


A Review of Advancements and Evidence Gaps in Diabetic Retinopathy Screening Models

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Abstract: Diabetic retinopathy (DR) is a microvascular complication of diabetes with a prevalence of ~35%, and is one of the leading causes of visual impairment in people of working age in most developed countries. The earliest stage of DR, non-proliferative DR (NPDR), may progress to sight-threatening DR (STDR). Thus, early detection of DR and active regular screening of patients with diabetes are necessary for earlier intervention to prevent sight loss. While some countries offer systematic DR screening, most nations are reliant on opportunistic screening or do not offer any screening owing to limited healthcare resources and infrastructure. Currently, retinal imaging approaches for DR screening include those with and without mydriasis, imaging in single or multiple fields, and the use of conventional or ultra-wide-field imaging. Advances in telescreening and automated detection facilitate screening in previously hard-to-reach communities. Despite the heterogeneity in approaches to fit local needs, an evidence base must be created for each model to inform practice. In this review, we appraise different aspects of DR screening, including technological advances, identify evidence gaps, and propose several studies to improve DR screening globally, with a view to identifying patients with moderate-to-severe NPDR who would benefit if a convenient treatment option to delay progression to STDR became available.

Keywords: telescreening, non-proliferative diabetic retinopathy, risk-stratification, systematic, opportunistic

Plain Language Summary

Diabetic retinopathy is a common complication of diabetes and is one of the leading causes of blindness in adults of working age.

Regular screening and early detection, before diabetic retinopathy progresses to the sight-threatening stage, is needed to provide treatment to prevent sight loss.

The increasing number of patients with diabetes means there are major challenges to carrying out accurate, cost-effective screening on a large scale, including:

- A lack of agreement on the best screening methods and how often they should be used
- Limited resources and infrastructure in some cases because many countries do not have country-wide healthcare systems or diabetic retinopathy care plans
- Patients with diabetes not attending their screening appointments

We reviewed current diabetic retinopathy screening methods and found that telescreening, whereby ophthalmologists visit communities or digital pictures are taken and graded later by an expert, combined with artificial intelligence (AI) to automatically detect diabetic retinopathy, may be a solution:

- Telescreening cost savings increase when carried out on a larger scale

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- AI automated detection has been developed for handheld cameras, unmanned kiosks, and smartphones, increasing accessibility
- Telescreening programs and patient education improve screening attendance

To provide the evidence needed to adopt these new techniques, future studies should focus on developing telescreening methods that are cost-effective across all healthcare systems. Other studies should investigate the reliability of AI automated detection and the ease of use of handheld devices and other new technologies.

Introduction

Diabetes is a global problem, afflicting more than 425 million people worldwide, which could rise to 629 million by 2045.¹ Diabetic retinopathy (DR) is a microvascular complication of diabetes, with an average prevalence of about 35% among people with diabetes, and is one of the leading causes of blindness in people of working age in most developed countries.¹ The earliest stage of DR is non-proliferative DR (NPDR). NPDR may progress from mild through moderate, then severe stages, to sight-threatening DR (STDR), such as proliferative DR (PDR) and diabetic macular edema (DME).² Approximately one-third of patients with DR have STDR,² so regular active screening of patients with diabetes and early detection of DR are necessary for early intervention to prevent sight loss and blindness. For example, after the introduction of national systematic screening programs in England and Wales, inherited retinal disorders accounted for more cases of certified blindness than DR in 2009–2010.³

Optimization of glycemic control, blood pressure, and serum lipid control are recommended to reduce the risk or slow the progression of DR. Nevertheless, even with optimal systemic control, a substantial proportion of patients with diabetes will develop DME or proliferative changes

requiring intervention.⁴ Currently, treatment options that specifically target NPDR and DME are limited to panretinal photocoagulation, intravitreal corticosteroids, and intravitreal vascular endothelial growth factor (VEGF) inhibitors.^{5–7} While these treatments are effective for many patients, they may be inconvenient, uncomfortable, and in some cases, associated with permanent eye damage.^{5,8} An effective systemic therapy delivered as an oral formulation would provide a more convenient treatment option that could be administered to patients with moderate-to-severe NPDR identified through active screening to delay progression to STDR.

