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Diabetic retinopathy: Looking forward to 2030

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Diabetic retinopathy (DR) is the major ocular complication of diabetes mellitus, and is a problem with significant global health impact. Major advances in diagnostics, technology and treatment have already revolutionized how we manage DR in the early part of the 21st century. For example, the accessibility of imaging with optical coherence tomography, and the development of anti-vascular endothelial growth factor (VEGF) treatment are just some of the landmark developments that have shaped the DR landscape over the last few decades. Yet, there are still more exciting advances being made. Looking forward to 2030, many of these ongoing developments are likely to further transform the field. First, epidemiologic projections show that the global burden of DR is not only increasing, but also shifting from high-income countries towards middle- and low-income areas. Second, better understanding of disease pathophysiology is placing greater emphasis on retinal neural dysfunction and non-vascular aspects of diabetic retinal disease. Third, a wealth of information is becoming available from newer imaging modalities such as widefield imaging systems and optical coherence tomography angiography. Fourth, artificial intelligence for screening, diagnosis and prognostication of DR will become increasingly accessible and important. Fifth, new pharmacologic agents targeting other non-VEGF-driven pathways, and novel therapeutic strategies such as gene therapy are being developed for DR. Finally, the classification system for diabetic retinal disease will need to be continually updated to keep pace with new developments. In this article, we discuss these major trends in DR that we expect to see in 2030 and beyond.

KEYWORDS

diabetic retinopathy, future trends and predictions, epidemiology, pathophysiology, imaging modalities, artificial intelligence, new treatments, classification and staging system

1 Introduction

Diabetic retinopathy (DR) is the major ocular complication of diabetes mellitus, and occurs in about 30 to 40% of diabetic individuals (1, 2). Globally, more than 100 million individuals are living with DR, and DR is a leading cause of blindness and visual impairment, especially among the working-age adult population (1, 3). Fortunately, much of the visual loss from DR is preventable, and the rates of vision loss from diabetes and DR have steadily declined over the past few decades (4, 5). Such improvements in visual outcomes for DR are multifactorial, and are due in large part to a combination of better systemic risk factor control, coupled with advances in ocular disease assessment, screening, imaging and treatment in recent years. For example, the universal adoption of DR classification systems such as the Early Treatment of Diabetic Retinopathy Study (ETDRS) and International Classification of Diabetic Retinopathy (ICDR) severity scales that effectively prognosticate the risk of disease progression, coupled with large-scale DR screening programs around the world, have allowed for appropriate surveillance and early intervention to prevent the onset of vision-threatening complications (5–7). Panretinal laser photocoagulation (PRP) helps to prevent severe vision loss due to proliferative DR (PDR), and the introduction of pattern scan laser (PASCAL) has made the procedure quicker, easier to perform, and more comfortable for patients (8–10). The widespread availability and use of non-invasive imaging such as optical coherence tomography (OCT), together with the introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatments have revolutionized the assessment and treatment of diabetic macular edema (DME), and dramatically improved visual outcomes for this complication of DR (11–13). Surgical outcomes for tractional retinal detachments and diabetic vitrectomies have also improved over the years, with the availability of more advanced instrumentation and surgical adjuncts such as pre-operative anti-VEGF injections (14–16).

Despite the tremendous progress that the field of DR has already seen, there are yet more exciting advances being made. Looking forward over the next decade, many of these ongoing developments are likely to further transform the clinical and research landscapes. In this article, we review some of the recent progress that has been made, and suggest how these developments may continue to shape the field in 2030 and beyond.

2 Shifts in epidemiology and disease burden

The global prevalence and disease burden of DR is expected to increase significantly over the next few decades, from about 103 million individuals in 2020, to 130 million in 2030, and 161 million in 2045 (17). Such projections are due to a variety of factors, including the increasing prevalence of diabetes around the world, lifestyle changes, and increasing lifespans and aging global populations (17). This sharp increase in DR disease burden by more than 25% in just 10 years, is likely to further strain healthcare systems and resources that are already stretched. The economic costs associated with DR and its complications are substantial. Direct healthcare costs related to DR in the USA were estimated at $493 million per year in 2004 (18). More recent data is lacking, but it is notable that these estimates were arrived at prior to the introduction of anti-VEGF treatment for DME. Subsequent studies have found that economic costs are significantly higher for patients with DME than without, and much of this is due to the need for costly anti-VEGF treatment (19, 20). Global prevalence of DME is also projected by increase by about 25%, to about 24 million individuals by 2030 (17). The resultant increase in healthcare costs are expected to be staggering.

Perhaps just as important as the overall increase in disease burden, is the projected pattern of increase. Based on epidemiologic projections to 2030, the rates of increase in DR prevalence for traditionally high-income regions such as North America and Europe appear to be relatively low, ranging from 10.8 to 18.0%. In contrast, the rates of increase in middle- and low-income regions such as the Western Pacific (WP), South and Central America, Asia, Africa, the Middle East and North Africa (MENA) are much higher, ranging from 20.6% to as high as 47.2%. In absolute terms, the largest increases by far are projected to occur in MENA, and WP, where the numbers of individuals with DR are expected to rise by more than 6 million in each region respectively (17). This geographic shift in disease burden towards Asia, Africa and WP means that global health strategies to combat DR will need to pivot to follow the shifting disease demographic. Healthcare resources for DR screening, diagnosis, follow-up, and treatment are urgently needed in these areas. Large-scale systematic, rather than opportunistic, DR screening programs that target all patients with diabetes in these regions will allow for early detection and intervention, will be cost-effective, and will reduce rates of vision loss, but they require significant investment in infrastructure and time to set up (21–24).

