**, The new vessels in the right eye at the intersection of the vertical (crimson) and horizontal (green) lines on optical coherence tomography (OCT) angiography are shown cross-sectionally on the OCT image (bottom panel) as red signals attached to the vitreous scaffold. **b**, In the left eye, the area of retinal non-perfusion highlighted at the intersection of the vertical (crimson) and horizontal (green) lines corresponds to the area of thinning of the inner retina on the OCT image (bottom panel).

and intraretinal microvascular abnormalities, and visualization of microaneurysms within the deep capillary plexus<sup>45</sup> (Fig. 2).

Importantly, OCT-A provides prognostic information beyond structural imaging<sup>24,46,47</sup>. Capillary-level changes are often more sensitive indicators of disease progression than alterations in larger vessels<sup>46</sup>. Diabetic macular ischaemia identified on OCT-A predicts diabetic retinopathy progression, DMO development and visual acuity decline<sup>48</sup>. Vessel density and perfusion metrics from intermediate and deep capillary plexuses appear more predictive of clinically significant outcomes than superficial plexus parameters, and OCT-A measures are increasingly incorporated as end points in clinical trials<sup>49</sup>.

Despite these advantages, challenges remain, including lack of standardization across devices, motion and projection artefacts, and limited availability of longitudinal datasets<sup>50</sup>. Notably, macular OCT-A perfusion metrics correlate with peripheral non-perfusion on UWFI, suggesting a potential role for measuring perfusion using OCT-A as a non-invasive, surrogate test for peripheral ischaemia, particularly in patients unable to undergo fluorescein angiography<sup>51</sup>.

## UWFI

UWFI extends assessment beyond the posterior pole to the mid-retinal periphery and far retinal periphery. Predominantly peripheral retinal lesions, defined as lesions with >50% distribution outside standard seven-field ETDRS regions, occur in 30–40% of eyes and are associated with increased diabetic retinopathy severity and progression<sup>52</sup> (Fig. 3). The presence of predominantly peripheral retinal lesions and peripheral retinal non-perfusion confers a substantially increased risk of diabetic retinopathy progression and conversion to proliferative diabetic retinopathy (PDR) over 4 years<sup>53</sup>.

Diabetic retinopathy severity grading using ultrawide-field colour fundus photography shows moderate to substantial agreement with standard ETDRS grading within overlapping regions and has demonstrated similar outcomes in analyses from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study, supporting its use in longitudinal studies<sup>54</sup>. Approximately 70% of retinal non-perfusion occurs outside the posterior pole, and ultrawide-field fluorescein angiography captures peripheral ischaemia, which is strongly associated with diabetic retinopathy

worsening, better than does ultrawide-field colour fundus photography. Consequently, UWFI–fluorescein angiography has been proposed as a component of future diabetic retinopathy staging systems, although the requirement for intravenous dye remains a limitation<sup>20</sup>.

## Adaptive optics

Adaptive optics retinal imaging systems achieve a lateral resolution of approximately 2–3  $\mu\text{m}$ , compared with ~10–15  $\mu\text{m}$  for conventional fundus imaging<sup>55</sup>. The axial resolution depends on the underlying modality, such as adaptive optics with OCT and adaptive optics with scanning laser ophthalmoscopy (AO-SLO) but is typically 3–5  $\mu\text{m}$ , allowing near-cellular-level visualization, which enables visualization of individual photoreceptors, capillaries and microaneurysms<sup>56</sup>. AO-SLO has demonstrated early photoreceptor loss and altered capillary flow even before clinically apparent diabetic retinopathy<sup>56–58</sup>. The observed early increase in retinal blood flow in eyes of patients with diabetes mellitus could represent a compensatory mechanism in response to subclinical retinal ischaemia or could be driven by the release of vasoactive mediators<sup>59</sup>. Regions of capillary non-perfusion identified with AO-SLO show notable alterations in photoreceptor morphology and density compared with areas of intact capillary perfusion, even at early stages of disease involving both the retina and choroid. These microstructural changes are associated with a measurable reduction in retinal sensitivity, reflecting NVU dysfunction and early neurodegeneration based on studies of low to moderate quality<sup>60</sup>. Overall, AO-SLO is best regarded as a research imaging modality with strong biological plausibility but insufficient evidence at present to support routine clinical use for quantifying neurodegeneration in diabetic retinopathy or DMO<sup>17</sup>.

