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Current research and future strategies for the management of vision-threatening diabetic retinopathy

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ABSTRACT

Diabetic retinopathy (DR) is a major ocular complication of diabetes and the leading cause of blindness and visual impairment, particularly among adults of working-age adults. Although the medical and economic burden of DR is significant and its global prevalence is expected to increase, particularly in low- and middle-income countries, a large portion of vision loss caused by DR remains preventable through early detection and timely intervention. This perspective reviewed the latest developments in research and innovation in three areas, first novel biomarkers (including advanced imaging modalities, serum biomarkers, and artificial intelligence technology) to predict the incidence and progression of DR, second, screening and early detection of referable DR and vision-threatening DR (VTDR), and finally, novel therapeutic strategies for VTDR, including diabetic macular oedema (DME), with the goal of reducing diabetic blindness.

1. Introduction

Diabetic retinopathy (DR) is a major ocular complication of diabetes, affecting approximately 30–40 % of individuals with diabetes.[1–3] Globally, over 100 million people with diabetes suffer from DR, with DR a leading cause of blindness and visual impairment, particularly among adults of working age.[4,5] Besides the direct clinical impact (ie, blindness) on patients with diabetes, the wider socio-family-economic costs associated with DR and its related complications are substantial.[6] For example, diabetes-related blindness costs the USA about $500 million annually.[7] In addition, patients with DR have noticeably higher medical costs than those with other diabetes-related conditions.[8] Of importance are the smaller groups of patients with vision-threatening DR (VTDR), comprising diabetic macular oedema (DME) and proliferative DR (PDR). For example, regarding DME, newer studies have demonstrated that the economic burden is substantially greater for patients with DME compared to those without the condition.[9,10] A considerable portion of this increased cost can be attributed to the necessity for life-long treatment with expensive anti-vascular endothelia derived growth factor (VEGF) therapies.[9] The global prevalence of DME is also projected to increase by about 25 % to about 24 million individuals by 2030.[11] It is anticipated that the resultant escalation in healthcare expenditures for treating patients with DME will be substantial.

To compound the public health impact of DR, the disease burden of DR is distributed unevenly globally, disproportionally affecting low- and middle-income countries (LMICs).[11,12] This is because as populations in LMICs become older and with increasing 'Western' lifestyles and dietary habits, diabetes and DR have increased dramatically. According to the epidemiologic projections for 2030, the projected increases in the prevalence of DR in high-income regions are relatively modest, ranging

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from 10.8 % to 18.0 %.[11] In contrast, the anticipated increases in LMICs are much higher, ranging from 20.6 % to as high as 47.2 %.[11] Many of the healthcare systems in LMICs are not yet prepared to deal with the surge in diabetes and its complications. Thus, there is an even more urgent need for using the latest technology and medical advances, such as artificial intelligence (AI), in supporting healthcare resources dedicated to diabetes and DR, including new strategies in DR screening, diagnosis, follow-up, and treatment in LMICs.[12]

Despite these substantial challenges in DR management globally, there are positive news and major advances. Much of the visual loss resulting from DR continues to be preventable, and in developed high-income countries, the rates of vision loss from diabetes and DR have steadily declined over the past few decades.[13] Such improvements in visual outcomes for DR are multifactorial, largely attributable to a synergistic effect of improved systemic risk factor management (eg, glucose and blood pressure control) and recent advancements in DR screening and anti-VEGF treatment. Looking ahead to the next decade, it is anticipated that numerous ongoing research, innovation, and advancements will continue to significantly reshape both the healthcare landscapes in this field with a focus on reducing inequity in DR management globally. This holds promise for LMICs.

In this perspective, we review the clinical and public health challenges in DR and then the latest developments in reducing diabetic blindness, covering three major aspects (Fig. 1): first, the prediction of DR incidence and progression with novel diagnostics; second, screening and early detection of patients with DR, and finally, the latest treatment strategies for patients with VTDR, including DME.