Although the incidence of DR development is higher for patients with type one diabetes (T1D) compared with type two diabetes (T2D),^{9,10} T2D is more prevalent than T1D, accounting for 90–95% of all diabetes cases and the majority of DR cases.^{10,11} One of the biggest challenges in managing DR is the prevalence of undiagnosed diabetes because DR may progress to STDR before a diagnosis of diabetes is established, resulting in people presenting with symptomatic complications of diabetes, both because the onset of T2D is usually slow and because the presentation may involve a long pre-detection period.^{1,2}

Table 1 shows the estimated prevalence of diabetes globally and illustrates the gravity of the problem of undiagnosed diabetes – the prevalence of diabetes worldwide is 9.3%, rising to 13.3% in North America and the Caribbean.¹ Another challenge faced in most countries with no DR care pathway is that as patients are asymptomatic, they are reluctant to present themselves for treatment, or they cannot afford out-of-pocket expenses for treatment.

In this review, we aim to identify the research required to improve DR screening globally, with a view to detecting

Table 1 Global Diabetes Prevalence in Adults Aged 20–79 (2019)¹

Region	Adult Population, N, Millions	Prevalence of Diagnosed Diabetes, % (95% CI)	Prevalence of Undiagnosed Diabetes, %
Worldwide	5000	9.3 (7.4–12.1)	NR
Africa	501	3.9 (2.1–7.1)	59.7
Europe	665	8.9 (7.0–12.0)	40.7
Middle East and North Africa	426	12.8 (7.2–17.6)	44.7
North America and the Caribbean	357	13.3 (10.5–15.8)	37.8
South and Central America	335	9.4 (7.8–11.7)	41.9
Southeast Asia	997	8.8 (7.1–11.1)	56.7
Western Pacific	1700	9.6 (8.6–11.9)	55.8

Abbreviations: CI, confidence interval; NR, not reported.

patients with moderate-to-severe NPDR who would benefit if a convenient treatment option to delay progression to STDR became available in the near future.

DR Screening

As opposed to other branches of medicine where patients receive tests when a disease is suspected, DR screening seeks to identify a previously undetected complication of diabetes in otherwise healthy individuals.¹² Patients with diabetes who do not receive DR screening are at four-fold higher risk of STDR;¹³ therefore, the broad goal of DR screening is to prevent progression to STDR. Screening for DR is cost effective compared with the costs of vision loss from undetected DR,¹⁴ and further cost savings can be made if high-risk groups are screened at shorter intervals than low-risk groups.¹⁵

DR screening is instrumental in disease management, including making treatment decisions; for example, early intervention in moderate-to-severe NPDR before it develops into PDR or DME may reduce both the disease burden for patients and societal costs.¹⁶ The benefit could be even more substantial after the introduction of an oral therapy for moderate-to-severe NPDR. From a holistic perspective, DR screening can also offer a further advantage in the detection of retinal and microvascular conditions other than DR.^{17,18} While there is broad agreement about the need for DR screening programs and currently several different approaches, there is a lack of consensus on the optimal approach in terms of cost effectiveness and/or logistical options in different healthcare systems.

Types of DR Screening

International and national guidelines recommend annual screening for DR for all patients with diabetes,^{19,20} and this is performed in some countries such as the UK, Iceland, and Hong Kong using systematic national screening programs.^{3,21,22} Systematic screening for DR involves the selective identification of all individuals at risk of DR (ie any patients with diabetes) and uses quality-assured predetermined screening processes to ensure adequate coverage of the chosen patient population.²² Systematic screening is probably the most effective way of detecting STDR; however, it is difficult to perform in many healthcare systems where there are multiple healthcare providers without a centralized database of patients with diabetes. Hence, in most other countries, opportunistic methods, such as local hospital-based projects or community-based screening programs, are used if any screening is performed

and tend to cover fewer patients and be less cost effective in the long term than systematic screening. Opportunistic screening is much more common,²² this may be offered by a healthcare professional, requested by a patient, or occur as a result of an assessment for another complaint, but it is not offered to all individuals at risk of DR.