## Electrophysiology

Electrophysiological testing provides objective functional assessment of retinal neurons that complements structural imaging. In diabetes mellitus, abnormalities in oscillatory potentials, b-wave amplitude and implicit times often precede visible retinopathy, suggesting early neuronal dysfunction<sup>61</sup>. Multifocal electroretinography (mfERG) and pattern electroretinography detect localized functional deficits that predict future lesion development<sup>62,63</sup>.

## Review article

Traditionally, electrodiagnostics requires specialized equipment and is time-consuming in routine clinical practice. However, emerging advances include portable and faster electrophysiology devices and integration with AI for automated interpretation. Electrophysiological metrics are also being used as functional biomarkers in clinical trials.

A comprehensive 2014 review reframed diabetic retinopathy as a neurodegenerative disease by synthesizing human, animal, electrophysiological and imaging evidence, and explicitly argues that neuroretinal dysfunction precedes microvascular pathology<sup>64</sup>. The article provides strong justification for neuroprotective and experimental medicine



**Fig. 3 | Ultrawide field fundus colour photograph and corresponding ultrawide field fundus angiography.** The ultrawide field fundus (UWFF) photograph of the left eye with proliferative diabetic retinopathy (panel **a**) shows new vessels on the disc and elsewhere, and the corresponding UWFF angiography image (panel **b**) shows extensive areas of predominantly peripheral retinal non-perfusion.



approaches targeting neurodegeneration<sup>64</sup>. In fact, the EUROCONDOR trial provided compelling proof-of-concept that retinal neurodegeneration is an early and modifiable component of diabetic retinopathy. In the EUROCONDOR trial, using mfERG as a functional end point, topical neuroprotective agents stabilized or improved retinal neuronal function in patients with early disease, whereas placebo-treated eyes showed progressive functional decline, despite minimal vascular change. These findings establish mfERG readings as a sensitive surrogate biomarker for neuroprotection and validate experimental medicine approaches targeting the neuroretinal component of diabetic retinopathy<sup>65</sup>.

## Digital innovations from screening to patient-centric health care

The increasing prevalence of diabetes mellitus, combined with a growing global shortage of health-care professionals, has led to increased use of digital technologies and telehealth systems<sup>66</sup>. These technologies and systems can expand access to care, lessen the burden on people with diabetes mellitus, improve efficiencies and reduce the unsustainable financial liability on health systems and payers<sup>66</sup>. The synergistic services utilizing teleophthalmology, digital and technological innovations and AI have the potential for large-scale implementation at fairly low cost, if appropriately integrated into clinical practice, to tackle the challenges of health coverage and sustainability<sup>5</sup>. Multimodal imaging could also serve as a core facet of modern retinal examination, as it is well suited to telehealth initiatives.

Conversely, it can be argued that the current implementation of digital technologies in clinical care is associated with high costs and might not adequately reach the populations most in need. Furthermore, the proliferation of numerous, often fragmented digital solutions has, in some cases, increased complexity and created additional challenges for efficient health-care delivery. Despite these concerns, it is important to embrace the digitization of care pathways<sup>67</sup>, as this can be done in ways that minimize negative effects and have a net benefit for patients.

## AI

In diabetic retinopathy, AI models have evolved from simple detection towards risk prediction and disease monitoring, supporting longitudinal assessment, clinical decision-making, and scalable deployment in screening, telemedicine and remote monitoring contexts<sup>68</sup>.

There are several examples of how AI has been incorporated into the clinical workflow of diabetic retinopathy management<sup>21,69</sup>. Deep learning, particularly convolutional neural networks, forms the backbone of digital innovation in this area, as imaging is a key part of assessing diabetic retinopathy<sup>70,71</sup>. Key tasks performed by deep learning include automated, scalable screening and diagnosis. Deep learning algorithms are used to assess image quality, detect the presence or absence of diabetic retinopathy, grade disease severity and identify referable diabetic retinopathy. In addition, deep learning enables lesion detection and localization, often supported by heat maps and saliency maps to enhance explainability<sup>68</sup>. Since the FDA approval of the first autonomous AI screening tool for diabetic retinopathy in 2018, several other algorithms have been developed and approved by the FDA and EMA<sup>69–71</sup>.

