Eye (2021) 35:2685–2698
https://doi.org/10.1038/s41433-021-01572-4

The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Recently updated global diabetic retinopathy screening guidelines: commonalities, differences, and future possibilities

Taraprasad Das[1,2] · Brijesh Takkar[1] · Sobha Sivaprasad[3,4] · Thamarangsi Thanksphon[5] · Hugh Taylor[6] · Peter Wiedemann[7] · Janos Nemeth[8,9] · Patanjali D. Nayar[10] · Padmaja Kumari Rani[1] · Rajiv Khandekar[11,12]

Received: 21 November 2020 / Revised: 28 March 2021 / Accepted: 21 April 2021 / Published online: 11 May 2021

Abstract

Diabetic retinopathy (DR) is a global health burden. Screening for sight-threatening DR (STDR) is the first cost-effective step to decrease this burden. We analyzed the similarities and variations between the recent country-specific and the International Council of Ophthalmology (ICO) DR guideline to identify gaps and suggest possible solutions for future universal screening. We selected six representative national DR guidelines, one from each World Health Organization region, including Canada (North America), England (Europe), India (South- East Asia), Kenya (Africa), New Zealand (Western Pacific), and American Academy of Ophthalmology Preferred Practice Pattern (used in Latin America and East Mediterranean). We weighed the newer camera and artificial intelligence (AI) technology against the traditional screening methodologies. All guidelines agree that screening for DR and STDR in people with diabetes is currently led by an ophthalmologist; few engage non-ophthalmologists. Significant variations exist in the screening location and referral timelines. Screening with digital fundus photography has largely replaced traditional slit-lamp examination and ophthalmoscopy. The use of mydriatic digital 2-or 4-field fundus photography is the current norm; there is increasing interest in using non-mydriatic fundus cameras. The use of automated DR grading and tele-screening is currently sparse. Country-specific guidelines are necessary to align with national priorities and human resources. International guidelines such as the ICO DR guidelines remain useful in countries where no guidelines exist. Validation studies on AI and tele-screening call for urgent policy decisions to integrate DR screening into universal health coverage to reduce this global public health burden.

✉ Taraprasad Das
tpd@lvpei.org

1 Srimati Kanuri Santhamma Centre for Vitreoretinal Diseases, L V Prasad Eye Institute, Hyderabad, India

2 Regional Chair, International Agency for the Prevention of Blindness, South East Asia, Hyderabad, India

3 NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK

4 UCL Institute of Ophthalmology, London, UK

5 Former Director, Healthier Populations and Non-Communicable Disease, WHO Regional Office for South- East Asia Region, New Delhi, India

6 Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

7 Department of Ophthalmology, University Leipzig, Leipzig, Germany

8 Department of Ophthalmology, Semmelweis University, Budapest, Hungary

9 Regional Chair, International Agency for the Prevention of Blindness, Europe, Budapest, Hungary

10 Regional Advisor, Disability & Injury Prevention and Rehabilitation, Healthier Populations and Non-Communicable Disease, WHO Regional Office for South- East Asia Region, New Delhi, India

11 Department of Research, Ophthalmic epidemiology & Low Vision, King Khalid Eye Hospital, Riyadh, Kingdom of Saudi Arabia

12 British Columbia Centre for Epidemiologic & International Ophthalmology, University of British Columbia, Vancouver, BC, Canada

Table 1 Key elements in global status of diabetes [2].

Components	AFR 47 countries		EUR 57 countries		MENA 21 countries		NAC 24 countries		SACA 19 countries		SEA 7 countries		WP 36 countries	
	2019	2030	2019	2030	2019	2030	2019	2030	2019	2030	2019	2030	2019	2030
Adult population (20–79 years)	501.3m	703.9m	665.4m	673.8m	426.3m	533.8m	357.1m	393.5m	335.1m	381.0m	997.4m	1.2b	1.7b	1.8b
DM regional prevalence	3.9%	4.1%	8.9%	9.8%	12.8%	14.2%	13.3%	14.2%	9.4%	10.6%	8.8%	9.7%	9.6%	11.0%
DM age-adjusted prevalence	4.7%	5.1%	6.3%	7.3%	12.2%	13.3%	11.1%	12.3%	8.5%	9.5%	11.3%	12.2%	11.4%	12.4%
DM people	19.4m	28.6m	59.3m	66.0m	54.8m	76.0m	47.6m	56.0m	31.6m	40.2m	87.6m	115.1m	162.6m	196.5m
DM undiagnosed prevalence	59.7%	-	40.7%	-	44.7%	-	37.8%	-	41.9%	-	56.7%	-	55.8%	-
DM undiagnosed people	11.6m	-	24.2m	-	24.5m	-	18.0m	-	13.3m	-	49.6m	-	90.8m	-
T1 DM people	25,800	-	296,500	-	149,400	-	224,900	-	127,200	-	184,100	-	102,200	-
DM deaths	366,200	-	465,900	-	418,900	-	301,700	-	243,200	-	1.15m	-	1.26m	-
DM health expense USD[a]	9.7b	12.7b	161.4b	168.5b	24.9b	32.5b	324.5b	338.8b	69.7b	80.4b	8.1b	10.1b	162.2b	181.8b
IGT. Regional prevalence	9.0%	9.5%	5.5%	5.9%	8.3%	8.9%	15.5%	16.3%	10.1%	10.8%	3.1%	3.3%	8.0%	8.7%
IGT. Age-adjusted prevalence	10.1%	10.5%	4.4%	4.9%	9.2%	9.7%	12.3%	13.2%	9.7%	10.3%	7.7%	7.9%	10.4%	11.0%
IGT. People	46.3m	66.8m	36.6 m	39.7 m	35.5 m	47.3 m	55.5 m	64.0 m	33.9 m	41.0 m	30.6 m	39.1 m	136.5 m	155.9 m