2. Clinical and Public Health Challenges in DR

2.1. Prediction of the incidence and progression of DR

The incidence and progression of DR among people with diabetes are highly variant. In addition to DR stages (ie, the risk of VTDR and blindness is higher in patients with more severe DR stages), the risk of DR incidence and progression is influenced by several systemic risk factors. Modifiable risk factors include hyperglycaemia, hypertension, dyslipidaemia and obesity, smoking, anaemia, pregnancy, low health literacy, inadequate access to health care, and poor adherence to therapy.[14,15] Non-modifiable risk factors include ethnicity, family history or genetics, age at onset of diabetes, type of diabetes, and duration of diabetes.[14,15] However, the lack of simple and validated individualised risk prediction models for DR progression makes it hard for physicians and the healthcare system to effectively stratify people with diabetes, to focus and allocate more healthcare resources to such high-risk individuals, and to prevent visual loss. Thus, establishing novel biomarkers in DR and using existing and new data, with new technology to risk-stratify people with diabetes could empower personalised preventive strategies for people at high risk of DR incidence and progression.

2.2. Screening and timely detection of patients with referable DR

Despite the recognised advantages of routine DR screening for individuals with diabetes, identifying those who have 'referable DR' (typically defined as moderate DR or worse and/or with DME), only a limited number of truly comprehensive, nationwide DR screening programs exist globally. Classic examples include those in the United Kingdom (UK), Singapore, Denmark, and Iceland.[16] In contrast, many other developed nations, such as the United States, and notably the majority of LMICs, including China and India, lack systematic, sustainable nationwide DR screening programs.

The present landscape of DR screening, which primarily relies on the evaluation of colour fundus photographs (CFP) either by retina specialists, general ophthalmologists, optometrists, or trained professional graders, continues to result in a significant number of patients remaining undiagnosed and under-referred.[17,18] Consequently, these individuals often receive medical intervention too late, which is partly attributed to low adherence to and limited access to retina screening appointments.[17] In-person retinal examinations using standard (table-top, nonportable) retinal cameras are impractical and unsustainable given the increasing size of global populations with diabetes.[19] Currently, screening all people with diabetes at regular yearly intervals is also not a feasible option due to the lack of manpower. Thus, leveraging new technologies, including handheld imaging devices, teleophthalmology, and AI, could potentially help to address and resolve many challenges and inequity in real-world DR screening programs, especially in LMICs.[20–24]

2.3. Limited sustainable strategies for patients with vision-threatening DR

Despite the major progress in intravitreal anti-VEGF therapy, which is now widely recognised as the first-line treatment for centre-involved DME and has also been validated as an effective treatment option for PDR, there continue to be challenges.[25–28] Although anti-VEGF therapy induces regression of vascular lesions and an apparent reduction in DR severity, studies indicate that the underlying retinal ischemia remains unaltered, and that lesions and retinopathy frequently recur soon after

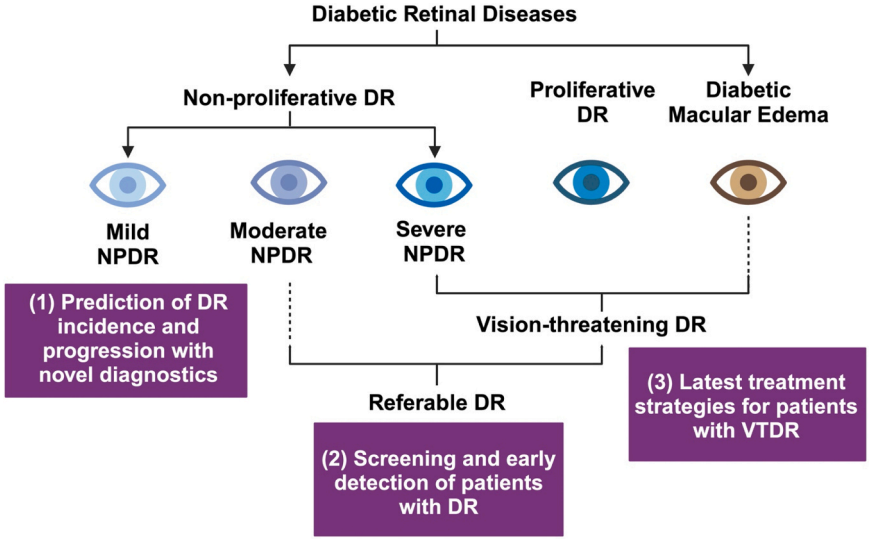

Fig. 1. Schematic Diagram Illustrating the Key Aspects in Reducing Diabetic Blindness.

