Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings

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Guidelines on Diabetic Eye Care

The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings

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Diabetes mellitus (DM) is a global epidemic and affects populations in both developing and developed countries, with differing health care and resource levels. Diabetic retinopathy (DR) is a major complication of DM and a leading cause of vision loss in working middle-aged adults. Vision loss from DR can be prevented with broad-level public health strategies, but these need to be tailored to a country's and population's resource setting. Designing DR screening programs, with appropriate and timely referral to facilities with trained eye care professionals, and using cost-effective treatment for vision-threatening levels of DR can prevent vision loss. The International Council of Ophthalmology Guidelines for Diabetic Eye Care 2017 summarize and offer a comprehensive guide for DR screening, referral and follow-up schedules for DR, and appropriate management of vision-threatening DR, including diabetic macular edema (DME) and proliferative DR, for countries with high- and low- or intermediate-resource settings. The guidelines include updated evidence on screening and referral criteria, the minimum requirements for a screening vision and retinal examination, follow-up care, and management of DR and DME, including laser photocoagulation and appropriate use of intravitreal anti−vascular endothelial growth factor inhibitors and, in specific situations, intravitreal corticosteroids. Recommendations for management of DR in patients during pregnancy and with concomitant cataract also are included. The guidelines offer suggestions for monitoring outcomes and indicators of success at a population level. *Ophthalmology 2018;■:1−15 © 2018 by the American Academy of Ophthalmology*

Diabetic mellitus (DM) is a global epidemic with significant morbidity and mortality, affecting not only populations in highly developed countries such as the United States, the United Kingdom, and those of Western Europe, but increasingly also developing countries, including China, India, South America, and Africa.[1−6] By 2040, of the 600 million people worldwide with DM, 400 to 500 million will live in low- and middle-income countries.[7] Thus, the impact of DM poses a substantial challenge to the health care systems in many developing countries.[8−10]

Diabetic retinopathy (DR) is a common and specific microvascular complication that develops over time.[11] Severe stages of DR, including proliferative dR (PDR) and diabetic macular edema (DME),[11] result in visual impairment and blindness without treatment. Epidemiologic studies have shown that approximately 1 in 3 persons with DM has DR, and 1 in 10 has PDR or DME.[12−15] Based on these rates, between 100 million and 120 million people have DR and possibly 20 million to 30 million have PDR or DME. However, of concern is that population surveys consistently show that half of persons with DM remain undiagnosed[16−18] and that many are unaware of their risk of DR and other complications.[19]

There are highly effective and cost-effective treatments for PDR and DME, demonstrated over 3 decades with landmark randomized clinical trials that show up to 98% of the blindness could be prevented by timely treatment with laser photocoagulation therapy and vitrectomy surgery,[20] and, in the past decade, intraocular injections of anti−vascular endothelial growth factor (VEGF) inhibitors for DME.[11,21] There is also evidence that intravitreal injections of corticosteroids may be useful for DME management, particularly in eyes with previous cataract surgery.[11,22] These treatments, coupled with the concept of earlier detection and systemic management of DM, such as intensive glucose and blood pressure control, have led to observations of declining rates of vision loss resulting from DR in the United States, Western Europe, and many countries over time.[23,24]

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From a public health perspective, vision loss resulting from DR can be prevented with a broad-based systems-level approach: first, by increasing public knowledge with targeted health care education; second, by well-implemented community-level or national screening programs for all persons with DM; third, with timely referral for more severe levels of DR; and finally, with appropriate treatment for advanced DR such as PDR and DME.[25–27] Although such broad public health programs based on best evidence have been, or could be, implemented in high-income countries with the necessary health care structure and resources in terms of funding, trained health care manpower, appropriate medications, and diagnostic and surgical facilities (i.e., in high-resource settings),[28–30] they remain a substantial challenge for countries with low or intermediate resources.[24] In these latter countries and communities, the shortage of trained eye care professionals, including ophthalmologists or optometrists, the lack of equipment (e.g., fundus cameras, lasers) and drugs, and poorly structured health care policies limit what can be achieved based on current evidence.[31,32] For example, intraocular anti-VEGF agents now are used widely for DME in countries with high-resource settings, but in low- or intermediate-resource settings, the access, availability, and administration of anti-VEGF agents are erratic and may be financially unsustainable, although they have been included in the World Health Organization List of Essential Medicines.[33]

Importantly, in many countries, the standard care pathway for DR is not always clear. Most available evidence-based guidelines for DR management are based on very country-specific requirements, and typically only those in a high-resources setting.[34–36] Some are specific to one aspect of DR care, such as management of DME.[37–39] Few comprehensive guidelines are available in low- or intermediate-resource countries.[40,41] A recent survey of 50 Asian countries showed that only 11 have some form of guidelines, of which 9 pertain to general DM care and only 2 are specific to DR.[42] Thus, a recurring problem that health care providers and policy makers face is the lack of clear understanding and guidance within a resource-specific context to design policies, to structure programs, and to monitor for success in implementation. In contrast, there are resource-specific guidelines on management of other major diseases, such as cancer and cardiovascular diseases.[43–45]

To address this critical gap from a global perspective, in 2013, the International Council of Ophthalmology (ICO)[46] initiated and developed guidelines based on best evidence from clinical data, incorporating practical real-world clinical experience from different countries and stakeholders. The aim of the 2013 ICO Guidelines for Diabetic Eye Care was to propose a feasible, sustainable, cost-effective set of recommendations for management of DR[47] with considerations for resource-based setting(s). The ICO consulted widely with ophthalmologists, physicians, and public health professionals with diverse experience and expertise from different nationalities and regions to design the 2013 guidelines, which were disseminated first in 2014. The 2013 guidelines have been translated into 7 languages.

These were updated in 2017 as the ICO Guidelines for Diabetic Eye Care.[46] This report summarizes the 2017 guideline recommendations for management for DR in both high-resource and low- or intermediate-resource settings, with a specific focus on screening, referral, follow-up, and timely treatment. Specific and detailed management of DR, including PDR and DME, is covered in other reviews[11,21,39,48,49] and on the ICO website[50] and is not addressed here.

Methods

In 2013, the ICO appointed the Diabetic Eye Care Task Force of 12 ophthalmologists from 11 different countries (see Appendix for list of members), who met over the course of 18 months for an in-depth review of the literature and the writing of the guidelines. The ICO invited national bodies (e.g., the American Academy of Ophthalmology) and international agencies (e.g., the International Diabetes Federation) to nominate members to be on the task force, with a view to having broad representations from different geographic regions and countries with varying resource levels, as well as a diverse mix of expertise ranging from retinal specialists to public health researchers. These guidelines were published in 2014.

For the 2017 guidelines, a new task force was established (see Appendix for list of members) to review the 2014 guidelines and make recommendation for new evidence since the last guidelines were published. Specific sections on epidemiology of DR, classification of DR and DME, screening guidelines, referral guidelines, detailed ophthalmic assessment of DR, treatment of DR, treatment of DME, indications for vitrectomy, list of suggested indicators for evaluation of DR programs, and equipment were assigned to the specific members of the committee. A new section on management of DR in special circumstances that describes the management of DR and DME in patients with cataracts or who are pregnant also was incorporated in the 2017 edition.

The members communicated via e-mail and teleconferences and met at major scientific conferences; first at Asia-Pacific Academy of Ophthalmology (APA02016), followed by Association for Research in Vision and Ophthalmology (ARV02016). Experts from the World Health Organization[33] and the International Agency for the Prevention of Blindness and other national and international committees were invited to meetings to discuss recommendations. Revised drafts were reviewed for comments and the committee reached a unanimous concurrence before finalizing the guidelines for official launch at the International Agency for the Prevention of Blindness General Assembly Meeting in Durban, South Africa, in November 2016.

High- versus Low- or Intermediate-Resource Settings

Recommendations were made for DR and DME in terms of screening, referral, follow-up schedules, and types of treatment for high-resource and low- or intermediate-resource settings, broadly classified on country income level as defined by the World Bank and World Health Organization[51] as follows: (1) high-resource settings, advanced or state-of-the-art screening and management of DR based on current evidence and clinical trials; (2) low- or intermediate-resource settings, essential or core to midlevel service for screening and managing DR with consideration for availability and access to care in different settings.

Summary of the International Council of Ophthalmology Guidelines

Overview of Diabetic Retinopathy

Diabetic retinopathy is the most common specific microvascular complication of DM.[11] Diabetic retinopathy develops

over time in a person with DM, progressing from milder stages of nonproliferative DR (NPDR) to more advanced vision-threatening levels of DR that include PDR and DME. The pathogenesis of DR involves interrelated pathways related to hyperglycemia, including genetic and epigenetic factors, free radicals and advanced glycosylation end products, inflammatory factors, and VEGF.

