Strategies to Tackle the Global Burden of Diabetic Retinopathy: From Epidemiology to Artificial Intelligence

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Keywords

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Abstract

Diabetes is a global public health disease projected to affect 642 million adults by 2040, with about 75% residing in low- and middle-income countries. Diabetic retinopathy (DR) affects 1 in 3 people with diabetes and remains the leading cause of blindness in working-aged adults. There are 3 broad strategic imperatives to prevent blindness caused by DR. Primary prevention requires preventing or delaying the onset of DR in those with diabetes by systems-level lifestyle modifications such as increasing physical activity or dietary modifications, pharmacological interventions for glycaemic and blood pressure control, and systematic screening for the onset of DR. Secondary prevention requires preventing the progression of DR in patients with DR by continuing systemic risk factor control, regular screening to monitor for the progression of mild DR to vision-threatening stages, and the development and implementation of evidence-based guidelines for managing DR. In this aspect, telemedicine-based DR screening incorporating artificial intelligence technology

has the potential to facilitate more widespread and cost-effective screening, particularly in low- and middle-income countries. Tertiary prevention of DR blindness has been the main focus of the clinical ophthalmology community, classically based on laser photocoagulation treatment and ocular surgery but with an increasing use of anti-vascular endothelial growth factor (anti-VEGF) for vision-threatening DR. Evidence from serial epidemiological studies shows blindness due to DR has declined in high-income countries (e.g., the USA and UK) due to coordinated public health education efforts, increased awareness, early detection by DR screening, sustained systemic risk factor control, and the availability of effective tertiary level treatment. However, the progress made in reducing DR blindness in high-income countries may be overwhelmed by the increasing numbers of patients with diabetes and DR in low- and middle-income countries (e.g., China, India, Indonesia, etc.). Thus, to tackle DR at a global level, a paradigm shift in strategic focus from tertiary towards secondary and primary prevention measures with a multi-pronged whole-of-society approach at regional and national levels is urgently needed.

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Introduction

It is well known that diabetes is a global “epidemic”. In 2015, an estimated 415 million people had diabetes globally, and this number is projected to increase to 642 million by 2040 [1]. Less commonly recognized is that about three-quarters of those with diabetes reside in low- and middle-income countries (sometimes termed “developing countries”) rather than in high-income countries (developed countries). Furthermore, with rapid industrialization and urbanization in the last 50 years, many traditionally classified low- and middle-income countries (e.g., China and India) are facing an alarming increase in the incidence of diabetes in a relatively short time [2]. For example, from 1994 to 2008, diabetes prevalence in China increased by 300% [3].

Diabetic retinopathy (DR), the leading cause of blindness and visual impairment in working-aged adults, is associated with a poor quality of life, lower levels of psychosocial well-being, and an increased risk of other diabetes complications and mortality [4–6]. It has been estimated that more than one-third of those with diabetes worldwide have some form of DR and nearly 1 in 10 have vision-threatening levels of DR (VTDR) including proliferative DR (PDR) and diabetic macular edema (DME) [7].

Some recent studies have provided “good news,” with blindness due to DR showing a declining trend in high-income countries (e.g., the USA and UK) due to the combination of a concerted public health effort, increased awareness, regional- or national-level DR screening, and the availability of improved therapies including anti-vascular endothelial growth factor (anti-VEGF) agents [8–10]. However, with the rising prevalence of diabetes, and growing and ageing population worldwide, the absolute number of people with DR is expected to increase. Furthermore, low- and middle-income countries which bear the brunt of the diabetes epidemic are unlikely to reflect similar trends of declining DR blindness to those seen in high-income countries, due to a lack of planning, eye-care resources, and limited access to quality and affordable eye-care.

Like any global public health chronic disease, strategies to tackle the DR epidemic can broadly be classified into primary, secondary, and tertiary prevention strategies (Fig. 1). Primary prevention includes preventing or delaying the onset of the disease (in this case, mild DR in those with diabetes). It requires an increasing awareness of the risk of DR and blindness in patients with diabetes, systems-level lifestyle modifications such as

more physical activity or dietary modifications, pharmacological interventions for glycaemic and blood pressure control, and systematic screening for the onset of DR. Secondary prevention requires the implementation of programmes to delay the progression of DR with an emphasis on systemic risk factor control, regular DR screening to monitor for the progression of mild DR to vision-threatening stages, and the development and implementation of evidence-based guidelines for managing DR. Traditionally, ophthalmologists, particularly in high-income countries, have focused on the tertiary prevention of DR blindness based on timely laser photocoagulation treatment and ocular surgery, but increasingly on the widespread use of anti-VEGF for VTDR, including DME and PDR.

We propose that, to effectively tackle DR at a global level, a paradigm shift in focus from tertiary towards secondary and primary prevention measures is required, particularly in low- and middle-income countries.

What Is the Current Understanding of the Epidemiology of Diabetes and DR?

In 2010, the International Diabetes Federation estimated that 285 million adults aged 20–79 years were affected by diabetes worldwide. By 2040, this number is expected to almost triple to 642 million [1]. Due to the rapid and ongoing socioeconomic transition, the increase in number of people with diabetes is expected to be substantial in low- and middle-income countries. For example, between 2010 and 2030, the number of adults with diabetes will increase by 69% in low- and middle-income countries compared to only 20% in high-income countries [11]. In fact, globally, two-thirds of diabetes patients live in low- and middle-income countries, particularly India and China. Furthermore, the classic risk profile of diabetic patients in low- and middle-income countries differs from that in high-income countries. While the increasing prevalence of diabetes in high-income “western” societies has been largely attributed to the increased life expectancy of the population, in low- and middle-income countries with rapid urbanization and industrialization, several risk factors like weight gain and obesity due to sedentary lifestyle, unhealthy diet, high blood pressure and high cholesterol have been shown to contribute. In addition, Asians tend to develop diabetes at least a decade earlier and at a lower BMI than whites. These differences suggest that the health care systems of countries with different economic status and different populations should focus on different public health strategies to control diabetes prevalence [2].