the therapy is discontinued.[29,30] Furthermore, there continues to be very significant undertreatment due to low adherence and persistence in maintaining therapy. Thus, it is an important research direction to develop sustainable management approaches for referable DR and VTDR by expanding access to cost-effective therapies. Although anti-VEGF therapy is the standard of care, it imposes a significant treatment burden on patients. Therefore, it is imperative for clinicians to leverage new tools for early detection for effective management of diabetes and DR.[31] Furthermore, emerging treatments that promise to significantly alter or reverse DR stages (eg, from severe to mild, or mild to no DR) will be important in the future DR treatment landscape over the coming decade. These include targeting multiple novel pathophysiological pathways and enhancing the longevity of treatment effects.[28]

3. Novel biomarkers to predict the incidence and progression of DR

3.1. New imaging modalities

New imaging technologies, including ultra-widefield (UWF) retinal imaging and optical coherence tomography angiography (OCTA), have been available for both research purposes and clinical applications for several years[32,33] UWF retinal imaging offers a field of view ranging from approximately 110° to 220°, facilitating the evaluation of the retinal periphery and encompassing a substantially larger retinal surface area compared to standard CFP.[34,35] The inclusion of the retinal periphery in UWF images could lead to a classification of greater DR severity in 10–19 % of eyes.[28] Additionally, longitudinal cohort studies have demonstrated that various peripheral DR lesions are independently correlated with an increased risk of progression to PDR.[36] OCTA is another imaging platform that would be increasingly important in DR assessment and prognostication.[37] OCTA is a non-invasive, non-contact system that can provide angiographic information and better visualization of the capillary microvasculature.[28,38–40] OCTA could provide a multitude of quantitative retinal vascular parameters, and several longitudinal cohort studies have started to elucidate the prognostic potential of quantitative biomarkers derived from OCTA in predicting important clinical outcomes among people with diabetes, such as DR progression, incidence of DME, and visual loss.[41]

3.2. Serum biomarkers in DR

Conventionally, haemoglobin A1c (HbA1c) is a recognised serum biomarker associated with the incidence and progression of DR. Although maintaining blood glucose levels within a target HbA1c of less than 7 % can effectively prevent DR from deterioration, HbA1c only accounted for a 6.6 % risk variation associated with DR.[42] Therefore, it is urgent to discover more reliable serum biomarkers for DR risk prediction and monitoring because of the complexity of DR pathogenesis. Promisingly, substantial progress has been made in exploring effective DR-related biomarkers, particularly in extracellular vesicles, metabolomics, lipidomics, and proteomics. Of note, a multiplatform metabolomic profile revealed metabolic disturbances correlated with DR.[43] A biomarker panel encompassing 12-hydroxyeicosatetraenoic acid and 2-piperidone in serum was identified, exhibiting superior diagnostic accuracy for distinguishing DR from diabetes. Another prospective study was conducted to establish a cohort of glucose-well-controlled diabetic patients (GW-DR) and performed targeted metabolomics to delineate the metabolic signature of GW-DR.[44] The study identified ethanolamine as a promising marker associated significantly with GW-DR risk.

Alterations in lipid metabolism, especially in ceramides, could also serve as a potential biomarker for DR development.[45] Mesenchymal stem cell-derived small extracellular vesicles might play an important role as key facilitators for the pathogenesis and treatment of DR by improving retinal function and reducing retinal apoptosis, inflammation, and angiogenesis.[46] Reduced estimated glomerular filtration rate (eGFR) is found to be significantly correlated with the development of PDR in patients with type 2 diabetes, highlighting the potential role of kidney function monitoring in preventing DR progression.[47]

3.3. Artificial intelligence to predict the incidence and progression of DR

In the last few years, AI, particularly deep learning (DL) technology has shown great potential in screening and detecting the presence and severity of DR.[48–55] These studies are discussed below.