DR Screening Methodology

Various methods of screening can be used to diagnose and monitor DR provided that the recommended sensitivity and specificity levels are met. The National Institute for Health and Care Excellence (NICE) guidelines propose that any screening program for DR should have at least 80% sensitivity and 95% specificity, with a technical failure rate of <5%.¹⁹

Mydriasis in DR Screening

Mydriatic retinal photography was traditionally believed to be the most effective DR screening strategy;²³ however, mydriasis needs to be performed by a qualified professional and is relatively time-consuming because the eye drops need at least 20 minutes to take effect, thus creating an administrative burden. New approaches to DR screening often omit mydriasis to improve the screening experience and overall acceptance by patients – by not dilating the pupil, the time in the clinic can be minimized and the screening efficiency improved (by taking fewer photographs and not having to wait for the dilating drops to take effect), allowing larger numbers of patients to be screened more quickly than traditional surveillance techniques.²⁴ A 2015 meta-analysis showed that although diagnostic accuracy was higher with mydriasis, adequate levels of sensitivity and specificity can be reached without mydriasis.²⁵ Different instruments can be used for screening (eg a direct or indirect ophthalmoscope, slit lamp, photographic film, scanning laser, or digital photography). The number of photographic fields, mydriatic status, and the experience or qualifications of the grader can vary.²⁶ For example, different numbers of photographic fields can be used for detecting retinopathy, trading ease of execution and cost for sensitivity.

Imaging in Single or Multiple Fields

The gold-standard DR detection method is 30° stereoscopic color fundus photography in seven standard fields;²⁷ however, this method is time-consuming and may be uncomfortable for the patient, as well as impractical for large-scale screening programs.²² The use of digital fundus photography allows for

a greater viewing angle, with most screening programs currently using 45°, enables the use of fewer fields, and is more convenient as it is quicker, requires less light exposure, and is often performed without mydriasis; however, sensitivity and specificity are reduced.²⁸ Compared with mydriatic ophthalmoscopy, the sensitivity and specificity for detecting DR with one-, two-, three-, and five-field non-mydriatic 45° color photography is 71–88% and 76–99%; 94% and 69%; 100% and 79%; and 85% and 99%, respectively.^{29,30} The American Academy of Ophthalmology reported that there is sufficient evidence to suggest that single-field fundus photography with interpretation by trained readers can serve as a screening tool to identify patients with DR, without the need for mydriasis in the majority of cases;²⁸ however, sensitivity and specificity values are diminished (non-mydriatic 45°: 61–78% and 85–86%; dilated 45°: 72–74% and 88%, respectively),²⁸ and it produces a higher number of unreadable images that require further referral³¹ compared with seven-standard field photography.

In the Comparison Among Methods of Retinopathy Assessment (CAMRA) study, the sensitivity and specificity of non-mydriatic three-field fundus photography (45° foveal, nasal, and temporal) for detecting any DR was 81% and 94%, respectively, and 54% and 99%, respectively, for detecting STDR.³² A cross-sectional study carried out in a Thai hospital compared single-field (45° central posterior) and five-field (45° central posterior, temporal, nasal, superior, and inferior) digital non-mydriatic fundus photography and found that both were acceptable for the detection of any DR by a primary care physician (sensitivity and specificity were 70.7% and 99.3%, respectively, for single-field fundus photography, and 84.5% and 98.6%, respectively, for five-field fundus photography), although the single-field approach occasionally missed peripheral retinal lesions and underestimated the DR grade.³⁰ Moreover, a report suggested that although single-field 45° digital non-mydriatic imaging can detect the presence of DR (sensitivity and specificity 71% and 96%), three 45° fields may be necessary for grading (sensitivity and specificity 82% and 92%),³³ representing a good compromise on sensitivity, specificity, and ease.³⁴

Digital Imaging

Digital modalities have largely superseded traditional fundoscopy and are a current focus for development in retinal screening technology. The introduction of digital technology allows fundus photography to be performed by non-ophthalmologists, with images sent to ophthalmologists or trained graders; digital