In DMO, AI-based approaches enable automated identification and quantification of OCT biomarkers, supporting objective assessment of disease severity and treatment response<sup>27</sup>. In addition, image domain transformation techniques have been developed to infer fluorescein angiography-like leakage information from OCT-A, providing adjunctive insights into vascular permeability that are not directly captured by OCT-A<sup>72</sup>.

Beyond structural analysis, AI models trained on large imaging datasets have been used to uncover novel disease biomarkers and predict functional outcomes. For example, deep learning algorithms have demonstrated the ability to estimate best corrected visual acuity from colour fundus photographs in eyes with DMO<sup>73</sup>. More recently, multimodal AI systems integrating imaging and functional data have been proposed for the detection of centre-involved DMO associated with visual impairment<sup>74</sup>. These models are also used to predict the risk of disease progression. Importantly, advances have been made in multimodal risk prediction, combining retinal images with additional diabetic retinopathy risk factors to generate patient-specific risk scores<sup>68</sup>.

Another important application of AI in diabetic retinopathy care is the use of large language models (LLMs) for clinical reasoning and communication<sup>75</sup>. While LLMs do not directly analyse retinal images, they add value by supporting interpretation, workflow optimization and human interaction. LLMs can translate deep-learning outputs into actionable recommendations that align with established clinical guidelines<sup>76</sup>. They can also automatically generate medical reports tailored to ophthalmologists, primary care physicians, or patients. Furthermore, LLMs enhance patient education and engagement by providing personalized advice in plain language, with the added benefit of multilingual support for global screening programmes. LLMs can also reduce administrative burden by assisting with clinical documentation, coding, regulatory compliance and summarization of electronic health record data<sup>75</sup>.

More recently, foundation models have emerged. These models are pre-trained on large, diverse datasets and adapted across multiple tasks to provide scalable and generalizable intelligence, thus expanding upon the capabilities of both deep learning and LLMs<sup>77</sup>. Their main functions include: universal retinal feature learning across different ethnicities, camera types and health-care settings; cross-task generalization; and multimodal learning that integrates retinal images with clinical text and laboratory data to enable more accurate and holistic assessment. The advantages of foundation models include strong performance with limited labelled data, which is an important consideration in low-income and middle-income countries as well as for improved robustness, bias reduction, fairness and sustainability for global deployment.

## Telemedicine

Telehealth for diabetic retinopathy enables remote screening, monitoring and follow-up by capturing retinal images outside traditional ophthalmology clinics and transmitting them for specialist review<sup>78</sup>. Hand-held and portable fundus cameras, including smartphone-based devices, facilitate retinal imaging in primary care, community clinics and low-resource or rural settings<sup>79,80</sup>. These devices improve access to screening for populations with limited availability of eye-care specialists, and support earlier detection of diabetic retinopathy. Images acquired using hand-held cameras can be assessed by trained graders or augmented with AI to triage normal and referable cases. Telehealth models reduce the need for in-person visits, increase screening uptake, and help address workforce and capacity constraints<sup>81</sup>. When integrated with secure digital platforms and clear referral pathways, teleophthalmology using hand-held cameras provides a scalable and cost-effective approach to diabetic retinopathy care<sup>82,83</sup>.

## Virtual clinics

Virtual clinics for stable diabetic retinopathy, also known as digital or asynchronous clinics, are care models in which clinical data are

collected by ophthalmic technicians without a face-to-face ophthalmologist visit and reviewed remotely by clinicians<sup>84,85</sup>. They are designed for patients with no diabetic retinopathy or stable, non-sight-threatening disease, allowing specialist clinics to focus on higher-risk cases. Data acquisition is typically performed by trained technicians in community or primary-care settings, and includes retinal imaging including OCT and wide-field retinal imaging, visual acuity testing and relevant clinical information. Images and data are uploaded to secure platforms and reviewed asynchronously by certified graders, ophthalmologists and increasingly with AI-supported decision tools<sup>86</sup>. AI can be used to assess image quality, triage normal or stable cases and flag referable disease, acting as a first reader or safety net rather than a replacement for clinicians. Structured digital reports are generated and integrated into electronic health records, with results communicated to patients and primary-care teams. Clear escalation pathways ensure that patients with disease progression, ungradable images or new symptoms are referred for face-to-face assessment. Virtual clinics reduce unnecessary hospital visits, improve access to care and increase service capacity<sup>84</sup>. They support more efficient use of specialist time while maintaining safety and clinical oversight. As the prevalence of diabetic retinopathy continues to rise, virtual clinics offer a scalable and sustainable model for managing stable disease.

