Lecture

The Diabetic Retinopathy "Pandemic" and Evolving Global Strategies: The 2023 Friedenwald Lecture

Tien Yin Wong[1–3] and Tien-En Tan[1,2]

[1]Singapore Eye Research Institute, Singapore, Singapore National Eye Centre, Singapore
[2]Duke-National University of Singapore, Singapore
[3]Tsinghua Medicine, Tsinghua University, Beijing, China

Correspondence: Tien Yin Wong, Senior Vice Chancellor and Chair Professor, Tsinghua Medicine, Tsinghua University, Beijing, China and Senior Advisor, Singapore National Eye Centre, Singapore;
wongtienyin@tsinghua.edu.cn.

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Diabetes mellitus and diabetic retinopathy (DR) are diseases that pose global public health challenges on a massive scale. Professor Andrew Boulton, President of the International Diabetes Federation (IDF), recently declared diabetes a "pandemic of unprecedented magnitude," alongside the release of the latest epidemiologic estimates of the global disease burden.[1] The latest report from the IDF estimates that 10.5%, or over 1 in 10, of the world's adult population currently lives with diabetes, which in absolute terms accounts for more than half a billion individuals.[2] Projections indicate that this burden is set to rise sharply, to almost 800 million individuals by 2045. Crucially, this disease burden is not restricted to any particular country or region, but has a major impact on all countries around the world, regardless of income and development status.[2,3] Diabetes, along with other "noncommunicable diseases" were traditionally considered predominantly afflictions of high-income, developed countries, but this is no longer true, and in absolute terms there are now more individuals with diabetes living in the developing world than established developed countries.[2,3]

DR is a key microvascular end-organ complication of diabetes, occurring in 30% to 40% of all diabetic individuals, and the rise in diabetes prevalence is clearly paralleled in DR.[4,5] A recent meta-analysis estimated that the current global prevalence of DR is about 103 million individuals, which is projected to rise further to 161 million individuals by 2045.[6] As with diabetes, from a public health perspective, it may be more informative to consider the pattern of growth, rather than just the overall increase in DR burden. Based on recent epidemiologic projections to 2030, the rates of increase in DR prevalence in middle- to low-income regions, such as the Western Pacific, the Middle East, North Africa, and Africa, range from 20.6% to 47.2%, which far outstrips the projected rates in high-income regions, such as Europe and North America.[5,6] These are also the areas that will see the largest increase of disease burden in absolute terms.

Clearly, the DR pandemic is a pressing global problem that needs to be addressed with urgency. Broad, system-wide strategies are needed to tackle the pandemic (see the Fig.): (1) evolving understanding of the epidemiology, risk factors, and public health challenges in DR, (2) evolving strategies to develop effective biomarkers in DR, and (3) evolving screening strategies for DR, leveraging technologies, such as telemedicine and artificial intelligence (AI).

Evolving Understanding of the Epidemiology, Risk Factors, and Public Health Challenges in DR

The first step to being able to mount an effective response to a problem lies in understanding its scale and breadth. Large concerted efforts to understand the epidemiology of DR started primarily in White populations in the 1980s. In the early 1980s, Barbara and the late Ronald Klein started the pivotal Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), funded by the National Eye Institute (NEI) in the United States.[7,8] This study provided a wealth of new information about the incidence, progression, and risk factors for DR, first with 4-year follow-up, then 10-year follow-up, and even up to 25-year follow-up data.[8–11] However, this study cohort consisted of mainly non-Hispanic White participants in an affluent, high-income country. Other large, influential epidemiologic cohort studies that were established in the early 1990s, such as the Rotterdam Study and the Blue Mountains Eye Study, were also carried out in White populations, and it was unclear if these epidemiologic observations and risk factors would generalize to other populations and socioeconomic settings as well.[12,13] By the late 2000s, epidemiologic data on DR prevalence and burden started to become available from population-based cohorts in Asia, including India, China, and Singapore.[14–17] With the data available from more geographically and ethnically diverse cohorts, this allowed for better definition of the global DR disease burden, through meta-analyses of large pooled cohorts.[4] The latest update to this meta-analysis was in 2020/2021, where global DR prevalence was estimated at 103 million, and projected to increase to 161 million by 2045.[6] Current diabetic macular edema (DME) prevalence was also estimated at 19 million individuals, and projected to increase to 29 million by 2045.[6] Data from diverse cohorts in different regions allowed for detailed projection of growth rates stratified by region. Such detailed, region-specific data are crucial

