

Current status and future possibilities of retinal imaging in diabetic retinopathy care applicable to low- and medium-income countries

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Diabetic retinopathy (DR) is a leading cause of blindness among adults and the numbers are projected to rise. There have been dramatic advances in the field of retinal imaging since the first fundus image was captured by Jackman and Webster in 1886. The currently available imaging modalities in the management of DR include fundus photography, fluorescein angiography, autofluorescence imaging, optical coherence tomography, optical coherence tomography angiography, and near-infrared reflectance imaging. These images are obtained using traditional fundus cameras, widefield fundus cameras, handheld fundus cameras, or smartphone-based fundus cameras. Fluorescence lifetime ophthalmoscopy, adaptive optics, multispectral and hyperspectral imaging, and multicolor imaging are the evolving technologies which are being researched for their potential applications in DR. Telemedicine has gained popularity in recent years as remote screening of DR has been made possible. Retinal imaging technologies integrated with artificial intelligence/deep-learning algorithms will likely be the way forward in the screening and grading of DR. We provide an overview of the current and upcoming imaging modalities which are relevant to the management of DR.

Key words: Artificial intelligence, diabetic retinopathy, fundus camera, handheld fundus cameras, optical coherence tomography, optical coherence tomography angiography, smartphone-based fundus cameras, telemedicine, widefield fundus cameras

Diabetic retinopathy (DR) is a leading cause of blindness in adults in developed countries. According to the International Agency for the Prevention of Blindness, over 4 million people are suffering from vision loss due to DR worldwide.^[1] These numbers are projected to rise with time. The International Diabetes Federation states that 79% of people with diabetes mellitus (DM) are living in low-medium-income countries (LMICs).^[2] For every person living with some form of visual impairment due to DR, there are many more people in the early stages of DR who are likely to suffer from vision loss without timely intervention.

Vision loss in diabetes occurs due to diabetic macular edema (DME), macular ischemia, and complications of proliferative diabetic retinopathy (PDR). The early stages of DR may be asymptomatic. Camera technology in the form of fundus cameras is useful for screening and diagnosing DR. Jackman and Webster captured the first fundus image and published their technique in 1886.^[3] Around the same time, Elmer Starr and Lucien Howe published a recognizable image of the fundus.^[4,5] With developments in instrumentation and camera technology, significant improvements were made in

retinal imaging in the subsequent decades. The footprint of these initial camera systems, however, was large, and thus, not practical for commercialization. Thorner was the first to introduce stereoscopic fundus photography in 1909.^[6] Then, in 1926, the first fundus cameras to be commercially available were introduced by Carl Zeiss and were able to capture a 20° field of the fundus.^[7] Following this, cameras capturing 30–45° field of the fundus were introduced. Even larger fields could be obtained by montaging these images. Incorporating fiber-optic illumination technology, Pomerantzeff introduced the trans-equatorial fundus camera in 1975.^[8] It could capture a 148° field of the retina and was the first described widefield fundus camera. In 1998, the Optos Panoramic 200 was launched which could capture ultra-widefield (UWF™) (200°) images of the retina.^[9]

Fundus Photography

The fundus photos are essential for the diagnosis and monitoring of many retinal conditions. Digital images can be obtained immediately, stored, reproduced, and transferred with ease. These images can also be magnified for a more detailed inspection of the fundus findings. The currently available fundus cameras include desktop fundus cameras,

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handheld cameras, smartphone-based cameras, and widefield cameras.