AFR Africa, *EUR* Europe, *DM* diabetes mellitus, *MENA* middle east and north Africa, *NAC* North America & Caribbean, *SACA* South And Central America, *SEA* South East Asia, *T1DM* Type 1 DM, *WP* Western Pacific, *USD* US dollars, *IGT* impaired glucose tolerance, *b* Billion, *m* million.

[a]Direct cost.

Introduction

The vision loss expert group (VLEG) reported that diabetic retinopathy (DR) accounted for 1.07% of blindness and 1.25% of moderate to severe visual impairment (MSVI) in 2015 [1]. Despite global efforts to reducing visual impairment, the prevalence of DR is increasing (Crude prevalence 1990: 0.03%; 2015: 0.04%) while the prevalence of all other causes of visual impairment is decreasing consequent to concerted global efforts [1]. This disparity is explained by the estimated global demographic changes between 2019 and 2030–24.8% increase in people with diabetes (International Diabetes Federation, IDF, 2019 estimation: 463 million; 2030 projection: 578 million) [2], 10.7% increase in population (2019 estimate: 7.71 billion; 2030 projection: 8.54 billion) [3], 13.1% longer longevity of people (life expectancy: 2019 estimation: 64.2 years; 2030 projection: 72.6 years) [3], and the increasing aging population of 65+ years (2019 estimate: 9.1%; 2030 projection: 11.7%) [3]. Table 1 lists the key elements of diabetes care in the world [2].

There is a concurrent rise in the worldwide cost of diabetes care; in 2030, the direct cost could be USD 825 billion (2019 estimate: USD 760 billion) [2] and total cost, both direct and indirect, could be USD 2.1–2.5 trillion (2015 cost: USD 1.3 trillion) [4]. However, there is gross inequity on planned expenditure on diabetes and its complications globally (the region with higher prevalence and the low-middle income countries, LMIC, are spending less). As one of the six building blocks of the WHO health system, health finance is an important consideration. In less developed countries, the consideration of the cost of DR care assumes more significance for three reasons: (a) higher resource allocation for cataract surgery and uncorrected refractive error; (b) a significant amount of out-of-pocket spending, and occasionally, catastrophic health expenditure; (c) late presentation of patients with advanced diabetic retinopathy and vision loss.

Progression of DR follows a particular pattern from non-proliferative DR (NPDR) to proliferative DR (PDR). Typically, it takes years for NPDR to convert to sight-threatening diabetic retinopathy (STDR). The STDR includes macular edema and proliferative diabetic retinopathy (PDR). Using retinal photography, a recent review estimated the global burden of DR in people with diabetes mellitus (DM) could be as high as 27% [5]. The estimated quality-adjusted life years (QALY) loss due to visual impairment is also high (−74.93 years per 100,000 person-years in a study from Korea) [6].

The key to reducing visual impairment and blindness for a chronic disease like DR is early detection and treatment of STDR. Screening is a useful tool, and DR meets nearly all criteria laid down by Wilson and Jungner [7]. Screening for

DR has also added benefit to identifying people at risk of other diabetes-related complications such as neuropathy, nephropathy, cardiovascular disease (CVD), stroke, and peripheral vascular disease [8].

The regional and national perspectives have been evolving globally to incorporate newer advances and innovations in DR screening. However, there are variations as per the existing public health requirements and available resources. The objective of this review was to identify potential areas for improvement to enable global coverage with DR screening. We reviewed the currently available and recently updated DR screening guidelines across the globe, one from each region of the World Health Organization (WHO)/International Agency for the Prevention of Blindness (IAPB). We compared them with the International Council of Ophthalmology (ICO) guidelines for evaluating the similarities and variations in screening for STDR.

Methods

A search of available electronic databases, including the WHO, ICO, IAPB, VISION 2020 Right to Sight, American Academy of Ophthalmology (AAO) sources, was completed to identify the existing country or professional ophthalmological society- approved DR guidelines for people with type 1 (T1) DM and type 2 (T2) DM. The reference terms were "diabetic retinopathy," "screening," "guidelines," and "practice pattern." We reviewed 12 guidelines available in the English-language published or updated in the last 5 years and selected one from each region of the IAPB. The publication period was chosen as the previous 5 years to include only those guidelines that have possibly incorporated the recent DR screening updates (Table 2a, b).

The final section of the guideline and reason for such selection is as follows: Canada (2018; North America-Canada practices systematic tele-screening), England (2017; Europe-England practices national screening), India (2019; South-East Asia-India is home to the second largest population of DM), Kenya (2017; Africa- Kenya has developed a detailed DM/DR protocol), New Zealand (2016; Western Pacific- New Zealand practices systematic national DR screening), and AAO Preferred Practice Pattern (PPP) (2019; guidelines used in Latin America and Eastern Mediterranean countries) [9–14]. All these guidelines were compared between them and against the ICO (2017) guidelines (Table 2a, b) [15].