More recently, AI/DL may now be able to prospectively predict the incidence and progression of DR (Table 1). Using nine nonocular, systemic risk factors, a machine learning (ML) XGBoost algorithm was developed and validated to identify patients with diabetes who would develop PDR, DME, and referable DR in the future.[56] Using baseline CFPs, DL algorithms were developed to predict the risk of DR progression, defined as two-step worsening on the Early Treatment Diabetic Retinopathy Diabetic Retinopathy Severity Scale, over the time course of two years.[57] The performance of one of these models (prediction at month 12) resulted in an area under the curve equal to 0.79. Similarly, DL algorithms were developed and validated to predict the risk of DR incidence within two years using baseline CFPs.[58] Kaplan-Meier analyses showed that the DL algorithm's prognostication generalised to predicting incident DR beyond two years and predicting moderate DR and VTDR. More recently, a DL system (termed DeepDR Plus) was developed and validated to predict time to DR progression within five years solely from baseline CFPs.[59] For predicting time to DR progression, the DeepDR Plus system achieved concordance indexes of 0.754–0.846 and integrated Brier scores of 0.153–0.241 for all times up to five years. Furthermore, the system was validated in real-world cohorts of participants with diabetes. The integration with clinical workflow could potentially extend the mean screening interval from twelve months to 31.97 months, while delayed detection of progression to VTDR was 0.18 %. Another two studies demonstrated that DL algorithms could utilize baseline UWF retinal images[60] or OCTA images[61] to predict DR progression. The accuracy and feasibility of automated ML models for identifying DR progression developed using UWF images were also demonstrated, especially for the prediction of two-step or greater DR progression within one year.[60] It is also shown that the presence of diabetic macular ischemia (DMI) on OCTA images identified by an automated binary algorithm demonstrates prognostic value for DR progression, DME development, and visual acuity deterioration.[61]

Together, the integration of UWF colour fundus photography, OCTA, 'omic' and other biomarker research, artificial intelligence, and statistical modelling is likely to facilitate new DR classifications even before visible DR lesions are seen in the current two-field retinal screening. The clinical deployment of such predictive algorithms for DR incidence and progression could potentially promote patient-specific risk assessment and further personalised care for DR management.

4. Screening and timely detection and referral of patients with referable DR

4.1. Handheld retinal imaging device

To address the significant public health need to identify VTDR, it is necessary to have broad-based DR screening programs. However, the necessity to traverse extensive distances and the limited availability of standard retinal cameras represent significant impediments to the clinical implementation of DR screening in rural regions and LMICs. The adoption of low-cost, handheld mobile devices and teleophthalmology screening programs emerges as potential solutions to these challenges. Compared with traditional nonportable retinal cameras, the pooled sensitivity and specificity for the detection of DR using handheld retinal imaging devices were 87 % and 95 %, respectively.[62]

Furthermore, significant progress in AI-integrated hand-held cameras is being made.[63] Though the best-performing AI algorithms met the

Table 1
Artificial Intelligence for Diabetic Retinopathy Screening and Prediction.