Traditional fundus cameras

The Early Treatment of Diabetic Retinopathy Study (ETDRS) seven-field stereoscopic fundus images are considered the gold standard for the evaluation of DR and covers 75° of the retina. This imaging protocol, however, requires time, patient cooperation, and expertise for acquiring these images. Two-field, 45° images of the posterior pole centered on the disk and the macula are less time-consuming alternatives to the seven-field stereoscopic fundus images. A review of the studies comparing single-field fundus photography with or without mydriasis and seven-field ETDRS standard photography or ophthalmologist performed dilated funduscopy showed that, even though the single-field fundus photography does not substitute for a comprehensive eye examination, it is a suitable alternative for the screening of DR and referral for further management.^[10]

Multiple mydriatic/non-mydriatic retinal cameras are currently available. Some of these cameras such as the CX-1 hybrid digital mydriatic/non-mydriatic retinal cameras, VX-20 alpha mydriatic/non-mydriatic combination retinal camera, Visucam NM/FA include color fundus photo, red-free photo, fluorescein angiography (FA), and fundus autofluorescence (AF) modes in the same device. The non-mydriatic cameras can capture fundus images in the eyes with a minimum pupil diameter of 3.7 mm. In comparison to the mydriatic fundus cameras, the non-mydriatic systems offer the benefit of lower cost, rapid image acquisition, and patient comfort by eliminating the need for pupil dilation. The fundus is focused using infrared rays which allows dilation of the pupil in a dimly lit room and a flash is produced to capture the image. But the images obtained without mydriasis may be of lower quality, and hence, ungradable due to over or underexposure, or due to loss of clarity from media opacity.^[11] The field of view may also be lesser than that of standard photography.

Handheld fundus cameras

In LMICs, where the number of ophthalmologists per million population is less than 10, DR screening is best carried out by non-ophthalmic personnel. A suitable approach would be to screen the patients with DM visiting their primary care physician for routine care. This can be best carried out using handheld non-mydriatic cameras. These low-cost portable devices are not power-consuming and occupy less space. These not only help in addressing the needs of underserved areas but also decrease the burden to the health care system by only directing individuals with significant or “referral-warranted” DR to a specialist. This might be the only form of DR screening accessible in certain areas, and hence, demands high-quality images. The disadvantage with the handheld cameras is poor stability while acquiring images and a smaller field of view.

Smartphone-based fundus cameras

Smartphone-based cameras are portable and do not need highly qualified technicians to obtain the images. Even though they are not highly sensitive or specific for diagnosing DR they are inexpensive alternatives for screening in resource-limited countries. The smartphone app enables image transfer and can be paired with the patient’s electronic health records. A meta-analysis performed to analyze the accuracy of the

smartphone-based fundus cameras concluded that with increasing severity of DR, the sensitivity and specificity for detecting DR is increased.^[12]

Widefield fundus cameras

The devices which capture information up to the posterior edge of the vortex vein ampulla in a single image are considered widefield fundus cameras and those which capture beyond the vortex vein ampulla (~110° of the fundus) in a single image are considered ultra-widefield fundus (UWF) cameras.^[13] The Pomerantzef trans-equatorial fundus camera captures a 148° field of the retina.^[8] The Staurengli lens is a widefield contact lens which may be used with scanning laser ophthalmoscopy (SLO) cameras and provides a 150° field of view of the retina.^[14] The Spectralis (Heidelberg Engineering, Heidelberg, Germany) multimodal imaging platform provides 55° field of view of the retina.^[15] With its available widefield attachment, up to 102° of the retinal field can be imaged.

Optos UWF imaging (OPTOS, Dunfermline, United Kingdom) is a non-contact system which produces pseudocolor images by combining red and green light^[9] [Fig. 1]. It captures a 200° field of view, and hence, covers 82% of the fundus. In the study by Hafner *et al.*,^[16] a higher grade of DR was noted in 39.8% of the eyes with Optos UWF images in comparison to the 45° fundus images. The peripheral lesions not covered by the traditional 45° camera were noted in 51.3% of the eyes using the UWF system.^[16] One limitation of the Optos system is that the lid and lash artifact can sometimes limit visualization of the far peripheral superior and inferior fundus. Steering images inferiorly and superiorly, and then, generating a montage, however, may allow a more complete assessment of the fundus.