## Remote monitoring tools

As longer-acting therapies for DMO and neovascular age-related macular degeneration become more widely available, remote (home) monitoring tools have emerged as a way of providing closer monitoring, which could help in earlier identification of patients whose disease is not responding to treatment or is responding suboptimally<sup>87</sup>. Such monitoring could increase opportunities for prompt intervention and improve outcomes<sup>87</sup>. In addition, it also allows monitoring of the second eye when people with only one affected eye require less frequent office visits. Prompt treatment, with good presenting vision, is a major factor in determining the final visual acuity after treatment<sup>88,89</sup>.

The first patient-operated, home-use OCT device was authorized by the FDA for remote retinal imaging in 2024 (ref. 90). It allows patients

to perform their own OCT scans at home in less than a minute, capturing high-resolution, cross-sectional images of the retina that can be transmitted wirelessly to the clinician for review. The device is paired with an AI-based image analysis algorithm providing clinicians with longitudinal structural information between scheduled in-office visits without replacing standard examinations. A trial on implementation of home monitoring OCT for patients with DMO is underway in China (NCT06610747)<sup>91</sup>.

Visual function applications (apps) are emerging digital tools that support the remote assessment and monitoring of visual function in people with diabetic retinopathy (Table 1). These smartphone-based or tablet-based apps can measure parameters such as visual acuity, contrast sensitivity, colour vision and metamorphopsia outside the clinic setting<sup>92</sup>. They enable more frequent monitoring between scheduled appointments and can help detect functional changes that are not immediately apparent on retinal imaging alone. Vision function apps can be integrated into telehealth and virtual clinic pathways, allowing results to be securely shared with clinicians and used to guide follow-up or escalation<sup>66</sup>. When appropriately validated and used alongside clinical imaging, these apps offer a patient-centred, accessible complement to traditional diabetic retinopathy care<sup>66</sup>.

As advanced multimodal imaging and AI mature, digital technologies should evolve from isolated tools into an integrated, learning health-care system supporting early detection, precision diagnosis, personalized treatment and efficient long-term monitoring (Box 1). When thoughtfully implemented, they offer the opportunity to improve outcomes, reduce inequities and future-proof diabetic retinopathy care pathways (Box 1).

## Advances in management of diabetic retinopathy and DMO

### Anti-VEGF agents

As VEGF is a key mediator of vascular permeability, inflammation and pathological neovascularization, intravitreal anti-VEGF therapy has become a component of the therapeutic armamentarium for PDR and the mainstay of treatment for DMO<sup>93,94</sup>.

**Table 1 | Visual function monitoring applications**

| Application                                      | Function test employed  | Parameter assessed  | Target population                                     |
|--|---|---|---|
| OdySight   | Visual acuity, contrast sensitivity, Amsler grid                    | Visual acuity, contrast sensitivity, metamorphopsia and scotoma | Patients with chronic eye diseases                    |
| Verana Vision Test (previously Checkup)          | Visual acuity (letter identification), Amsler grid                  | Visual acuity, metamorphopsia and scotoma                       | Patients with AMD or diabetic retinopathy             |
| Home Vision Monitor (previously myVisionTrack)   | Shape discrimination hyperacuity                                    | Hyperacuity   | Patients with maculopathy (AMD, diabetic retinopathy) |
| Alleye   | Alignment hyperacuity   | Hyperacuity   | Patients with AMD or DMO                              |
| MultiBit Test                                    | Rarebit perimetry   | Visual field integrity  | Patients with macular disease                         |
| Central retinal sensitivity                      | Retinal sensitivity to luminance                                    | Visual field integrity  | Patients with AMD                                     |
| Hyperacuity app or hyperacuity examination (HAC) | Line distortion hyperacuity task                                    | Hyperacuity   | Patients with AMD and risk of conversion to nAMD      |
| OKKO Health                                      | Line distortion, visual acuity                                      | Metamorphopsia, hyperacuity                                     | Patients with AMD                                     |
| Macular tester                                   | Amsler grid   | Metamorphopsia  | Patients with AMD                                     |
| KeepSight journal                                | Magazine-style tool and game-like test                              | Hyperacuity, metamorphopsia                                     | Patients with AMD                                     |
| ForeseeHome                                      | Includes a home device that uses preferential hyperacuity perimetry | Hyperacuity   | Patients with AMD                                     |

AMD, age-related macular degeneration; DMO, diabetic macular oedema; nAMD, neovascular AMD.