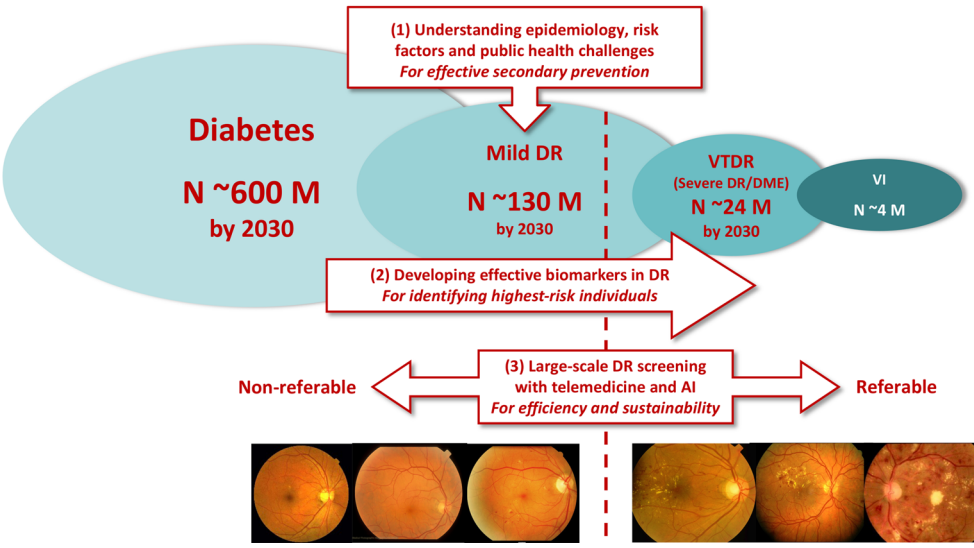

Figure. Schematic diagram illustrating the systems-wide strategies needed to tackle the DR pandemic. DR, diabetic retinopathy; VTDR, vision-threatening diabetic retinopathy; DME, diabetic macular edema; VI, visual impairment; M, million; AI, artificial intelligence.

for planning public health interventions targeted at the DR pandemic.

Continued efforts to provide up-to-date, accurate epidemiologic data in DR are essential to detect changing trends, and to allow for appropriate resource allocation in the years to come. Interestingly, the future of epidemiologic studies may turn out to be quite different from the existing, resource-intensive model. In current studies, significant resources are generally devoted to human grading of color fundus photographs (CFPs) and other retinal imaging modalities gathered from thousands of participants, across multiple study time points. However, some groups have recently validated approaches to leverage on AI and deep learning algorithms to grade large-scale epidemiologic data quickly, accurately, and efficiently. For example, Ting et al. applied an AI system for automated DR grading to a large dataset consisting of more than 90,000 CFP images, and compared this AI system against human graders, who are the existing standard of care. They showed that both methods of grading identified similar DR prevalence rates, and could reproduce the exact same epidemiologic risk factors for DR. However, the automated AI model was able to achieve its grading of the large dataset in about 1 month, which was much shorter than the estimated 2 years required by the human graders.[18] Similarly, innovative application of AI and other new technologies to existing large-scale datasets could accelerate the findings from epidemiologic studies, or even potentially generate new insights to guide policy-making and public health strategies.

Besides providing estimates of disease burden, epidemiologic studies also provide essential information on potentially modifiable risk factors, which can be targeted for effective secondary prevention (see the Fig.). Analysis of the available cohort studies has provided many important insights in this regard. First, the most important risk factors for DR incidence and progression are diabetes duration, glycemic control (usually measured in glycated hemoglobin A1c [HbA1c] levels), and blood pressure or hypertension control.[4,10,11,19] Of these major risk factors, the latter two are clearly modifiable. Second, these risk factors have been consistently demonstrated across many diverse cohorts, regardless of differences in ethnicity.[20,21] Third, these risk factors have also been shown to be remarkably consistent across both urban and rural populations.[22,23]