What Do We Know about the Trends in DR Blindness?

Globally, in 2010, DR was ranked the fifth-most common cause of blindness and moderate-to-severe vision loss; of the 32.4 million blind and 191 million visually impaired, 0.8 million were blind and an additional 3.7 million were visually impaired due to DR [12]. However, in high-income countries, population-based and screening studies suggest a declining trend in the rates of DR-related blindness. Evidence from long-term prospective studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that the incidence of PDR has declined since the late 1990s [13]. This trend is supported by serial screening studies in Europe that showed a greater than two-thirds reduction in the prevalence of blindness after the introduction of free DR screening services [14]. In a pooled meta-analysis with data on from multiple time points in high-income countries, the incidence of PDR as well as severe visual loss after 4 years is substantially lower at a later time period (1986–2008), 2.6 and 3.2%, respectively, than previously (1975–1985), i.e., 19.5 and 9.7%, respectively [8]. This decline in high-income countries has been attributed to concerted public health prevention efforts including improved glycaemic and blood pressure control and reduced smoking rates, coupled with educational and screening programmes for the early detection and timely treatment of VTDR [13]. There is no evidence to support a similar trend in low- and middle-income countries which face challenges in systematic screening and timely intervention.

As recently as 2 decades ago, most of the epidemiological data on the prevalence and incidence of DR was based on earlier studies from white populations such as the WESDR [15–18]. In recent years, substantially more data on DR in other ethnic groups in Asia [19–21] and Africa is now available. In 2010, a global meta-analysis was performed, estimating that 35% were affected by any DR, 10% of which had VTDR [7]. The lifetime risk of developing DR is estimated to be 50–60% in patients with type 2 diabetes [15] and up to 90% in those with type 1 diabetes [22].

Although widely studied, it remains unclear if there are perceptible variations in the prevalence and risk of DR across countries or racial/ethnic groups. Previously, some studies suggested the prevalence of DR is higher in western than Asian populations: 29–40% in the USA, 27% in Canada, and 30% in the UK and Australia, with corresponding estimates of 15.8% in South Korea, 18% in In-

dia, and 23% in China [23]. Although these figures may indicate that Asian countries have a lower prevalence than western populations, more recent study and a meta-analysis of 72 studies conclude that DR prevalence may actually be higher in Asian countries and that the previously reported lower rates may have been due to a lack of awareness, late detection of DR, and poor access to health care. With regard to racial/ethnic variations, DR prevalence has been reported to be higher in minority ethnic groups and migrant populations. In the USA, African-Americans and Mexicans are reported to have a higher prevalence of DR as well as VTDR than whites [24], attributed to poorer glycaemic control and lower screening and treatment rates in these minority ethnic groups. In the UK, south Asians have a significantly higher prevalence of DR than white Europeans (45 vs. 37% of any DR; 16 vs. 12% of VTDR) as well as higher levels of modifiable risk factors and early onset of diabetes [25]. In Singapore, Indians were found to have higher prevalence than Malays and Chinese [26]. Within the large immigrant Indian populations in Singapore, second-generation Indians have a higher prevalence of diabetes and DR than first-generation Indians. It has been speculated that the acculturation to a western lifestyle has contributed to this higher prevalence in immigrant populations [27]. Untangling possible variations in the epidemiology of DR according to country, region, or race/ethnicity is complex and may be impossible.

Are Risk Factors for DR Different across Populations?

Another important epidemiological question is whether there are variations in risk factor associations for DR, and therefore a need for population-specific systemic control strategies? It appears that, despite some reported variations in the prevalence of DR in high-income and low- to middle-income societies, across ethnic groups, and in new immigrant versus native populations, systemic risk factors for DR have largely been consistent across studies. These include the classic “big three” risk factors: a longer diabetes duration, hypertension, and hyperglycaemia.

The classic epidemiological data shows that after 20 years of having diabetes, nearly all patients with type 1 and 60% of those with type 2 have some form of retinopathy. In the global meta-analysis study, when compared to those with <10 years of type 2 diabetes, those with ≥20 years had a 2.5 times increased risk of any DR and 6.3 times increased risk of VTDR after accounting for poor metabolic control; corresponding estimates for type 1 diabetes were 2.7 times for any DR and 8.7 times for VTDR

[7]. Almost all of the studies have consistently shown that poor glycaemic control is associated with the development and progression of DR across populations; this includes prospective studies on both type 1 [28] and type 2 [19, 20, 29] diabetes. Similarly, hypertension and higher systolic blood pressure are important risk factors for DR, again demonstrated in many studies including prospective studies on type 1 [30] and type 2 [19, 31, 32] diabetes. The relationship of dyslipidaemia as a risk factor for DR is less consistently demonstrated in epidemiological studies.

The consistency of findings from epidemiological studies on the importance of control of systemic risk factors for DR is strongly supported by data from landmark randomized controlled trials. This includes the effectiveness of tight glycaemic control and hypertension control in reducing the risk and progression of DR in both type 1 and type 2 diabetes, shown in the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS). There are 3 important observations from these trials. First, the DCCT showed that, in type 1 diabetes, intensive glycaemic control is extremely important and that patients randomized to a tight glycaemic control regimen have their risk of DR cut by 75% and progression of DR by 54% over 6.5 years. Furthermore, tight glycaemic control has broad ocular benefits, with patients experiencing a 35–50% reduction in the need for diabetes-related ocular surgery including cataract surgery and vitrectomy. Second, tight glycaemic control appears to not be crucial in type 2 diabetes. In the UKPDS, involving type 2 diabetes, when compared to the conventional treatment group, patients randomized to intensive glycaemic control had their DR risk cut by only 25%. This was confirmed by a recent meta-analysis of type 2 diabetes from 7 trials, in which intensive glycaemic control reduced the risk of DR by only 20% [33]. Third, hypertension control may be more important in type 2 diabetes. In the UKPDS, hypertensive patients allocated to tight BP control (<150/85 mm Hg) had their risk of progression of DR cut by 34% and the risk of deterioration in visual acuity reduced by 47% over a 9-year period. In the Steno-2 study, multi-factorial intervention of hyperglycaemia, hypertension, dyslipidemia, and microalbuminuria, with glucose-lowering drugs, angiotensin-converting enzyme inhibitors, and statins, reduced the risk of macro- and microvascular events including DR by about 50%, demonstrating the benefit of a proactive, target-driven multi-factorial risk reduction approach to optimizing outcomes in people with type 2 diabetes [34].