Clarus™ (CLARUS 500, Carl Zeiss Meditec AG, Jena, Germany) is a true color imaging device covering up to 133° field of the retina in a single image. A 200° image could theoretically be obtained by montaging two separate images. In a study comparing Clarus and Optos for grading images with DR according to the ETDRS severity level, a higher severity level of DR was noted in a marginal number of eyes.^[17] In this study, this was explained as possibly due to an increased area obscured by the artifacts on the Optos images in comparison to the montaged Clarus images.

In addition to color fundus photos, fundus FA, fundus AF imaging, and near-infrared reflectance (NIR) images can be captured by many of the available fundus cameras and these may aid in a more accurate characterization of the level of DR. Unlike in age-related macular degeneration, however, AF and NIR are not currently used routinely in the diagnosis and management of DR.

Fundus Fluorescein Angiography

FA in DR helps in visualizing microaneurysms, macular leakage, foveal avascular zone, macular ischemia, areas of peripheral capillary non-perfusion, intraretinal microvascular abnormalities (IRMAs), and neovascularization of the disk (NVD)/neovascularization elsewhere (NVE). The source of the leakage can be identified on FA which serves as a guide for focal or grid macular laser.^[18] DME is classified into focal and diffuse categories based on the characteristic of the leakage associated with microaneurysms on FA.^[19] FA helps

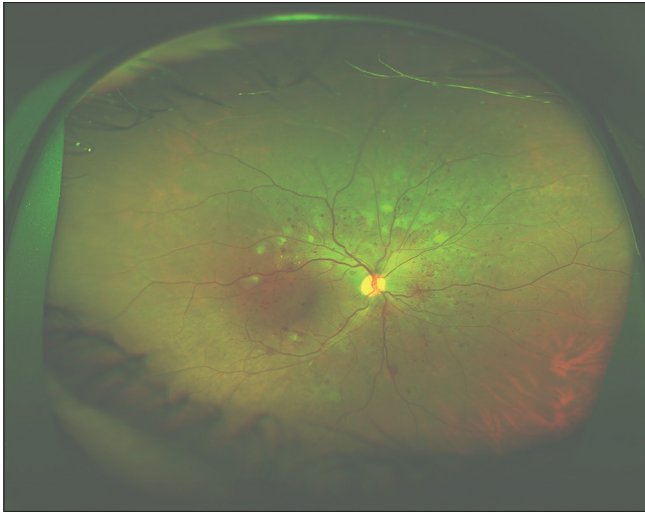


Figure 1: Ultra-widefield retinal image of the right eye of a patient with proliferative diabetic retinopathy captured using the Optos UWF fundus camera. Numerous hemorrhages, microaneurysms, cotton wool spots can be seen along with a large area of neovascularization elsewhere, nasal to the disk

in determining the cause of unexplained visual loss in DR by evaluating the macular perfusion status.

With the development of widefield fundus cameras, peripheral lesions not appreciated by seven-field standard FA or two-field FA are now being recognized [Fig. 2]. Finberg reported that with ultra-wide fluorescein angiography (UWFA), significantly more diabetic retinal pathology can be visualized in a single image than with conventional systems, but with reduced image clarity.^[20] Wessel *et al.*^[21] found 3.9 times more area of retinal non-perfusion and 1.9 times more area of neovascularization with UWF angiography compared to the standard 7 field FA. Oliver *et al.*^[22] described a new entity using the UWF angiogram called the peripheral vessel leakage (PVL), a phenomenon characterized by late leakage from the retinal veins and arteries, and hypothesized this feature to be an indicator of active retinopathy. PVL is associated with the area of peripheral non-perfusion and neovascularization. Studies using UWF angiography have reported a correlation between the area of peripheral retinal non-perfusion and the presence of neovascularization and FAZ.^[23-25] DR lesions with a greater extent outside versus inside the standard ETDRS fields were defined as predominantly peripheral lesions. Silva *et al.*^[26] reported the presence and increasing extent of predominantly peripheral lesions to be associated with the increased risk of DR progression over 4 years.