Epidemiologic Features of Diabetic Retinopathy. In many countries, DR is the most frequent cause of preventable blindness in working-age adults. A meta-analysis reported that 1 in 3 such persons (34.6%) had DR in the United States, Australia, Europe, and Asia and 1 in 10 such persons (10.2%) had vision-threatening DR (i.e., PDR, DME, or both); thus, based on the 2010 world DM population, more than 92 million adults have DR, 17 million have PDR, and 20 million have DME.[14] The Global Burden of Disease Study showed in that in 2010, there were 0.8 million blind persons and 3.7 million persons who had visual impairment because of DR.[6]

Diabetic retinopathy develops with longer duration of DM and is associated with poor control of blood sugar, blood pressure, and blood lipids.[11,22] Tight glycemic control has been shown in major trials to reduce the incidence and progression of DR.[26,27] To a lesser extent, tight blood pressure control, particularly in diabetic persons with hypertension, also has been shown to reduce DR risk and progression and, importantly, cardiovascular complications.[11,21] However, good glycemic and blood pressure controls by themselves may not necessarily reduce the lifetime risk of DR developing to negligible levels, so persons with DM remain at risk of DR over time.

The overall prevalence of DR in a community is influenced by the number of people with DM.[52] In high-resource settings with good health care systems, more people with early DM will have been diagnosed through screening. The prevalence of DR in people with newly diagnosed DM will be low, resulting in a lower overall prevalence of DR. In low- or intermediate-resource settings with less advanced health care systems, fewer people with early DM will have been diagnosed. Because the early stage of DR is asymptomatic, many people may be diagnosed with DM only when symptoms or complications have occurred. Thus, the prevalence of DR among people with newly diagnosed DM will be high, resulting in a somewhat higher overall prevalence of DR.

Definition and Classification of Diabetic Retinopathy. The classic retinal lesions of DR are well described and include microaneurysms, intraretinal hemorrhages, venous beading (venous caliber changes consisting of alternating areas of venous dilation and constriction), intraretinal microvascular abnormalities, hard exudates (lipid deposits), and retinal neovascularization (Figs 1 and 2). These findings can be used to classify eyes as having the following overlapping spectrum of DR.

Nonproliferative Diabetic Retinopathy. Eyes with NPDR have not yet developed neovascularization, but may have any of the other classic DR lesions. Eyes progress from having no DR through a spectrum of DR severity that includes mild, moderate, and severe NPDR and subsequently vision-threatening levels of PDR and DME. The stages of DR can be categorized using the simple International Classification of DR scale[53] (Table 1). Correct identification of the DR severity level of an eye allows a prediction of risk of DR progression and visual loss, and thus determination of appropriate referral, follow-up intervals, and treatment recommendations.

Proliferative Diabetic Retinopathy. Proliferative DR is the most advanced stage of DR and represents an angiogenic response of the retina to extensive ischemia from capillary closure. Retinal neovascularization typically is characterized as being new vessels on the disc or new vessels "elsewhere," typically along the vascular arcades. New vessels often occur at the interface between perfused and nonperfused areas of retina.

Diabetic Macular Edema. Diabetic macular edema is an additional important vision-threatening manifestation of DR that is assessed separately from the stages of DR because DME can be seen in eyes at any DR severity level and can run an independent course. Conventionally, based on the International Classification, DME has been defined and classified based on a clinical examination or retinal photography results according to its proximity to fovea. In the current guidelines,[46] the definition and classification of DME are updated with information from OCT, if available (Table 1): (1) no DME, absence of retinal thickening or hard exudates in the macula region; (2) non−center-involving DME, retinal thickening in the macula that does not involve a central subfield zone that is 1 mm in diameter; and (3) center-involving DME, retinal thickening in the macula that involves a central subfield zone that is 1 mm in diameter. The determination of DME severity based on these 3 categories also will determine the need for treatment and follow-up recommendations. It is important to note that advanced stages of DR and DME may be present even in patients who are not experiencing visual symptoms.

Screening, Referral, and Follow-up

Screening. Screening for DR is an important cost-effective aspect of DM management.[29,30] However, even if an adequate number of ophthalmologists are available, using ophthalmologists to screen every person with DM usually is not feasible and is likely to be an inefficient use of resources.[54–57] A screening examination theoretically could include a complete ophthalmic examination with best-corrected visual acuity after refraction, pupil dilation, and latest retinal imaging, such as with wide-field retinal photography and OCT.[55,56] However, such screening examinations are not performed routinely even in high-resource settings. The current guidelines suggest the minimum screening examination components to ensure appropriate referral should include a screening vision examination (before pupil dilation if this is necessary) and a retinal examination adequate for DR classification. This can vary depending on high-resources settings or low- or intermediate-resources settings.

The screening vision examination should be completed by appropriately trained personnel, including general practitioners, nurses, and health care workers in community settings, in any of the following ways, depending on resource availability: (1)

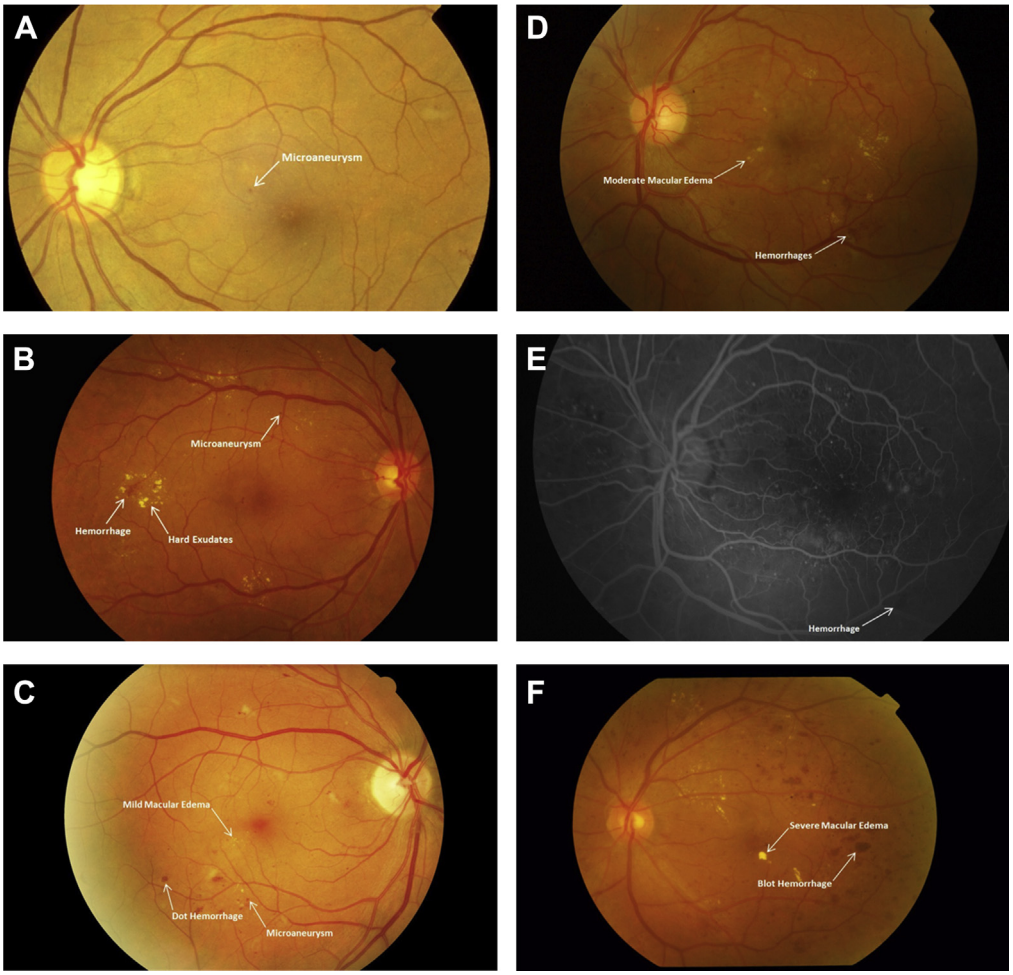

Figure 1. Fundus photographs and fluorescein angiogram showing features of mild and moderate to severe stages of nonproliferative diabetic retinopathy. **A**, Fundus photograph showing mild nonproliferative diabetic retinopathy with microaneurysms. **B**, Fundus photograph showing moderate nonproliferative diabetic retinopathy with hemorrhages, hard exudates, and microaneurysms. **C**, Fundus photograph showing moderate nonproliferative diabetic retinopathy with mild diabetic macular edema. **D**, Fundus photograph showing moderate macular edema. **E**, Fluorescein angiogram showing moderate nonproliferative diabetic retinopathy with non–center-involving diabetic macular edema. **F**, Fundus photograph showing severe nonproliferative diabetic retinopathy with center-involving diabetic macular edema.

refracted visual acuity examination using 3- or 4-m visual acuity lane and a high-contrast visual acuity chart; (2) presenting visual acuity examination using a near or distance eye chart and pin-hole option if visual acuity is reduced; and (3) presenting visual acuity examination using a 6/12 (20/40) equivalent handheld chart consisting of at least 5 standard letters or symbols and a pin-hole option if visual acuity is reduced.