copies of the images are retained and can be remotely reviewed and subsequently graded. Using smartphone-based retinal cameras with specialized adaptors, skilled operators can capture high-quality, wide-field fundus images; furthermore, these embedded systems are capable of acquisition, storage, and even analysis of images.³⁵ However, mydriasis is necessary for optimizing sensitivity with this approach and therefore it is not feasible in all circumstances. In the CAMRA study, the sensitivity and specificity for smartphones to detect any DR was 50% and 94%, respectively, and 59% and 100%, respectively, for detecting STDR.³² However, artificial intelligence (AI)-based automated software in conjunction with a smartphone-based device has demonstrated a sensitivity and specificity for the detection of any DR of 96% and 80%, respectively, and 99% and 80%, respectively, for the detection of STDR.³⁶ Another novel technique for retinal imaging is the miniaturized non-mydriatic wide-field fundus camera, which uses dual light sources – near infrared (for retinal guidance) and white (for color retinal imaging) – to successfully achieve reflection-free and artefact-free fundus photography; furthermore, these cameras are constructed from off-the-shelf components³⁷ so may become an affordable solution. The FDA-approved, handheld Pictor portable LED camera offers another non-mydriatic approach for obtaining high-quality retinal images (with minimal training) from which STDR could be identified by graders with a broad level of experience.³⁸ Unlike smartphone-based imaging, these novel approaches do not require mydriasis and are potentially the next generation of telemedicine and point-of-care assessment devices for eye diseases. Although currently available non-mydriatic cameras tend to be expensive and bulky,³⁹ a current research focus includes the development of smaller, handheld retinal cameras to obtain fundus images without mydriasis^{37,38,40} and allow screening in underserved hard-to-reach communities, as demonstrated in urban slum populations.⁴¹ Another approach is through the use of healthcare kiosks located in public places, such as supermarkets and pharmacies, that already offer automated vision tests⁴² or screening for several chronic diseases, including diabetes.^{43,44} Including fully automated non-mydriatic fundus cameras in pre-existing or new, dedicated healthcare kiosks may encourage patients with diabetes to initiate opportunistic screening. This raises the question of who should fund such an initiative. Existing kiosks have been sponsored by healthcare companies, supermarkets and pharmacies, but often at a local level,⁴² or by employers via health insurance coverage,⁴⁵ so access may be sporadic.

Screening Based on the Posterior Pole vs the Entire Retina

It was estimated that up to 15% of DR lesions and 27% of PDR lesions may lie outside of the area covered by a standard 45° field image.²³ Increasing a single field of view to 60° covers 60% of the area covered by seven 30° fields and may increase the chance of detecting early retinopathy; however, the wider angle reduces magnification.⁴⁶ Ultra-wide-field (UWF) imaging devices, such as the Optos P200MA/P200C⁴⁷ or Optos Daytona⁴⁸ (Optos Plc, Dunfermline, UK), address the limitations imposed by conventional fundus photography by broadening the view of the retina from 30° up to 200° in a single image, with a high level of sensitivity.⁴⁷ The ungradable image rate per patient is lower using UWF imaging than with conventional fundus photography, leading to a reduction in the number of ungradable images overall.⁴⁸ Furthermore, peripheral lesions that would not have been identified using standard Early Treatment of Diabetic Retinopathy Study (ETDRS) fields may have prognostic significance; they are suggestive of more severe DR in ~10% of patients,⁴⁸ and their predominance outside the standard ETDRS field is associated with a 4.7-fold increased risk of progression to PDR.⁴⁹ Using a smartphone, a lens adaptor, and a high-definition television, self-monitoring UWF retinal photography (“retinal selfie”) is currently being investigated, highlighting the improved accessibility and cost effectiveness brought by technological advances.⁵⁰

Other Diagnostic Tools for DR Retinal Fundus-Related Electrophysiological Responses

Aspects of retinal function, such as fundus-related electrophysiological responses, can vary at different stages of DR. RETeval-DR™ (LKC Technologies, Inc., Gaithersburg, MD, USA; Welch Allyn, Inc., Skaneateles Falls, NY, USA), a new handheld device for measuring oscillatory potentials,^{51,52} has demonstrated accuracy in detecting DR once the operator has undergone minimal training.⁵² The performance of RETeval-DR™ has been compared with standard seven-field fundus photography and found to be highly accurate (99%), with a very short testing time (2.3 minutes),⁵² and RETeval-DR™ can differentiate STDR from non-STDR quickly, without mydriasis.^{51,52} Furthermore, 63.5% of patients preferred RETeval-DR™ screening over other imaging techniques, compared with 22.8% who preferred digital fundus photography, which could positively impact patient adherence and aid

patient management.^{51,52} Nevertheless, the cost of these devices is likely to be problematic for some providers.