Because of the consistency of epidemiological studies and large trials across populations, a uniform strategy to manage systemic risk factors is possible for all diabetic patients with and without DR around the world. In this respect, many guidelines, including those of the International Council of Ophthalmology (ICO), recommend that all patients with diabetes should aim to have maintenance of glycaemic control, with HbA_{1c} levels <7%, and treatment of hypertension and dyslipidemia.

What Are the Strategies to Tackle Global Blindness due to DR?

Extrapolating the age-standardized prevalence of DR estimated by Yau et al. [7] in 2010 to the 2040 diabetic population [1], we estimate that ~93 million adults will have any DR and ~38 million will have VTDR by 2040, assuming that DR prevalence remained the same in 2010 and 2040. These numbers are substantial. Thus, similar to other major global public health problems (e.g., coronary heart disease, stroke, dementia, and cancers), tackling DR requires broad, population-based strategies, classically divided according to the stage of intervention as primary, secondary, or tertiary (Fig. 1).

Primary prevention is applied to individuals with diabetes but without evidence of DR, and aims to prevent or delay the onset of DR. Secondary prevention is applied to those with early stages of DR, with the goal of preventing the progression of DR to vision-threatening stages. Tertiary prevention is applied to those with VTDR, and aims to prevent blindness, restore vision, and improve the quality of life of those with visual losses.

Primary prevention includes a variety of measures:

- Lifestyle and behavioural modifications before the development of diabetes or DR
- An improved awareness of DR
- Self-management of diabetes and hypertension
- Pharmacological interventions to improve glycaemic and blood pressure control
- DR screening for the early detection of DR.

Secondary prevention strategies can include any or all of the following measures:

- Continuation of pharmacological interventions to improve glycaemic and blood pressure control
- DR screening and monitoring for the progression of early DR to VTDR
- Implementation of guidelines and policy across all countries specific to their health care system for the management of DR.

Fig. 1. Prevention strategies for tackling the epidemic of diabetic retinopathy. DR, diabetic retinopathy; DME, diabetic macular edema; VI, visual impairments; M, 1 million people.

Tertiary prevention includes:

- Laser photocoagulation for PDR
- Anti-VEGF therapy for DME and PDR
- Vitrectomy in those with more advanced DR
- Improved quality of life by visual rehabilitation among those with DR blindness.

Traditionally, the ophthalmology community, particularly in high-income countries, has focused their efforts largely on the tertiary prevention of DR blindness, based on improving the delivery of laser photocoagulation treatment and ocular surgery, but also increasingly the widespread use of anti-VEGF for VTDR including DME and PDR. Some of these measures have been driven by industry which has actively promoted the use of anti-VEGF therapy even in low- and middle-income countries. However, we and others have now suggested that, in order to effectively tackle DR at a global level, a major paradigm shift is necessary and the community should move from tertiary towards secondary and primary prevention measures, particularly in low- and middle-income countries.

What Challenges Are Involved in the Primary and Secondary Prevention of DR?

Implementing secondary and primary prevention measures, even in high-income countries, is complex and challenging. We identify some immediate challenges and major barriers that need to be addressed before such a strategy can be effective. Some of these are listed in

Table 1 along with strategies to improve primary and secondary prevention of blindness due to DR.

Suboptimal Awareness of DR in Diabetes Patients by Physicians Continues to Limit the Delivery of Evidence-Based Care and the Implementation of Guidelines

Diabetes, like many chronic diseases, affects multiple organ systems. Improving awareness and knowledge about the natural history of diabetes and the risk of complications, including DR, is therefore recognized as an important public health strategy. However, awareness of DR in diabetes patients continues to be suboptimal in both low- and middle-income and high-income countries. In the USA, in the National Health and Nutrition Examination Survey (NHANES), 73% of patients with DR were unaware of their disease status. Correspondingly, 80% in the Singapore Epidemiology of Eye Diseases (SEED) Study [35] and 73% in the Andhra Pradesh Eye Disease Study in India were unaware of their DR status. Even among patients with advanced DR needing treatment, 25% in Singapore and 60% in Iran were not aware of the disease [35]. Unfortunately, the availability of even simple DR education materials is limited in low- and middle-income countries and is almost non-existent in extremely low-income settings like Africa.

Adherence to DR screening, even if it were available, is also suboptimal. The International Diabetes Management Practice Study that evaluated diabetes treatment

Table 1. Challenges and possible solutions to improve prevention strategies for DR