Questions

The ICO guidelines on diabetic eye care provide a framework for developing regionally applicable DR screening guidelines. We reviewed the ICO guidelines and identified questions relevant to DR screening. The answers to these questions are central components for any DR screening program.

1. Classification of DR: Which classification is easy to use and reliable that could be applied with optimal training of human resources?
2. Systemic factors in DR: What are the target parameters associated with DM care that impacts DR outcome?
3. Screening and referral for DR: Why, Who, How, and What?

Results

The following answers to the questions derived from the review of the guidelines are included in this communication.

Definition and classification of DR: what is easy to use and yet reliable?

The earliest classification of DR is the Airlie House classification [16]. The proposed classification, with little modification, was, used in the Diabetic Retinopathy Study (DRS) and, for the first time, the standards of photo-documentation using stereo photographs of 7 standard fields (around the optic disc and macula) were laid [17]. Later, this classification was further modified and used in the Early Treatment of Diabetic Retinopathy Study (ETDRS) [18]. The ETDRS introduced a new term- the clinically significant macular edema (CSMO) [18]. The ETDRS also measured the DR severity scale into 13 levels.

The ETDRS classification became the new gold standard of the DR severity scale; it was suitable for research but suffered from its complexity. In 2003 the Clinical Disease Severity Scale for DR proposed a new classification, the International Classification of Diabetic Retinopathy (ICDR) [19]. There are five categories in DR; diabetic macular edema (DMO), when present, was classified into three categories. (Table 3). Using the optical coherence tomography heatmap, the DMO is also classified into "center involving" and "non-center involving" DMO [20]. All examined/selected guidelines currently follow the ICDR classification, and color fundus photography is the recommended standard for DR screening.

Systemic factors in DR: what are the target parameters?

Control of diabetes mellitus and many associated co-morbidities is necessary for maximum treatment benefit to

Table 2 Literature review of DR and DM screening.

(A) Diabetic retinopathy [9–15]

Region	Country	Commissioning authority	Publication year
North America	Canada	Clinical Practice Guidelines Expert Com	2018
Latin America	LA	AAO PPP	2019
East Mediterranean	EMR	AAO PPP	2019
Africa	Kenya	Division on NCD, Kenya	2017
South-East Asia	India	Indian institute of public health	2019
Europe	England	NHS DR screening program	2017
West Pacific	New Zealand	Ministry of health, New Zealand	2016
International Council of Ophthalmology (ICO)			2017

(B) Diabetes mellitus [26–32]

Region	Country	Commissioning authority	Publication year
North America	USA	ADA	2019
South America	LA	AAO PPP	2019
East Mediterranean	Pakistan	WHO CC, Pakistan	2019
Africa	South Africa	SEMDSA	2017
South East Asia	India	ICMR	2018
Europe	-	EASD	2017
West Pacific	Australia	Diabetes Australia	2014
	Japan	Japan Diabetes Society	2016

AAO American Academy of Ophthalmology, *ADA* American Diabetes Association, *DR* Diabetic retinopathy, *EASD* European Association for the study of diabetes, *ICMR* Indian Council of Medical Research, *LA* Latin America, *PPP* preferred practice pattern, *NCD* non-communicable disease, *NHS* National Health Service, *SEMDSA* Society of Endocrinology, Metabolism, and Diabetes of South Africa; *WHO CC* World Health Organization Collaborating Center.

Table 3 International classification of diabetic retinopathy (ICDR) classification [19].

Disease severity	Findings observable upon dilated ophthalmoscopy
Diabetic retinopathy (DR)	
No apparent DR	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than Severe NPDR, (microaneurysms with other signs like intraretinal hemorrhages, hard exudates, cotton wool spots)
Severe NPDR	Any of the following: (4:2:1) 1 More than 20 intraretinal hemorrhages in each of 4 quadrants 2 Definite venous beading in 2+ quadrants 3 Prominent intraretinal microvascular abnormalities IRMA in 1+ quadrant (And no signs of PDR)
PDR	One or more of the following: 1. Neovascularization 2. Vitreous/preretinal hemorrhage
Diabetic macular edema (DME) by clinical appearance	
No apparent DME	No retinal thickening or hard exudates at macula
Mild DME	Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
Moderate DME	Retinal thickening or hard exudates approaching the center of the macula but not involving the center
Severe DME	Retinal thickening or hard exudates involving the center of the macula
DME classification by Center of macula involvement using Optical Coherence Tomography (OCT)	
Non-central involving DME	Retinal thickening in the macula that does not involve central subfield zone in OCT (1 mm diameter)
Center involving DME	Retina thickening in the macula that involves the central subfield zone in OCT (1 mm diameter)

DR diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *DME* diabetic macular edema.

people with STDR [21–25]. This consists of a variable combination of retinal laser and intravitreal anti-vascular endothelial growth factor (VEGF) injection and vitreoretinal surgery [21].