Author (Year)	Objectives	Number of Participants	Inputs	AI Methods	Key Findings
Screening and Detecting DR and DME					
Gulshan et al. (2016)[51]	Detect referable DR and diabetic macular oedema	Model development & Internal validation: Images = 128,127 External validation: N = 5871, Images = 11,711;	Colour fundus photos	Convolutional neural network (Inception-v3)	**External Validation** Referable DR AUROC: 0.990–0.991; Sensitivity: 87.0 %–97.5 %; Specificity: 93.4 %–98.5 % Diabetic Macular Oedema Sensitivity: 90.4–90.8 %; Specificity: 98.7 %–98.8 %
Ting et al. (2017)[52]	Detect referable and vision-threatening DR	Model development & Internal validation: N = 14,880, Images = 71,896 External validation: Images = 40,752	Colour fundus photos	Convolutional neural network (Adapted VGGNet)	**Internal Validation** Referable DR AUROC: 0.936; Sensitivity: 90.5 %; Specificity: 91.6 % Sight-threatening DR AUROC: 0.958; Specificity: 100 %; Specificity: 91.1 % **External Validation** Referable DR AUROC: 0.889–0.983; Sensitivity: 91.8–100 %; Specificity: 73.3–92.2 %
Abràmoff et al. (2018)[49]	Detect More than mild DR (mtmDR)	N = 900	Colour fundus photos	IDx-DR (Multilayer convolutional neural network)	**Fully Analyzable Populations** mtmDR Sensitivity: 87.2 %; Specificity: 90.7 %
Bhaskaranand et al. (2019)[53]	Detect referral-warranted DR (more than mild NPDR)	N = 101,710	Colour fundus photos	EyeArt system v2.0 (Multiple convolutional neural networks)	**Populations with known DR Levels** Referral-Warranted DR Sensitivity: 91.3 %; Specificity: 91.1 %
Dai et al. (2021)[50]	Image quality assessment, lesion segmentation, and DR detection across early-to-late stages	Model development: N = 121,342, Images = 466,247 Internal validation: N = 52,004, Images = 200,136 External validation: Images = 209,322	Colour fundus photos	Convolutional neural network (ResNet and Mask-RCNN)	**Internal Validation** Referable DR AUROC: 0.973; Sensitivity: 0.941; Specificity: 0.897 **External Validation** Referable DR AUROC: 0.946–0.973; Sensitivity: 0.928–0.945; Specificity: 0.813–0.883
Predicting the incidence and progression of DR and DME					
Arcadu et al. (2019)[57]	Predict DR progression in untreated eyes over the course of two years	N = 529,528 and 499 at 6th-, 12th- and 24th-month intervals respectively	Colour fundus photos	Convolutional neural network (Inception-v3)	**Validation Dataset** 6th month Interval AUROC: 0.68; Sensitivity: 66 %; Specificity: 77 % 12th month Interval AUROC: 0.79; Sensitivity: 91 %; Specificity: 65 % 24th month Interval AUROC: 0.77; Sensitivity: 79 %; Specificity: 72 %
Bora et al. (2021)[58]	Predict onset of DR over the course of two years	Model development: Eyes = 575,431 Internal validation: Eyes = 3678 External validation: Eyes = 2345	Colour fundus photos	Convolutional neural network (Inception-v3)	**Internal Validation** AUROC: Fundus only: 0.79; Risk factors only: 0.72; Hybrid: 0.81 **External Validation** AUROC: Fundus only: 0.70; Risk factors only: 0.62; Hybrid: 0.71
Dai et al. (2024)[59]	Predict DR progression over the course of five years	Model development: N = 179,327, Images = 717,308 Internal validation: N = 19,100 External validation: N = 10,768 Real-world cohort validation: N = 5214	Colour fundus photos	Convolutional neural network (ResNet−50)	**Predicting Time to DR Progression in Internal and External Validation Datasets** Concordance Indexes: 0.754–0.846 and integrated Brier scores of 0.153–0.241 for all times up to five years **Real-world Prospective Study Integrating the System into the Clinical Workflow** Potential extension of the mean screening interval from 12–31.97 months with a low rate of delayed detection of progression to vision-threatening DR (0.18 %)
Silva et al. (2024)[60]	Predict DR progression over the course of three years using baseline ultra-widefield retinal images	Development: 1179 deidentified UWF images with mild (n = 380) or moderate (n = 799) NPDR Validation: 328 images	Ultra-widefield retinal images	Google AutoML platform	**Validation Dataset for Eyes with Baseline Mild NPDR** Sensitivity: 0.72; Specificity: 0.63 **Validation Dataset for Eyes with**