So, if we know where the problem is, and how to effectively reduce the risk of DR incidence and progression, why has this not yet translated to significant improvements? What are the public health challenges that need to be addressed? The first key challenge is a lack of disease awareness. In a cross-sectional study from the United States in the mid-2000s, about 55% to 74% of individuals with DR and/or DME were found to be unaware of their diabetic eye disease.[24] In a population-based survey in Singapore also from the mid-2000s, more than 80% of individuals with DR, and about 50% of individuals with severe DR were undiagnosed and unaware of their disease.[25] Clearly, even in affluent, well-developed countries with good healthcare access, there exist major gaps in disease awareness and diagnosis. Data from other, lower-income countries and regions is lacking, but is likely to show similar or even lower levels of disease awareness. The second key challenge is that systemic risk factor control among diabetic and DR populations remains almost uniformly poor. This is despite clear, robust evidence that glycemic control and blood pressure control are powerful modifiable risk factors for DR. For example, a cross-sectional survey of patients with diabetes attending a tertiary ophthalmology clinic in Australia found that only 30% of patients had blood pressure levels within target, and less than half were aware of the importance of blood pressure control.[26] A different survey targeted at ophthalmologists in the same country found that only 55% of ophthalmologists regularly reviewed blood pressure levels in their management of patients with DR.[27] In Singapore, among patients with DR in a population-based cohort, fewer than 20% of patients achieved their targets for optimal glycemic or blood pressure control.[28] Nevertheless, whereas statistics from studies like this can be somewhat surprising or disheartening, they do provide clear direction in terms of the public health challenges that need to be addressed, to improve DR outcomes at the population level. Without proper definition or understanding of the key challenges, it would be impossible to formulate effective or useful solutions.

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Evolving Strategies to Develop Effective Biomarkers in DR

The second essential key strategy for tackling the DR pandemic is the development of new, effective prognostic biomarkers for DR progression and visual loss (see the Fig.). A "biomarker" is defined by the US Food and Drug Administration (FDA) as a "defined characteristic that is measured as an indicator of … pathogenic processes, or responses to an exposure of intervention."[29] The FDA defines different categories of biomarkers, but in this context we are concerned specifically with "prognostic biomarkers," which are "used to identify likelihood of a clinical event, disease recurrence, or progression."[29] DR follows clearly defined stages of disease, progressing from no or subclinical disease to mild DR, and then to vision-threatening DR (VTDR) in about 5% to 10% of patients, where they have DME or are at high risk for proliferative complications, which lead to visual loss and blindness.[4,6] This pattern of disease progression provides a clear opportunity for early intervention to prevent vision loss in the later stages of disease. However, the sheer scale of the diabetic population (currently more than half a billion individuals worldwide) necessitates that we have effective ways of identifying this subset of patients who progress to VTDR, and who are at greatest risk of visual loss, so that they can be targeted for intervention (see the Fig.). Herein lies the need for effective prognostic biomarkers in the early stages of DR.[4]

Attempts to identify biomarkers for DR from retinal imaging are not new. Film-based CFP imaging was first used as the basis for early DR severity classification systems from the 1960s, including the Hammersmith classification and the original Airlie House classification.[30–32] Modified Airlie House classifications, including the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale and the WESDR classification systems also started out using film-based CFP images.[33(p10),34] Eventually, these were replaced by digital CFP imaging, but the biomarkers and disease severity scales graded within the images remained the same.[35–38] The ETDRS severity scale graded on CFP images is still widely considered the gold standard in DR severity staging and prognostication.[33] This severity scale is based on the identification and qualitative grading of various retinal vascular lesions, such as retinal hemorrhages and microaneurysms (H/MAs), venous beading (VB), intra-retinal microvascular abnormalities (IRMAs), and new vessels (NVs).[33] The ETDRS severity scale was validated as a prognostic biomarker on longitudinal natural history data from 3711 eyes with untreated DR in the ETDRS study in the 1980s, where it was demonstrated that the severity scale could effectively predict the risk of progression to proliferative diabetic retinopathy (PDR) at 1-, 3-, and 5-year time points.[39] The ETDRS and the subsequently simplified International Clinical Diabetic Retinopathy (ICDR) severity scales as prognostic biomarkers for progression to PDR, have been the basis for much of clinical DR management and research over the past few decades.[40] DR severity classification has been used to determine appropriate clinical surveillance intervals, escalation from teleophthalmology screening programs, thresholds for laser treatment with panretinal photocoagulation (PRP), and as surrogate end points for clinical trials.[41,42]