There are several modifiable systemic factors of DM, but the two risk factors with the most convincing evidence and affordable treatment are hyperglycemia and hypertension. The ACCORD and its follow-up studies provided recent evidence that intensive glycaemic control remains beneficial for reducing DR progression. The legacy effect is evident in people with type 2 DM [22, 24]. The Diabetes Control and Complications Trial (DCCT) evaluated intensive control of hyperglycemia in Type 1 DM, and long term results showed definite benefits in risk reduction of DR [25]. The United Kingdom Prospective Diabetes Study (UKPDS) has shown a decreased incidence of DR with tight control of blood pressure and glucose in patients with Type 2 DM [23]. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), diastolic blood pressure was a significant predictor for DR progression to PDR over 14-year follow-up in people with T1DM [26]. The DM guidelines from different countries of the region [27–33] have set targets for diabetes, blood pressure, and cholesterol control (Table 4). Other important systemic factors are kidney disease (greater association with T1DM) [34], microalbuminuria, anemia (for retinopathy progression and DMO) [35], and obesity (strong relationship with insulin resistance) [36]. With the recent surge of novel anti-diabetes strategies, the initial worsening of DR should be monitored before the retina begins to stabilize, as observed with insulin therapy initiation [37]. A multi-disciplinary approach and close interaction between the diabetologist and ophthalmologist helps, and housing them together is beneficial.

Screening and referral for DR: Why Who, How, and When

Why should DR screening be established?

The vast majority of patients who develop DR have no symptoms until the late stages due to DMO and PDR complications, such as vitreous hemorrhage or tractional retinal detachment. The late presentation of people with an advanced disease state is a worldwide phenomenon related to a lack of public knowledge, awareness, and social deprivation [38–41]. Direct medical costs for DR care are substantial, so also the indirect costs of visual impairment with respect to loss of productivity, increasing hospital

Table 4 Recommended systemic and lifestyle targets for non-pregnant adults with DM [26–32].

Region/ country	HbA1C% (in IFCC units)	FPG (mg/dl)	BP (mm Hg)	HDL (mg/dl)	LDL (mg/dl)
USA	<7.0% (<53.0)	80–130	<140/90 if not high risk, else <130/80	>39	<70 if high risk[a]
Europe	<7.0% (<53.0)	<126	120–130 /70–80 120–139/70–80 (≥65 years)	NS	<70 if high risk
Australia	<7.0% (<53.0)	106–145	<130/80	>39	<77
Japan	<7.0% (<53.0)	<130	<130/80	>40	<100
MENA	6.5–7.0% (47.5–53.0)	80–120	<140/90	NS	NS
South Africa	<7.0% (<53.0)	72–126	<140/90	>39 for men	<70
India	<7.0% (<53.0)	80–110	<130/80	>40 for men	<70 for high risk

MENA Middle East and North Africa, *NS* not specified, *IFCC* International Federation of Clinical Chemistry (mmol/mol).

[a]High risk refers to patients at high risk for macrovascular complications as defined by regional organizations, e.g., established cerebral vascular disease (CVD), smoking, obesity, hypertension, family history of premature CVD and evidence of other vascular disease [32].

admissions, and decreased quality of life [42]. From a public health perspective, blindness, and its treatment cost results in poverty at the individual level and retards economic development at the national level [43]. Good health and wellbeing (Sustainable Development Goal, SDG 3) is intimately connected with SDG 1 and 2 (No poverty and Zero hunger) [44]. All guidelines agree to screen for diabetic retinopathy, and DR screening fits all chronic disease screening criteria [45].

Who should perform DR screening?

In the past, countries have relied on ophthalmologists and physicians to screen all people with diabetes. With the shift from ophthalmoscopy to digital retinal photography, technically trained and certified screeners such as optometrists and allied ophthalmic personnel, including trained retinal photographers, are more cost-effective [46]. The reliability of screening by optometrists and/or retinal photographers has reached 91% sensitivity, and 78% specificity [47] against the National Institute for Clinical Excellence (NICE, UK) recommended acceptance level for DR screening at 80% sensitivity, 95% specificity (and clinical failure rate <5%) [48]. In many countries, the existing law does not allow optometrists to dilate pupils without ophthalmologist supervision. This is a barrier, but reading and grading fundus photos obtained in a non-mydriatic camera could overcome this barrier with the current technology.

How often and where should DR screening be done

Most guidelines suggest that people with T2DM are screened first at the time of diagnosis, and people with T1 DM are screened first at puberty or five years after the diagnosis.

The follow-up care depends on the disease severity; it could vary from 1 to 2 years when there is no retinopathy to half-yearly review once the retinopathy is stabilized after adequate treatment. Longer intervals of follow-up have also been suggested after cohort studies on T2 DM [49]. There are different opinions on the time of retinal examination during pregnancy (Table 5). Examining all people with DM at fixed facilities (eye hospital/ophthalmology services) may not always be feasible in many low-middle income countries (LMICs) and in countries/regions that do not have enough workforce and technology resources. In most countries, there is no standardized, systematic nation-wide screening for DR. In the studied guidelines, only England and New Zealand practice a national DR screening policy. Maintaining a national registry of patients with DM will help direct patients with DM for periodic screening efficiently. Annual eye evaluation may not be cost-effective for low-risk patients [50].