3 Non-vascular aspects of diabetic retinal disease

The clinically-visible retinal lesions associated with DR, such as microaneurysms, hemorrhages and hard exudates, are primarily the result of retinal microvascular damage. Consequently, the focus on DR pathophysiology, diagnosis and assessment has traditionally always centered around the vascular

aspect of the disease. However, with the availability of better structural retinal imaging modalities and functional assessments, evidence has accumulated over the years of significant retinal neural dysfunction as well, which occurs together with, or in some cases precedes, the development of vascular abnormalities. These structural and functional changes have collectively been termed "diabetic retinal neurodegeneration" (DRN) (25–28).

OCT studies have shown that patients with diabetes demonstrate significant thinning of the inner retinal layers, including the retinal nerve fiber layer (RNFL), and ganglion cell layer (GCL) (26, 29–31). Retinal thinning is progressive over time, and can precede the development of clinically-visible DR lesions (26, 30). Histological studies on enucleated eyes also corroborate these findings, showing reductions in retinal ganglion cell density in eyes with DR (32). Functional assessments in diabetes reveal reductions in contrast sensitivity, visual field defects, electrophysiologic deficits, and impaired pupillary responses (33–38).

Despite the clear evidence of DRN occurring in diabetic retinal disease, there remain many important unanswered questions in this area. What is the prognostic significance of DRN in terms of ocular or systemic outcomes in diabetes? What is the functional impact of DRN on quality of life? How and when should DRN be assessed and quantified? Current OCT studies on DRN measure different retinal layers (e.g. RNFL, GCL), and in different, non-standardized locations. Functional assessments such as electrophysiology, visual field perimetry and pupillometry are often time-consuming and resource-intensive. Recently, a portable, handheld chromatic pupillometer was shown to able to provide rapid, clinic-based assessment of retinal neural function in diabetes (38). Such findings, however, need to be replicated and validated in larger cohorts. There is also much ongoing work to determine the prognostic impact of DRN, and to incorporate such assessments of DRN into routine DR classification and staging systems (28, 39, 40). These efforts are likely to change the way we routinely assess and manage DR in the next few decades.

4 New imaging modalities and biomarkers

New imaging modalities such as ultra-widefield (UWF) retinal imaging and OCT angiography (OCTA) have been available for research and commercial clinical use for a number of years now. UWF retinal imaging provides a field of view of about 110° to 220°, and allows for visualization up to at least the anterior edge of the ampullae of the vortex veins (41). These platforms can be used for UWF color or pseudocolor photography (UWFCP), as well as UWF fluorescein angiography (UWFFA). UWF imaging platforms are non-contact and often do not require pupillary mydriasis, but their most important advantage, is that they provide for assessment of the retinal peripheries, and overall a much larger retinal surface area than standard color fundus photography (CFP). With standard CFP, the typical 7 standard ETDRS fields cover only about 30% of total retinal surface area (39, 42). In contrast, UWF imaging systems allow for assessment of approximately 80% of retinal surface area, which is a major advantage (42).

Assessment of the retinal peripheries with UWF images in DR has significant prognostic and management implications. For one, inclusion of the peripheries in UWFCP images results in a greater DR severity level in 10 to 19% of eyes (43–46). Furthermore, studies from a longitudinal cohort showed that various peripheral DR lesions, such as predominantly peripheral lesions (PPLs), and number, surface area, and distance of hemorrhages/microaneurysms and cotton-wool spots from the optic nerve head, were independently associated with greater risk of progression to PDR (47, 48). However, the prospective longitudinal Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol AA study recently concluded that PPLs in UWFCP images were not correlated with DR worsening, whereas PPLs and non-perfusion on UWFFA were (49, 50). Unfortunately, UWFFA has some major drawbacks that limit its universal use in all DR patients, including the need for invasive dye administration, time needed for acquisition, and the need for tertiary specialist interpretation. At present, the ideal modality for peripheral assessment and the best way to do so in DR remain unclear. Nevertheless, it is clear that as we better define the role of the retinal peripheries, UWF imaging platforms are sure to play an important role in DR assessment and management over the next decade.

OCTA is another imaging platform that will be increasingly important in DR assessment and prognostication. OCTA is a non-invasive, non-contact system that can provide angiographic information without the need for invasive dye administration like fluorescein. Other advantages of OCTA over dye-based fluorescein angiography are better visualization of the capillary microvasculature, and depth-resolved segmentation of the superficial, middle and deep capillaries plexuses, which are differentially affected in diabetes and DR (51–53). OCTA can provide quantitative metrics relating to the retinal microvasculature, and many of these, such as lower vessel density, lower fractal dimension, greater tortuosity, and greater foveal avascular zone area, have been associated in cross-sectional studies with greater DR severity (51–55). The impact of such cross-sectional associations in clinical practice is limited, but the major impact from OCTA will be realized when such OCTA metrics are eventually linked to clinical outcomes of interest on longitudinal studies. At present, longitudinal prospective OCTA studies are limited, but hopefully this need will be addressed in the next few years (56–59). Other barriers to widespread adoption and clinical impact of OCTA include scan quality and gradability, as well as the use of multiple different commercial OCTA machines, with proprietary algorithms and

quantitative metrics that are not standardized or interchangeable between devices. As these barriers are addressed, it is likely that OCTA will become a powerful, non-invasive prognostic tool for clinical assessment in DR.