The retinal examination may be accomplished in the following ways: (1) direct or indirect ophthalmoscopy or slit-lamp biomicroscopic examination of the retina; (2) retinal (fundus) photography, including any of the following: 30° to wide field, monophotography or stereophotography, and dilated or undilated photography. This could be done with or without accompanying OCT. Low-cost cameras are now widely available. The retinal examination also could include telemedicine approaches. For the retinal examination, a medical degree may not be necessary, but the examiner must be well trained to perform ophthalmoscopy or retinal photography and be able to assess the severity of DR in retinal images.

So for high-resource settings, screening could take the form of a visual acuity test with refraction and retinal photography, whereas in low-/intermediate-resource settings, screening should be a visual acuity test using pin-hole and a clinical retinal examination with pupil dilation. Figure 3 shows an example of the screening process for DR.

A screening program for DR must be coupled with access to adequate and timely referral for ophthalmologic care.[55,56] The guidelines suggest that without appropriate and timely access to ophthalmologic care, screening patients with positive results will have no benefit from the DR screening program. Thus, DR screening programs should be started only after ensuring appropriate access to facilities with access to minimum treatment, including the availability of a laser machine and typically within 3 months of screening. Minimum referral guidelines are as follows: (1) visual acuity

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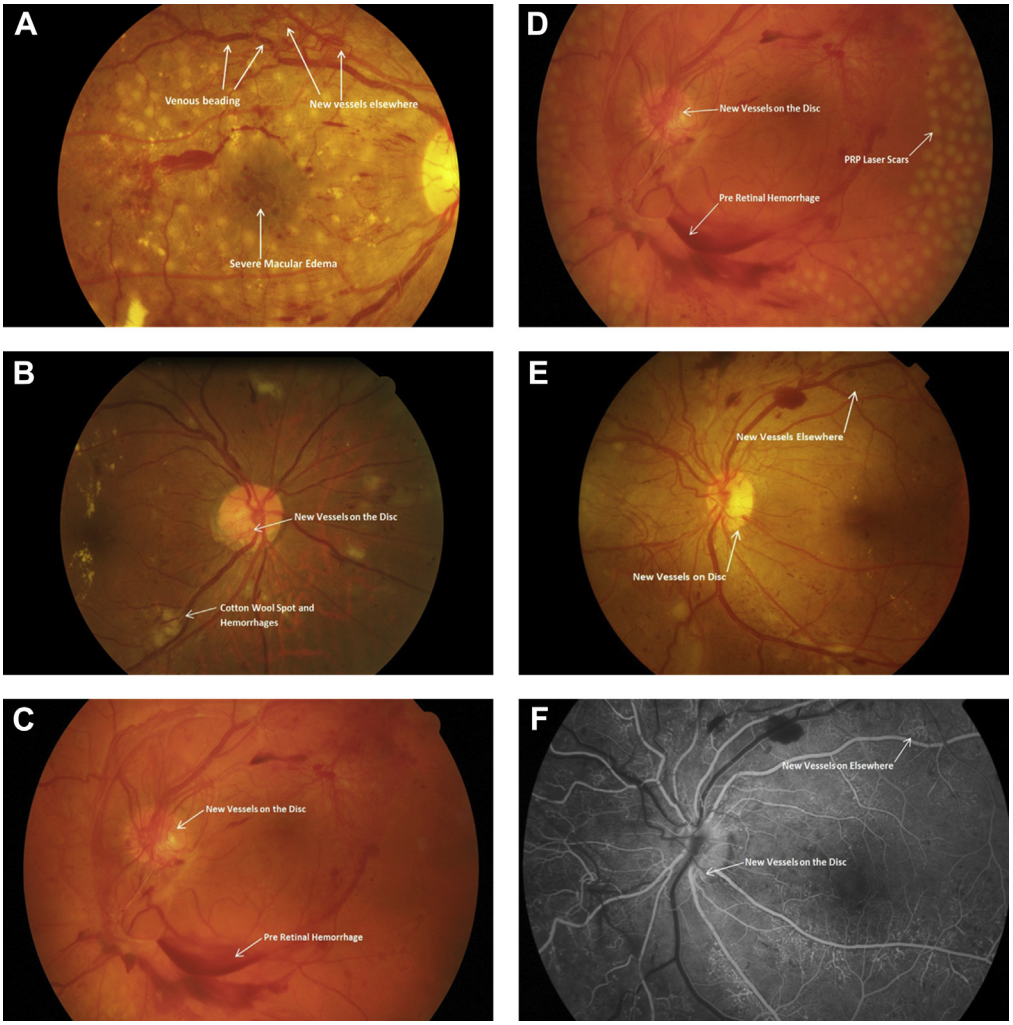

Figure 2. Fundus photographs and fluorescein angiogram showing features of severe stages of proliferative diabetic retinopathy and diabetic macular edema. **A**, Fundus photograph showing proliferative diabetic retinopathy with venous beading, new vessels elsewhere, and severe diabetic macular edema. **B**, Fundus photograph showing high-risk proliferative diabetic retinopathy with new vessels at the disc. **C**, Fundus photograph showing high-risk proliferative diabetic retinopathy with preretinal hemorrhage and new vessels on the disc. **D**, Fundus photograph showing high-risk proliferative diabetic retinopathy with new panretinal photocoagulation (PRP) scars. **E**, Fundus photograph showing proliferative diabetic retinopathy. New vessels appear on the disc and elsewhere. **F**, Fluorescein angiogram showing proliferative diabetic retinopathy. New vessels appear on the disc and elsewhere.

worse than 6/12 (20/40) or symptomatic vision reports; (2) if DR can be classified according to the simplified International Classification of DR (Table 1), they should be referred based on recommendations for management (Tables 2 and 3).

If screening visual acuity or retinal examination cannot be obtained, referral should be made. The guidelines suggest that patients with less than adequate retinal assessment should be referred unless it is obvious that there is no DR, or at most, only mild NPDR (microaneurysms only). Additionally, persons with unexplained visual acuity loss should be referred.

The suggested requirement, screening schedules, and referral to an ophthalmologist are similar for stages of no apparent DR, mild NPDR, and no DME; severe NPR; and PDR severity levels of DR between high-resource settings (Table 2) and low- or intermediate-resource settings (Table 3). However, the guidelines suggest that screening schedules for mild NPDR and moderate NPDR can be less frequent (1−2 years and 6−12 months, respectively) for low- or intermediate-resource settings (Table 3).

In countries with low- or intermediate-resource settings, ophthalmologists could encounter resource problems such as equipment scarcity and shortage in laser equipment available for treatment of DME. The committee took this into consideration and proposed that referral for patients seeking treatment with non−center-involved DME and normal vision is not required in countries with low or intermediate resource availability. However, a referral to an ophthalmologist should be viewed as a preferred option for the patient should there be adequate access to laser equipment in these settings (Table 3).

Referral Examination by Ophthalmologist. For patients referred, a medical history and clinical examination would

Table 1. International Classification of Diabetic Retinopathy and Diabetic Macular Edema

Disease	Findings Observable on Dilated Ophthalmoscopy*
Diabetic retinopathy	
No apparent DR	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	Microaneurysms and other signs (e.g., dot and blot hemorrhages, hard exudates, cotton wool spots), but less than severe nonproliferative DR
Severe nonproliferative DR	Moderate nonproliferative DR with any of the following: intraretinal hemorrhages (≥20 in each quadrant); definite venous beading (in 2 quadrants); intraretinal microvascular abnormalities (in 1 quadrant); and no signs of proliferative retinopathy
Proliferative DR	Severe nonproliferative DR and 1 or more of the following: neovascularization, vitreous/preretinal hemorrhage
Diabetic macular edema	
No DME	No retinal thickening or hard exudates† in the macula
Non–center-involving DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1 mm in diameter
Center-involving DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter

DME = diabetic macular edema; DR = diabetic retinopathy.
*Clinical findings as reported and observed from dilated ophthalmoscopy performed for DR and dilated binocular, stereoscopic ophthalmoscopy for DME.[75]
†Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening, and this requires a 3-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy, stereo fundus photography, or both.

include assessment of visual symptoms, visual acuity, measurement of intraocular pressure, gonioscopy when indicated, slit-lamp biomicroscopy, and fundus examination. In the medical history and examination, assessment of visual symptoms, glycemic status (hemoglobin A1c), and systemic and medical status (e.g., pregnancy, blood pressure, serum lipid levels, renal status) should be performed.