Contradicting reports of a correlation between peripheral ischemia and DME have been published.^[24,27] UWFA also aids in identifying the peripheral ischemic areas for targeted retinal photocoagulation, which is a safe alternative to conventional pan-retinal photocoagulation and has favorable outcomes.^[28]

Optical Coherence Tomography

Optical Coherence Tomography (OCT) is a non-invasive imaging modality which captures cross-sectional images of the retina and volumetric or 3-D imaging. It provides high-resolution images of the retinal anatomy. It has evolved



Figure 2: Corresponding ultra-widefield fluorescein angiogram of the patient's eye shown in Fig. 1. The red circle denotes the area covered by a traditional 45° fundus camera. The regions of capillary non-perfusion and areas of neovascularization can be seen beyond the central 45°, highlighting abnormalities that may have been missed without the use of wider field imaging

from time-domain OCT to spectral-domain OCT and swept-source OCT (SSOCT), with progressively increasing scanning speeds. OCT is vital in the qualitative and quantitative analyses of retinal changes in the DME. Currently, the diagnosis and monitoring treatment response to pharmacotherapeutics for DME relies heavily on OCT.

In DR, the breakdown of the blood-retinal barrier results in the accumulation of fluid in the retinal layers of the macula. Based on the findings on OCT, the morphology of DME is classified as sponge-like retinal swelling, cystoid macular edema, and/or serous retinal detachment.^[29] Commonly used quantitative parameters from OCT include central retinal thickness, mean thickness in each of the nine subfields, and macular volume within the ETDRS grid [Fig. 3]. Since the macular thickness was found to have a poor correlation with the visual function, the relationship between other parameters on OCT and visual acuity was explored.

The macula in diabetics without retinopathy has been found to be thinner and this can be explained by the retinal neuronal abnormalities which occur before the manifestation of vascular abnormalities.^[30] The retinal nerve fiber layer is found to be thinner in diabetics and correlates with the duration of diabetes.^[31] The ganglion cell layer + inner plexiform layer thinning has also been noted in diabetics without retinopathy.^[32]

The disorganization of the retinal inner layers (DRIL) characterized by the inability to identify the boundaries between the outer plexiform layer, inner nuclear layer (INL), and the ganglion cell layer-inner plexiform layer complex on OCT has been described in the eyes with DR. The presence of DRIL correlates with poor visual acuity in the eyes with DME and with areas of macular non-perfusion.^[33,34] Similar to DRIL, reduced photoreceptor outer segment length, disruption of the external limiting membrane (ELM), and disruption of the inner and outer segments of the photoreceptors can be noted on OCT and also correlate with poor visual acuity.^[35-37]

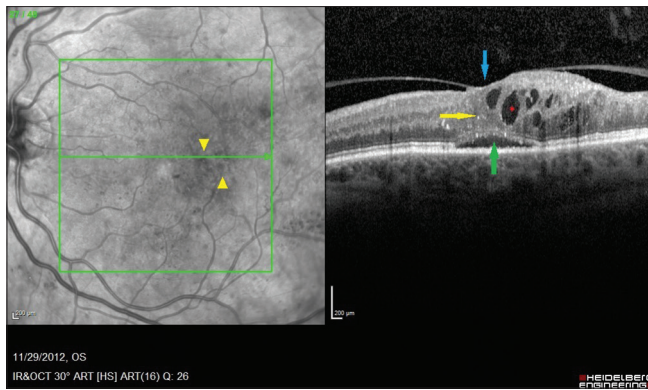


Figure 3: Near-infrared (NIR) reflectance image and B-scan optical coherence tomography (OCT) image of the left eye of a patient with DME. The OCT image shows evidence of foveal subretinal fluid (green arrow), intraretinal cystoid spaces (asterisk), and hyperreflective foci (yellow arrow). The posterior hyaloid is attached at the fovea and detached perifoveally (blue arrow). The corresponding NIR reflectance image shows multiple circular regions with a subtle rim of hyperreflectivity and central hyporeflectivity corresponding to the accumulation of fluid in intraretinal cystoid spaces (yellow arrowhead)