5 Artificial intelligence

Artificial intelligence (AI) and deep learning (DL) algorithms will play an increasingly important role over the next decade in the areas of medical diagnostics, screening, prognostication, and assisting with management or treatment decisions. Ophthalmology has been a leader in developing AI algorithms for clinical use, and automated diagnosis or detection of DR from CFP images was one of the first use cases developed, from as early as 2016 (60–62). Initial studies already demonstrated that AI algorithms developed on large datasets could reach very high levels of diagnostic performance for detection of referable DR and vision-threatening DR (61, 62). About 5 years later, there are now multiple AI-based systems for DR screening that have been approved for clinical use. IDx-DR (IDx LLC, Coralville, IA, USA) and EyeArt (Eyenuk, Inc., Woodlands Hills, CA, USA) have both received approval by the USA Food and Drug Administration (FDA), and are already in clinical use (63, 64). 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 suggested that incorporation of such an AI algorithm as an assistive tool in a large scale DR screening program will be associated with significant cost savings (65). It is likely that by 2030, we will see AI algorithms routinely deployed in many large-scale DR screening programs around the world, either as fully autonomous systems, or in hybrid systems where the algorithms function as assistive tools (65). However, there are still some challenges that need to be overcome for widespread acceptance of large-scale AI screening systems. Retinal images frequently contain signs of other ocular or systemic diseases besides DR, and the medicolegal aspects of this are still uncertain. IDx-DR, for example, only detects DR, and the FDA approval for its use clearly states that the algorithm does not diagnose any other ocular disease. Other AI-based systems take a different approach to this; SELENA+ detects DR, as well as 2 other major eye diseases – age-related macular degeneration and glaucoma (62). Poor image quality can also adversely affect the accuracy of such algorithms, but most commercial AI systems now have in-built automated image quality assessments (62, 63).

Beyond just diagnosis and screening of DR, there are other potential use cases for AI algorithms that are also being developed. AI-based detection of DME from CFP images is promising, and could help to improve and reduce false positive referral rates from DR screening programs (66). Some imaging modalities such as OCT and OCTA have in-built software and segmentation algorithms that provide quantitative parameters, such as central subfield thickness (CST) in OCT, or capillary vessel density in OCTA. However, the capability of these automated software algorithms to provide detailed quantitative information is limited to a few parameters, and is dependent on the accuracy and resolution of automated segmentation. Using AI to improve retinal layer segmentation and to provide precise quantification of fluid volumes in different fluid compartments could have major impact in terms of prognostication, and guiding treatment decisions for DME (67–71). Similarly, there has been a shift in emphasis towards quantitative assessment in modalities that are typically assessed qualitatively or categorically, such as number, size and location of retinal vascular lesions on CFP or UWFCP images, or areas of retinal non-perfusion on UWFFA images (48, 50, 72–74). Manual grading and assessment of these quantitative parameters would be impractical, and AI algorithms for automated quantification will go a long way to making such quantitative parameters accessible, and clinically useful. Finally, the use of AI to process multimodal clinical and imaging data in DR, to provide more accurate prognostication of long-term outcomes, such as visual outcomes, risk of developing incident DME, and anti-VEGF treatment burden in DME, is an exciting area to look forward to (75).

6 New treatment strategies

Intravitreal anti-VEGF therapy is the established first line treatment for center-involved DME, and has also been shown to be a valid treatment option for PDR (12, 76, 77). Observations from the registration trials for anti-VEGF therapy in DME showed that anti-VEGF therapy can also result in significant improvements in DR severity for patients with non-proliferative DR, and this has been confirmed in more recent prospective clinical trials as well (78–81). As a result, intravitreal aflibercept is now FDA-approved for treatment of non-proliferative DR, as well as PDR and DME. However, at this point, it seems unlikely that anti-VEGF therapy will be used on a large scale for routine treatment of non-proliferative DR. The DRCR.net Protocol W trial showed that anti-VEGF therapy for non-proliferative DR could prevent the onset of PDR and DME, but that final visual outcomes were no different from a strategy of initial observation, with treatment for PDR or DME initiated as-needed (81). Furthermore, while anti-VEGF therapy results in regression of vascular lesions and apparent “improvement” in DR severity, reports show that the underlying retinal ischemia is unchanged, and that lesions and retinopathy often recur rapidly after cessation (82, 83). Finally, the cost-effectiveness of treating non-proliferative DR with regular anti-VEGF therapy has not been well-examined, but it is difficult to imagine widespread use outside of high-resource clinical settings.

Instead, new treatments that are more likely to have significant impact on the DR landscape over the next decade are those targeting new pathophysiologic pathways, and those

that improve the durability of treatment effect. For example, faricimab is a bi-specific monoclonal antibody that provides dual inhibition of both the VEGF and the angiopoietin (Ang) and tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Tie) pathways (84, 85). Inhibiting Ang-2 on top of VEGF-A is thought to provide a synergistic effect, with better vascular stability and reduction in vascular leakage (84). The recent phase 3 YOSEMITE and RHINE clinical trials demonstrated that intravitreal faricimab for DME provided substantial visual gains comparable to aflibercept, but with superior anatomic outcomes. More importantly, faricimab had a durable treatment effect, with more than 70% and 50% of eyes reaching dosing intervals of every 12 to 16 weeks, and 16 weeks respectively at 1 year (85). Other promising treatment strategies to provide increased durability and reduced treatment burden include high-dose aflibercept (8 mg), sustained delivery of ranibizumab through a refillable port delivery system (PDS), and gene therapy with agents such as RGX-314 and ADVM-022 for long-term VEGF suppression (86–89). By providing more durable treatment effect, these approaches aim to address real unmet needs in DME treatment, where high treatment burden, problems with compliance to therapy, and under-treatment limit real world visual outcomes (90–93). These treatment approaches will play a major role in DME management in the near future.