OCT is now regarded as the most sensitive method in the detection and assessment of DME.[11] The retinal map scan is useful in locating the area with retinal thickening; single line scans are useful in detailing the specific DME morphologic changes such as intraretinal cysts, subretinal fluid or detachment, and vitreoretinal traction. However, because of the high costs of the imaging equipment as well as requirement of skilled training of ophthalmologists, assessment of DME by OCT is currently considered feasible only for countries with high resources.

Fundus photography is a useful way of recording the disease activity and it is also useful in determining detailed severity of the disease. This provides a feasible method of examination for countries with low or intermediate resources.

Fluorescein angiography is not required to diagnose DR, PDR, or DME, all of which are diagnosed by means of fundus examination. However, it should be noted that fluorescein angiography can be used as a guide to evaluate retinal nonperfusion area, presence of retinal neovascularization, and microaneurysms or macular capillary nonperfusion in DME. Also, in some cases, fluorescein angiography may be useful to differentiate intraretinal microvascular abnormalities from new blood vessels seen in PDR.

Follow-up. In general, the follow-up history should be similar to the initial examination. The assessment of new visual symptoms and visual acuity, measurement of intraocular pressure, and fundus examination are essential. Like screening schedules, the follow-up schedules generally are the same except for mild NPDR and moderate NPDR, where patients in countries with low- or intermediate-resource settings are advised to have their follow-up visits in 1 to 2 years, or 6 to 12 months' time, respectively (Table 4). Countries with high resources can consider early panretinal laser photocoagulation (PRP) as a method of management for DR in the severe NPDR and PDR stages (Table 5). In contrast, PRP has been proposed for management of PDR for countries with low or intermediate resources only if DR progresses to PDR (Table 4). For the management of non–center-involved DME, the guidelines propose that countries with high-resource settings should consider focal or grid laser photocoagulation (Table 5), whereas this recommendation is deemed to be impractical for countries where resources are lacking.

Patient Education. Patient education imparted from the physician or other health care providers to the patient plays a pivotal role in a successful attempt to prevent blindness. It is important that the health care provider, physician, or ophthalmologist discuss the test or examination results and their implications. For example, patients with DM but without DR should be strongly encouraged to undergo screening DR examinations. Patients should be duly informed of the importance of timely intervention, despite good vision and no ocular symptoms, for effective treatment of DR. Health care providers, physicians, and ophthalmologist also should educate their patients on the need to maintain near-normal glucose levels and near-normal blood pressure as well as the need to exercise good serum lipid level control. To ensure effective patient education, there should be effective communication between the ophthalmologist and the general physician (e.g., family physician, internist, or endocrinologist) regarding ocular findings. Finally, for patients whose conditions fail to respond to treatment and surgery or for whom treatment is unavailable, where appropriate, referrals for counseling, rehabilitative, or social services could be considered. Vision rehabilitation and social services also can be referred for patients with reduced visual function.

Management

Management for Diabetic Retinopathy and Proliferative Diabetic Retinopathy. There have been many reviews on specific management of DR.[11,21] In principle, systemic

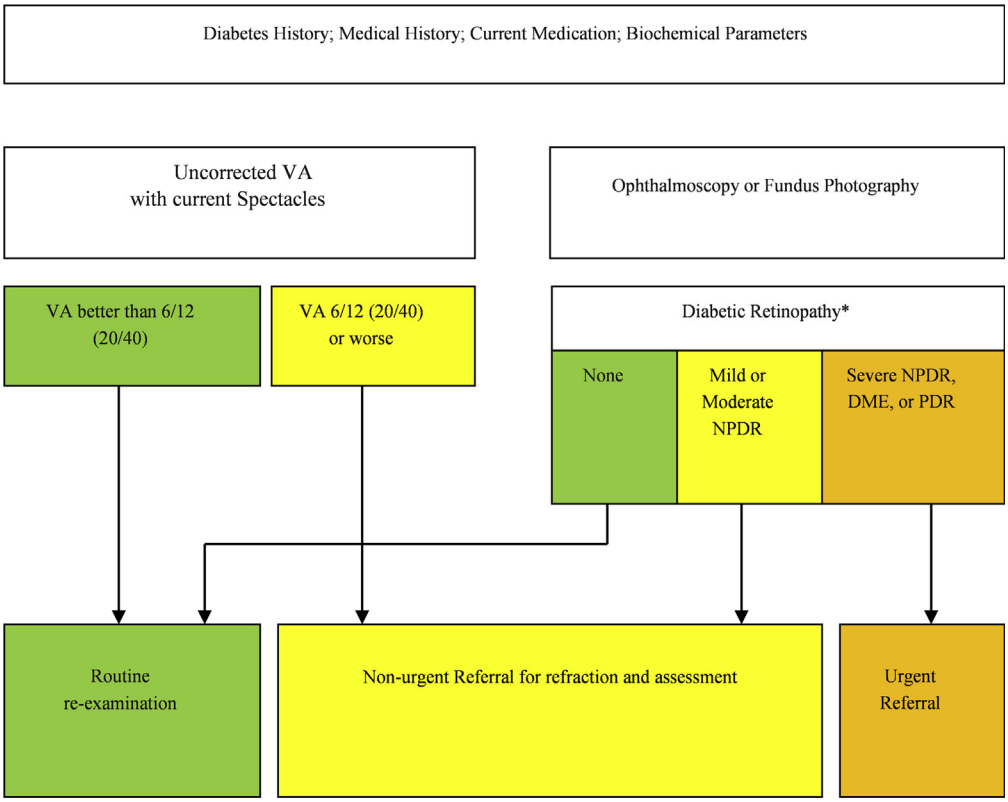

Figure 3. Flowchart showing screening for diabetic retinopathy. DME = diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VA = visual acuity. *Need to optimize medical treatment; glycemic control, hypertension, and lipids.

medical control is critical for all patients with DM with and without DR. Recommendations include maintenance of glycemic control to hemoglobin A1c less than 7.0%, treatment of systemic hypertension, and dyslipidemia.[36]

Laser PRP is considered the mainstay of treatment for PDR[58,59] and also can be considered for certain high-risk patients with severe NPDR.[11] This includes factors such as poor compliance with follow-up, impending cataract extraction or pregnancy, and status of the fellow eye (e.g., blind or advanced DR in the fellow eye).

There is increasing evidence from clinical trials demonstrating anti-VEGF injections as a safe and effective treatment of PDR through at least 2 years.[60] This has been demonstrated for ranibizumab and aflibercept,[61] but other intravitreal anti-VEGF agents such as bevacizumab also are effective against retinal neovascularization.

For low- or intermediate-resource settings, recommendations for management generally are similar to those in high-resource settings. Where resources permit, PRP should be considered the preferred choice of treatment of severe NPDR and all stages of PDR. The contemporary PRP approach uses short-pulse 20- to 30-ms laser with 2000 to 4000 treatment burns depending on the PDR grade/severity.[62]

Table 2. Screening and Referral Recommendations Based on International Classification of Diabetic Retinopathy* and Diabetic Macular Edema for High-Resource Settings

Classification	Re-examination or Next Screening Schedule	Referral to Ophthalmologist
DR		
No apparent DR, mild nonproliferative DR, and no DME	Re-examination in 1–2 yrs	Referral not required
Mild nonproliferative DR	6–12 mos	Referral not required
Moderate nonproliferative DR	3–6 mos	Referral required
Severe nonproliferative DR	<3 mos	Referral required
Proliferative DR	<1 mo	Referral required
DME		
Non–center-involving DME	3 mos	Referral required
Center-involving DME	1 mo	Referral required

DME = diabetic macular edema; DR = diabetic retinopathy.
*In cases where diabetes is controlled.

Table 3. Screening and Referral Recommendations Based on International Classification of Diabetic Retinopathy* and Diabetic Macular Edema for Low- or Intermediate-Resource Settings

Classification	Re-examination or Next Screening Schedule	Referral to Ophthalmologist
DR		
No apparent DR, mild nonproliferative DR, and no DME	Re-examination in 1–2 yrs	Referral not required
Mild nonproliferative DR	1–2 yrs	Referral not required
Moderate nonproliferative DR	6–12 mos	Referral required
Severe nonproliferative DR	<3 mos	Referral required
Proliferative DR	<1 mo	Referral required
DME		
Non–center-involving DME	3 mos	Referral not required (referral recommended if laser sources available)
Center-involving DME	1 mo	Referral required

DME = diabetic macular edema; DR = diabetic retinopathy.
*In cases where diabetes is controlled.