Studies from India, Malawi, and the USA have shown that screening closer to people and/or coupled with the application of laser to eyes with STDR detected in screening improves compliance and is cost-effective, including the gain in quality-adjusted life years (QALY) [51–53]. Based on the current resources, we suspect reaching people with mobile services or opportunistic screening in mass medical congregations would continue for quite some time in all LMICs.

What should be included in DR screening?

The ICO screening guideline suggests a record of disease and treatment history (duration, status, and medication). The basic eye examinations include presenting (and spectacles corrected, if any) vision and fundus photography [15]. A comprehensive eye examination would also include slit-lamp examination, intraocular pressure measurement (gonioscopy when intraocular pressure is high), and dilated eye examination. However, essentially, a screening examination should be short enough for people to adopt it and yet informative enough for intelligent referrals.

Table 5 DR Screening strategy [8–15].

Question	Condition	Strategy	County guidelines						
			Canada	Latin Am	England	India	Kenya	NZ	AAO PPP
Who	All DM	Trained personnel	+	-	+	+	+	+	+
		Ophthalmologist	+	+	+	+	+	+	+
		Teleophthalmology	+	-	+	+	-	+	+
How	All DM	Fundus photo	+	+	+	+	+	+	+
		Ophthalmoscopy	+	+	+	+	+	+	+
		National screening	-	-	+	-	-	+	
When	T2DM	At diagnosis	+	+	+	+	+	+	
	T1DM	On basis of puberty			-	+			+
		Review on basis of age	+ (>15 years)	+ (>15 years)	12 years and above	+ (>10 years)		+ (>10 years)	
		Review on basis of duration of DM(5-year interval)	+	+		+	+	+	+
	Pregnancy	Pre-existing DM only	+		+	+		+	
		All gestational DM		+			+	+	+
Basic tests	ALL DM	Visual acuity	+	+	+	+	+	+	+
		Fundus\camera preference	Non-mydriatic	Mydriatic	Non-mydriatic	Non-mydriatic	Mydriatic	Non mydriatc	Color
		Fundus field	7-field/UWF	NS	2×45^0	Variable	NS	4–750	Not specified
		Mydraisis prefered	+	+	+	+	+	+	+
Referral	Disease severity	Non STDR	Annual	Annual	R0–R3[a]	Annual	Annual	R0–R5[a] M0-M6[a]	Annual
		STDR	Urgent	Urgent		Urgent	Urgent		Urgent
ICO	Referral by disease and county economics				Referral criteria by VA, disease, infrastructure				
	No/mild NPDR. Referral	LMIC: 1–2 years	HIC-6–12 months		Vision	<20/40; VA reduction symptoms			
	Mod- Severe NPDR & worse	LMIC-Urgent	HIC-Urgent		Disease status	Mod/severe NPDR & worse			
	Pregnancy. Pre-existing DM	LMIC-28 weeks	HIC- 16–20 weeks		Infrastructure	VA, retinal exam not obtained			

DM diabetes mellitus, *NS* not specified, *NZ* New Zealand, *UWF* Ultra-widefield.

[a]Based on disease severity of disease.

What are the follow-up and referral criteria

The key indicators of DR screening's success are the robustness of the referral system and compliance with these referrals. Three outcomes could emerge from a DR screening episode (a) a routine re-examination when there is no or mild retinopathy, (b) non-urgent referral for moderate non-sight-threatening DR and (c) urgent referral for sight-threatening DR. Most guidelines agree that annual eye check-up is necessary when retinopathy is not detected (some countries recommend two years) and this interval is reduced depending on the degree of retinopathy. The ICO has suggested different guidelines for LMIC- it is twice longer for mild retinopathy (1–2 years in LMIC and 6–12 months in high-income countries, HIC). England and New Zealand guidelines have a systematic referral pattern: England (R0–R3) and New Zealand (R0–R5), depending on the disease severity. All guidelines are unanimous on the referral of all people with STDR and those with reduced visual symptoms. However, crucial to the right referral is the quality of the retinal image and grading of these images. All guidelines suggest referrals of all people with ungradable fundus photographs. Table 5 lists the DR screening strategy [8–16].

Discussion

All the included guidelines uphold the fundamental aim of DR screening to identify STDR. There are many similarities and a few variations in the screening guidelines (Table 5). It appears that two regions, the Eastern Mediterranean and Latin America region, follow the AAO PPP. We also believe the ICO guideline is used in many LMICs that have not yet developed their DR guidelines. Important areas of dissimilarity are the technical details, screening personnel, the need for mydriasis, and the choice of retinal camera.

Screening personnel

A 2015 ICO survey estimated 232,866 ophthalmologists globally, and they were unequally distributed, much less in low-income countries (3.7/million population) than in high-income countries (76.2/million population), and within the LMICs, they were located more in urban than in rural areas [54]. In the same year, 2015, there were 415 million people with diabetes globally, and 75% of them lived in LMICs [55]. Given that the global annual growth of the number of ophthalmologists is 2.9% and the yearly global increase in people with diabetes is 4.47% [2], it would be impossible for ophthalmologists alone to screen all people with diabetes all the time. Therefore, we advocate that non-ophthalmologists be trained to capture retinal images and use computer-aided grading of DR images, where available.