7 An updated classification system for diabetic retinal disease

As a consequence of these many exciting advances in the field of DR over the past few decades, our DR classification and severity staging systems need to be updated to keep pace with the latest developments (39, 40, 94). The ETDRS and ICDR severity scales that are in routine use have made tremendous impact to research trials and clinical management, but they are now 2 to 3 decades old, and have significant limitations (7, 95). Some of the key areas that need to be addressed in an updated classification system are: (1) Inclusion of relevant prognostic information from the retinal peripheries that can now be reliably imaged with UWF systems, (2) Recognition and assessment of non-vascular aspects of diabetic retinal disease, such as retinal neural dysfunction or DRN, (3) Incorporating information and biomarkers from available imaging modalities such as OCT and OCTA, (4) Greater emphasis on, and clinically-relevant severity classification for DME, which is now the most common cause of visual impairment from DR, and which drives management decisions, and (5) Accurate prognostication of eyes that have undergone intravitreal anti-VEGF or other treatments.

There are major international efforts ongoing to update the DR classification system, such as the Diabetic Retinal Disease Staging System Update Effort, a project which is part of the Mary Tyler Moore Vision Initiative, which brings together leading scientists and experts on DR, with the overall aim of preventing vision loss from diabetes (94). There are still many gaps and unmet needs in the literature that need to be addressed, to inform a robust, evidence-based updated classification system. Nevertheless, it is likely that we will see a new and improved DR classification and staging system soon, that will have major impact on how we practice and manage DR in 2030. Such a classification system will no doubt need to be validated, regularly reviewed, and further updated to keep pace with new developments in the field. Furthermore, various widely-used international DR management guidelines, such as those by the International Council of Ophthalmology (ICO), will also need to be updated in accordance with new classification systems (76).

8 Conclusion

Clearly, many important strides have been made in the field of DR over the past few years, which will shape and transform the clinical and research landscapes in the years to come. Here, we have attempted to anticipate and predict some of these trends that are likely to be influential over the next decade. While many of these new imaging, assessment and treatment modalities have the potential to significantly improve clinical outcomes in DR, it is important that these advances are translated equally to both high- and low-resource settings around the world. As we have discussed above, epidemiologic projections suggest a continued shift towards increased disease burden in low-resource settings, and advances in DR management must be accessible to these patient populations, if we hope to see continued reductions in the rates of visual loss and blindness from DR in 2030 and beyond.

Author contributions

T-ET and TYW both contributed to conception of the study, and drafting and revising of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

TYW is a coinventor, with patents pending, for a deep learning system for diabetic retinopathy, glaucoma, and age-related macular degeneration (SG Non-Provisional Application number 10201706186V), and a computer-implemented method for training an image classifier using weakly annotated training data (SG Provisional Patent Application number 10201901083Y), and is cofounder and shareholder of EyRIS Pte Ltd, Singapore.

The remaining author declares that the research was conducted in the absence of any other commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* (2012) 35:556–64. doi: 10.2337/dc11-1909

2. Ruta LM, Magliano DJ, Lemesurier R, Taylor HR, Zimmet PZ, Shaw JE. Prevalence of diabetic retinopathy in type 2 diabetes in developing and developed countries. *Diabetes Med* (2013) 30:387–98. doi: 10.1111/dme.12119

3. Ting DSW, Cheung GCM, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: A review. *Clin Exp Ophthalmol* (2016) 44:260–77. doi: 10.1111/ceo.12696

4. Wong TY, Mwamburi M, Klein R, Larsen M, Flynn H, Hernandez-Medina M, et al. Rates of progression in diabetic retinopathy during different time periods: A systematic review and meta-analysis. *Diabetes Care* (2009) 32:2307–13. doi: 10.2337/dc09-0615

5. Sabanayagam C, Yip W, Ting DSW, Tan G, Wong TY. Ten emerging trends in the epidemiology of diabetic retinopathy. *Ophthalmic Epidemiol* (2016) 23:209–22. doi: 10.1080/09286586.2016.1193618

6. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* (1991) 98:823–33.

7. Wilkinson CP, Ferris FL, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* (2003) 110:1677–82. doi: 10.1016/s0161-6420(03)00475-5

8. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* (1991) 98:766–85.