Treatment of Diabetic Macular Edema. Focal or grid laser photocoagulation has been determined to be an effective treatment for clinically significant macular edema, a term defined by the Early Treatment Diabetic Retinopathy Study group based on clinical fundus examination.[63,64] In general, the modified Early Treatment Diabetic Retinopathy Study focal or grid laser photocoagulation protocol has been proposed as a preferred protocol for laser treatment of clinically significant macular edema.[65] Although clinically significant macular edema continues to be used widely, the guidelines recommend DME be classified into center-involving and non–center-involving DME according to clinical findings and OCT results where available. Patients with non–center-involving DME may be observed until there is progression to central involvement, or focal laser can be performed to treat leaking microaneurysms if DME is threatening the fovea (Fig 4), according to the modified Early Treatment Diabetic Retinopathy Study focal or grid laser photocoagulation protocol. No treatment should be applied to lesions closer than 300 to 500 μm to the center of the macula.

Treatment of Center-involving Diabetic Macular Edema with Anti–Vascular Endothelial Growth Factor Agents and Steroids. In recent years, intravitreal administration of anti-VEGF agents has been demonstrated to be the standard of care with favorable outcomes in preventing vision loss in patients with DME, and this should be considered by countries with high resources.

Where the patient seeks treatment with center-involving DME and good visual acuity (better than 6/9 or 20/30), 3 treatment options are possible and are currently being evaluated in an ongoing clinical trial: (1) careful follow-up with anti-VEGF treatment only for worsening DME; (2) intravitreal anti-VEGF injections; or (3) focal or grid laser photocoagulation with anti-VEGF, if necessary. Where the patient demonstrates center-involving DME and associated vision loss (6/9 or 20/30 or worse), intravitreal anti-VEGF treatment with ranibizumab (Lucentis; Novartis, Switzerland) 0.3 or 0.5 mg, bevacizumab (Avastin; Roche, Switzerland) 1.25 mg, or aflibercept (Eylea; Bayer, Germany) 2 mg therapy can be considered. Treatment with aflibercept may provide the best visual outcomes over 1 year, especially in eyes with baseline visual acuity of 6/15 (20/50) or worse. However, by 2 years of therapy, ranibizumab-treated eyes achieve similar visual results as those given aflibercept do. Treatment with bevacizumab provides similar visual outcomes to the other 2 agents in eyes with only mild visual impairment at baseline (20/32–20/40), but is not as effective at reducing retinal thickening as aflibercept or ranibizumab therapy.

Table 4. Follow-up Schedule and Management Based on Diabetic Retinopathy Severity for High-Resource Settings

Disease	Follow-up Schedule for Management by Ophthalmologists
DR severity	
No apparent DR	Re-examination in 1–2 yrs; this may not require re-examination by an ophthalmologist
Mild nonproliferative DR	6–12 mos; this may not require re-examination by an ophthalmologist
Moderate nonproliferative DR	3–6 mos
Severe nonproliferative DR	<3 mos; consider early panretinal photocoagulation
PDR	<1 mo; consider panretinal photocoagulation
Stable (treated) PDR	6–12 mos
DME severity	
Non–center-involving DME	3–6 mos; consider focal laser photocoagulation
Center-involving DME	1–3 mos; consider focal laser photocoagulation or anti-VEGF therapy
Stable DME	3–6 mos

DME = diabetic macular edema; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; VEGF = vascular endothelial growth factor.

Table 5. Follow-up Schedule and Management Based on Diabetic Retinopathy Severity for Low- to Intermediate-Resource Settings

Disease	Follow-up Schedule for Management by Ophthalmologists
DR severity	
No apparent DR	Re-examination in 1–2 yrs; this may not require re-examination by an ophthalmologist
Mild nonproliferative DR	1–2 yrs; this may not require re-examination by an ophthalmologist
Moderate nonproliferative DR	6–12 mos
Severe nonproliferative DR	<3 mos
PDR	<1 mo; consider panretinal photocoagulation
Stable (treated) PDR	6–12 mos
DME severity	
Non–center-involving DME	3–6 mos
Center-involving DME	1–3 months; consider focal laser photocoagulation or anti-VEGF therapy
Stable DME	3–6 mos

DME = diabetic macular edema; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; VEGF = vascular endothelial growth factor.

Although there are different treatment regimens, the guidelines recommend a regimen that includes an initiation of monthly loading-dose injections followed by treatment interruption and reinitiation based on visual stability and OCT findings (Fig 5). Patients should be monitored almost monthly with OCT to consider the need for treatment. Typically, the number of injections is 6 to 8 in the first year, 2 or 3 during the second year, 1 to 2 during the third year, and 0 to 1 in the fourth and fifth years of treatment.

For eyes with persistent retinal thickening despite anti-VEGF therapy, consider laser treatment after 24 weeks. Treatment with intravitreal triamcinolone also may be considered (2 mg/0.05 ml, 4 mg/0.1 ml), especially in pseudophakic eyes. For patients who have concomitant glaucoma or ocular hypertension or who are steroid responders, intravitreal triamcinolone should be given with caution, and only if intraocular pressure can be monitored during the course of therapy.[66] Vitrectomy surgery also may be offered, particularly when there is evidence of vitreoretinal traction. Vitrectomy surgery has been postulated to improve DME even in the absence of vitreoretinal traction by increasing oxygenation of the vitreous cavity.[66] For patients with DME that is associated with PDR, monotherapy with intravitreal anti-VEGF therapy should be considered with re-evaluation for the need for laser PRP or continued anti-VEGF after the DME resolves.

In countries with low or intermediate resources, where possible, physicians can consider off-label alternatives such as bevacizumab (Avastin) to more expensive drugs such as ranibizumab (Lucentis) or aflibercept (Eylea).[11] Otherwise, focal or grid laser treatment should be considered as a primary method of treatment for DME in low- or intermediate-resource settings.

Management of Diabetic Retinopathy in Special Circumstances

The 2017 guidelines included recommendation on the management of DR in 2 special circumstances.

Pregnancy. For pregnancy,[66] this included the following recommendations. First, patients with pre-existing DM planning pregnancy should be informed of the need for assessment of DR before and during pregnancy. Pregnant women with pre-existing DM should be offered a screening retinal assessment after their first antenatal clinic appointment and again at 28 weeks if results from the first assessment are normal. If any DR is present, additional retinal assessment should be performed at 16 to 20 weeks. Second, DR should not be considered a contraindication to rapid optimization of glycemic control in women with high hemoglobin A1c levels early in pregnancy, but retinal assessment is essential. Third, DR should not be considered a contraindication to vaginal birth.

Cataract Surgery. Because DR severity and DME are known to progress faster after cataract surgery,[67,68] the guidelines propose the following as principles of management. For mild cataract, carefully assess DR status. Patients without vision loss with a clear fundus view may not require cataract surgery. For moderate cataract, carefully assess DR status. Attempt to treat any severe NPDR with laser PRP and any DME with focal or grid laser or anti-VEGF therapy before cataract surgery. After DR or DME is stable, consider cataract surgery to improve vision. For severe to advanced cataract with poor fundus view, if DR status cannot be assessed adequately, consider early cataract surgery followed by assessment and treatment as necessary. If DME is present, consider anti-VEGF before surgery, at the time of surgery, or after surgery if DME is discovered when the medium is cleared.

Discussion

The 2017 ICO Guidelines for Diabetic Eye Care serve as a general comprehensive guide for physicians, ophthalmologists, and health care providers with broad recommendations, incorporating best evidence-based management principles with practical, real-world experience in different settings. The key features of the guidelines are recommendations for diagnosis and definition, screening and referral, and follow-up and management options based on resource settings, which are divided broadly into high-resource settings (e.g., United States, United Kingdom, and Western Europe) versus low- or intermediate-resource settings (e.g., rural areas in China, India, Africa, and South America).