Despite the success of the ETDRS severity scale, the search for new and better biomarkers in DR has continued, as imaging and image analysis technology have improved. Retinal vessel caliber and geometry have been investigated for years as potentially useful biomarkers in DR. From as early as the 1960s, observations were made from clinical ophthalmoscopy and film-based CFP images that retinal vessel caliber was different in patients with and without diabetes.[43] However, more widespread investigation and application of these insights were limited by the technology available at the time, as there was no way to rapidly and accurately measure these parameters. In the 1990s, the development of computer-assisted semi-automated quantification techniques, such as the Singapore I Vessel Assessment (SIVA) allowed for more rigorous evaluation of these potential biomarkers.[40,44,45] Analysis of longitudinal epidemiologic datasets with these tools showed that retinal vessel caliber was associated with incident diabetes in otherwise healthy persons.[46–48] Subsequent studies also demonstrated that retinal vessel caliber could predict the risk of DR progression, progression to PDR, and other diabetic microvascular complications.[49–52] Besides just vascular caliber, other quantitative metrics in relation to retinal vascular geometry, such as vascular tortuosity and fractal dimensions, were also independently linked to incidence and progression of DR, and other diabetic microvascular complications.[53,54] More recently, the development of AI and deep learning techniques has allowed for fully automated AI-enabled segmentation and quantification of retinal vessels from CFP images, which have now been validated as powerful predictors of systemic cardiovascular risk and outcomes.[55,56]

With the introduction of new retinal imaging modalities, the search for more effective DR biomarkers has continued in earnest. Widefield and ultra-widefield (UWF) retinal imaging platforms are now in regular clinical and research use, which can reproducibly image much more of the retinal periphery. Standard CFP imaging typically captures 45 degrees to 50 degrees in a single image, and the standard 7-field ETDRS images cover only about 30% of total retinal surface area.[32,57] In contrast, UWF imaging platforms can now capture up to 200 degrees in a single image, or about 80% of the retinal surface area.[32,57] Some longitudinal cohort studies have now shown that DR lesions in the peripheral retina imaged either with color/pseudocolor photography, or with fluorescein angiography (FA), may have important prognostic implications for outcomes such as progression to PDR, or DR progression.[58–60] However, some of the results of these studies have been inconsistent, and the optimal method of grading and quantifying peripheral DR lesions has yet to be established.[58,60–64] "Traditional" ETDRS severity scale grading also changes when the peripheral retina is taken into account, and the prognostic implications of this are still an area of active study.[65–67] Updating the current gold standard DR severity classification and grading system to improve the predictive ability of our prognostic biomarkers is a priority for the field.[35,68,69]

Optical coherence tomography (OCT) and OCT angiography (OCTA) are also compelling noninvasive retinal imaging modalities with a wealth of information for new DR biomarkers. OCT studies have shown that patients with diabetes have evidence of retinal neural thinning and neurodegeneration, which often precedes the development of clinically-visible retinopathy.[70–72] Functional studies with modalities, such as electrophysiology, psychophysical testing, and pupillometry, have also revealed evidence of diabetic retinal neural dysfunction early in the disease process.[73–75] The evidence pointing to diabetic retinal neurodegeneration (DRN) occur-

ring early in the disease process from multiple different assessment modalities indicates the potential for DRN to be an important prognostic, monitoring, or pharmacodynamic/response biomarker in DR.[29] Studies looking at validating these DRN biomarkers are in progress. Meanwhile, OCTA allows for noninvasive, depth-resolved assessment of the retinal capillary microvasculature, and can provide angiographic information without the need for dye administration.[76] OCTA provides a multitude of quantitative retinal vascular parameters, such as foveal avascular zone (FAZ) measures, as well as vessel density and perfusion indices from the superficial, intermediate, and deep capillary plexuses, and even the choriocapillaris and deeper choroidal layers.[76] Some longitudinal cohort studies have begun to demonstrate the prognostic capability of some of these quantitative OCTA biomarkers in predicting clinical outcomes, such as DR progression, DME, and visual loss.[77–79] However, barriers and challenges that need to be solved include standardization and cross-validation of OCTA metrics between different devices and scan protocols, as well as the need for more consistent, prospective longitudinal data.[80]