9. Alasil T, Waheed NK. Pan retinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. *Curr Opin Ophthalmol* (2014) 25:164–70. doi: 10.1097/ICU.0000000000000048

10. Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. *Retina* (2010) 30:452–8. doi: 10.1097/IAE.0b013e3181c70127

11. Fujimoto J, Swanson E. The development, commercialization, and impact of optical coherence tomography. *Invest Ophthalmol Vis Sci* (2016) 57:OCT1–OCT13. doi: 10.1167/iovs.16-19963

12. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* (2016) 123:1351–9. doi: 10.1016/j.ophtha.2016.02.022

13. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* (2012) 119:789–801. doi: 10.1016/j.ophtha.2011.12.039

14. Berrocal MH, Acaba LA, Acaba A. Surgery for diabetic eye complications. *Curr Diabetes Rep* (2016) 16:99. doi: 10.1007/s11892-016-0787-6

15. Gupta B, Sivaprasad S, Wong R, Laidlaw A, Jackson TL, McHugh D, et al. Visual and anatomical outcomes following vitrectomy for complications of diabetic retinopathy: the DRIVE UK study. *Eye (Lond)* (2012) 26:510–6. doi: 10.1038/eye.2011.321

16. Zhang Z-H, Liu H-Y, Hernandez-Da Mota SE, Romano MR, Falavarjani KG, Ahmadieh H, et al. Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: a meta-analysis of randomized controlled trials. *Am J Ophthalmol* (2013) 156:106–15.e2. doi: 10.1016/j.ajo.2013.02.008

17. Teo ZL, Tham Y-C, Yu M, Chee ML, Rim TH, Cheung N, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: Systematic review and meta-analysis. *Ophthalmology* (2021) 128:1580–91. doi: 10.1016/j.ophtha.2021.04.027

18. Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ, McCall N, et al. The economic burden of major adult visual disorders in the united states. *Arch Ophthalmol* (2006) 124:1754–60. doi: 10.1001/archopht.124.12.1754

19. Romero-Aroca P, de la Riva-Fernandez S, Valls-Mateu A, Sagarra-Alamo R, Moreno-Ribas A, Soler N, et al. Cost of diabetic retinopathy and macular oedema in a population, an eight year follow up. *BMC Ophthalmol* (2016) 16:136. doi: 10.1186/s12886-016-0318-x

20. Chen E, Looman M, Laouri M, Gallagher M, Van Nuys K, Lakdawalla D, et al. Burden of illness of diabetic macular edema: Literature review. *Curr Med Res Opin* (2010) 26:1587–97. doi: 10.1185/03007995.2010.482503

21. Nguyen HV, Tan GSW, Tapp RJ, Mital S, Ting DSW, Wong HT, et al. Cost-effectiveness of a national telemedicine diabetic retinopathy screening program in Singapore. *Ophthalmology* (2016) 123:2571–80. doi: 10.1016/j.ophtha.2016.08.021

22. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med* (1996) 124:164–9. doi: 10.7326/0003-4819-124-1_part_2-199601011-00017

23. Javitt JC, Canner JK, Sommer A. Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. *Ophthalmology* (1989) 96:255–64. doi: 10.1016/s0161-6420(89)32923-x

24. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, et al. Screening for diabetic retinopathy: New perspectives and challenges. *Lancet Diabetes Endocrinol* (2020) 8:337–47. doi: 10.1016/S2213-8587(19)30411-5

25. Sohn EH, Han IC, Abramoff MD. Diabetic retinal neurodegeneration-should we redefine retinopathy from diabetes? *JAMA Ophthalmol* (2019) 137 (10):1132–3. doi: 10.1001/jamaophthalmol.2019.2536

26. Sohn EH, van Dijk HW, Jiao C, Kok PHB, Jeong W, Demirkaya N, et al. Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. *Proc Natl Acad Sci USA* (2016) 113: E2655–2664. doi: 10.1073/pnas.1522014113

27. Lynch SK, Abràmoff MD. Diabetic retinopathy is a neurodegenerative disorder. *Vision Res* (2017) 139:101–7. doi: 10.1016/j.visres.2017.03.003

28. Abramoff MD, Fort PE, Han IC, Jayasundera KT, Sohn EH, Gardner TW. Approach for a clinically useful comprehensive classification of vascular and neural aspects of diabetic retinal disease. *Invest Ophthalmol Vis Sci* (2018) 59:519–27. doi: 10.1167/iovs.17-21873

29. Chen X, Nie C, Gong Y, Zhang Y, Jin X, Wei S, et al. Peripapillary retinal nerve fiber layer changes in preclinical diabetic retinopathy: A meta-analysis. *PloS One* (2015) 10:e0125919. doi: 10.1371/journal.pone.0125919

30. Lim HB, Shin YI, Lee MW, Park GS, Kim JY. Longitudinal changes in the peripapillary retinal nerve fiber layer thickness of patients with type 2 diabetes. *JAMA Ophthalmol* (2019) 137(10):1125–32. doi: 10.1001/jamaophthalmol.2019.2537

31. Aschauer J, Pollreisz A, Karst S, Hülsmann M, Hajdu D, Datlinger F, et al. Longitudinal analysis of microvascular perfusion and neurodegenerative changes in early type 2 diabetic retinal disease. *Br J Ophthalmol* (2022) 106(4):528–33. doi: 10.1136/bjophthalmol-2020-317322

32. Obara EA, Hannibal J, Heegaard S, Fahrenkrug J. Loss of melanopsin-expressing retinal ganglion cells in patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci* (2017) 58:2187–92. doi: 10.1167/iovs.16-21168

33. Sokol S, Moskowitz A, Skarf B, Evans R, Molitch M, Senior B. Contrast sensitivity in diabetics with and without background retinopathy. *Arch Ophthalmol* (1985) 103:51–4. doi: 10.1001/archopht.1985.01050010055018

34. Han Y, Adams AJ, Bearse MA, Schneck ME. Multifocal electroretinogram and short-wavelength automated perimetry measures in diabetic eyes with little or no retinopathy. *Arch Ophthalmol* (2004) 122:1809–15. doi: 10.1001/archopht.122.12.1809