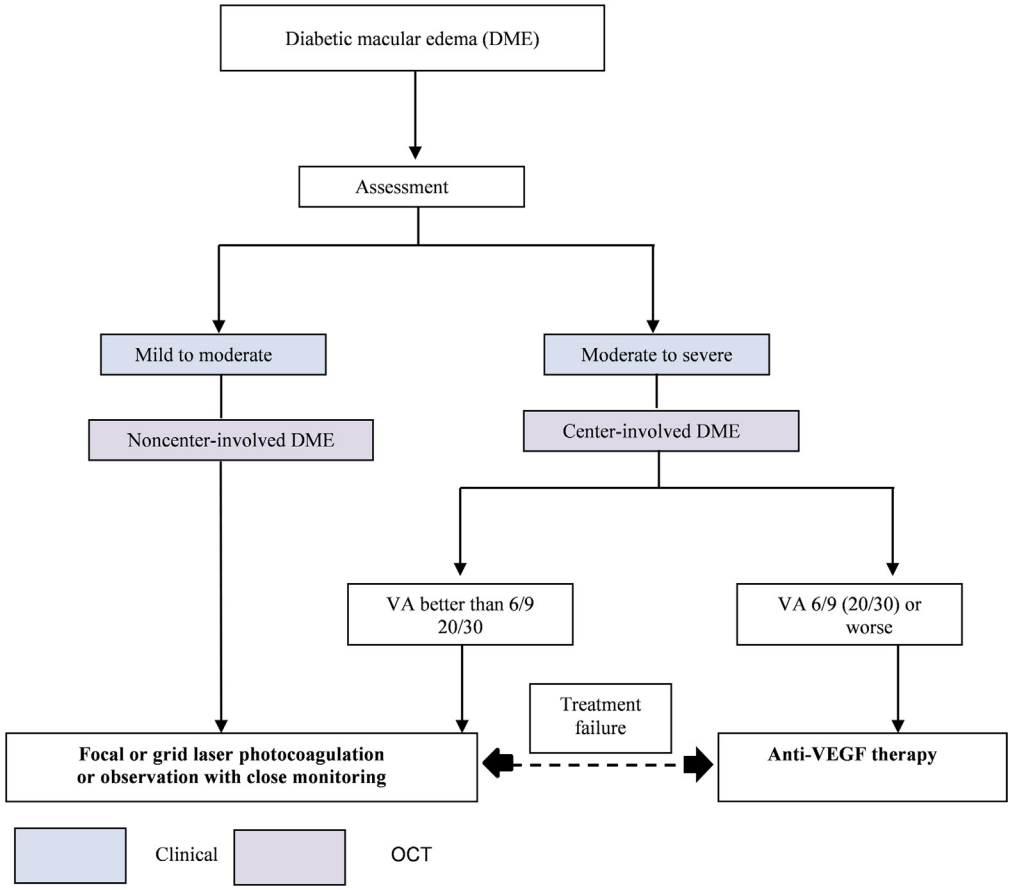

Figure 4. Flowchart showing treatment decision tree for diabetic macular edema (DME) based on center involvement and vision. VA = visual acuity; VEGF = vascular endothelial growth factor.

There are many recommendations in the ICO guidelines that may differ from other major reviews and national guidelines. With regard to screening, countries such as the United Kingdom already have well-established national DR screening programs for all persons with DM, generally with fundus photography incorporating telemedicine and centralized reading centers.[69] Some screening groups also have incorporated OCT into the screening workflow as a secondary measure to detect DME, although the use of OCT has not yet been accepted fully as cost effective.[70] Other investigators have suggested that wide-field retinal photography may be more sensitive at detecting cases of DR that are missed with traditional fundus photography.[70] Although such ideal screening programs based on evolving best evidence could be implemented in high-resource setting countries, they remain a substantial challenge for countries with low or intermediate resources. In such communities, multiple factors affect the ability to design, construct, and sustain a DR screening program; these factors include the shortage of trained eye care professionals, the lack of funding for equipment such as a fundus cameras, and inability to refer patients to facilities for treatment. Therefore, in the ICO guidelines, specific minimum requirements for vision and retinal examination are proposed so that even in low- or intermediate-resource settings, screening programs can be implemented over time.

Screening schedules and referral guidelines also differ somewhat in different publications. The ICO guidelines recommend that for vision-threatening levels of DR (i.e., severe NPDR and PDR), the timing for referral should be similar between high-resource settings (Table 2) and low- or intermediate-resource settings (Table 3). However, for mild NPDR and moderate NPDR, because of resource constraints, the timing for referral can be longer (1−2 years and 6−12 months, respectively) for low- or intermediate-resource settings (Table 3). Nevertheless, it remains a significant challenge to design, implement, and sustain cost-effective screening programs for DR, even in high-resource countries. In the United States, for example, screening is patchy and suboptimal and up to 50% of the population is not screened as recommended.[66]

Regarding treatment for DR and DME, most other reviews and guidelines have been based on the highly cost-effective treatments for PDR and DME that have been developed over the past 3 decades and that have been demonstrated in landmark randomized clinical trials. These have provided very specific evidence and guidelines for systemic glycemic and blood pressure control, the use of both PRP and focal or grid laser photocoagulation therapy, and use of intravitreal anti-

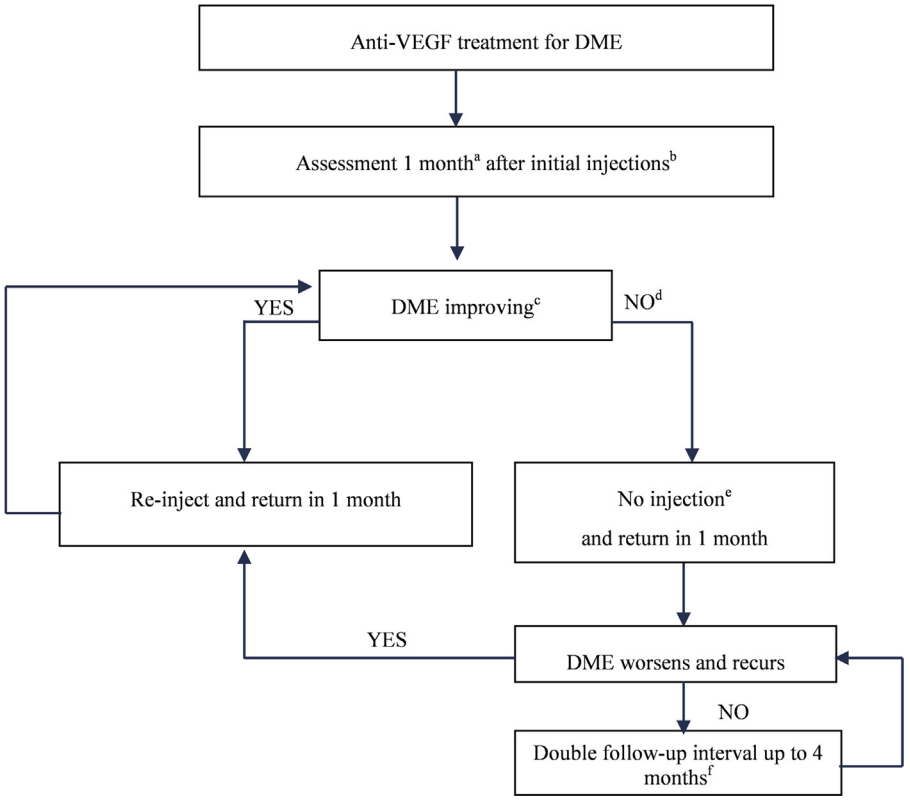

Figure 5. Flowchart showing anti–vascular endothelial growth factor (VEGF) treatment decision tree based on the Diabetic Retinopathy Clinical Research Network (DRCR.net) re-treatment and follow-up schedule. a. In the DRCR.net study, 4-week, not 1-month, intervals were used. b. The DRCR.net study required 4 injections of intravitreal ranibizumab every 4 weeks initially; it is not known whether a different number of injections initially would have worked as well. DRCR.net also required 2 additional injections at months 5 and 6 if edema persisted and success had not been met, even in the absence of improvement. c. Relevant details from the DRCR.net study: 1) DRCR.net "improvement" on Zeiss Stratus OCT >10% decrease in central subfield thickness; 2) Even if no longer improving on OCT, injections continued if visual acuity (VA) "improvement" (unless 6/6 or better); 3) VA improvement defined as 5 or more letter increase on Electronic ETDRS Visual Acuity Test. d. In the DRCR.net study, if focal/grid laser was deferred at baseline, it was added at or after 24 weeks if edema still present and OCT central subfield and vision no longer improving. e. In the DRCR.net study, all patients received at least 4 injections 4 weeks apart. The decision to re-inject was at investigator discretion, starting at 16 weeks for "success", defined as VA better than 6/6 or OCT central subfield <250μm. Starting at 24 weeks, re-injection was also at investigator discretion if no improvement in OCT central subfield or vision. f. The DRCR.net study continued to follow-up every 4 weeks through the 52-week visit and did not permit extension of follow-up until after the 52 week visit. If injection was withheld due to no improvement or success at 3 consecutive visits following the week 52 visit, follow-up interval was doubled to 8 weeks and then again to 16 weeks if still no change. DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study.

VEGF therapy for DME.[26,27,60,71–73] The current 2017 ICO guidelines have incorporated many of these best-evidence practices into its recommendations, but have differed in some important areas. For example, intravitreal anti-VEGF agents are now used widely for DME in countries with high-resource settings, but in low- or intermediate-resource settings, issues with access, availability, and administration of anti-VEGF agents may not allow the intensive treatment schedule and regimen needed (Figs 4 and 5) to provide the outcomes seen in clinical trials. Thus, laser photocoagulation continues to be emphasized, particularly for non–center-involving DME. The guidelines also have suggested that treatment with intravitreal triamcinolone also may be considered, especially in pseudophakic eyes with DME. In addition, sustained-release steroid implants have been used to treat DME effectively and may have longer duration of action and fewer side effects.[11,74,75] However, sustained-release steroid implants are unlikely to play a significant role in DME management in low-resource settings and thus are not covered in these guidelines.