Finally, the evolution of AI and deep learning techniques has begun to unlock the potential of hypothesis-free biomarkers from retinal imaging, which may ultimately prove to be more powerful at prognostication than focusing on specific lesions or parameters alone. Bora et al. developed deep learning algorithms for prediction of developing incident DR within 2 years that used only CFP images as algorithm input. The AI models that they developed were able to provide relatively accurate predictions of progression, and also provided independent prognostic information over and above established clinical risk factors, such as duration of diabetes and glycemic control.[81] So far, this sort of hypothesis-free AI and deep learning techniques have only been applied successfully to CFP imaging, but with the wealth of rich, complex information available from UWF imaging, FA, OCT, and OCTA images, it seems highly likely that a hypothesis-free approach with these other imaging modalities holds significant promise as well.

Ultimately, the development of better, and more accurate prognostic biomarkers in DR will allow us to effectively risk stratify the sizable global population with diabetes, so as to be able to focus and allocate resources on the highest-risk individuals, and prevent visual loss on a large scale.

Evolving Screening Strategies for DR: From Telemedicine to AI

Good biomarkers for DR progression and risk are only useful in combating the DR pandemic, if they can be widely applied to screening patients with diabetes at the population level, to prevent vision loss in an efficient and cost-effective manner (see the Fig.). The benefits of DR screening are clear and universally acknowledged. In 1989, based on estimates of treatment benefit from clinical trials on PRP, Rohan et al. made the case for the benefits of "an effectively managed community based screening program encompassing detection, referral, treatment, and follow up" in England and Wales.[82] In one of the earliest demonstrations of translating these recommendations in practice, Bäcklund et al. showed that the implementation of a DR screening program in 1990 resulted in a 47% reduction in the incidence rates of diabetes-related blindness in Stockholm Country in Sweden over the next 5 years.[83] Subsequent studies also showed that DR screening for prevention of visual loss was clearly cost-effective.[84,85] As a result, regular DR screening for individuals with diabetes is now universally recommended by many international guidelines published by ophthalmologists and endocrinologists alike.[41,86]

However, despite the acknowledged benefits of large-scale DR screening, there exist only a few truly nationwide DR screening programs around the world, such as in the United Kingdom, Singapore, and Iceland. Many other large, developed countries, including the United States, and certainly most developing countries, do not have established nationwide DR screening programs. Implementing large-scale DR screening programs in these settings presents a huge opportunity to reduce preventable visual loss around the world. However, the challenges to implementing such population-based or community-based DR screening programs need to be acknowledged, including: (1) significant investment in infrastructure, (2) lack of human capital in the form of doctors or trained non-physician graders, (3) increased workload on tertiary ophthalmic services generated by screening, (4) establishing a framework for appropriate follow-up, referral and treatment, (5) reimbursement and other legislative barriers, and (6) sustainability and cost-effectiveness. Nevertheless, the technologies now available to us, including teleophthalmology and AI, can help to address and resolve many of these challenges.

In this regard, it is worth examining the establishment and evolution of the national DR screening program in Singapore as a case study. In 2004, based on the available evidence and in consultation with expert workgroups, the Singapore Ministry of Health issued a recommendation for regular DR screening for all patients with diabetes at the national level. At the time, DR screening was initiated on an ad hoc basis, by primary care physicians and endocrinologists caring for patients with diabetes, and CFP images were being graded by primary care family physicians. This national recommendation led to the development of the Singapore Integrated Diabetic Retinopathy Program (SIDRP), which was a nationwide teleophthalmology-based DR screening program set up in 2010.[87] In the SIDRP setup, digital CFP images were acquired by nurses at government-funded primary care clinics across Singapore, and these images were transferred to centralized reading centers through a secure cloud-based teleophthalmology information technology infrastructure. Images were read by trained, non-physician, professional image graders, and then screening reports with referral recommendations based on standardized referral criteria were transmitted back to the primary clinics, with a turnaround time of less than 1 hour. Key advantages of this teleophthalmology system over the traditional model of screening in Singapore at the time were: (1) rapid turnaround time of 1 hour, versus 2 to 4 weeks, (2) freeing up family physician manpower and resources for other tasks, (3) modified standardized referral criteria to only refer patients with referable DR (previously patients with mild DR were being referred as well), (4) greater diagnostic accuracy, and (5) greater cost-effectiveness.[87,88] Over the next decade, the SIDRP screening program was progressively expanded to eventually include all government-funded primary care clinics throughout Singapore, and now to handling more than 110,000 DR screening encounters annually. Data collected in Singapore after implementation has demonstrated that the SIDRP screening program provides similar outcomes to the previ-