Pupillary Light Reflexes

The pupillary light response can be used as an index of intrinsically sensitive retinal ganglion cell function, which in turn may provide insight into inner retina dysfunction in patients with diabetes. A study investigating the effects of diabetes on the various pupillary measures showed that patients with diabetes at all stages of NPDR can have abnormalities in pupil responses, such as decreased pupillary light response elicited by flashes of light under melanopsin-mediated conditions, and for patients with moderate-to-severe NPDR, under cone-mediated conditions.⁵³ Furthermore, mean dark-adapted steady-state pupil size was significantly reduced at all stages of NPDR ($p < 0.001$), whereas the mean light-adapted steady-state pupil size was only significantly reduced for patients with moderate-to-severe NPDR ($p = 0.008$).⁵³ Significant changes in mean dark-adapted pupillary re-dilation velocity were detected in patients with diabetes without DR and in those with mild and moderate NPDR and PDR ($p \leq 0.05$).⁵⁴ Another study reported that reduced pupillary dilatation amplitude was detected in hyperglycemic patients with DR,⁵⁵ which may assist in patient diagnosis and stratification by severity. Smartphone LEDs have been used as stimuli in combination with infrared video pupillometry,⁵⁶ and now entirely iPhone-based pupillometry can provide similar results to infrared pupillometry.⁵⁷ Further studies are required to determine the relative accuracy, costs, and ease of these pupillary light response tests, or a combination thereof, for sensitivity and specificity for diagnosing DR and determining its severity. Smartphone approaches are promising as they permit patients to detect DR themselves, without the need for ophthalmologists or optometrists, and instead, pupillary response recordings can be sent to an expert for interpretation.

Developments in DR Screening: Telescreening and AI

Telescreening, whereby ophthalmologists visit communities and/or digital pictures are taken and graded later by an expert, represents the single most promising innovation in DR screening for large populations. Meta-analysis suggests that telescreening reduces clinic workload, is cost effective, and can increase patient compliance when provided free of charge to remote communities.⁵⁸ Telescreening approaches may include temporary mobile DR screening services whereby teams visit communities for short periods, centralized image analysis, or

a combination of both.^{59–62} Telescreening is usually cheaper and preferred by patients compared with traditional surveillance techniques.⁶³ Telescreening has been used in different screening programs, including the OPHDIAT® program in France;⁵⁹ the Remote Outreach DR Screening Service in Australia, which increased screening rates four-fold;⁶⁴ and the Sankara Nethralaya Teleophthalmology Project (SNTOP) and Aravind Teleophthalmology Network (ATN) in India, which estimated that 150 patients could be screened per day, with a single ophthalmologist making the final diagnoses remotely.⁶⁵ In China, the “Lifeline Express” initiative, which consists of custom-built trains and eye centers nationwide, has successfully extended its initial service beyond cataract surgery treatment to large-scale DR screening.⁶⁰

Another transformative advance in DR screening is the use of automated DR detection and AI, including automated machine learning and deep learning algorithms that are capable of recognizing DR lesions.^{66–68} After “training” with data sets that may include several thousand images, deep learning systems have achieved a sensitivity and specificity of $\geq 80\%$.^{67,69} AI has been successfully integrated into smartphone-based systems and on-site systems such as the FDA-approved IDx-DR system.^{36,70–72} Cheaper and accessible handheld cameras with incorporated AI will lead to a reduction in DR screening costs in a similar manner to the outsourcing and streamlining of blood tests and diagnosis, and this may be the key to the rapid assessment of large numbers of retinal images. The capturing and sharing of digital fundus photographs may also be useful in other conditions: Google AI can predict the risk of stroke using fundus photographs, suggesting that this approach may have the ability to provide standardized measurements.⁷³

To improve access for the majority of patients with DR, telescreening is likely to be the basis of most DR screening programs in the future; however, imaging and analysis depend on equipment and training, which can be cost prohibitive, especially in communities that are not supported by centralized healthcare systems or governments.⁷⁴

Strategies to Improve the Uptake of DR Screening

Despite the wealth of evidence supporting the effectiveness of DR screening, coverage is inconsistent and may be below recommended levels in certain groups, such as younger patients, those with T1D, or those in deprived areas, even in

countries where systematic screening is employed.⁷⁵ Screening non-attendance is not only a missed opportunity for detecting STDR, but can also result in financial consequences through the treatment of more advanced retinopathy.⁷⁶ The use of telescreening presents an immense opportunity to manage the steadily increasing demand for eye care; however, challenges remain in the delivery of practical, viable, and clinically proven solutions. The cost savings of telescreening approaches are more significant when carried out on a greater scale;⁷⁷ therefore, cooperation and agreement on screening approaches within nations is required to organize screening over greater areas, to ensure high standards and cost savings. The lack of DR awareness and its potential impact on sight, in addition to poor delivery of DR screening services and their associated costs, have been reported as important barriers to accessing treatment in both developing and developed countries.^{78–81} The following section explores how DR screening uptake could be improved.