Challenge	Solution
Awareness of DR among patients remains poor	Availability of patient education materials at primary and secondary care centers and structured education for people with diabetes to manage their condition and inform them about the risks to their sight early in the management of diabetes care, to ensure good compliance with regular eye checks
Awareness of DR remains suboptimal among primary care physicians	Structured education programmes for primary care physicians. Good communication between primary care physicians and ophthalmologists regarding patients' ocular findings, efficient referral practices, and a clear care pathway
Motivating patients to make behavioral modifications (lifestyle, medication adherence)	Focused educational and media campaigns to promote healthy food choices or reduce the consumption of unhealthy foods. The primary care physician, in discussion with patients, diabetologists, and other specialists should develop an individualized plan tailored to the patient's level of motivation and preference. Empower diabetic patients to self-manage their own disease through diet and exercise, blood pressure and glucose monitoring, and insulin administration where indicated, by deploying emerging technologies like wearable devices to track activities that promote lifestyle changes, the use of smart phones, and mobile apps for monitoring glycaemic and blood pressure levels, setting reminders for medications, etc
Variability of DR management guidelines across settings and difficulty in implementing guidelines in resource-limited settings	Adoption of DR management based on the type of resource setting as recommended in the ICO guidelines
Limited access to DR screening and coverage in poor/intermediate-resource settings	Telemedicine-based DR screening and task-shifting. Engagement of voluntary organizations/private partners to implement DR screening programmes and management, e.g., establishing a DR eye unit, training eye care professionals, screening for DR and treatment, providing medical equipment, establishing visual rehabilitation services and facilities, etc
Sustainability of DR screening programmes is questionable	Integrating DR screening into existing public health programmes such as healthy lifestyle initiatives, disease control, etc. AI-based screening methods with careful planning and design. Personalized screening based on risk stratification, e.g., extending the screening interval from annually to every 2 years in low-risk cases. To avoid over-referral, use OCT as a second-line screening tool for patients referred for DME based on fundus photography
Inadequate capacity of health care services to deliver primary and secondary prevention services in low- and middle-income countries	Partnering with non-governmental organizations, private partners, international agencies, etc. to improve DR care by providing screening, treatment, rehabilitative services, medicine, equipment, and training of eye care professionals
Eye health often receives inadequate resources, so securing the commitment of high-level decision-makers in the Ministry of Health to promote the prevention of avoidable blindness and improve eye health is crucial	Policy changes creating an enabling environment for making lifestyle changes like taxing unhealthy foods, providing food labels at supermarkets, building neighbourhood parks/exercise tracks, instituting smoking restrictions in public places, etc. Integrating eye care into routine diabetes care/primary care and integrating DR policies, guidelines, and training into all relevant national health policies and guidelines. Developing national action plans for addressing DR in consultation with relevant stakeholders across diabetic and eye health care, patients, the private sector, and provincial government, and then integrating these plans into national diabetes strategies. Including eye health considerations in workforce planning for services to be provided at primary/secondary/tertiary-level health care facilities. Promote surveillance and research for assessing the burden of DR, population needs and evaluating the cost-effectiveness of interventions, particularly in low- and middle-income countries

practices over a 5-year period in low- and middle-income countries reported that a quarter of those with type 2 diabetes in Asia and Latin America had never been screened for DR.

The DR Barometer Study, that assessed the level of awareness and provision of screening and treatment for

DR and DME from the perspective of 2,329 health care professionals involved in the management of adults with diabetes/DR/DME from 41 countries, found that more than one-third of the diabetes specialists surveyed reported that they did not discuss eye care with their diabetic patients and just over one-third of ophthalmologists re-

ported that they had sufficient information on diabetic eye complications [36]. The most common barriers to eye health in diabetic patients reported by eye care professionals were patients' lack of knowledge about DR/DME (43%), the lack of importance given to eye examinations by patients (33%), and the high cost of care (32%). Late screening (66%) and a lack of patient education materials (55%) were cited as barriers to optimal eye health by ophthalmologists. The study findings emphasized the need for health care professionals to be sufficiently trained and supported for providing optimal eye care to diabetic patients. However, a trial evaluating the effectiveness of patient education materials, aimed at family physicians to increase retinal screening of diabetic patients in Ontario where eye examinations including retinal screening is offered free for all those with diabetes, failed to demonstrate any impact of such materials on screening uptake (eye exam rates were 31.6% for patients of control physicians vs. 31.3% for those who received a short directive message, and 32.8% for those who received detailed information and reminders) [37]. This suggests that the use of educational materials alone is not a useful strategy for closing this evidence-practice gap among family physicians and emphasizes the importance of exploring alternative behavioral change interventions.

Effective communication between the ophthalmologist and the general physician (family physician/endocrinologist) regarding ocular findings also appears to sub-optimal. Diabetes management requires patients to visit different specialists besides ophthalmologists, and sub-optimal communication and referral practices between specialists were found to hinder effective care in the Barometer Study [36]. Good communication, efficient referral practices, and a clear care pathway are essential to ensure that each specialist has the appropriate information about the patient.

Behavioural Modifications to Lifestyle Measures and Systemic Control Are Challenging to Implement

It is well known that adopting a healthy lifestyle, i.e., exercising regularly and having a healthy diet (e.g., avoiding energy-dense food and eating more fruits and vegetables), is effective in preventing or delaying the onset of diabetes and also DR in those with diabetes. However, motivating patients to make lifestyle modifications is challenging. For patients with type 2 diabetes, a long-term weight loss goal of 5% of their body weight is recommended but also setting small behavioral targets like exercising regularly, controlling food portions, and tracking these changes to achieve the long-term goal of 5% weight

reduction. When primary care physicians discuss an individualized plan with patients, empower them to self-monitor their goals, assess the targets at each visit, and adjust their goals accordingly, this has been effective in making lifestyle changes.

For coronary heart disease and stroke, the American Heart Association has identified evidence-based strategies that are effective in improving diet and physical activity and reducing smoking habits. There are 6 domains: (1) sustained media and educational campaigns to improve diet, e.g., promoting the consumption of healthy food (fruits/vegetables) or reducing the consumption of unhealthy foods (fast foods/energy-dense foods/sugary drinks), (2) labelling and providing information on specific nutrients/calories on food items to improve food purchasing choices, (3) taxing unhealthy foods and providing subsidies for healthy choices, (4) wellness initiatives and availability of healthier food at workplaces, (5) making local environments conducive to lifestyle changes, such as building parks, playgrounds, and exercise facilities in neighbourhoods, and (6) restrictions and mandates that prohibit smoking in public places as well as allocating designated areas for smoking [38]. However, implementing these changes requires the substantial and sustained commitment and engagement of many stakeholders at various levels including policy-makers, public health officials, advocacy groups, clinicians, researchers, and private partners.