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ous physician-based screening model, but at significantly lower cost, with estimated future cost savings of almost SGD $30 million over a lifetime horizon.[87]

Although this teleophthalmology screening model has proven to be effective and economically viable, there remain concerns about future scalability and sustainability, as the diabetes prevalence and disease burden continues to increase. Therefore, it is essential to see how new technologies such as AI can be safely and effective integrated into the system, to further enhance its efficiency and long-term sustainability. Multiple different AI-based systems have been developed and validated for DR screening around the world, with some systems already having obtained regulatory approval in some countries, and being deployed for clinical use.[89–92] From Singapore, the SELENA+ (EyRIS Pte Ltd., Singapore) AI-based DR screening system was developed primarily on images and screening data from the SIDRP, and has since been validated and tested on numerous datasets from other countries.[90,93] SELENA+ has received European CE Mark approval, and is currently being piloted for implementation in the SIDRP, before a potential nationwide rollout.[5] Preliminary data from the prospective pilot study has demonstrated acceptable accuracy compared to the existing standard of care (unpublished data). Demonstrating diagnostic accuracy of an AI-based system for DR screening is one thing, but how best to integrate an AI system into existing screening workflows is an unresolved question. With this in mind, Xie et al. conducted an economic analysis modeling study with the SELENA+ algorithm, and compared a "replacement" approach, where the AI model completely replaced human graders in the existing workflow, against a "triage" approach, where the AI model was used as a first-pass "triage" tool, to screen out the majority of low-risk cases and reduce human grader workload, and to refer only a subset of cases to human graders for second grading and confirmation.[94] The authors demonstrated that the "triage" workflow approach resulted in the greatest cost savings, and recommended this approach. Although the SELENA+ algorithm started out initially as an academic project in Singapore, it has since been licensed to a commercial start-up company (EyRIS Pte Ltd., Singapore) to manage operational, regulatory, and commercial aspects, to accelerate eventual implementation.

One of the key takeaways from our experience in the design and preliminary implementation of an AI-based system in our national DR screening program is the addition of an AI model as a specific, narrow, and incremental, change to the existing workflow, with an assistive rather than disruptive role, combined with teleophthalmology, and in a manner that does not adversely impact ophthalmologists in the system.

Concluding Observations

The DR pandemic is a truly global challenge, that will affect every country and every healthcare setting. The scale of the problem is massive, with the numbers of individuals with diabetes and DR projected to rise to 800 million and 161 million respectively around the world by 2045.[2,6]

However, not all the news is bad. Significant progress has already been made over the past few decades in the fight against this pandemic, and we are already beginning to the see some of the positive effects. Due in part to a combination of better systemic management, penetrance of DR screening programs, in some parts of the world, and access to better ocular treatments such as laser photocoagulation and intravitreal therapy, we are seeing encouraging signs that the rates of PDR and DR-related blindness are coming down in many countries. For example, long-term 25-year data from the WESDR has shown that patients diagnosed with DR in recent years have lower rates of progression to PDR that in the 1980s.[9] When a different, multi-ethnic cohort of patients in the United States were examined first in the early 2000s, and then again 8 years later, it was found that almost a quarter of participants had shown improvements in DR severity.[95,96] In the United Kingdom, where nationwide DR screening programs have been implemented for many years, the rates of DR-related blindness have dropped significantly, such that "for the first time in at least five decades, diabetic retinopathy/maculopathy is no longer the leading cause of certifiable blindness among working age adults in England and Wales."[97] A meta-analysis of prospective studies on DR has also shown significant reductions in the rates of progression to PDR and visual loss over the past few decades.[98]

Epidemiologic data like this over the decades provides strong encouragement that we are making progress in the war against DR. However, there is still much to be done. Given the scale of the problem, and the impact of diabetes and DR across the globe, it is clear that systemwide strategies are needed to tackle this pandemic going forward. With a combination of systemwide strategies, such as better understanding of the remaining public health challenges, continued development of more effective prognostic biomarkers in DR, and with the implementation of sustainable AI-based large-scale screening programs for DR, we can have confidence that we have the necessary tools to fight this pandemic, and ultimately save vision for millions of people around the world.

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