Patient Education and Engagement

Health literacy in diabetes and its complications may be insufficiently developed for optimal participation in DR screening. Studies of the provisions of DR screening and treatment have identified a lack of awareness of the relationship between diabetes and DR until after vision is affected; furthermore, this was acknowledged by physicians as a key barrier that impacts outcomes of adults with DR.⁸² Improved patient education and access to clinics may increase DR screening rates and attendance at follow-up appointments, and therefore should be included in public health programs.^{79,80} Various studies show that educational interventions (both targeted at DR and diabetes in general) improve DR screening rates: a 2018 meta-analysis (including studies in the USA, Canada, Australia, China, and Europe) demonstrated a 5% improvement in DR screening rates after DR-specific and general diabetes educational intervention;⁸³ an educational intervention study performed in the USA doubled the rate of ophthalmic examination achieved with a routine medical care group (from 27.3% to 54.7%);⁸⁴ another study in the USA revealed that patients receiving an educational intervention and personalized letter compared with usual care (schedule letter and automated phone call) were more likely to arrange (63% vs 40%; $p < 0.0001$) and attend their appointment (48% vs 30%; $p < 0.0001$);⁸⁵ and a study in Tanzania showed that an educational intervention and a referral for free screening improved uptake from 29% to 47%.⁸⁶ Tailoring health education to high-risk subgroups, for example younger people,^{87,88} is a valid strategy, although the effectiveness of targeting populations

based on baseline demographics remains unclear.⁸³ Studies have shown that perceptions of barriers to DR screening can differ between patients and healthcare providers, and as such, active patient community engagement should be considered when formulating new educational programs.⁸⁹ For instance, intervention mapping using patient interviews and surveys has been used to develop leaflets targeting young people with T2D,⁸⁷ and direct telephone engagement with patients has been shown to increase DR screening attendance by 74% in patients with diabetes in an urban healthcare setting in the USA.⁹⁰

Changes to DR Screening Service Delivery

Patients with inconvenient journeys to screening appointments are associated with delayed DR screening;⁹¹ screening and health checks performed in more conveniently located healthcare settings, such as high street dental surgeries and community pharmacy settings, may offer a solution. Community-based screening programs for various non-communicable diseases, including osteoporosis, cardiovascular disease, peripheral arterial disease, and diabetes have shown promising results for this type of intervention;⁹² furthermore, stakeholders were in broad support of this approach. Using their unique position, pharmacists can identify candidates for DR screening based on their medication histories and can use the screenings as an opportunity to encourage patients to seek DR care from their physicians.⁹² Community settings may also facilitate effective interventions, such as on-the-spot counselling and friendly reminders, that could be effective for motivating patients to self-manage their conditions. DR screening in a primary care setting by trained non-physician/ophthalmologist photographic graders may offer a further solution,^{93,94} provided adequate levels of sensitivity and specificity are met.¹⁹ Trained photographers can acquire the images, which can be saved and analyzed at a future date, and the uptake of automated diagnostic systems and AI may add efficiency and value to existing telescreening programs.⁷⁰ Other aspects of task-sharing in DR management – such as carrying out regular follow-up appointments for those not currently showing signs of DR – could also reduce the burden on ophthalmologists.⁹⁵ Adequate training underpins the success of this approach; ophthalmic personnel generally outperform non-ophthalmic personnel in DR grading, so referral to ophthalmologists must be an option when

necessary.⁹⁶ Infrastructure improvements, focused on increased collaboration and information sharing between providers, have the potential to increase screening uptake by reaching more patients.⁹⁷ For instance, bespoke software produced by the Portuguese Diabetes Association (APDP [APDPSoft]) integrates with the Portuguese Ministry of Health systems to track screening requests and appointments, and also manages clinical data, fundus photography, and retinography reports.^{98,99} Automated interrogation and extraction of electronic primary care data may identify additional candidates for screening.¹⁰⁰

Financial Incentives and Reimbursement for Screening Systems

Deprivation remains a factor in non-attendance for DR screening, even in countries with a systematic approach, such as the UK.^{101,102} High-income countries such as Australia and Canada report significantly lower DR screening rates and inadequate diabetes care in their remote Indigenous populations,^{103,104} therefore, a concerted effort is needed to screen hard-to-reach communities.¹⁰⁵ Reimbursement of retinal screening can be complex and extra considerations such as patient selection, camera utilization, and use of non-mydriatic cameras may affect reimbursement claims.^{106,107} A study in Trinidad and Tobago revealed that private sector ophthalmologists performed 80% of all eye care, but only 19.3% of the adult population had private healthcare insurance, leading to significant out-of-pocket expenditure.¹⁰⁸

