The Evolution of Diabetic Retinopathy Screening

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Abstract

Diabetic retinopathy (DR) is a leading cause of preventable blindness and has emerged as a global health challenge, necessitating the development of robust management strategies. As DR prevalence continues to rise, advancements in screening methods have become increasingly critical for timely detection and intervention. This review examines three key advancements in DR screening: a shift from specialist to generalist approach, the adoption of telemedicine strategies for expanded access and enhanced efficiency, and the integration of artificial intelligence (AI). In particular, AI offers unprecedented benefits in the form of sustainability and scalability for not only DR screening but other aspects of eye health and the medical field as a whole. Though there remain barriers to address, AI holds vast potential for reshaping DR screening and significantly improving patient outcomes globally.

Introduction: The Diabetic Retinopathy Pandemic

Diabetes has rapidly become a global health crisis, labelled as a 'pandemic of unprecedented magnitude' by the International Diabetes Federation (IDF)[1]. Data from the latest 2021 IDF report shows that one in ten (10.5%) of the world's adult population is currently living with diabetes, a rise of 16% from the previous 2019 estimates[2]. This proportion is projected to surge by 46% to one in eight adults or 800 million individuals across the globe, by 2045. Contrary to previous belief, diabetes is no longer predominantly a disease of the affluent West. Developing and populous nations such as China and India are seeing high rates of increase in diabetes prevalence, linked partly to their rapid urbanisation and economic growth[3]. More than four-fifths of the total global diabetes burden now affects individuals residing in low- and middle- income countries (LMICs), cementing its status as a worldwide pandemic[2].

Diabetic retinopathy (DR) is the major ophthalmic complication of diabetes, characterized by damage to the retina. DR is the leading cause of blindness and vision impairment in working-age adults, and is linked to poorer quality of life, elevated depressive symptoms and an increased risk of overall mortality[4-6]. Global data show that just over one-third of individuals with diabetes suffer from DR, with 1 in 10 experiencing forms of vision-threatening diabetic retinopathy (VTDR) such as proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DME)[7]. There are promising trends of declines in blindness due to DR in Europe and North America, reflecting the efforts of concentrated public health efforts, effective screening and increased availability of novel therapies such as anti-VEGF agents[8, 9]. In contrast, low- and middle- income countries are expected to see a 20-45% increase in DR rates. This is double the rate projected for the high-income regions of Europe and North America[10, 11]. These regions are unlikely to see such declining trends due to limited healthcare resources for DR diagnosis, screening and treatment. Moreover, due to the growing and ageing global population, the increase in the global burden of DR is projected to echo the rising prevalence of diabetes with a 55% rise from 2020 levels, affecting an estimated 160 million individuals in 2045[11].

The scale of the problem is thus immense. In just over half a decade, it is projected that 4 million individuals will suffer from visual impairment due to severe vision-threatening DR[7, 12]. Early identification allows patients at risk of VTDR to receive treatment that can significantly reduce their risk of visual impairment and blindness[13]. However, though DR evolves in a predictable sequence of steps – from no or subclinical disease to mild DR to VTDR with PDR or DME, culminating in visual impairment and blindness – we still lack effective reliable measures to identify which individuals will develop the most severe vision-threatening forms of the disease[14]. The Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale, developed in the 1980s from analyses of retinal vascular lesions on film-based colour fundus photographs (CFPs), could accurately predict progression to PDR[15, 16]. Subsequently simplified into the International Clinical Diabetic Retinopathy (ICDR) severity scale as a prognostic biomarker, it has been the gold-standard for clinical DR management and research since[17, 18]. The advent of new retinal imaging modalities has sparked renewed interest in the search for new and more powerful prognostic biomarkers. Though these early results show promise[19-22], they have also produced inconsistent data and require optimisation, standardisation and validation before they can be routinely implemented[23-25].

Given our current limits on prediction and stratification of DR patients at risk of visual impairment with existing biomarkers, comprehensive regular screening emerges as the most invaluable tool for early detection and intervention of severe DR. Moreover, even as new biomarkers are refined and validated, these will necessitate systematic screening of patients with diabetes at the population-level in order to be applied efficiently. Such screening approaches will need to be capable of keeping pace with the growing and ageing population. Achieving these goals in DR screening will require three major transformations (Figure): (1) a shift from specialist to generalist approaches, (2) the adoption of teleophthalmology and (3) the integration of human expertise and artificial intelligence (AI).