35. Falsini B, Porciatti V, Scalia G, Caputo S, Minnella A, Di Leo MA, et al. Steady-state pattern electroretinogram in insulin-dependent diabetics with no or minimal retinopathy. *Doc Ophthalmol* (1989) 73:193–200. doi: 10.1007/BF00155037

36. Aung MH, Kim MK, Olson DE, Thule PM, Pardue MT. Early visual deficits in streptozotocin-induced diabetic long evans rats. *Invest Ophthalmol Vis Sci* (2013) 54:1370–7. doi: 10.1167/iovs.12-10927

37. Feigl B, Zele AJ, Fader SM, Howes AN, Hughes CE, Jones KA, et al. The post-illumination pupil response of melanopsin-expressing intrinsically photosensitive retinal ganglion cells in diabetes. *Acta Ophthalmol* (2012) 90: e230–234. doi: 10.1111/j.1755-3768.2011.02226.x

38. Tan T-E, Finkelstein MT, Tan GSW, Tan ACS, Chan CM, Mathur R, et al. Retinal neural dysfunction in diabetes revealed with handheld chromatic pupillometry. *Clin Exp Ophthalmol* (2022) 50(7):745–56. doi: 10.1111/ceo.14116

39. Jampol LM, Tadayoni R, Ip M. Need for a new classification of diabetic retinopathy. *Retina* (2021) 41:459–60. doi: 10.1097/IAE.0000000000003070

40. Sun JK, Aiello LP, Abràmoff MD, Antonetti DA, Dutta S, Pragnell M, et al. Updating the staging system for diabetic retinal disease. *Ophthalmology* (2021) 128 (4):490–3. doi: 10.1016/j.ophtha.2020.10.008

41. Choudhry N, Duker JS, Freund KB, Kiss S, Querques G, Rosen R, et al. Classification and guidelines for widefield imaging: Recommendations from the international widefield imaging study group. *Ophthalmol Retina* (2019) 3:843–9. doi: 10.1016/j.oret.2019.05.007

42. Byberg S, Vistisen D, Diaz L, Charles MH, Hajari JN, Valerius M, et al. Optos wide-field imaging versus conventional camera imaging in Danish patients with type 2 diabetes. *Acta Ophthalmol* (2019) 97:815–20. doi: 10.1111/aos.14118

43. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. *Ophthalmology* (2013) 120:2587–95. doi: 10.1016/j.ophtha.2013.05.004

44. Aiello LP, Odia I, Glassman AR, Melia M, Jampol LM, Bressler NM, et al. Comparison of early treatment diabetic retinopathy study standard 7-field imaging with ultrawide-field imaging for determining severity of diabetic retinopathy. *JAMA Ophthalmol* (2019) 137:65–73. doi: 10.1001/jamaophthalmol.2018.4982

45. Price LD, Au S, Chong NV. Optomap ultrawide field imaging identifies additional retinal abnormalities in patients with diabetic retinopathy. *Clin Ophthalmol* (2015) 9:527–31. doi: 10.2147/OPTH.S79448

46. Silva PS, El-Rami H, Barham R, Gupta A, Fleming A, van Hemert J, et al. Hemorrhage and/or microaneurysm severity and count in ultrawide field images and early treatment diabetic retinopathy study photography. *Ophthalmology* (2017) 124:970–6. doi: 10.1016/j.ophtha.2017.02.012

47. Silva PS, Cavallerano JD, Haddad NMN, Kwak H, Dyer KH, Omar AF, et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. *Ophthalmology* (2015) 122:949–56. doi: 10.1016/j.ophtha.2015.01.008

48. Sadda SR, Nittala MG, Taweebanjongsin W, Verma A, Velaga SB, Alagorie AR, et al. Quantitative assessment of the severity of diabetic retinopathy. *Am J Ophthalmol* (2020) 218:342–52. doi: 10.1016/j.ajo.2020.05.021

49. Marcus DM, Silva PS, Liu D, Aiello LP, Antoszyk A, Elman M, et al. Association of predominantly peripheral lesions on ultra-widefield imaging and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol* (2022) 140 (10):946–54. doi: 10.1001/jamaophthalmol.2022.3131

50. Silva PS, Marcus DM, Liu D, Aiello LP, Antoszyk A, Elman M, et al. Association of ultra-widefield fluorescein angiography–identified retinal nonperfusion and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol* (2022) 140(10):936–45. doi: 10.1001/jamaophthalmol.2022.3130

51. Chua J, Sim R, Tan B, Wong D, Yao X, Liu X, et al. Optical coherence tomography angiography in diabetes and diabetic retinopathy. *J Clin Med* (2020) 9 (6):1723. doi: 10.3390/jcm9061723

52. Tan T-E, Nguyen Q, Chua J, Schmetterer L, Tan GSW, Wong CW, et al. Global assessment of retinal arteriolar, venular and capillary microcirculations using fundus photographs and optical coherence tomography angiography in diabetic retinopathy. *Sci Rep* (2019) 9:11751. doi: 10.1038/s41598-019-47770-9

53. Sun Z, Yang D, Tang Z, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: An updated review. *Eye (Lond)* (2021) 35 (1):149–61. doi: 10.1038/s41433-020-01233-y