Need for mydriasis

Mydriatic examination generally allows screening of a greater retinal area compared to an undilated fundus view. Pupil dilatation enables the ophthalmologists to have a good view of the retina and a photographer to obtain artifact-free retinal photographs. However, dilatation for all patients and a routine mydriatic screening test that makes the person wait for at least 30 min and incapacitates the individual for near work for the next couple of hours may not always be necessary. With newer technology of non-mydriatic devices (such as non-mydriatic retinal camera and optical coherence tomography angiography), one could reserve pupillary dilatation to people where a readable/gradable image could not be obtained and obviously for those who need treatment. To achieve universal coverage in countries with steep increases in numbers of people with diabetes, innovative approaches in using non-mydriatic cameras should be encouraged. Policies that prevent mydriasis by non-clinician or non-clinical environment should be reviewed, risk-assessed, and situation-specific strategies tailored to facilitate mydriasis.

Creating referral system

One of the prime motivating factors of a screening program for DR is the evidence-based standardized care for all levels of STDR that includes laser, intravitreal anti-VEGF injection, and vitreoretinal surgery [56–59]. The detailed referral system practiced in England and New Zealand national screening is not practically possible everywhere, certainly not in LMICs. Ideally, countries must develop/revise their country-specific DR screening and treatment guidelines based on the local resources and trained human resources for health. The global benchmark, such as the ICO guideline that has taken different resources into account, is a good option as a national guideline or a template to develop/revise national policies.

Future of DR screening

Borne out of technological advances and policy planning, there are emerging game-changers. These should be considered in new or revised DR screening guidelines. These include camera technology, artificial intelligence, e-health, and universal health coverage.

Camera technology

The concept of 7-field fundus photography (30^0 views) originated with the DRS in the early 1970s. The 7-field fundus photos were arranged around the optic disc in a particular sequence [17, 18]. Since then, camera technology

and techniques have undergone sweeping changes. In brief, these changes are black and white to color photography, film-based to digital photography, narrow (30^0) field to wide (45^0–50^0, and ultra-wide (200^0) field imaging. Recent studies have demonstrated that digital photography is as good as film-based photography [60]; monoscopic digital fundus photographs also match the rigor of stereo photos [61]; and a mosaic of four- or five- 45^0 fields could create a field of view reaching the area covered by classic 7-field fundus photography [62]. Single ultra-widefield color fundus photo is also reported good for DR grading [63]. One drawback of digital retinal imaging is its inability to identify and grade macular edema accurately. Over the years, the camera hardware technology has advanced to produce less bulky and hand-held cameras, smartphone-based cameras, and non-mydriatic fundus cameras. This has immensely increased the opportunity to reach people closer to their home and transmit their images to a remotely located reading site for grading and management planning. In the last two decades, the quality of handheld cameras has considerably improved with better prediction capability [64, 65]. A good-quality fundus image is one where both disc and macula are captured in the same frame with good focus and illumination; a poor-quality fundus image captures either disc or macula and has poor illumination (Fig. 1).

A technical comparison of the currently available non-mydriatic cameras is listed in Table 6. Technology has improved over the years; the questions at present are (1) what is the minimum field required for DR screening in most instances; (2) what are financial resources, as the camera cost steeply increases with an increase in the field of view; (3) what is the choice between mydriatic and non-mydriatic camera for retinal photography and its applicability in DR screening. A systematic review on the use of non-mydriatic cameras reported that two-field retinal photographs were predictable (sensitivity 91%, specificity 94%). It matched the predictability of images obtained by the mydriatic fundus camera once the ungradable images (18.4%) are excluded [66].

Artificial intelligence

Artificial intelligence (AI) in health care uses complex algorithms to emulate human cognition to analyze complex medical data without direct human input. It provides a well-defined output to the end-user. In several large studies, deep learning (one of the tools of AI) in DR has shown good sensitivity (87% to 100%), specificity (87% to 98%), and receiver operating characteristic curve (AUC; 0.93 to 0.99) for referable DR and/or STDR [67–69]. The current technology cannot capture macular edema (would improve once OCT images are included). AI has not addressed the issue of images captured in different cameras, the image quality, and the field of view. Despite technological advances, deep learning is still not tried in a real-world screening of DR.