The First Evolution in DR Screening: Specialists to Generalists

DR screening put in the hands of primary care providers (PCPs) allows for monitoring of a larger population of patients with diabetes at risk of developing retinopathy, with appropriate lifestyle interventions to ameliorate risk of progression alongside escalation to tertiary ophthalmic centres in cases of severe disease (Figure).

The evidence base for the benefits of DR screening is unanimous. One of the earliest demonstrations of this benefit was by Bäcklund et al. who showed a 47% reduction in diabetes-related blindness rates in Stockholm Country, Sweden in the five years after the implementation of a screening program in 1990[26]. Thirteen years later, in England and Wales, the rollout of the 2003 national DR screening programme resulted in a 18.6% reduction in the proportion of DR-related blindness by 2009-2010[27]. Indeed, this was the first time in fifty years that DR was no longer the leading cause of certifiable blindness in working-age adults in the country. DR screening has been shown to be cost-effective[28, 29] and is universally recommended by many international guidelines[18, 30]. Despite this, there are only a few truly effective national DR screening programs around the world – including the United Kingdom, Iceland and Singapore (Table 1). Notably, large high-income countries such as the US and LMICs do not have national screening programs. Considering the global patterns of epidemiology of the DR pandemic away from high-income countries towards developing economies, this is of particular concern.

Whilst the benefits of nationwide DR screening are undisputed, there clearly exist multiple barriers to their implementation across the world. These include the significant infrastructure investment required, lack of trained manpower and consequent extra pressure on PCPs and tertiary ophthalmic services, the design of suitable guidelines for referral, follow-up and intervention at each stage, legislative barriers and long-term concerns around sustainability and cost-effectiveness. To address these, further transformations in the screening set-up are vital.

The Second Evolution in DR Screening: Film to Telemedicine

In 2018, the Global Diabetic Retinopathy Advocacy Initiative identified four key areas for strengthening the development of an integrated approach between PCPs and eye specialists for the secondary prevention of DR. These areas focused on integrating routine eye and diabetes care in both PCP and primary eye care settings through tools such as screening, while establishing systems for improving patient recall, follow-up and treatment[31]. Crucially, this compendium highlighted one of the major challenges facing DR screening – its integration into routine care by PCPs. As frontline generalists, PCPs manage numerous aspects of a patient's health, and adding DR screening to their list of tasks imposes an additional burden on an often already stressed system. Moreover, interpretation of CFPs requires specialised knowledge and expertise in DR, an investment that is not practical for PCPs who already balance multiple competing demands on their time. While teleretinal services that utilise ophthalmologists for image interpretation offer a potential solution, they also exhibit significant flaws. Firstly, the same principles of competing demands on the time of eye specialists combined with the already existing inadequate numbers of these specialists pose problems[32]. Secondly, data reveal low rates of patient uptake of follow-up care likely due to the long times between assessment and diagnosis and consequent lack of face-to-face counselling, reducing the effectiveness of this strategy[33-35]. Telemedicine, utilising non-physician graders, emerges as an ideal solution to these challenges, providing a rapid, efficient and specialised remote platform through which PCPs can submit CFPs and receive eye care reports that can be actioned easily in a standardised manner (Figure).

Singapore's Integrated DR Program (SiDRP) lends itself for discussion as a case study of a successful screening paradigm utilising telemedicine. Previously, DR screening in Singapore was carried out on an ad hoc basis by PCPs and endocrinologists with PCPs interpreting CFPs. In 2010, following the recommendations of the Singapore Ministry of Health for regular nationwide DR screening for all patients with diabetes, the SiDRP was established. Under the SiDRP, CFP images were captured by nurses at primary care clinics and securely transferred to centralised remote reading centres via a cloud-based teleophthalmology system. Trained CFP graders would review the images in real-time and return screening reports with referral recommendations based on standardised criteria to primary care clinics within an hour[36].

Starting with just over 2000 patients and expanding over a decade to >120,000 patients across all primary care clinics in the country, the SiDRP exemplifies a model that addresses the key areas identified by the Global Diabetic Retinopathy Advocacy Initiative. The teleophthalmology system reduces the burden on PCPs by investing in, and outsourcing to trained graders, consequently improving diagnostic accuracy[37]. Its significantly faster turnaround times of less than an hour, compared to days or weeks, and use of standardised referral criteria improve patient follow-up care uptake. Indeed, multiple trials of smaller-scale telemedicine systems in different regions globally have demonstrated clear benefits of increased uptake, higher patient satisfaction and reduced vision loss[38-41]. Finally, whilst maintaining health outcomes on par with the previous system, the SiDRP has proven to be extremely cost-effective, with a predicted lifetime cost savings of almost SGD $30 million[36].