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Objectives	Number of Participants	Inputs	AI Methods	Key Findings
		(including 50 progressors) with mild NPDR and 425 images (including 95 progressors)			**Baseline Moderate NPDR** Sensitivity: 0.80; Specificity: 0.72
Yang et al. (2023)[61]	Investigate whether an automated binary DMI algorithm using OCTA images provides prognostic value on DR progression, DME development, and VA deterioration	321 eyes from 178 patients with diabetes	OCTA images	Convolutional neural network (DenseNet−161)	**Incremental Value of Adding the Presence of DMI at the Baseline Computed by the Deep Learning Algorithm for Predicting Clinical Outcomes** DR Progression Concordance Indexes: 0.73–0.78 DME Development Concordance Indexes: 0.72–0.78 VA Deterioration Concordance Indexes: 0.70–0.74

DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; DME, diabetic macular oedema; DMI, diabetic macular ischemia; OCTA, optical coherence tomography angiography; VA, visual acuity; CI, confidence interval; AUROC, area under the receiver operating curve

criteria for effective DR screening for referable DR screening using handheld fundus cameras in a real-world setting, there was significant variability in the performance of these algorithms, highlighting the importance of external validation before clinical application.[64] In real-world DR screening, another issue is that incorporating additional peripheral fields could enhance the DR screening accuracy of handheld retinal imaging protocols.[65]

Smartphone-based DR screening is another promising research direction. Smartphone-based fundus imaging approaches can meet the requirements for DR screening in an outreach environment and might aid in reducing the burden of DR screening, particularly in LMICs.[66] A prospective, comparative study was conducted to assess the effectiveness of Selfie Fundus Imaging for DR screening. This innovative method shows promise in supporting timely and efficient screening efforts for DR, potentially improving access to care and sustaining regular screening in diverse settings.[67] In fact, even diabetic kidney disease and diabetic neuropathy may be identified from retinal images and retinal vasculature also predicts macrovascular complications emphasising the wealth of information that can be obtained from retinal images.[68–70] Indeed, with time, it is anticipated that retinal screening may provide holistic screening for complications of diabetes.

4.2. Teleophthalmology screening strategies

Teleophthalmology screening strategies possess the capability to enhance both the accuracy and efficiency of DR screening in LMICs. Specifically, these strategies could mitigate the shortfall of trained healthcare professionals capable of interpreting DR lesions in retinal fundus images within resource-limited settings. Such strategies would typically entail the establishment of a central grading centre to receive and analyse retinal images sourced from local clinics. It has been demonstrated that teleophthalmology screening is highly effective for referable DR screening and enhances patient compliance, particularly in underserved areas.[71] However, a number of factors that could improve the quality of such settings were identified,[72] including ensuring sufficient numbers and sizes of retinal fields, undertaking mydriatic retinal examinations and stereoscopic imaging, and using licensed eye care providers to evaluate retinal fundus images at the reading centres. It was demonstrated that teleophthalmology DR screening strategies could lead to substantial cost savings, particularly in low-income countries and rural populations,[73] and it was reported that such a teleophthalmology DR screening program is projected to yield a saving of 29.4 million Singapore dollars for the healthcare community in Singapore over a lifetime horizon.[12]

In Denmark, diabetologists have traditionally been unaware of the DR status of patients. To address this, and to reduce the burden of frequent healthcare visits for persons with diabetes, the concept of same-day-complication-screening has now been partly implemented nationally. In essence, DR screening is now performed in diabetes departments throughout the country. Using telemedicine, retinal images and OCT are then transferred for evaluation to ophthalmology-based central screening centres. Evaluations are then returned to the diabetologists within one hour. In the meanwhile, additional DR parameters (eg, glycaemic regulation, blood pressure, and lipids) and other microvascular complications have also been evaluated, which provides the diabetologist with an excellent overview of the full complication status. This leads to a better integrated care and substantially reduces the number of health care visits for patients.