Hyperreflective foci (HRF) are small dot-like lesions found in the neurosensory retina of the eyes with DME [Fig. 3]. Their precise origin remains inconclusive and may be varied, but they have been proposed to be subclinical hard exudates, or migrating retinal pigment epithelium (RPE) cells, or degenerated photoreceptor cells or aggregates of cells involved in a retinal inflammatory response, such as activated microglia.^[38,39] HRF in the outer retina is associated with disrupted ELM and ellipsoid zone (EZ; formerly termed the inner segment-outer segment junction) and decreased visual acuity.^[40] The reduction in the number of HRF may be observed with complete resolution of the edema.

Various vitreoretinal interface abnormalities have been noted on the OCT in the eyes with DR [Fig. 3]. These include vitreomacular traction, epiretinal membrane, and a thick posterior hyaloid which may contribute to the non-resolving DME.^[41] Vitreoschisis is reported to be more frequent in the eyes with DR than in those without DR.^[42] With SSOCT the *in vivo* microstructural characteristics of *in vivo* neovascular complexes can be identified.^[43] Intraoperative OCT helps in dissecting the proliferative membranes in tractional retinal detachment due to PDR.^[44] Studies have published contradicting reports regarding *in vivo* choroidal thickness measured on OCT in different stages of DR and in DME, and this remains a topic of active research interest.^[45]

OCT Angiography

The recent development of OCT angiography (OCTA) has enabled non-invasive visualization of the retinal microvasculature at different levels of the retina. The OCTA identifies pixels of decorrelation among multiple B-scans from the same location as evidence of motion which is interpreted as flow.

Microaneurysms have been localized mainly to the deep capillary plexus using OCTA.^[46] Microaneurysms not seen on dilated fundus examination or FA have been identified using OCTA^[47] [Fig. 4]. At the same time, not all microaneurysms visualized on FA can be identified on OCTA.^[46] Foveal avascular

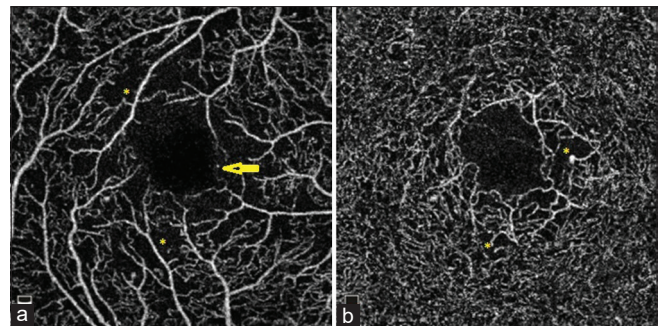


Figure 4: Optical coherence tomography angiography (OCTA) en face images at the level of the superficial capillary plexus (a) and deep capillary plexus (b) of the right eye of a patient with diabetic retinopathy without macular edema. The enlargement and loss of circularity of the foveal avascular zone may be appreciated. A few microaneurysms (yellow arrow), as well as some perifoveal capillary dropout (yellow asterisk), are evident

zone area, perimeter, shape, and circularity, which are measures of macular perfusion status can be measured on OCTA [Fig. 4]. These parameters are known to be altered in diabetic patients, even before the development of clinically detectable DR.^[48] Macular vascular parameters can be measured on OCTA using various automated algorithms. These measurements are likely more accurate with OCTA than with FA as *in vivo* OCTA images are not obscured by dye leakage. The vessel density which is defined as the percentage of blood vessels in the area of interest can be calculated from a binarized image. As the accuracy of the diameter of capillaries on OCTA is limited by the image resolution, the vessel density or perfusion density measured in this way may be an overestimate of the true value. As an alternative, a skeletonized vessel density or vessel length density can be computed. It only considers the vessels that exist per unit area, regardless of the vessel diameter. Fractal dimension is another measure of macular perfusion status. It evaluates the complexity of the vascular branching pattern. Several studies have reported the enlargement of the FAZ area, decrease in FAZ circularity, and decrease in vessel density, and fractal dimension to be significantly associated with the worsening DR.^[48]

On OCTA, cystoid spaces appear oblong with smooth borders and are devoid of flow, and do not follow the distribution of the surrounding capillaries. The areas of capillary non-perfusion are grayer and have irregular borders.^[49] OCTA has shown lower reliability in the eyes with DME, as the intraretinal fluid can influence the segmentation on OCT and lead to erroneous results.