Table 1: Features and key outcomes of established national screening programs for diabetic retinopathy around the world.

Country	Population (million)	National Level of Income	Year	Screening Location	Screening Method	Reported DR Prevalence	Reported DR Screening Uptake
Botswana	2.63	Higher middle-income	2009	Hospital-based screening	Fundus photography	17.7%[42]	Not reported.
Denmark	5.90	High-income	2013	Ophthal-mology clinic	Fundus photography	16.5%[43]	Attendance (timely and delayed) at ~88.5%.[43]
Iceland	0.38	High-income	1980	Ophthal-mology clinic	Fundus photography & clinical examination	4-year incidence of retinopathy recorded as 38.1%.[44]	Not reported.
Ireland	5.12	High-income	2013	Screening centres	Fundus photography	31.8% (mean) detectable retinopathy over 5 rounds of screening[45].	Uptake in 2021 recorded at 67.2%[45].
Malta[46, 47]	0.53	High-income	2015	Diabetes clinic or health centres	Clinical examination	Not reported.	Not reported.
Singapore	5.63	High-income	2010	Primary care	Fundus photography, telemedicine	15.8%[48]	Not reported.
Slovenia	2.11	High-income	2016	Community screening centres	Fundus photography, telemedicine	25.8%[49]	Not reported.
United Kingdom	66.97	High-income	2003	Primary care	Fundus photography, telemedicine	36.6% from a regional study[50].	Uptake in 2015 recorded at 82.8%[51].

Despite the clear success of this nationwide teleophthalmology program, a key question persists: how can this service be sustained and scaled to perform to high standards in the face of ever-increasing demand? This brings us to the third key advancement in screening processes – the integration of AI.

The Third Evolution in DR Screening: Humans to AI

Deep learning (DL) and AI, a major focus of technological innovation in recent years, provide an ideal source of the computational power needed to enhance screening processes. When incorporated into the existing teleophthalmology system, AI has the potential to significantly enhance screening efficiency with faster turnaround times and streamlined workflows (Figure). Most importantly, the incorporation of AI promises a viable route to scaling and sustaining enhanced workflows, even in the face of increased demand.

The first algorithm to employ DL components for the automated detection of referable DR and VTDR was developed by Abràmoff and colleagues in 2016 using a dataset of ~1750 retinal images[52]. The DL-enhanced system outperformed a previous algorithm that had relied purely on traditional machine learning methods[53]. The system, IDx-DR, has been validated on data collected prospectively from primary care clinics within the US and abroad[54-56] and is the first autonomous AI to receive regulatory approval from the US Food and Drug Administration (FDA) for detecting severe DR in adults with diabetes[57]. A further major step was a large study by Google Healthcare that used over 120 000 retinal images to develop a DL system for detecting referable DR. This system achieved extremely high levels of sensitivity (>87%), specificity (>90%) and area under the receiver operating characteristic curve (AUC) (99.1%) in its external validation with two public datasets[58]. These results attracted considerable publicity within both the ophthalmology world and the mainstream media[59-62]. A number of groups have since reported similar results with their own DL algorithms developed and validated in different datasets around the globe[63-65].

In Singapore, the DL algorithm SELENA+ was developed and validated using retinal images collected from the SiDRP as well as ten additional multiethnic cohorts representing diverse populations with diabetes from different countries. In the primary dataset (>71 000 images), the system demonstrated an AUC of 93.6% for detecting referable DR with high sensitivity (90.5%) and specificity (91.6%). In the secondary validation datasets (>40 000 images), AUCs ranged between 88.9% and 98.3%[66]. Moreover, SELENA+ maintained this consistently accurate performance even in an 'extreme' population in Zambia, where the algorithm had not been previously trained[67]. Whilst diagnostic accuracy of these DL systems is undisputed, the question remains as to the most effective route to implementation. Xie et al.[68] examined exactly this question, modelling the economic costs of two approaches to AI integration in the existing system. In one, SELENA+ fully replaced primary human graders and in the other, SELENA+ was used as a 'triage' tool to screen out low-risk cases and refer on a subset of cases to human graders for secondary confirmatory grading. Interestingly, the triage approach showed the highest cost savings at $62/patient compared to $66/patient in the replacement approach and $77/patient in the existing system.