4.3. Artificial intelligence for DR screening and detection

Teleophthalmology screening strategies for DR screening have demonstrated both effectiveness and economic viability. However, concerns persist regarding their scalability and sustainability in the face of rising diabetes prevalence and an increasing disease burden. Recent advancements in AI/DL hold the potential to significantly improve the efficiency and long-term viability of these teleophthalmology screening approaches for DR (Table 1). Automated diagnosis or detection of referable DR/VTDR from CFP images was one of the first use cases in the field of medical AI, from as early as 2016.[51] Initial studies already demonstrated that AI algorithms developed on large datasets could reach very high levels of diagnostic performance for the detection of referable DR and VTDR.[51,52] Later in 2021, a DL system, named DeepDR, was developed and validated to detect early-to-late stages of DR. DeepDR was trained for real-time image quality assessment, lesion detection, and DR/DME grading across the disease spectrum.[50] Now, several AI-based systems for DR screening have been approved for clinical use, including IDx-DR (IDx LLC, Coralville, IA, USA)[49] and EyeArt (Eyenuk, Inc., Woodlands Hills, CA, USA).[53] SELENA+ (EyRIS Pte Ltd, Singapore) has received European CE Mark Approval, and is planned to be deployed as part of the national DR screening program in Singapore soon. An economic modelling study demonstrated that the incorporation of AI algorithms as an assistive tool in large-scale DR screening programs will be associated with significant cost savings.[74] Recently, a portable AI screening tool (AEYE-DS with Optomed Aurora) has obtained regulatory approval from the US FDA.[75] It has also been revealed that the AI-human hybrid teleophthalmology technology could both reduce reliance on human specialists while simultaneously enhancing diagnostic accuracy.[76]

It is likely that in the near future, we will see AI/DL algorithms routinely deployed in many large-scale DR screening programs across the world, either as fully autonomous systems to give diagnosis alone or in hybrid systems where the AI/DL algorithms function as assistive tools for physicians to make the final diagnosis.[74] Additionally, the advent of

large language models (LLMs) represents a significant breakthrough as they enable interactive, human-like conversations.[77,78] Specifically in DR screening, LLMs offer unique opportunities to optimize digital eye care, address clinical workflow inefficiencies, and enhance patient experiences.[79] Recently, an integrated image-language system (termed DeepDR-LLM) was developed and validated,[80] combining a large language model (the LLM module) and image-based deep learning (the DeepDR-Transformer module), to provide individualised diabetes and DR management recommendations to primary care physicians.

5. New treatment strategies for patients with VTDR

The anti-VEGF therapy revolutionised DR management.[81] Intravitreal injections of aflibercept gained FDA approval for non-PDR (NPDR), PDR, and DME.[82,83] Despite the remarkable achievements of conventional anti-VEGF regimens over the past two decades, findings from the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol W revealed that while early intervention with intravitreal aflibercept in NPDR reduces the risk of developing DME and PDR, it did not confer additional visual acuity gains,[84] underscoring the complexity in balancing costs and benefits in anti-VEGF treatments. Furthermore, some patients exhibit an incomplete or no response to standardised therapy, or experience diminishing treatment effects over time.[85,86] Added to these challenges are issues of neurotoxicity, local and systemic side effects, as well as the financial and adherence burden imposed by the short half-life of traditional anti-VEGF agents.[87] While effectively targeting angiogenesis, current anti-VEGF therapies fail to alleviate retinal nonperfusion, leaving the underlying ischemic state unaltered.

To address these limitations, some strategies have been devised, including reducing dosing frequency, dual targeting approaches, novel drug delivery methodologies, and developing agents that target non-VEGF-dependent mechanisms. With the FDA's approval in August 2023, 8 mg aflibercept, compared to the traditional 2 mg counterpart, extends the interval to eight to 16 weeks for DME and eight to 12 weeks for DR, thereby significantly decreasing injection frequency.[88] Faricimab, a bispecific antibody targeting both angiopoietin-2 (Ang-2) and VEGF-A, mitigates inflammation and leakage more effectively with a quarterly dosing schedule.[89] It has also been demonstrated that clinically meaningful visual acuity gains from baseline, anatomic improvements, and extended durability with intravitreal faricimab up to every 16 weeks were maintained through year 2. Faricimab given as a personalised treat-and-extend (T&E)-based dosing regimen supports the role of dual angiopoietin-2 and VEGF-A inhibition to promote vascular stability and to provide durable efficacy for patients with DME.[90] OPT-302, by inhibiting VEGF-C and VEGF-D activity, complements anti-VEGF therapies like aflibercept or conbercept, broadening the therapeutic scope to encompass the entire VEGF family.[91] Innovations in drug delivery systems, such as the refillable port delivery system (PDS) for sustained release of ranibizumab, also exemplify efforts to streamline administration and enhance patient compliance.[92] KSI-301 represents another breakthrough, characterised by a unique design: an anti-VEGF IgG1 antibody fused to a high molecular weight biopolymer, a stable phosphocholine-based biomaterial. This intricate conjugation enables an extended intravitreal half-life of approximately six months.[93] Gene therapy is being investigated as a durable option for the management of VTDR. Anti-ceramide immunotherapy was also regarded as a new strategy for DR treatment target.[94] Oral and topical therapies are also being evaluated and it is hoped that such easy and cheaper treatment options are likely to widen the reach of treatment options for all people with diabetes worldwide. Anti-inflammatory drugs, such as topical bromfenac[95] and ketorolac,[96] could improve the efficacy of intravitreal ranibizumab in DME treatment without significantly raising the risk of corneal side effects.