For PDR, in high-resource settings, clinicians are increasingly treating highly compliant patients with anti-VEGF therapy. Even then, there remains uncertainty regarding the cost effectiveness and long-term durability of anti-VEGF therapy for PDR, and in many situations (e.g., poorly compliant patients), laser PRP continues to be the standard of care for PDR. Thus, anti-VEGF therapy for treatment of PDR is not recommended in the guidelines for low-resource settings. These concepts may change over time when results of new clinical trials and cost-effective studies are released.[61]

Some areas do not have clear consensus, such as timing for PRP for the treatment of PDR. The guidelines recommend that PRP should be administered only if DR progresses to PDR for countries with low or intermediate resources (Table 4). However, one of the key problems for low-resource settings is tracking and referring patients who need treatment on a timely basis. Thus, it can be argued that in a low-resource environment, if a patient with severe or very severe NPDR has been identified by screening

programs, it would be appropriate to consider PRP at that time. This prevents the possibility of not being able to follow up and bring the patient back for treatment when PDR eventually develops, realizing that the progression from severe and very severe NPDR to PDR is rapid and almost universal. Such an approach should be considered if access to laser treatment is possible in these settings.

Some novel technologies may be useful for screening, diagnosis, and management of DR, but are not covered in the current guidelines. For example, OCT angiography is an emerging technology with the capability to visualize the retinal microvasculature and capillary network without the need for injection of fluorescein dye, and thus is a potential replacement for invasive fluorescein angiography.[76] Studies show OCT angiography−measured retinal capillary network changes are associated with severity of DR,[77,78] nonperfusion, diabetic macular ischemia,[79] visual acuity,[80] and systemic risk factors.[81] However, the exact role of OCT angiography in the assessment and management of DR and DME remains to be determined. Similarly, the use of automated computer software, including new artificial intelligence algorithms, to detect DR from fundus photographs is extremely promising,[81,82] but it is unclear how such automated systems fit within existing DR screening programs at present.[83]

A recent position statement by the American Diabetes Association (ADA) has documented its recommendations for screening and follow-up on the management of DM.[36] The ADA position statement is largely targeted at the US health care system and may be applicable to other high-resource settings, and it does not make specific recommendations according to the types of resource availability. Some differences between the ADA and ICO should be highlighted. First, regarding screening schedules, the ADA suggests annual DR screening examination may not be necessary for patients with DM who have no evidence of DR for one or more annual DR screening examinations, and screening every 2 years thus can be considered for these patients. If any level of DR is present, subsequent examinations should be repeated at least annually or more frequently if the DR is progressing or sight threatening.[36] These were taken into consideration in developing the recommendation for screening for no DR or mild NPDR in the current ICO guidelines (Tables 2 and 3). Second, there was no follow-up schedule recommended by the ADA for stable and treated PDR or DME. The ICO guidelines incorporated this because it covers a large portion of the population with DM. Third, regardless of the resources status, the ICO guidelines recommended a slightly more intensive follow-up schedule for center-involved DME as compared with the ADA's recommendation, taking on a tighter preventive measure in an attempt to reduce the risk of DME progression as the main cause of vision loss. Fourth, in terms of treatment, the ADA recommends intravitreal steroidal treatment as an alternative to anti-VEGF therapy for DME. However, it was believed that steroid therapy may carry the risk of cataract and glaucoma that may not be possible to detect or manage in lower-resource settings.

It is important to emphasize that the ICO guidelines are not a systematic review of the literature and do not reflect the latest developments reported in major clinical trials. Thus, because this report was not conducted as a systematic review, references are not graded according to levels of evidence. There are also important details on specific concepts not addressed in these guidelines. For example, the guidelines suggest that for DR screening, the "retinal examination could include telemedicine approaches," but do not define the parameters for such programs, including issues related to type of camera, the need for pupil dilation, the quality of photographs, the grading of images, among others; these are covered in other reviews and studies.[84−86]

In summary, with DM estimated to affect more than 600 million by 2040, with the vast majority living in developing countries with low and intermediate resources, comprehensive yet practical guidelines are necessary for diagnosis, definition, screening, referral, follow-up, and management. The 2017 ICO guidelines provide a basis for many countries and communities to develop more specific programs targeted at reducing the risk of vision loss resulting from DR.

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References

1. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301(20):2129−2140.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(1):4−14.
3. Werfalli M, Engel ME, Musekiwa A, et al. The prevalence of type 2 diabetes among older people in Africa: a systematic review. *Lancet Diabetes Endocrinol*. 2016;4(1):72−84.
4. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet*. 2006;368(9548):1681−1688.
5. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. *Lancet Diabetes Endocrinol*. 2015;3(12):1004−1016.
6. Leasher JL, Bourne RR, Flaxman SR, et al. Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. *Diabetes Care*. 2016;39(9):1643−1649.
7. International Diabetes Foundation. Diabetes: facts and figures. http://www.idf.org/about-diabetes/facts-figures. Accessed December 1, 2017.
8. Abegunde DO, Mathers CD, Adam T, et al. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet*. 2007;370(9603):1929−1938.
9. Beran D, Yudkin JS. Diabetes care in sub-Saharan Africa. *Lancet*. 2006;368(9548):1689−1695.
10. Mbanya JC, Motala AA, Sobngwi E, et al. Diabetes in sub-Saharan Africa. *Lancet*. 2010;375(9733):2254−2266.
11. Tan GS, Cheung N, Simo R, et al. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143−155.
12. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141(3):446−455.

13. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005−2008. *JAMA*. 2010;304(6):649−656.
14. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556−564.
15. Mathenge W, Bastawrous A, Peto T, et al. Prevalence and correlates of diabetic retinopathy in a population-based survey of older people in Nakuru, Kenya. *Ophthal Epidemiol*. 2014;21(3):169−177.
16. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin Pract*. 2014;103(2):150−160.
17. Zhang X, Geiss LS, Cheng YJ, et al. The missed patient with diabetes: how access to health care affects the detection of diabetes. *Diabetes Care*. 2008;31(9):1748−1753.
18. Gakidou E, Mallinger L, Abbott-Klafter J, et al. Management of diabetes and associated cardiovascular risk factors in seven countries: a comparison of data from national health examination surveys. *Bull World Health Organ*. 2011;89(3):172−183.
19. Bressler NM, Varma R, Doan QV, et al. Underuse of the health care system by persons with diabetes mellitus and diabetic macular edema in the United States. *JAMA Ophthalmol*. 2014;132(2):168−173.
20. Ferris 3rd FL. How effective are treatments for diabetic retinopathy? *JAMA*. 1993;269(10):1290−1291.
21. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124−136.
22. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med*. 2012;366(13):1227−1239.
23. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology*. 2009;116(3):497−503.
24. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol*. 2016;44(4):260−277.
25. Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care*. 2009;32(12):2307−2313.
26. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329(14):977−986.
27. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837−853.
28. Fong DS, Aiello LP, Ferris 3rd FL, Klein R. Diabetic retinopathy. *Diabetes Care*. 2004;27(10):2540−2553.
29. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med*. 1996;124(1 Pt 2):164−169.
30. Rohan TE, Frost CD, Wald NJ. Prevention of blindness by screening for diabetic retinopathy: a quantitative assessment. *BMJ*. 1989;299(6709):1198−1201.
31. Resnikoff S, Felch W, Gauthier TM, Spivey B. The number of ophthalmologists in practice and training worldwide: a growing gap despite more than 200,000 practitioners. *Br J Ophthalmol*. 2012;96(6):783−787.
32. Burgess PI, Msukwa G, Beare NA. Diabetic retinopathy in sub-Saharan Africa: meeting the challenges of an emerging epidemic. *BMC Med*. 2013;11:157.
33. World Health Organization. WHO model list of essential medicines. http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1. Accessed December 1, 2017.
34. Hooper P, Boucher MC, Colleaux K, et al. Contemporary management of diabetic retinopathy in Canada: from guidelines to algorithm guidance. *Ophthalmologica*. 2014;231(1):2−15.
35. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA*. 2007;298(8):902−916.
36. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(3):412−418.
37. Bandello F, Midena E, Menchini U, Lanzetta P. Recommendations for the appropriate management of diabetic macular edema: light on DME survey and consensus document by an expert panel. *Eur J Ophthalmol*. 2016;26(3):252−261.
38. Das T, Aurora A, Chhablani J, et al. Evidence-based review of diabetic macular edema management: consensus statement on Indian treatment guidelines. *Indian J Ophthalmol*. 2016;64(1):14−25.
39. Mitchell P, Wong TY, Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for diabetic macular edema. *Am J Ophthalmol*. 2014;157(3):505−513.e501−e508.
40. Rajavi Z, Safi S, Javadi MA, et al. Diabetic retinopathy clinical practice guidelines: customized for Iranian population. *J Ophthalmic Vis Res*. 2016;11(4):394−414.
41. Ziemssen F, Lemmen K, Bertram B, et al. National guidelines for treatment of diabetic retinopathy: second edition of the national guidelines for treatment of diabetic retinopathy. *Ophthalmologe*. 2016;113(7):623−638.
42. Wang LZ, Cheung CY, Tapp RJ, et al. Availability and variability in guidelines on diabetic retinopathy screening in Asian countries. *Br J Ophthalmol*. 2017;101(10):1352−1360.
43. Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries. In: Sloan FA, Gelband H, eds. *Cancer Control Opportunities in Low- and Middle-Income Countries*. Washington (DC): National Academies Press (US); 2007. ISBN-13: 978-0-309-10384-8ISBN-10: 0-309-10384-3.
44. Owolabi M, Miranda JJ, Yaria J, Ovbiagele B. Controlling cardiovascular diseases in low and middle income countries by placing proof in pragmatism. *BMJ Global Health*. 2016;1(3). pii: e000105. eCollection 2016.
45. Yip CH, Anderson BO. The Breast Health Global Initiative: clinical practice guidelines for management of breast cancer in low- and middle-income countries. *Expert Rev Anticancer Ther*. 2007;7(8):1095−1104.
46. International Council of Ophthalmology. ICO guidelines for diabetic eye care. http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf. Accessed December 1, 2017.
47. International Council of Ophthalmology. ICO guidelines for diabetic eye care: available in English, Chinese, French, Portuguese, Serbian, Spanish, and Vietnamese. http://www.icoph.org/resources/309/ICO-Guidelines-for-Diabetic-Eye-Care-available-in-English-Chinese-French-Portuguese-Serbian-Spanish-and-Vietnamese.html. Accessed December 1, 2017.
48. Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I, et al. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. *Cochrane Database Syst Rev*. 2014;(11), CD008721.