Alibhai *et al.*^[50] showed a statistically significant increase in the percentage of non-perfusion area on widefield OCT angiography, with increasing severity of DR. OCTA color-coded perfusion density maps have also been used to analyze the progressive retinal perfusion changes in DR.^[51] For IRMAs and NVEs/NVDs, widefield OCTA has higher detection rates than color fundus photo or clinical examination.^[52,53] OCTA is also helpful in characterizing these vascular abnormalities and differentiating IRMAs from NVEs.^[52] Unlike IRMAs which are intraretinal, NVDs and NVEs appear as flow signal within the preretinal hyperreflective material.

Diabetes can also affect the choroidal circulation characterized by aneurysms, dilatation, and obstruction of the

vessels, vascular remodeling with increased vascular tortuosity, vascular dropout, and focal vascular non-perfusion.^[54] OCTA helps in non-invasive imaging of the choriocapillaris. Loria *et al.*^[55] reported significantly increasing choriocapillaris flow void area with increasing stage of the DR stage. The appearance of these flow void areas precedes the development of clinically detectable DR.

Fundus Autofluorescence

Autofluorescence refers to the ability of certain materials to fluoresce when excited with a light of a suitable wavelength. In the eye, the cornea, lens, and retina all exhibit AF due to the endogenous fluorophores present in these tissues. The fluorophores present in the retina include lipofuscin, a product of the oxidative breakdown of the photoreceptor outer segments in the RPE, and melanolipofuscin present in the RPE cell/choroid complex. Short wavelength AF originates from lipofuscin and near-infrared wavelength is thought to primarily originate from melanin.

Autofluorescence images can be obtained using flash fundus cameras or an SLO-based system. In DME, various patterns of AF have been described, including normal, spot increased, cystoid increased, and irregular decreased AF.^[56] Increased AF has been reported in the regions of cystoid DME and is thought to be due to the displacement of macular pigment (xanthophyll), which normally blocks the underlying fluorescence from the RPE to the periphery of the cysts. This also results in decreased AF at the margins of the cysts. The macular pigment optical density (MPOD) can also be measured using AF imaging. AF imaging has shown increased MPOD measurements surrounding the cysts and decreased MPOD in the area of the cystoid lesion itself.^[57]

It is also postulated that the photoreceptors damaged due to DR are phagocytosed by the RPE cells which lead to increased production of lipofuscin.^[56] Pece postulated that hyperfluorescence could be pseudofluorescence due to the light reflected from the fluid within the retinal cysts.^[58] The accumulation of advanced glycation end products induced by activated microglial cells is also said to cause increased AF.^[59] Macular hyperautofluorescence without foveal hyperautofluorescence has been noted to occur in individuals with DM without any clinical sign of DR.^[60] Decreased AF has been reported in the parafoveal area. The cause for decreased AF in DR is suspected to be due to the edematous retinal parenchyma in DME and/or the components from extravasated blood in the outer plexiform layer blocking the underlying RPE fluorescence.^[61] Hard exudates are also said to absorb the AF resulting in decreased AF. The photoreceptor loss caused by DR may ultimately result in reduced phagocytosis of the outer segments, and hence, reduced production of lipofuscin.^[56] Quantitative measurement of color AF has revealed the increased intensity of green and red AF in people with diabetes mellitus compared to that with healthy individuals and in the eyes with DME compared to that without DME.^[59]

Vujosevic found a strong correlation between increased AF in DME and decreased central field sensitivity on microperimetry, indicating the decrease in the function of the neurosensory retina.^[62] McBain *et al.*^[63] found 81% sensitivity and 69% specificity in diagnosing DME with AF when compared with FA. The sensitivity is higher in florid macular edema. AF imaging, hence, detects DME non-invasively and

quickly and can be offered to patients with severe allergic/anaphylactic reaction to the fluorescein dye. The need for clear ocular media and the wide availability of the OCT, which provides an excellent assessment of the photoreceptors and RPE, limits its routine use in the management of DR.