## Box 1 | Potential ways of integrating of digital approaches into diabetic retinopathy care pathway

### Screening

At the screening stage, artificial intelligence (AI) can facilitate automated grading of diabetic retinopathy and image quality control. Digital enablers such as hand-held cameras can allow providers to perform imaging even in low-resource settings. These technologies can be implemented using scalable platforms and offer community-based, low-cost options.

### Diagnosis and stratification

Predictive and prognostic AI algorithms can also assist with diagnosing and triaging patients. At this stage, it is important for clinicians handling different aspects of patient care to work together to design appropriate treatment pathways based on information gathered through digital approaches.

### Treatment planning and delivery

AI can also be used in validated clinical decision support tools and to integrate information collected during early stages of care into patients' electronic health records. A phased roll-out of such systems is key so that any issues with such tools can be identified and addressed, prior to widespread use.

### Follow-up and monitoring

Validated clinical decision support tools that use AI can also be helpful during follow-up. These tools can be integrated in optical coherence tomography devices that patients can use to collect images at home or at local primary care facilities. These images can then be shared with clinicians, allowing them to monitor a patient's condition without requiring an in-person visit.

Currently, PDR is most commonly managed with panretinal photocoagulation, although clinical trials such as DRCR Protocol S, CLARITY and PROTEUS have shown that intravitreal anti-VEGF therapy can induce more rapid regression of retinal neovascularization<sup>95–97</sup>. However, anti-VEGF treatment is not considered a sustainable long-term strategy for PDR, owing to its short intravitreal half-life and its inability to address key underlying disease mechanisms, including retinal non-perfusion<sup>98</sup>. As a result, improvements in diabetic retinopathy severity scores are often not durable and have not consistently translated into meaningful visual functional benefits, and the high treatment burden of repeated injections has limited widespread adoption as primary therapy<sup>99,100</sup>. Nevertheless, anti-VEGF agents have received regulatory approval for the treatment of diabetic retinopathy in some jurisdictions, including by the FDA.

By contrast, several anti-VEGF agents are licensed as first-line therapy for DMO, with approximately half of patients achieving a gain of at least two lines of visual acuity as measured using the ETDRS chart in clinical trials<sup>89</sup>. In real-world practice, however, these outcomes are frequently attenuated. This attenuation is due to difficulties with adhering to intensive treatment regimens; broader patient eligibility, with some patients with limited potential for visual acuity improvement being treated in real-world settings, but not included in trials; and suboptimal responses or disease recurrence in up to 40% of treated eyes<sup>101</sup>. Persistent VEGF upregulation despite good systemic glycaemic control further underscores the multifactorial and heterogeneous nature of DRD. Together, these limitations highlight the need for novel therapeutic targets, improved drug delivery strategies and combination approaches that reduce treatment burden and improve outcomes across both DMO and PDR.

Over the past three decades, the development of intravitreal anti-VEGF therapies has advanced markedly, evolving from selective inhibition of VEGFA to targeting additional angiogenic pathways. Therapeutic formats have progressed from monoclonal antibodies (ranibizumab, bevacizumab and brolucizumab, which are all VEGFA inhibitors) to fusion proteins (aflibercept, which blocks VEGFA, VEGFB and PlGF) and, more recently, bispecific antibodies (faricimab, which blocks VEGFA and angiopoietin 2). Parallel efforts to increase molar drug concentrations and port delivery systems have aimed to improve durability and clinical outcomes while reducing treatment burden. The Diabetic

Retinopathy Clinical Research Network Protocol T trial compared three first-generation intravitreal anti-VEGF agents (bevacizumab, ranibizumab and aflibercept 2 mg) and showed that aflibercept 2 mg is more effective than bevacizumab or ranibizumab at improving vision in eyes presenting with worse initial visual acuity<sup>102</sup>. The visual outcomes for the three agents were similar for eyes with good (20/40 or better) baseline visual acuity. After a gap of a few years, second-generation anti-VEGF were developed. Clinical trial designs for these drugs (faricimab, brolucizumab and aflibercept 8 mg)<sup>103–105</sup> focused on proving the durability of these agents against fixed dosing of aflibercept 2 mg, the dose given in the summary product characteristics for aflibercept. This approach resulted in a lack of data on direct comparisons of clinical effectiveness and safety of these agents versus aflibercept 2 mg when dosed identically.