49. Mohamed QA, Fletcher EC, Buckle M. Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema. *BMJ Clin Evid*. 2016;Mar 16. pii: 0702; PubMed PMID: 27031563; PubMed Central PMCID: PMC4817243.
50. International Council of Ophthalmology. ICO diabetic eye care. http://www.icoph.org/enhancing_eyecare/diabetic_eyecare.html. Accessed December 1, 2017.
51. World Health Organization. Health statistics and information systems. http://www.who.int/healthinfo/global_burden_disease/definition_regions/en/. Accessed December 1, 2017.
52. Sabanayagam C, Yip W, Ting DS, et al. Ten emerging trends in the epidemiology of diabetic retinopathy. *Ophthal Epidemiol*. 2016;23(4):209–222.
53. Wilkinson CP, Ferris 3rd FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9): 1677–1682.
54. Bragge P, Gruen RL, Chau M, et al. Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol*. 2011;129(4):435–444.
55. Horton MB, Silva PS, Cavallerano JD, Aiello LP. Operational components of telemedicine programs for diabetic retinopathy. *Curr Diabetes Rep*. 2016;16(12):128.
56. Horton MB, Silva PS, Cavallerano JD, Aiello LP. Clinical components of telemedicine programs for diabetic retinopathy. *Curr Diabetes Rep*. 2016;16(12):129.
57. Jones S, Edwards RT. Diabetic retinopathy screening: a systematic review of the economic evidence. *Diabet Med*. 2010;27(3):249–256.
58. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1981;88(7):583–600.
59. Bressler NM, Beck RW, Ferris 3rd FL. Panretinal photocoagulation for proliferative diabetic retinopathy. *N Engl J Med*. 2011;365(16):1520–1526.
60. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015;314(20):2137–2146.
61. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical Efficacy of Intravitreal Aflibercept versus Panretinal Photocoagulation for Best Corrected Visual Acuity in Patients with Proliferative Diabetic Retinopathy at 52 Weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet*. 2017;389(10085):2193–2203.
62. Muqit MM, Marcellino GR, Henson DB, et al. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study report 4. *Eye*. 2011;25(11):1447–1456.
63. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study Research Group. *Arch Ophthalmol*. 1985;103(12):1796–1806.
64. Relhan N, Flynn Jr HW. The Early Treatment Diabetic Retinopathy Study historical review and relevance to today's management of diabetic macular edema. *Curr Opin Ophthalmol*. 2017;28(3):205–212.
65. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol*. 2007;125(4): 469–480.
66. Morrison JL, Hodgson LA, Lim LL, Al-Qureshi S. Diabetic retinopathy in pregnancy: a review. *Clin Exp Ophthalmol*. 2016;44(4):321–334.
67. Haddad NM, Sun JK, Abujaber S, et al. Cataract surgery and its complications in diabetic patients. *Semin Ophthalmol*. 2014;29(5–6):329–337.
68. Shah AS, Chen SH. Cataract surgery and diabetes. *Curr Opin Ophthalmol*. 2010;21(1):4–9.
69. Scanlon PH. The English national screening programme for sight-threatening diabetic retinopathy. *J Med Screening*. 2008;15(1):1–4.
70. Goh JK, Cheung CY, Sim SS, et al. Retinal imaging techniques for diabetic retinopathy screening. *J Diabetes Sci Technol*. 2016;10(2):282–294.
71. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Lachin JM, et al. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342(6):381–389.
72. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13): 1193–1203.
73. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–1589.
74. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014;121(10):1892–1903.
75. Augustin AJ, Kuppermann BD, Lanzetta P, et al. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmol*. 2015;15:150.
76. Spaide RF, Klancnik Jr JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015;133(1):45–50.
77. Kim AY, Chu Z, Shahidzadeh A, et al. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57(9): OCT362–OCT370.
78. Durbin MK, An L, Shemonski ND, et al. Quantification of retinal microvascular density in optical coherence tomographic angiography images in diabetic retinopathy. *JAMA Ophthalmol*. 2017;135(4):370–376.
79. Bradley PD, Sim DA, Keane PA, et al. The evaluation of diabetic macular ischemia using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57(2): 626–631.
80. Samara WA, Shahlaee A, Adam MK, et al. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. *Ophthalmology*. 2017;124(2):235–244.
81. Ting DSW, Tan GSW, Agrawal R, et al. Optical coherence tomographic angiography in type 2 diabetes and diabetic retinopathy. *JAMA Ophthalmol*. 2017;135(4):306–312.
82. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA*. 2016;316(22):2402–2410.

83. Wong TY, Bressler NM. Artificial intelligence with deep learning technology looks into diabetic retinopathy screening. *JAMA*. 2016;316(22):2366–2367.
84. Jani PD, Forbes L, Choudhury A, et al. Evaluation of diabetic retinal screening and factors for ophthalmology referral in a telemedicine network. *JAMA Ophthalmol*. 2017;135(7):706–714.
85. Shi L, Wu H, Dong J, et al. Telemedicine for detecting diabetic retinopathy: a systematic review and meta-analysis. *Br J Ophthalmol*. 2015;99(6):823–831.
86. Silva PS, Aiello LP. Telemedicine and eye examinations for diabetic retinopathy: a time to maximize real-world outcomes. *JAMA Ophthalmol*. 2015;133(5):525–526.

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Appendix. International Council of Ophthalmology Diabetic Eye Care Committee Members

2016 Diabetic Eye Care Committee: Tien Yin Wong, MBBS, PhD (Singapore), Chairman; Lloyd Paul Aiello, MD, PhD (USA); Frederick Ferris, MD (USA); Neeru Gupta, MD, PhD, MBA (Canada); Ryo Kawasaki, MD, MPH, PhD (Japan); Van Lansingh, MD, PhD (Mexico); Mauricio Maia, MD, PhD (Brazil); Wanjiku Mathenge, MD, PhD, MBChB (Rwanda); Sunil Moreker, MBBS (India); Mahi Muqit, FRCOphth, PhD (UK); Serge Resnikoff, MD, PhD (Switzerland); Paisan Ruamviboonsuk, MD (Thailand); Jennifer Sun, MD, MPH (USA); Hugh Taylor, AC, MD (Australia); Juan Verdaguer, MD (Chile); Peiquan Zhao, MD (China). 2013 Task Force on Diabetic Eye Care: Hugh Taylor, AC, MD, Chairman; Susanne Binder, MD; Taraprasad Das, MD, FRCS; Michel Farah, MD; Frederick Ferris, MD; Pascale Massin, MD, PhD, MBA; Wanjiku Mathenge, MD, PhD, MBChB; Serge Resnikoff, MD, PhD; Bruce E. Spivey, MD, MS, Med; Juan Verdaguer, MD; Tien Yin Wong, MD, PhD; Peiquan Zhao, MD.

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Abbreviations and Acronyms:
ADA = American Diabetes Association; **DM** = diabetic mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **ICO** = International Council of Ophthalmology; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **VEGF** = vascular endothelial growth factor.

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