Treatment targets and strategies should be based on a stepwise approach, e.g., managing hyperglycaemia, starting with a single-drug therapy to a dual combination, and advancing to triple-drug combination while balancing the benefits and risks of glycaemic control. Also, personalized management plans focusing on patient-centric care is recommended, e.g., setting a more stringent glycaemic target for newly diagnosed, younger adults with no systemic comorbidities, and a less stringent glycaemic target for those with a longer duration of diabetes, established vascular complications, or the elderly, taking into account the potential risk of hypoglycaemia and a patient's age and health status [39]. Glycaemic control, coupled with a comprehensive cardiovascular risk reduction programme including smoking cessation, adoption of a healthy lifestyle, and adequate blood pressure and lipid control, has been shown to be effective in preventing/delaying long-term complications of diabetes [34].

Many diabetic patients without complications are not often motivated and do not always follow recommendations made by their primary care physicians at the time of diagnosis. Thus, ophthalmologists have a special and

unique responsibility to make their patients aware of the importance of adopting a healthy lifestyle and actively making lifestyle changes to maintain near-normal blood glucose and blood pressure levels.

Systematic Screening Programmes for DR Are Lacking or Inconsistent in Many Countries

DR has long been recognized as a classic condition that will benefit from regular screening. It is common in people with diabetes, but remains asymptomatic until advanced, with strong evidence that earlier treatment prevents loss of vision. Screening for DR and timely and appropriate referral to eye care services has been shown to be cost-effective [40]. Furthermore, in the longer term, early detection of DR appears to motivate patients to better manage their diabetes with improved glycaemic and blood pressure control.

In this regard, many major national (the American Diabetes Association and American Academy of Ophthalmology) and international (the ICO, International Diabetes Foundation, and WHO) concerns recommend that people with type 2 diabetes should have an initial dilated-eye examination at the time of their diabetes diagnosis and subsequent yearly examinations (or more frequently if DR progresses).

However, despite broad-level consensus, recommendations, and guidelines, adherence to regular DR screening is low in many communities, due to a combination of a lack of resources and infrastructure (lack of equipment and medication), a lack of trained eye care professionals including ophthalmologists and optometrists, and sub-optimal access to care. Even in high-income settings, challenges remain in implementing a cost-effective and sustainable DR screening program. In the USA, DR screening is patchy, and up to 50% of the diabetic population is not screened. In the UK, where screening services are offered for free, more than one-third of patients with diabetes do not adhere to the screening guidelines [41].

There is increasing use of telemedicine-based DR screening programmes with digital fundus photography (FP) in different settings. This is well established in the UK [42] and has been successfully adopted in Singapore. The Singapore Integrated DR Program (SiDRP) covers up to 200,000 people with diabetes in 18 primary care facilities in Singapore. Retinal photos taken at point-of-care are transmitted by means of a tele-ophthalmology platform and then read centrally by trained graders. Their reports are sent back to primary care clinics on the same day (90% in <1 h) and patients are referred to ophthalmologists if required. Comparing telemedicine screening

to the existing physician-assessed model, the saving in terms of direct costs was only SGD 144/person (EUR 94.20). Extrapolating this to the SiDRP population, this translates to a lifetime saving of ~SGD 29 million [43]. Telescreening and appropriate task-sharing and task-shifting between clinicians and health professionals, e.g., trained graders instead of ophthalmologists reading retinal images, is a fast, accurate and cost-effective solution to DR screening in all resource settings, and coverage is improved.

There Are Only a Few Consistent Clinical Guidelines Available

Whilst the implementation of broad-based public health programmes for diabetes care is feasible in high-income countries, it remains a serious challenge in countries with poor/intermediate resources and constrained by a lack of trained eye care professionals, equipment, drugs, infrastructure, etc. In many countries, the standard care pathway for DR is not clear. Guidelines are important to improve care. However, few comprehensive guidelines are available in these settings. In a recent survey of 50 Asian countries, 11 had some form of guidelines; 2 were specific for DR and the rest were for general diabetes care [44].

What Are the Possible Strategies to Improve Primary and Secondary Prevention of DR Blindness?

Development of a Set of Universal Guidelines for DR Management Will Provide Standards for Care

In 2013, the ICO developed resource-specific guidelines for diabetic eye care based on best evidence from clinical data and input from stakeholders from different countries. The 2017 updated guidelines proposed a feasible, cost-effective, and sustainable set of recommendations for the management of DR specific for each resource setting, with a special focus on screening, referral, follow-up, and timely treatment [40]. The ICO suggests developing guidelines specific to resource setting. In high-resource settings, screening could include a visual acuity test with refraction and retinal photography. In poor/intermediate-resource settings, there should be a visual acuity test using the pinhole method and a clinical retinal examination with pupil dilation. The guidelines recommend that the screening timing for referral for VTDR should be the same (urgent referral) in all settings; however, for less severe stages, screening schedules for low- or intermediate-resource settings can be less frequent. A

suitable screening schedule for moderate, non-proliferative DR is 3–6 months for the high-resource setting and 6–12 months for settings with poor/intermediate resources. The use of optical coherence tomography (OCT), the most sensitive method for the detection of DME, is feasible for high-resource settings only, due to the costs and the need for skilled training of ophthalmologists. In poor/intermediate-resource settings, FP provides a feasible method of examining the presence and severity of DME. Screening could also be based on telemedicine-based approaches and task-shifting, where digital retinal photographs taken with non-mydriatic cameras in a primary care setting by nurses/technicians are then transmitted for remote interpretation by trained readers and consultation by ophthalmologists.