Since 2022, many biosimilars of ranibizumab and aflibercept have also been approved by regulators in various countries and are interchangeable with the original drugs. These new therapies are likely to lower the cost of the drugs without clinically meaningful differences in safety and effectiveness compared with the original forms<sup>106</sup>.

### Steroids and laser treatments

Before the development of anti-VEGF agents, intravitreal steroids and macular laser photocoagulation were the only treatment options available for DMO. In the ETDRS, focal laser treatment reduced the rate of moderate vision loss by at least 50% in eyes with clinically significant DMO compared with no treatment<sup>6</sup>. As traditional laser photocoagulation is destructive in nature and laser burns can increase over time, many researchers have evaluated the role of subthreshold laser burns, whereby shorter pulses using a low power are applied to minimize collateral thermal damage<sup>107</sup>. Currently, laser photocoagulation for DMO is restricted to non-centre-involving DMO that meets the criteria of clinically significant macular oedema, although these cases can also be managed by observation. Other patients with indications for laser photocoagulation include those on anti-VEGF therapy who require supplementary therapy or those in whom anti-VEGF therapy is contraindicated.

Intravitreal steroids have also been used for DMO for over two decades. In the era prior to availability of anti-VEGF agents, intravitreal triamcinolone was used, especially in eyes that did not respond to laser treatment<sup>108</sup>. However, robust evidence from the Diabetic Retinopathy

Clinical Research Network Protocol I trial showed that it is less effective than laser photocoagulation for DMO as a primary therapy<sup>109</sup>. Consequently, triamcinolone use was restricted to those eyes that are refractory to laser treatment. Since then, two sustained-release dexamethasone and fluocinolone acetonide intraocular implants have been approved for use<sup>110,111</sup>. They are mostly used in persistent DMO due to their known adverse effect of causing the development of cataract and glaucoma or increasing the progression of these conditions. Across major clinical trials, cataract surgery was required in approximately 30–80% of eyes with cataract progression over long-term follow-up, while clinically significant intraocular pressure elevation occurs in about 20–40% of patients, with a smaller proportion requiring glaucoma surgery (<5%). Rates of infectious endophthalmitis are low and similar to those associated with other intravitreal injections (<0.1%)<sup>109–111</sup>. In spite of these adverse events, there are considerable differences in the usage of intravitreal steroids in DMO, with some patients being offered this treatment as first line<sup>112</sup>.

## Surgical therapies

Despite panretinal photocoagulation being the established treatment for PDR and the effective regression of retinal neovascularization by anti-VEGF agents, advanced stages require surgery<sup>113</sup>. The major indications for pars-plana vitrectomy remain unchanged and include non-clearing vitreous haemorrhage, macular-threatening tractional retinal detachment, severe fibrovascular proliferation and tractional macular oedema. Modern vitrectomy instrumentation such as vitrectors with high cutting rates and 25-gauge or 27-gauge instruments allow for precise removal of fibrovascular membranes and the repair of tractional retinal detachments<sup>114</sup>. Vitrectomy for DMO and vitreoretinal traction in diabetic retinopathy remains controversial due to variable anatomical and visual outcomes. While vitrectomy can relieve vitreomacular traction and improve retinal oxygenation, it does not address the underlying inflammatory and vascular mechanisms of DMO. Anatomical improvement is more consistent in eyes with clear tractional pathology, but visual acuity gains are often modest and unpredictable, particularly in the absence of traction. In addition, vitrectomy carries surgical risks, including cataract progression and retinal detachment. Consequently, with the availability of effective intravitreal therapies, vitrectomy is generally reserved for selected patients with tractional components or refractory disease<sup>115</sup>.

Advances in vitrectomy for diabetic retinopathy have been supported by innovations such as surgical robotics, wide-viewing systems, intraoperative OCT and chromovitrectomy techniques. Robotic and robot-assisted platforms improve instrument stability, precision and tremor reduction, which is particularly valuable during delicate membrane peeling and manipulation of fragile neovascular tissue<sup>116</sup>. Wide-viewing systems provide panoramic visualization of the retina, enabling safer and more efficient identification and management of peripheral pathology and tractional retinal detachments<sup>117</sup>. Chromovitrectomy, using vital dyes such as trypan blue or brilliant blue G, enhances visualization of the vitreous membranes, epiretinal membrane and internal limiting membrane, facilitating more complete and controlled membrane removal<sup>118</sup>. Together, these technologies improve surgical safety, efficiency and outcomes in complex diabetic vitrectomy cases.