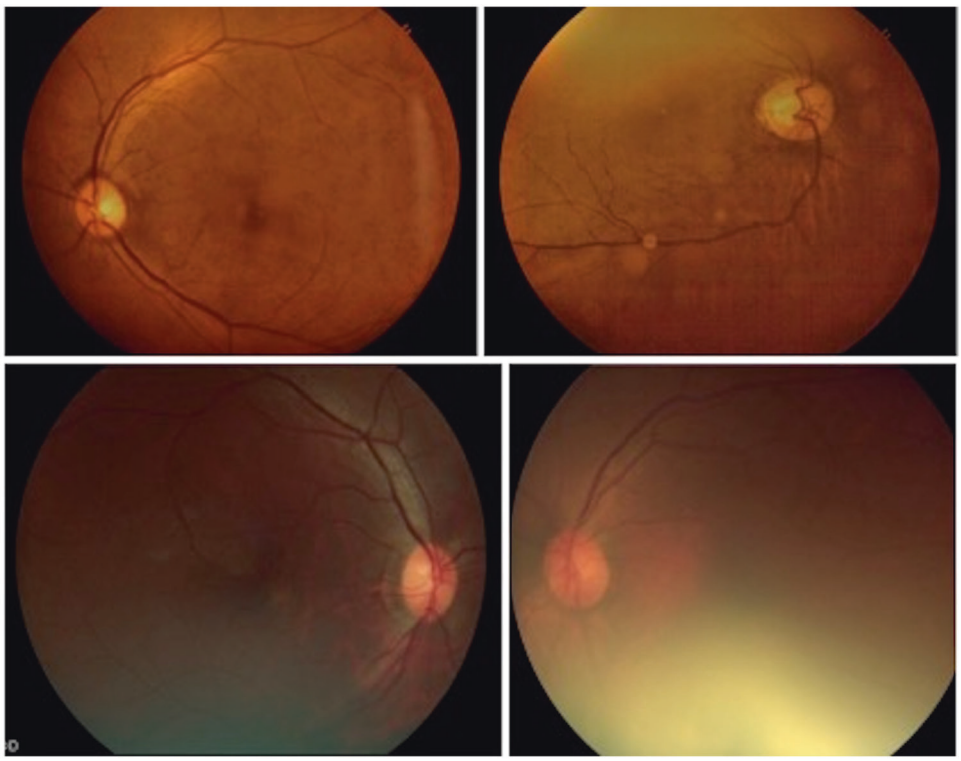

Fig. 1 Example of fundus photo obtained in DR screening using non-mydriatic camera. Upper panel: 3 Nethra™ (Forus, India)- good (left) and poor (right) quality fundus image. Lower panel: Visuscout™ (Zeiss, Germany)- good (right) and poor (left) quality fundus image.

Table 6 Technical comparison of commercially available non-mydriatic cameras.

Make and model[a]	Model	Type	Minimum pupil size (mm)	Field of view (degrees)	Autofocus	Imaging[c]	Other features
Zeiss	Visuscout 100	HH	3.5	40	+	C, RF, IR	Wi fi enable AI integration
Bosch	Fundus	HH	NS	40	+	C, RF, IR	-
Topcon	TRC-NW400	TT	>4	45	+	C	Image share with internet
Topcon	TRC-NW8F	TT	3.3	45	+	CC, RF, FFA, FAF	-
Optovue	Vivocon	TT	4	≥45	+	C	Wi fi enable
Welch Allyn	RetinaVue RetinaVue100	HH	NS	45	+	C	-
	RetinaVue 700	HH	2.5[b]	60	+	C	EMR integratable
	CenterVue DRS	TT	2.7[b]	45	+	C	EMR integratable
Forus	3nethra Royal	TT	NS	45	NS	C	EMR integratable AI integration
Canon	CR-2	TT	4	45	+	C, RF	Internal fixation
Kowa	VX-20	TT	4	45	+	C	Internal fixation
	Nonmyd DIII	TT	3.5	45/30	NS	C	Internal fixation
Nidek	AFC-330	TT	3.3	45	+	C	EMR integratable
	Verscam	HH	NS	45	+	C	slit-lamp attachment Internal fixation
Centervue	DRS camera	TT	4	45	+	C	Wi fi enable
	Eidon	TT	2.5	60	+	C, RF, IR	Confocal true color
Coburn	SK-650A	TT	3.3	45	No	C, RF, anterior	Internal fixation
Volk	Pictor plus	HH	2.7	40	+	C, anterior	Wi fi enable
EasyScan	Retinal imaging	TT	1.5	45	+	C, IR	Confocal SLO
Optos[d]	California	TT	NS	200	No	C, RF, FFA, FAF	Confocal SLO, EMR integratable
Optomed	Aurora	HH	3.1	50	+	C, RF, IR	EMR integratable Wi fi enable
Remedio	Fundus on phone camera	Hand held	3.3	45	No	C, RF, IR	Smart phone based, SL mount, tele med capable

The information presented in table has been compiled from the specifications mentioned at the websites of the respective manufacturers.

C color, *FAF* fundus auto fluorescence, *FFA* fundus fluorescein angiography, *HH* hand held, *IR* infra red, *NS* not specified, *RF* red free, *SL* slit-lamp, *TT* table top.

[a]Excluding small pupil modes and multi modal imaging systems.

[b]May need little chemical dilation.

[c]As available in the specifications.

[d]Technically not a non-mydriatic camera, but has been extensively used as the same.

The final barriers are the health policy of different countries and the trust of both clinicians and patients in the machine verdicts [70].

E-healthcare-ophthalmology

E-health refers to the intersection of medical informatics, public health, and business, referring to health services and information delivered or enhanced through the Internet and related technologies [71]. The World Health Assembly (WHA) 2018 acknowledged digital technologies' potential to play a major role in improving public health worldwide (WHA 71.7) [72]. The most integral part of e-health and telemedicine is robust information and communication technology (ICT). Broadly, telemedicine applications are divided into (1) "asynchronous" (Store-and-forward) that involves an exchange of pre-recorded data between two or more individuals; and (2) "synchronous" (Real-time) that involves the simultaneous presence of individuals for an immediate exchange of information. Both are possible, though; the asynchronous method is more suitable for DR screening. The patient's management information is shared

at the soonest possible time, and appropriate care is offered after that.