Following its success, SELENA+ has been licensed to a commercial start-up company (EyRIS Pte Ltd., Singapore) to manage the technical, operational and commercial aspects of its implementation into clinical practice[69]. While digital technologies such as telemedicine and AI are lauded as disruptive innovations, they also generate concerns about potential negative impacts on human jobs. Thus, an important point to draw from Singapore's AI-based DR screening program is the way in which AI has been utilised most effectively when implemented in a specialised narrow part of the clinical workflow, complementing, rather than replacing, human roles. By automating specific tasks such as image analysis, AI enhances the efficiency of healthcare professionals, enabling them to focus on higher-level tasks that require human expertise. This approach ensures that AI serves as a tool to augment, rather than diminish human capability and ultimately both safeguard human roles whilst producing the best screening outcomes.

The age of AI has only just begun to dawn. The field is expanding rapidly with multiple types of models showing massive burgeoning potential. Generative AI has marked a significant shift, with models able to generate new data based on existing datasets. Large language models (LLMs), a form of generative AI trained with massive amounts of linguistic data, have taken the world by storm. ChatGPT, an LLM developed by OpenAI, has drawn global headlines with its ability to engage in human-like conversation and answer questions on different topics[70, 71]. The potential of such LLMs in healthcare is vast. While DL algorithms have performed well in detecting eye disease, LLMs show promise in transforming clinical workflows, from streamlining triage and appointment scheduling to personalising patient visits, boosting healthcare adherence with patient education, automating medical record documentation and serving as a resource for medical training[72].

Healthcare is a complex field with varied forms of data, activities and tasks. Though AI has been developed to fit into narrow specialist domains, a novel challenge presents itself: can AI models be built to fulfil multiple different healthcare functions? Foundational AI models, pre-trained on broad data and able to adapt to a wide range of tasks, are a prime research focus for this question[73]. In ophthalmology, a key example is the development of RETFound, a foundational model trained via self-supervised learning on 1.6 million retinal images. Through subsequent fine-tuned supervised learning with annotated images, RETFound was adapted for disease detection, consistently outperforming other models in the diagnosis and prognosis of sight-threatening eye diseases[74]. A further striking innovation includes combining AI models. An integrated DL-LLM, merging an LLM module with a DL module based on retinal images, was developed to give individualised recommendations for patients in primary diabetes care. In a single-centre prospective study, it was shown that the quality and empathy of level of diabetes management recommendations were highest when PCPs were assisted by the AI. This translated through to better self-management by patients with newly diagnosed diabetes and greater adherence to DR referrals[75].

Despite the widespread benefits these systems may offer, there is equal concern about their limitations (Table 2). Nevertheless, we can anticipate a growing evolution in the development and use of medical AI, from specialized tasks to universally applicable models capable of broader abstract functions such as emulating physician empathy and intuition and integrating non-clinical data for wider public health maintenance and disease prevention[76].

Table 2: Advantages and limitations of medical AI models.

Advantages of Medical AI	**Limitations of Medical AI**
Enhanced diagnostic accuracy: AI systems are able to detect rates of disease such as DR extremely accurately, allowing for earlier intervention and management[66].	Dependence on quality data: AI is 'data-hungry' usually requiring vast amounts of datapoints to reach an adequate performance level. Training from a single dataset is prone to bias and exaggerates health inequity but acquiring diverse datasets can be difficult and costly[77].
Enhanced efficiency: AI has immense multi-functional capacity and has been shown to be able to detect multiple conditions from a single dataset[66, 78, 79]. This shows potential for further enhancing the efficiency of future screening initiatives.	Lack of interpretability: AI can function as a 'black box' and this lack of transparency into the mechanisms of performance hinder easy justification of diagnosis, treatment or outcomes that are predicted to patients and other users. It also does not allow us to monitor potential bias that may arise[63].
Sustainability and scalability: AI has immense processing power and is thus able to screen large volumes of data rapidly. This has the advantage of streamlining workflows such as in the DR screening program and being able to meet future demand.	Potential job displacement: Concerns exist related to the possibility of AI replacing human jobs – though this is somewhat mitigated by recent evidence suggesting AI produces the highest quality and most cost-effective outcomes in conjunction with human roles[68].
Cost-effectiveness: AI integration has been shown to lower costs associated with human grading in DR screening when effectively deployed as a triage tool[68].	Integration into medical practice: Though AI has been shown to work well in narrow specialist domains of healthcare, difficulties are likely to arise in attempts to integrate more universal models into existing clinical workflows[76].
Personalised medicine: AI is able to individualise patient recommendations based on provided information to tailor follow-up and treatment[75].	Regulatory and legal challenges: Defining responsibility, medico-legal ethics frameworks and other important aspects of implementation are crucial for safe deployment of these systems in clinical practice – such conversations are still in their infancy[80].