## Emerging therapies and delivery strategies for diabetic retinopathy and DMO

It is well established that, despite the availability of effective ocular therapies for vision-threatening complications of DMO and PDR, optimal

control of modifiable systemic risk factors including hyperglycaemia, dyslipidaemia and hypertension remains essential for preventing disease onset and progression. Newer classes of glucose-lowering therapies, such as dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists, as well as bariatric surgery, have improved glycaemic control and reduced the risk of diabetes mellitus-related complications<sup>119</sup>. However, the increased risk of early worsening of diabetic retinopathy observed in the SUSTAIN-6 trial among participants treated with semaglutide prompted the FOCUS trial (NCT03811561), which is evaluating the long-term effects of semaglutide versus standard care on diabetic retinopathy progression over 5 years, with retinopathy as the primary outcome<sup>120,121</sup>. Early worsening of diabetic retinopathy associated with rapid glycaemic improvement has also been reported with other pharmacological agents and following bariatric surgery, underscoring the importance of close retinal monitoring in patients with severe non-proliferative disease<sup>122,123</sup>.

In addition, antihypertensive therapies, particularly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, confer added benefit in reducing diabetic retinopathy progression<sup>124</sup>. Although statins and fibrates are primarily used to manage dyslipidaemia, their protective effects on diabetic retinopathy appear to be mediated largely through anti-inflammatory mechanisms, including activation of peroxisome proliferator-activated receptor- $\alpha$ , rather than lipid lowering alone<sup>125,126</sup>. The LENS trial, which included 1,151 participants with non-referable diabetic retinopathy or maculopathy, demonstrated a 27% reduction in the risk of progression to referable disease among patients treated with fenofibrate<sup>127</sup>. Two ongoing clinical trials are further evaluating fenofibrate with diabetic retinopathy as the primary outcome: NCT04661358, a 4-year study in individuals with type 1 diabetes mellitus or type 2 diabetes mellitus and mild-to-moderate non-proliferative diabetic retinopathy without centre-involving DMO, and NCT01320345, a 3-year Australian trial in individuals with type 1 diabetes mellitus and non-proliferative diabetic retinopathy<sup>128,129</sup>.

The landscape of therapeutic approaches specifically for diabetic retinopathy and DMO has broadened substantially. Box 2 shows therapies grouped according to their primary route of delivery, reflecting differences in pharmacokinetics, target tissue, durability and treatment burden<sup>130,131</sup>. Oral agents primarily modulate inflammatory, oxidative stress, and metabolic and cytoskeletal pathways through systemic exposure, and offer the theoretical advantage of continuous bilateral drug exposure<sup>132</sup>. Topical therapies target pathways that are accessible via the ocular surface but are limited by posterior segment bioavailability<sup>133</sup>. Intravitreal therapies include VEGF-dependent and VEGF-independent mechanisms and remain the mainstay of treatment for DMO<sup>131–136</sup>. Suprachoroidal delivery enables compartmentalized drug distribution to the posterior segment while potentially reducing anterior segment exposure<sup>130,131</sup>. Surgical approaches, including port delivery systems and rarely, subretinal gene therapies, are designed to provide sustained intraocular drug expression and reduce treatment burden<sup>130,137,138</sup>.

Caution is warranted with long-term VEGF neutralization, as VEGF is essential for retinal homeostasis, neuronal survival and maintenance of the choriocapillaris. Long-term or irreversible VEGF suppression, particularly with gene-based therapies that are difficult to titrate, can therefore increase the risk of retinal or choroidal atrophy. In addition, vector-induced inflammation remains a concern for ocular gene therapies, especially those employing adeno-associated viral vectors, which can elicit innate and adaptive immune responses that can cause intraocular inflammation or limit transgene durability<sup>138</sup>.