Studies have investigated the impact of DR costs (real and perceived), as well as the impact of incentivizing DR screening, and identified significant predictors of decreased adherence, including when participants believed their medical insurance did not sufficiently cover the costs of diabetic eye exams, had poorly controlled blood glucose, or had only recently been diagnosed with diabetes.¹⁰⁹ In a UK study, methods for encouraging patient engagement with DR screening were studied and it was revealed that financial incentives attracted fewer patients to screening than standard invites.¹¹⁰ Nevertheless, screening practices that detect DR early offer longer-term cost savings by avoiding the costs of preventable sight loss and blindness, including disability grants that could be avoided with early treatment;¹¹¹ an Australian pilot telescreening program for early DR was effective and costs were competitive with Medicare reimbursement costs for eye examinations.¹¹²

Recommendations for Future Studies

The studies presented here highlight the necessity of DR screening for preventing blindness due to escalating global diabetes prevalence. Given the exponential rise of diabetes globally, the manpower needed for DR screening is likely to be outpaced, and telescreening undoubtedly has the greatest potential to transform screening. Public health programs and population-based interventions should provide appropriate levels of diagnostic accuracy within the context of cost-effective evidence-based care. The findings reported herein suggest that telescreening for DR can be successful while also reducing travel time and costs for patients with diabetes, and despite higher referral numbers owing to ungradable images, patients appear to prefer this approach, thus improving patient adherence and engagement.

To plan and feasibly implement DR screening in public health policies globally, we propose several studies to assess the extent of DR and screening best practice. To employ successful DR screening programs that are cost effective and efficient, the best approach needs to be determined; incorporating the recent advances in technology and telescreening could impact DR screening, while balancing cost, practicality, and patient preference, as well as patient outcomes. Studies should focus on developing a telescreening methodology that can be applied on a large scale and across different regions. For example, a non-mydriatic or staged mydriatic methodology that would allow evaluation of the predictive accuracy of digital imaging in different populations using digital fundus photography in three fields may offer an acceptable compromise on sensitivity and ease of execution. Other studies should include the evaluation of AI automated detection versus traditional approaches and aim to standardize the second-tier referral process for patients requiring treatment and ungradable images. Research projects exploring whether the use of hand held devices, advanced optics, and newer technology (including UWF imaging and retinal function measurements) are feasible for future large-scale telescreening would be particularly helpful in terms of ease of use, reliability, and costs. The impact of patient-driven approaches such as smartphone pupillometry and automated non-mydriatic fundus cameras situated in public places should also be studied as a means to increase patient-driven screening.

Conclusions

This review is limited to the published data available; however, it is clear that great attempts are being made worldwide in the

fields of telescreening, automated detection using AI, and patient-initiated testing with smartphones and unmanned kiosks to diagnose and manage the escalating problem of diabetes and DR, despite the immense challenges with resources and infrastructure. However, despite these efforts, evidence gaps remain. Telescreening approaches and equipment need to be compared and ideally standardized, and AI and smartphone technologies need to be rigorously tested to ensure adequate sensitivity and specificity. We believe that a more standardized and collaborative approach would lead to the establishment of the best approach to DR screening practice, as well as data sharing for research purposes and cost efficiency.

In countries with inadequate primary care systems, a holistic approach to screening for diabetes is highly recommended to prevent end-organ damage in the absence of a routine screening program. This, at a minimum, should include retinal screening, as well as foot examinations, blood pressure monitoring, and urine albumin, HbA_{1c}, and lipid testing. A collateral benefit of DR screening, which may be underappreciated, is that it can also identify other conditions, including retinal disease and other microvascular conditions.

To protect the sight of the millions of patients at risk of DR, significant investment is required. Determining the best way forward is a challenge, especially with respect to funding initiatives such as healthcare kiosks and smartphone telescreening. Whether pharmaceutical companies, supermarkets and pharmacies, insurance companies, or healthcare authorities should contribute and/or collaborate is unclear, but doing nothing is more costly, both economically and to society. It is likely that DR-related visual disabilities will increase in the coming years; therefore, an organized public health approach must be adopted, with all stakeholders cooperating to control severe visual disabilities caused by DR.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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