Future Directions and Research

As DR screening evolves, new opportunities for innovation and improvement continue to emerge. Three key areas discussed here include the development of portable handheld retinal cameras to widen access, more intelligent AI algorithms capable of detecting a multitude of conditions and the incorporation of optical coherence tomography (OCT) for DME detection.

Firstly, current DR screening systems leave many patients undiagnosed and under-referred, often due to low adherence to screening appointments[81]. In LMICs, restricted access to retinal cameras exacerbates this issue. To address this, low-cost handheld mobile devices have been developed, demonstrating high sensitivity and specificity for DR detection[82]. Smartphone-based applications also show promise in supporting DR screening efforts and early integration with AI algorithms further strengthens the potential of these routes[83-86]. Secondly, the role and capabilities of AI in screening continue to rapidly expand. DL systems can now detect not only the presence and severity of DR, but also prospectively predict its incidence and progression, potentially paving the way to personalised screening intervals[87, 88]. The development of the DL system in Singapore from retinal images was notable for its ability to detect not only referable DR but also other sight-threatening diseases, such as glaucoma and age-related macular degeneration (AMD) with high sensitivity (>90%), specificity (>73%) and AUC (>89%)[66]. Other novel studies have taken this even further and developed algorithms capable of detecting non-ophthalmic conditions, such as chronic kidney disease and Alzheimer's disease, from retinal photos[78, 79]. This has given rise to the field of 'oculomics', which leverages AI-enhanced retinal imaging to predict a range of systemic conditions, including cardiovascular disease, cerebrovascular disease, stroke, schizophrenia, metabolic disease, hepatobiliary disease and even overall morbidity and mortality[89-94]. Further work is needed to better understand the underlying mechanisms of these associations and expand this exciting emerging field. Finally, while 2D fundus photography has been the primary screening tool for PDR and DME, it has limitations in DME detection, leading to both missed diagnoses and unnecessary referrals[95, 96]. Optical coherence tomography (OCT), with its higher sensitivity, has been proposed as complementary screening tool for DME and when integrated with existing methods, has shown increased cost-effectiveness with comparable health outcomes[97, 98]. DL algorithms for automated OCT-based detection of DME have demonstrated high accuracy in real-world applications[99, 100]. Further work is needed to examine the most effective ways of including, improving and automating OCT detection of DME in existing DR screening pathways.

Conclusions

Addressing the DR pandemic requires a comprehensive, multi-pronged approach. A clear shift from specialist to generalist is essential for effective screening while telemedicine expands the reach and ease of implementation of this approach. However, the potential of AI stands out as a game-changer. With its ability to enhance efficiency and scalability, AI has massive potential to upscale DR screening and management, broader aspects of eye health and indeed clinical practice as a whole. As these innovations continue to evolve, they offer a powerful path towards combating the global DR crisis and improving the lives of millions.

Conflict of Interest

Tien Y Wong is a consultant for Abbvie Pte Ltd, Aldropika Therapeutics, Bayer, Boehringer-Ingelheim, Carl Zeiss, Genentech, Iveric Bio, Novartis, Opthea Limited, Plano, Quaerite Biopharm Research Ltd, Roche, Sanofi, Shanghai Henlius,. He is an inventor, holds patents and is a co-founder of start-up companies EyRiS and Visre, which have interests in, and develop digital solutions for eye diseases.

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Figure Legend

Figure: Diagram illustrating the major transformations in DR screening that are needed to ensure effective, scalable population-level screening of patients with diabetes. 1: PCPs organize DR screening and staff upload digital retinal photos to server; 2: DR grading is carried out at centres, triaged with AI and confirmed by humans; 3: A report is generated based on DR grading; 4: The report is transmitted back to PCPs with standardized referral criteria; 5: If mild DR (non-referable), then PCPs manage risk factors and continue screening; 6: If severe DR (referable), then patients are referred to eye specialists for treatment. DR, diabetic retinopathy; VTDR, vision-threatening diabetic retinopathy; DME, diabetic macular oedema; VI, visual impairment; M, million; AI, artificial intelligence.