DME remains a leading cause of vision loss in individuals with diabetes.[11] Despite advances in anti-VEGF therapies, macular laser therapy remains crucial, particularly in non-centre-involved clinically significant macular oedema (CSME).[97] Traditional continuous wave lasers cause visible retinal burns (threshold therapy), while subthreshold micropulse laser (SML) has comparable efficacy and cost to SL therapy, which can avoid retinal damage and minimize the risk of foveal burns, allowing for safer, repeatable treatments over larger areas.[98] Additionally, intravitreal corticosteroids exert comprehensive anti-inflammatory effects by inhibiting the production of VEGF and other proinflammatory mediators, which also contribute to the treatment of DME. This therapy may benefit DME monotherapy in treatment-naive patients and anti-VEGF non-responders.[99]

DR involves intricate biochemical and metabolic disorders in almost all retina cells.[100] Beyond the focal investigation of angiogenesis, studies are progressively delving into therapies targeting inflammatory mediators and cells, antioxidant strategies, as well as neuroprotective agents, all of which are under exploratory and developmental stages.[24] Furthermore, stem cell therapies and genetic interventions have emerged as promising avenues, demonstrating the potential to mitigate retinal barrier breakdown, alleviate cellular apoptosis and dysfunction, and facilitate the restoration of healthy vasculature. The advent of genome-wide analyses, metabolomics, and proteomic profiling for DR marks a new frontier, wherein the realisation of personalised, precision medicine approaches become increasingly feasible.[28] This advancement, considering the dynamic evolution of key pathological features across varying stages of DR, holds the promise of administering the most efficacious therapies to patients at the optimally timed intervention points.

6. Conclusion and perspective

To address the growing global burden of DR and improve patient outcomes, several key strategies regarding DR treatment and management should be emphasised as follows, covering the three aspects we reviewed here: first, incorporating novel biomarkers to enhance the prediction of DR incidence and progression for precision and personalised medical decision-making, including both serum and imaging biomarkers; second, adopting innovative strategies for improving DR screening and early detection, such as integrating AI technologies and hand-held retinal cameras for DR screening, especially in LMICs; and third, developing sustainable management approaches for referable DR and VTDR by expanding access to cost-effective therapies.

Future directions in DR management could focus on integrating biomarkers for prediction models into electronic medical record (EMR) decision support systems to enable pre-emptive interventions. Implementation studies are crucial for translating AI/ML-based stratification tools into clinical practice, ensuring they effectively guide early detection and management strategies. In the management of VTDR, similar to other diabetic complications, such as chronic kidney disease and cardiovascular disease, primary prevention strategies—including improved awareness and adherence—significantly impact population health. Despite anti-VEGF therapy being the standard care for VTDR, its significant treatment burden highlights the need for early detection tools. Clinicians must leverage these innovations to improve diabetes and DR management. Digital health innovations, such as predictive algorithms using real-time data from wearables and sensors, can identify individuals at higher risk for diabetes complications. Integrating these tools into unified digital health platforms enables more informed decision-making, enhances patient engagement through personalised feedback, and improves adherence to lifestyle modifications, thereby reducing diabetic complications, including DR and blindness.

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