54. Ting DSW, Tan GSW, Agrawal R, Yanagi Y, Sie NM, Wong CW, et al. Optical coherence tomographic angiography in type 2 diabetes and diabetic retinopathy. *JAMA Ophthalmol* (2017) 135:306–12. doi: 10.1001/jamaophthalmol.2016.5877

55. Nesper PL, Roberts PK, Onishi AC, Chai H, Liu L, Jampol LM, et al. Quantifying microvascular abnormalities with increasing severity of diabetic retinopathy using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* (2017) 58:BIO307–15. doi: 10.1167/iovs.17-21787

56. Tsai ASH, Jordan-Yu JM, Gan ATL, Teo KYC, Tan GSW, Lee SY, et al. Diabetic macular ischemia: Influence of optical coherence tomography angiography parameters on changes in functional outcomes over one year. *Invest Ophthalmol Vis Sci* (2021) 62:9. doi: 10.1167/iovs.62.1.9

57. You QS, Wang J, Guo Y, Pi S, Flaxel CJ, Bailey ST, et al. Optical coherence tomography angiography avascular area association with 1-year treatment requirement and disease progression in diabetic retinopathy. *Am J Ophthalmol* (2020) 217:268–77. doi: 10.1016/j.ajo.2020.04.024

58. Custo Greig E, Brigell M, Cao F, Levine ES, Peters K, Moult EM, et al. Macular and peripapillary optical coherence tomography angiography metrics predict progression in diabetic retinopathy: A Sub-analysis of TIME-2b study data. *Am J Ophthalmol* (2020) 219:66–76. doi: 10.1016/j.ajo.2020.06.009

59. Sun Z, Tang F, Wong R, Lok J, Szeto SKH, Chan JCK, et al. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: A prospective study. *Ophthalmology* (2019) 126:1675–84. doi: 10.1016/j.ophtha.2019.06.016

60. Ting DSW, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, et al. Artificial intelligence and deep learning in ophthalmology. *Br J Ophthalmol* (2019) 103:167–75. doi: 10.1136/bjophthalmol-2018-313173

61. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA* (2016) 316:2402–10. doi: 10.1001/jama.2016.17216

62. Ting DSW, Cheung CY-L, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA* (2017) 318:2211–23. doi: 10.1001/jama.2017.18152

63. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med* (2018) 1:39. doi: 10.1038/s41746-018-0040-6

64. Bhaskaranand M, Ramachandra C, Bhat S, Cuadros J, Nittala MG, Sadda SR, et al. The value of automated diabetic retinopathy screening with the EyeArt system: A study of more than 100,000 consecutive encounters from people with diabetes. *Diabetes Technol Ther* (2019) 21:635–43. doi: 10.1089/dia.2019.0164

65. Xie Y, Nguyen QD, Hamzah H, Lim G, Bellemo V, Gunasekeran DV, et al. Artificial intelligence for teleophthalmology-based diabetic retinopathy screening in a national programme: an economic analysis modelling study. *Lancet Digit Health* (2020) 2:e240–9. doi: 10.1016/S2589-7500(20)30060-1

66. Varadarajan AV, Bavishi P, Ruamviboonsuk P, Chotcomwongse P, Venugopalan S, Narayanaswamy A, et al. Predicting optical coherence tomography-derived diabetic macular edema grades from fundus photographs using deep learning. *Nat Commun* (2020) 11:130. doi: 10.1038/s41467-019-13922-8

67. De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med* (2018) 24:1342–50. doi: 10.1038/s41591-018-0107-6

68. Hsu H-Y, Chou Y-B, Jheng Y-C, Kao Z-K, Huang H-Y, Chen H-R, et al. Automatic segmentation of retinal fluid and photoreceptor layer from optical coherence tomography images of diabetic macular edema patients using deep learning and associations with visual acuity. *Biomedicines* (2022) 10:1269. doi: 10.3390/biomedicines10061269

69. Roberts PK, Vogl W-D, Gerendas BS, Glassman AR, Bogunovic H, Jampol LM, et al. Quantification of fluid resolution and visual acuity gain in patients with diabetic macular edema using deep learning: A *Post hoc* analysis of a randomized clinical trial. *JAMA Ophthalmol* (2020) 138:945–53. doi: 10.1001/jamaophthalmol.2020.2457

70. Schmidt-Erfurth U, Reiter GS, Riedl S, Seeböck P, Vogl W-D, Blodi BA, et al. AI-Based monitoring of retinal fluid in disease activity and under therapy. *Prog Retin Eye Res* (2022) 86:100972. doi: 10.1016/j.preteyeres.2021.100972

71. Schlegl T, Waldstein SM, Bogunovic H, Endstraßer F, Sadeghipour A, Philip A-M, et al. Fully automated detection and quantification of macular fluid in OCT using deep learning. *Ophthalmology* (2018) 125:549–58. doi: 10.1016/j.ophtha.2017.10.031

72. Sears CM, Nittala MG, Jayadev C, Verhoek M, Fleming A, van Hemert J, et al. Comparison of subjective assessment and precise quantitative assessment of lesion distribution in diabetic retinopathy. *JAMA Ophthalmol* (2018) 136:365–71. doi: 10.1001/jamaophthalmol.2018.0070

73. Nicholson L, Ramu J, Chan EW, Bainbridge JW, Hykin PG, Talks SJ, et al. Retinal nonperfusion characteristics on ultra-widefield angiography in eyes with severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. *JAMA Ophthalmol* (2019) 137:626–31. doi: 10.1001/jamaophthalmol.2019.0440