Digital and Mobile Technology Can Assist Patients and Public Health Education

Mobile health interventions via automated text messages, smartphone applications (apps), and wearable devices are increasingly playing a role in diabetes education, self-management, and prevention [45]. For instance, mobile apps tracking physical activity, diet, weight loss, and sleep quality help to set goals to suit individual preferences, and personalized feedback messages/emails with educational and motivational content and reminders to take medications and monitor blood sugar have been shown to improve behavioral changes and glycaemic control.

Personalized Screening Intervals and New Retinal Imaging Technologies Including AI May Increase the Reach and Yield of DR Screening

Risk of DR progression has been shown to be significantly higher in those with background DR in both eyes, compared to those with no background DR [46]. Risk stratification models that take into account patients' retinopathy status and glycaemic control have shown that in low-risk patients, e.g., those with no retinopathy detected at 2 consecutive visits and who have adequate glycaemic control, extending the screening interval to 2 years showed no significant difference in clinical outcomes in the 1-year and 2-year screening intervals. Personalized screening intervals based on retinopathy status and risk factors could improve adherence to screening and reduce the resources needed to screen for DR.

New imaging technology has been introduced in ophthalmology in the last few years. This has substantial potential to be applied in DR screening. For example, ultra-wide field (UWF) FP can capture a larger area of the ret-

ina than traditional cameras. In a population-based DR teleophthalmology programme in the USA, Silva et al. [47] compared DR screening by means of traditional non-mydriatic camera multi-field FP and UWF imaging in 8,109 patients. They found that UWF imaging reduced the rate of ungradable eyes by 81% and increased the rate of DR detection 2-fold. Another recent advance in DR screening is combining FP with OCT for detecting DME. The diagnosis of DME requires identification of macular thickening, so screening by non-stereo FP tends to have a high false-positive rate of around 80%. OCT, by imaging retinal thickness and structure with a high resolution, provides a more objective and quantitative assessment of macular edema than detection by FP and is widely recognized as the new reference standard for the assessment of DME, even in the screening setting [48]. We note that UWF and OCT imaging technologies are feasible only in high-resource settings.

There is substantial potential for the use of artificial intelligence (AI) in DR screening. Current DR screening programmes require manual grading of DR which is not sustainable in the long run, even in high-resource settings. Therefore, scaling up and expanding to meet the growing diabetes epidemic is challenging. AI-based technology, including deep-learning systems, is gaining popularity in ophthalmology, particularly for DR screening and automated segmentation of OCT images for diagnosing DR and DME [49]. Gulshan et al. [50] from Google Health were the first to show an automated algorithm based on retinal images with a very high accuracy for detecting referable DR ($\geq 99\%$). Since then, several deep-learning algorithms have been developed and validated in diverse populations. Ting et al. [51] recently developed an AI deep-learning system for identifying other sight-threatening eye diseases such as age-related macular degeneration and glaucoma besides referable DR. They compared its performance with manual grading in several local and external validation cohorts. For identifying referable DR, the system had an accuracy of 94% in the development cohort and 90–98% in the external validation cohorts. The system had accuracy of around 94% for other eye diseases. The AI system developed by Abramoff et al. [52], called IDX-DR, has been approved by the US Food and Drug Administration for detecting DR levels greater than mild in adults with diabetes without the need for interpretation by a clinician. Besides high-income settings, AI-based technology can also be deployed in low- and middle-income settings with appropriate planning. A recent study conducted in Zambia evaluated the performance of AI-based deep learning showed the system

had 97–99% accuracy for detecting referable DR, VTDR, and DME [53]. The findings support the potential for an AI-based screening model to be applied for DR screening in under-resourced African populations. The application of AI in poor-resource settings might need more careful and comprehensive design and planning, taking into consideration the availability of specialists, the cost-effectiveness of the programme, and the long-term patient outcomes. The performance of AI in DR screening is very promising, but several challenges remain that limit its use in clinical medicine, e.g., identifying image features that are critical to image classification, large-scale implementation, and the medico-legal implications [54].

An Integrated Approach to Optimal DR Care across Eye Health and Diabetes

To reduce the incidence and burden of loss of vision loss due to DR, the Global Diabetic Retinopathy Advocacy Initiative group recommends an integrated approach across eye health and diabetes that ensures that services, support, and information are available and accessible for all patients with diabetes [55]. The group identified 4 different models: (1) the integration of eye care into routine diabetes care/primary care, e.g., provision of eye health examinations/screening services as part of routine diabetes care by service providers; (2) the integration of diabetes into comprehensive/primary eye care, e.g., enhancing the skills of eye health professionals including ophthalmologists/optometrists to understand the consequences of DR, identification and management of DR and diabetes and the complications; (3) horizontal and vertical integration of services, e.g., improved referral/recall pathways within and across all levels of the health care system; and (4) integration of DR policies, guidelines, and training into all relevant national health policies, e.g., including DR-specific policies in national diabetes plans, national noncommunicable disease strategic planning, and other relevant high-level government policies. The initiative also provides specific recommendations for initiating, fostering, and driving the integrated care at the level of primary, secondary, and tertiary care, and for government and donors/funding and investment partners. For instance, primary care providers can spearhead preventive actions such as improving health literacy and educating people with DR what action can be taken to avoid the progression of DR, secondary and tertiary care providers can take a leading role in collaborating with other components of the health system to overcome barriers, governments can accelerate integrated care by developing and strengthening regulations,

laws, and policies that support it, provide appropriate financial coverage of DR services in insurance and benefit schemes, invest in infrastructure and technology, and donors can work with national and local governments to prioritize the populations and regions in greatest need of integrated care and direct funding to support advancement.

Partnership and Collaboration across Countries and Disciplines Will Address Gaps in Diabetes Care

Primary and secondary prevention efforts in low- and middle-income countries could be improved by partnering with non-governmental organizations, research foundations, the private sector, and international agencies to provide screening, equipment, drugs, DR units, treatment, and care, including rehabilitation services. Domestic and international stakeholders in these countries need to strengthen their engagement with ministries of health at both a political and economic level to invest in eye health and prevent avoidable blindness due to conditions including DR [56]. High-income countries can also help to build the local capacity to improve research and surveillance of avoidable blindness due to DR and share best practices with low- and middle-income countries.