In India, remote screening has been used in DR successfully using a low-cost portable retinal camera [73, 74]. Realizing the importance of tele-screening, the Canadian Retina Research Network (CR2N) has recently laid guidelines to standardize tele-screening methodology in DR. The important elements of these guidelines are DR severity classification and recommendation for retinal photography (two-45^0 field fundus photo, one centered on the disc and the other centered on the macula; 60^0 horizontal and 45^0 vertical), and optical coherence tomography (imaging macula) standards [75]. Some of the important barriers of e-health that applies equally to tele-screening of DR include the availability of reliable ICTs in regions where it matters the most (such as in LMICs), the language of communication across different parts of the world, human, culture, and behavior of shifting from face-to-face encounters to virtual ones and the local legal requirements.

Universal health care

Universal health coverage (UHC) (equitable access, quality care, no catastrophic financial hardship) is the world's aspiration [76], and the continuum of health intervention by integrated people-centered eye care (IPCEC) is WHO's recommendation [77]. The IPCEC addresses the full spectrum of eye conditions, according to people's needs and throughout their life course [77]. It has four layers of care from community to tertiary care. Adhering to both the principles of UHC and IPCEC, different components of DR screening could be conveniently distributed from community level to tertiary level care [78] (Table 7).

Systemic care

Monitoring for systemic factors forms an essential aspect of the management of DM and DR. The targets for systemic care are generally uniform across the geographic territories, barring minor differences (Table 4). There is consensus that hyperglycemia and hypertension could be managed as per the available resources at primary through tertiary centers (Table 7). This would result in a decrease in microvascular (including DR) and macrovascular complications of DM. In line with the UHC, the closer this intervention is taken to the community, the higher likelihood of compliance.

Task sharing

Screening of DR in a cost-effective way is important and necessary when there is a huge burden of DM and a shortage of human resources, particularly in regions with a high prevalence of diabetic eye disease [79]. Effective and efficient use of the available trained human non-ophthalmologist workforce would free the ophthalmologists to perform a technically more difficult task in DR care, such as delivering retinal laser, performing intravitreal injections/vitreoretinal surgery, and follow up care of the treated patients.

Screening is not without limitations. These include: (a) screening can reduce the risk of developing a disease or its complications but cannot offer a guarantee of protection; (b) there is a minimum risk of false-positive and false-negative results; (c) false-positive results could lead to distress and possibly unnecessary treatment; (d) false-negative results could lead to false reassurance to patients and doctors. Screening is effective only when it is combined with proper referral and timely treatment. Therefore, it is imperative that screening is not established without creating suitable referral pathways, appropriate treatment, and follow-up care.

Weakness and strengths

The main weakness of this analysis is the limited number of guidelines examined and confined to the English language only. Incidentally, more countries have guidelines for DM (including one from the IDF for T2DM) than DR. The only global guideline for DR is the one recommended by the ICO. Also, we selected English-language DR guidelines, one from each IAPB region and the ones recently published.

The strength of this analysis was the evaluation of the most recent (2016–2019) published DR guidelines. Given

Table 7 DR screening activities at different levels of health care [78] along the WHO guidelines of integrated people-centered eye care.

Activity	DM center	Community	Primary	Secondary	Tertiary
DM/DR history	+	+	+	+	+
Blood test	+	−	+	+	+
VA measurement	+	+	+	+	+
Dilated eye exam	+/−	−	+	+	+
Fundus photo	+/−	+/−	+/−	+	+
Referral to next level	+	+	+	+	+
Advocacy	+	+	+	+	+

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the technological advances of devices used in DR detection, increased advocacy, and friendly eye health policy, the inclusion of the DR guidelines formulated in the recent five years was important. This report also compares the current commercially available non-mydriatic fundus camera, which is soon likely to be the standard of DR screening. The analysis also provided evidence on gaps in guidelines, and recommendations are made based on potential solutions from practices in different health systems.

In conclusion, a uniform protocol for DR screening in each country would help improve case detection. National guidelines on timely and evidence-based treatments should be put in place to complement a good screening program. Using newer technology of the camera, e-health, artificial intelligence, and the use of available health care personnel beyond ophthalmologists such as the allied eye health personnel will improve universal coverage of screening. International and national policies need to prioritize DR screening and treatment to align with universal health coverage to improve the efficiency of the screening programs in diabetic retinopathy.

Acknowledgements Hyderabad Eye Research Foundation for research support of TD, BT, and PKR.

Funding SS, TD, PKR: GCRF UKRI (MR/P207881/1). TD/BT/PKR: general funding support by HERF. TD, BT, PKR: Hyderabad Eye Research Foundation, Hyderabad, India (2020). SS, TD, PKR: GCRF UKRI (MR/P207881/1).

Author contributions Concepts: TD, BT, PDN. Design: TD, BT, SS, HT, JN, RK. Definition of intellectual content: TD, BT, SS, TT, ST, PW, JN, PDN, PKR, RK. Literature search: TD, BT, SS, TT, PW, JN, PDN, PKR, RK. Data acquisition: TD, BT, ST, JN. Data analysis: TD, BT. Statistical analysis: TD, BT. Manuscript preparation: TD, BT, SS, RK. Manuscript editing: TD, BT, SS, TT, HT, PW, JN, PDN, PKR, RK. Manuscript review: TD, BT, SS, TT, HT, PW, JN, PDN, PKR, RK. Guarantor: TD.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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