74. Ehlers JP, Jiang AC, Boss JD, Hu M, Figueiredo N, Babiuch A, et al. Quantitative ultra-widefield angiography and diabetic retinopathy severity: An assessment of panretinal leakage index, ischemic index and microaneurysm count. *Ophthalmology* (2019) 126:1527–32. doi: 10.1016/j.ophtha.2019.05.034

75. Tan T-E, Wong TY, Ting DSW. Artificial intelligence for prediction of anti-VEGF treatment burden in retinal diseases: Towards precision medicine. *Ophthalmol Retina* (2021) 5:601–3. doi: 10.1016/j.oret.2021.05.001

76. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on diabetic eye care: The international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology* (2018) 125:1608–22. doi: 10.1016/j.ophtha.2018.04.007

77. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial. *JAMA* (2015) 314:2137–46. doi: 10.1001/jama.2015.15217

78. Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. *Ophthalmol Retina* (2018) 2:997–1009. doi: 10.1016/j.oret.2018.06.005

79. Mitchell P, McAllister I, Larsen M, Staurenghi G, Korobelnik J-F, Boyer DS, et al. Evaluating the impact of intravitreal aflibercept on diabetic retinopathy progression in the VIVID-DME and VISTA-DME studies. *Ophthalmol Retina* (2018) 2:988–96. doi: 10.1016/j.oret.2018.02.011

80. Brown DM, Wykoff CC, Boyer D, Heier JS, Clark WL, Emanuelli A, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: Results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol* (2021) 139(9):946–55. doi: 10.1001/jamaophthalmol.2021.2809

81. Maturi RK, Glassman AR, Josic K, Antoszyk AN, Blodi BA, Jampol LM, et al. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: The protocol W randomized clinical trial. *JAMA Ophthalmol* (2021) 139(7):701–12. doi: 10.1001/jamaophthalmol.2021.0606

82. Couturier A, Rey P-A, Erginay A, Lavia C, Bonnin S, Dupas B, et al. Widefield OCT-angiography and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and edema treated with anti-vascular endothelial growth factor. *Ophthalmology* (2019) 126:1685–94. doi: 10.1016/j.ophtha.2019.06.022

83. Pearce E, Chong V, Sivaprasad S. Aflibercept reduces retinal hemorrhages and intravitreal microvascular abnormalities but not venous beading: Secondary analysis of the CLARITY study. *Ophthalmol Retina* (2020) 4:689–94. doi: 10.1016/j.oret.2020.02.003

84. Regula JT, Lundh von Leithner P, Foxton R, Barathi VA, Cheung CMG, Bo Tun SB, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med* (2016) 8:1265–88. doi: 10.15252/emmm.201505889

85. Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, Haskova Z, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet* (2022) 399:741–55. doi: 10.1016/S0140-6736(22)00018-6

86. Brown DM. Evaluation of 8 mg intravitreal aflibercept injection for neovascular age-related macular degeneration: Results from the phase 2 CANDELA study. *Investigative Ophthalmology Visual Sci* (2022) 63:1345–F0179.

87. Holekamp NM, Campochiaro PA, Chang MA, Miller D, Pieramici D, Adamis AP, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* (2022) 129:295–307. doi: 10.1016/j.ophtha.2021.09.016

88. Tan T-E, Fenner BJ, Barathi VA, Tun SBB, Wey YS, Tsai ASH, et al. Gene-based therapeutics for acquired retinal disease: Opportunities and progress. *Front Genet* (2021) 12:795010. doi: 10.3389/fgene.2021.795010

89. Xu D, Khan MA, Ho AC. Creating an ocular biofactory: Surgical approaches in gene therapy for acquired retinal diseases. *Asia Pac J Ophthalmol (Phila)* (2021) 10:5–11. doi: 10.1097/APO.0000000000000362

90. Blinder KJ, Dugel PU, Chen S, Jumper JM, Walt JG, Hollander DA, et al. Anti-VEGF treatment of diabetic macular edema in clinical practice: Effectiveness and patterns of use (ECHO study report 1). *Clin Ophthalmol* (2017) 11:393–401. doi: 10.2147/OPTH.S128509

91. Mitchell P, Sheidow TG, Farah ME, Mahmood S, Minnella AM, Eter N, et al. Effectiveness and safety of ranibizumab 0.5 mg in treatment-naïve patients with diabetic macular edema: Results from the real-world global LUMINOUS study. *PloS One* (2020) 15:e0233595. doi: 10.1371/journal.pone.0233595

92. Van Aken E, Favreau M, Ramboer E, Denhaerynck K, MacDonald K, Abraham I, et al. Real-world outcomes in patients with diabetic macular edema treated long term with ranibizumab (VISION study). *Clin Ophthalmol* (2020) 14:4173–85. doi: 10.2147/OPTH.S281501

93. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: A real-world analysis of 28 658 patient eyes. *Br J Ophthalmol* (2021) 105:216–21. doi: 10.1136/bjophthalmol-2020-315933

94. Sun JK, Gardner TW, Abramoff MD, Aiello LP, Colhoun H, Glassman AR, et al. Updating the diabetic retinal disease staging system through the restoring vision moonshot™. *Invest Ophthalmol Visual Sci* (2022) 63:2207–F0270.

95. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified airlie house classification. ETDRS report number 10. *Ophthalmology* (1991) 98:786–806.