In conclusion, we suggest that, while there has been major progress and advancement in understanding and managing DR in the past few years, DR is a global epidemic that needs significant innovative solutions as well as national and international strategies. Effective implementation of primary and secondary prevention strategies has the potential to significantly reduce blindness due to DR. Thus, a shift in focus from tertiary type DR treatment to primary and secondary prevention strategies is needed.

Disclosure Statement

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References

- Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017 Jun;128:40–50.
- Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. *Lancet*. 2010 Jan;375(9712):408–18.
- Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010 Mar;362(12):1090–101.
- Rees G, Xie J, Fenwick EK, Sturrock BA, Finger R, Rogers SL, et al. Association between Diabetes-Related Eye Complications and Symptoms of Anxiety and Depression. *JAMA Ophthalmol*. 2016 Sep;134(9):1007–14.
- Kramer CK, Rodrigues TC, Canani LH, Gross JL, Azevedo MJ. Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies. *Diabetes Care*. 2011 May;34(5):1238–44.
- Fenwick EK, Xie J, Ratcliffe J, Pesudovs K, Finger RP, Wong TY, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Invest Ophthalmol Vis Sci*. 2012 Feb;53(2):677–84.
- Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012 Mar;35(3):556–64.
- 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 Dec;32(12):2307–13.
- Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009–2010. *BMJ Open*. 2014 Feb;4(2):e004015.
- Claessen H, Kvitkina T, Narres M, Trautner C, Zöllner I, Bertram B, et al. Markedly Decreasing Incidence of Blindness in People With and Without Diabetes in Southern Germany. *Diabetes Care*. 2018 Mar;41(3):478–84.
- Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010 Jan;87(1):4–14.
- Leasher JL, Bourne RR, Flaxman SR, Jonas JB, Keeffe J, Naidoo K, et al.; Vision Loss Expert Group of the Global Burden of Disease Study. Global Estimates on the Number of People Blind or Visually Impaired by Diabetic Retinopathy: A Meta-analysis From 1990 to 2010. *Diabetes Care*. 2016 Sep;39(9):1643–9.
- Klein R, Klein BE. Are individuals with diabetes seeing better? A long-term epidemiological perspective. *Diabetes*. 2010 Aug;59(8):1853–60.
- Sabanayagam C, Yip W, Ting DS, Tan G, Wong TY. Ten Emerging Trends in the Epidemiology of Diabetic Retinopathy. *Ophthalmic Epidemiol*. 2016 Aug;23(4):209–22.
- Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol*. 1989 Feb;107(2):244–9.
- Looker HC, Krakoff J, Knowler WC, Bennett PH, Klein R, Hanson RL. Longitudinal studies of incidence and progression of diabetic retinopathy assessed by retinal photography in pima indians. *Diabetes Care*. 2003 Feb;26(2):320–6.
- McCarty DJ, Fu CL, Harper CA, Taylor HR, McCarty CA. Five-year incidence of diabetic retinopathy in the Melbourne Visual Impairment Project. *Clin Exp Ophthalmol*. 2003 Oct;31(5):397–402.
- Mitchell P. Development and progression of diabetic eye disease in Newcastle (1977–1984): rates and risk factors. *Aust NZ J Ophthalmol*. 1985 Feb;13(1):39–44.
- Raman R, Ganesan S, Pal SS, Gella L, Kulothungan V, Sharma T. Incidence and Progression of Diabetic Retinopathy in Urban India: Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS II), Report 1. *Ophthalmic Epidemiol*. 2017 Oct;24(5):294–302.
- Tam VH, Lam EP, Chu BC, Tse KK, Fung LM. Incidence and progression of diabetic retinopathy in Hong Kong Chinese with type 2 diabetes mellitus. *J Diabetes Complications*. 2009 May-Jun;23(3):185–93.
- Xu J, Xu L, Wang YX, You QS, Jonas JB, Wei WB. Ten-year cumulative incidence of diabetic retinopathy. The Beijing Eye Study 2001/2011. *PLoS One*. 2014 Oct;9(10):e111320.
- Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1989 Feb;107(2):237–43.
- Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)*. 2015 Sep;2(1):17.
- Zhang X, Saaddine JB, Chou CF, Cotch MF, Cheng YJ, Geiss LS, et al. Prevalence of diabetic retinopathy in the United States, 2005–2008. *JAMA*. 2010 Aug;304(6):649–56.
- Raymond NT, Varadhan L, Reynold DR, Bush K, Sankaranarayanan S, Bellary S, et al.; UK Asian Diabetes Study Retinopathy Study Group. Higher prevalence of retinopathy in diabetic patients of South Asian ethnicity compared with white Europeans in the community: a cross-sectional study. *Diabetes Care*. 2009 Mar;32(3):410–5.
- Tan GS, Gan A, Sabanayagam C, Tham YC, Neelam K, Mitchell P, et al. Ethnic Differences in the Prevalence and Risk Factors of Diabetic Retinopathy: The Singapore Epidemiology of Eye Diseases Study. *Ophthalmology*. 2018 Apr;125(4):529–36.
- Zheng Y, Lamoureux EL, Ikram MK, Mitchell P, Wang JJ, Younan C, et al. Impact of migration and acculturation on prevalence of type 2 diabetes and related eye complications in Indians living in a newly urbanised society. *PLoS One*. 2012;7(4):e34829.
- Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology*. 1998 Oct;105(10):1801–15.
- Kim YJ, Kim JG, Lee JY, Lee KS, Joe SG, Park JY, et al. Development and progression of diabetic retinopathy and associated risk factors in Korean patients with type 2 diabetes: the experience of a tertiary center. *J Korean Med Sci*. 2014 Dec;29(12):1699–705.
- Romero-Aroca P, Baget-Bernaldiz M, Fernandez-Ballart J, Plana-Gil N, Soler-Lluis N, Mendez-Marin I, et al. Ten-year incidence of diabetic retinopathy and macular edema. Risk factors in a sample of people with type 1 diabetes. *Diabetes Res Clin Pract*. 2011 Oct;94(1):126–32.
- Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001 Feb;44(2):156–63.
- Tudor SM, Hamman RF, Baron A, Johnson DW, Shetterly SM. Incidence and progression of diabetic retinopathy in Hispanics and non-Hispanic whites with type 2 diabetes. San Luis Valley Diabetes Study, Colorado. *Diabetes Care*. 1998 Jan;21(1):53–61.
- Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011 Nov;343:d6898.
- Gale R, Scanlon PH, Evans M, Ghanchi F, Yang Y, Silvestri G, et al. Action on diabetic macular oedema: achieving optimal patient management in treating visual impairment due to diabetic eye disease. *Eye (Lond)*. 2017 May;31 S1:S1–20.