## Box 2 | Routes of delivery for investigational therapies in diabetic retinopathy and diabetic macular oedema<sup>130,131</sup>

### Oral

- Tyrosine kinase inhibitors (TKIs)
- Kallikrein–kinin pathway modulation
- Connexin 43 modulation
- Neurometabolic pathway modulation
- NO–cGMP signalling modulation
- Redox factor 1 inhibition
- Lipid-lowering drugs

### Subcutaneous

- TKIs

### Topical

- Steroids
- TKIs
- p53 activation
- Connexin 43 mimetics

### Intravitreal

- VEGF inhibition
- Dual angiogenic pathway inhibitors (anti-VEGF–ANGPT2)

- ANG–TEK2 pathway inhibitors
- WNT– $\beta$ -catenin pathway modulators
- IL-6 inhibition
- Semaphorin 3A inhibition
- Endothelin 1 inhibition
- TGF $\beta$ 2 antisense oligonucleotides
- Gene therapy

### Suprachoroidal

- Steroids
- TKIs
- Kallikrein–kinin pathway modulation
- Gene therapy

### Surgical

- Port delivery systems
- Subretinal gene therapy

ANG, angiogenin; ANGPT2, angiopoietin 2; NO, nitric oxide; TEK, TEK receptor tyrosine kinase; TGF $\beta$ 2, transforming growth factor- $\beta$ 2; VEGF, vascular endothelial growth factor.

Alternative approaches, including photobiomodulation, suppression of rod photoreceptor function, senolytics and inhibition of VEGFC and VEGFD signalling, have not demonstrated efficacy to date<sup>139–142</sup>. A novel pathway to modulate retinal ischaemia by inhibiting semaphorin 3A is currently being investigated<sup>136</sup>.

### Potential therapies for diabetic retinopathy-related neurodegeneration and neuroinflammation

Emerging neuroprotective strategies target neuronal survival, microglial activation and inflammatory signalling. Agents such as brimonidine, somatostatin analogues and citicoline aim to preserve retinal neuronal function and reduce apoptosis<sup>65,143,144</sup>. Restoration of neurotrophic support through brain-derived neurotrophic factor pathways is another area of active investigation. Microglial inhibitors such as tetracycline or doxycycline, CX3CR1 pathway modulators, P2X7 receptor antagonists and TSPO ligands are potential targets for neuroinflammation<sup>145–148</sup>. Several lines of evidence also support targeting microglial signalling, inflammasome–IL-1 pathways and complement-mediated inflammation<sup>149</sup>. Other preclinical or translational cytokine-targeting biologics for diabetic retinopathy include TNF, IL-6 and IL-1 $\beta$ <sup>150</sup>. Müller cell-targeted strategies such as antioxidants (such as  $\alpha$ -lipoic acid) and inhibitors of osmotic stress pathways (such as aldose reductase inhibitors) are options being investigated for preserving the normal homeostatic functions of these cells and preventing their pathological activation (gliosis)<sup>151,152</sup>. Together, these approaches aim to complement vascular-targeted therapies by addressing the neural and inflammatory components of diabetic retinopathy.

### Conclusions

Diabetes mellitus is a global pandemic with increasing prevalence. Advances in treatments for diabetes mellitus and retinopathy provide

a promising outlook for mitigating sight-threatening effects. Early identification of diabetic retinopathy through frequent dilated retinal examinations is essential for prompt referral to the ophthalmologist and retinal specialist. Advances in diagnostics and digital technologies have prompted the emergence of novel clinical care pathways for diabetic retinopathy. Systemic management is also essential for the management of non-proliferative diabetic retinopathy and for the prevention of progression to DMO and PDR, with the primary care physician playing a pivotal role in the fight against vision loss in patients with diabetes mellitus. Treatment advances have demonstrated powerful improvements in the care of diabetic retinopathy, whereas trials of novel mechanisms and progress in standards of care hold promise for the future. Awareness of current guidelines, treatment protocols and new therapeutics among both generalists and specialists is essential for preserving sight in the population with diabetes mellitus.

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## Author contributions

The authors contributed equally to all aspects of the article.

## Competing interests

S.S. is a consultant for AbbVie Pte Ltd, Amgen, Adverum, Apellis, Bayer, Biogen, Boehringer-Ingelheim, Novartis, Eyebiotech, Eyepoint Pharmaceuticals, Janssen Pharmaceuticals, Ocular Therapeutix, Kriya Therapeutics, OcuTerra, Roche, Stealth Biotherapeutics and Sanofi; has received research support from Boehringer Ingelheim, Roche, Optos and Bayer; and is a Trial Steering Committee member for Novo Nordisk. S.V. is a consultant for AbbVie, Adverum, Alimera, Annexon, Apellis, Bayer, Boehringer-Ingelheim, Novartis, Roche and Zeiss.

## Additional information

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