- 35 Huang OS, Tay WT, Ong PG, Sabanayagam C, Cheng CY, Tan GS, et al. Prevalence and determinants of undiagnosed diabetic retinopathy and vision-threatening retinopathy in a multiethnic Asian cohort: the Singapore Epidemiology of Eye Diseases (SEED) study. *Br J Ophthalmol*. 2015 Dec;99(12):1614–21.
- 36 Cavan D, Makaroff LE, da Rocha Fernandes J, Karuranga S, Sylvanowicz M, Conlon J, et al. Global perspectives on the provision of diabetic retinopathy screening and treatment: survey of health care professionals in 41 countries. *Diabetes Res Clin Pract*. 2018 Sep;143:170–8.
- 37 Zwarenstein M, Shiller SK, Croxford R, Grimshaw JM, Kelsall D, Paterson JM, et al. Printed educational messages aimed at family practitioners fail to increase retinal screening among their patients with diabetes: a pragmatic cluster randomized controlled trial [ISRCTN72772651] [ISRCTN72772651]. *Implement Sci*. 2014 Aug;9(1):87.
- 38 Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, et al.; American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovasc. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation*. 2012 Sep;126(12):1514–63.
- 39 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015 Mar;58(3):429–42.
- 40 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 Oct;125(10):1608–22.
- 41 Schoenfeld ER, Greene JM, Wu SY, Leske MC. Patterns of adherence to diabetes vision care guidelines: baseline findings from the Diabetic Retinopathy Awareness Program. *Ophthalmology*. 2001 Mar;108(3):563–71.
- 42 Scotland GS, McNamee P, Fleming AD, Goatman KA, Philip S, Prescott GJ, et al.; Scottish Diabetic Retinopathy Clinical Research Network. Costs and consequences of automated algorithms versus manual grading for the detection of referable diabetic retinopathy. *Br J Ophthalmol*. 2010 Jun;94(6):712–9.
- 43 Nguyen HV, Tan GS, Tapp RJ, Mital S, Ting DS, Wong HT, et al. Cost-effectiveness of a National Telemedicine Diabetic Retinopathy Screening Program in Singapore. *Ophthalmology*. 2016 Dec;123(12):2571–80.
- 44 Wang LZ, Cheung CY, Tapp RJ, Hamzah H, Tan G, Ting D, et al. Availability and variability in guidelines on diabetic retinopathy screening in Asian countries. *Br J Ophthalmol*. 2017 Oct;101(10):1352–60.
- 45 Shan R, Sarkar S, Martin SS. Digital health technology and mobile devices for the management of diabetes mellitus: state of the art. *Diabetologia*. 2019 Jun;62(6):877–87.
- 46 Scanlon PH. Screening Intervals for Diabetic Retinopathy and Implications for Care. *Curr Diab Rep*. 2017 Sep;17(10):96.
- 47 Silva PS, Cavallerano JD, Haddad NM, Tolls D, Thakore K, Patel B, et al. Comparison of Nondiabetic Retinal Findings Identified with Nonmydriatic Fundus Photography vs. Ultra-wide Field Imaging in an Ocular Telehealth Program. *JAMA Ophthalmol*. 2016 Mar;134(3):330–4.
- 48 Virgili G, Menchini F, Casazza G, Hogg R, Das RR, Wang X, et al. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev*. 2015 Jan;1:CD008081.
- 49 Cheung CY, Tang F, Ting DS, Tan GS, Wong TY. Artificial Intelligence in Diabetic Eye Disease Screening. *Asia Pac J Ophthalmol (Phila)*. 2019 Apr.
- 50 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 Dec;316(22):2402–10.
- 51 Ting DS, Cheung CY, Lim G, Tan GS, 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 Dec;318(22):2211–23.
- 52 Abramoff MD, Lou Y, Erginay A, Clarida W, Amelon R, Folk JC, et al. Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning. *Invest Ophthalmol Vis Sci*. 2016 Oct;57(13):5200–6.
- 53 Bellemo V, Lim Z, Lim G, Nguyen Q, Xie Y, Yip M, et al. Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. *Lancet Digital Health*. 2019;1(1):e35–44.
- 54 Ting DS, Peng L, Varadarajan AV, Keane PA, Burlina PM, Chiang MF, et al. Deep learning in ophthalmology: the technical and clinical considerations. *Prog Retin Eye Res*. 2019 Apr;S1350-9462(18)30090-9.
- 55 IAPB. A global compendium on good practice: integrated care for diabetes and eye health [Internet] [cited 2018 Sep 25]. Available from: <https://www.iapb.org/tag/compendium-of-good-practice/>
- 56 Morone P, Cuenca EC, Kocur I, Banatvala N. Investing in eye health: securing the support of decision-makers. Geneva: WHO; 2012.