Near-Infrared Reflectance Imaging

NIR images are commonly obtained as companion images along with OCT scans, and thus, they can provide useful documentation of disease features when the companion color fundus images are not available. The long wavelength of NIR imaging allows the images to be captured even in the presence of a small pupil, media opacity, hemorrhage, subretinal fluid, and exudation. On NIR imaging, the regions with cystoid macular edema may be readily visualized [Fig. 3]. Neovascularization in the eyes with PDR commonly appears as hyporeflective irregular blood vessels.^[64,65] However, image artifacts are common which can make interpretation challenging.

While the previous sections summarize the commonly available and utilized imaging modalities in the assessment of the diabetic patient, the next section reviews technologies that may provide useful information but are still being researched for their potential applications in DR. Table 1 summarizes the advantages and limitations of the commonly used imaging modalities in DR.

Fluorescence Lifetime Ophthalmoscopy

Fluorescence lifetime ophthalmoscopy (FLIO) is a new modality, which has been most extensively studied in the context of age-related macular degeneration, macular telangiectasis, and neurodegenerative diseases (e.g., Alzheimer's).^[66-68] FLIO measures the time spent by a fluorophore in a high energy state before decaying to the ground state, also called the fluorescence decay time. Increased fundus fluorescence decay time was noted in the studies by Schweitzer *et al.*^[69] and Schmidt *et al.*^[70] in the patients with DM with or without NPDR, respectively. Accumulated advanced glycation end products have been postulated as the cause of increased fluorescence lifetimes.^[69,70]

Adaptive Optics

Adaptive optics (AO) imaging captures images with high resolution by compensating for ocular wavefront aberrations. Microaneurysms, IRMAs, and neovascularization which are at times difficult to be identified on fundus photo can easily be distinguished on AO imaging. With AO imaging, microaneurysms and intraretinal hemorrhages appear as hyporeflective dots. The retinal edema causes a blurring effect on the images and retinal cystoid spaces have a sharp hyporeflective demarcation line corresponding to the internal lining of the cyst wall. Hard exudates appear heterogeneous with distinct dark margins.^[71] Due to the ultrahigh resolution of the vessel wall, the flow within the microvasculature can be visualized which further aids in differentiating microaneurysms from intraretinal hemorrhage. Ultrastructural changes in the form of photoreceptor mosaic abnormalities can also be detected.^[72,73]

Multispectral and Hyperspectral Imaging

Multispectral imaging (MSI) and hyperspectral imaging (HSI) are novel technologies which capture information from

Table 1: Advantages and limitations of commonly used retinal imaging modalities for assessment of diabetic retinopathy

Imaging	Advantages	Limitations
Fundus photography	Non-invasive Widely available	Two-dimensional image Pupillary dilation usually needed
Fluorescein angiography	Provides information on dynamic blood flow Helps in distinguishing MAs and hemorrhages, IRMAs, and NVEs Identifies area of non-perfusion Better sensitivity for low-flow vascular lesions than OCTA	Invasive Time-consuming Contrast dye has potential adverse reactions Leakage of dye can obscure details of vascular structures Low resolution Not depth-resolved
Optical coherence tomography	Provides cross-sectional view of retinal structures Non-invasive Can quantify retinal thickness to assist in monitoring progress of diabetic macular edema and response to therapy Rapid and easy to acquire	Cannot visualize vascular alterations precisely Difficult to image the periphery Dense volumetric acquisitions require more time Segmentation errors may impact the accuracy of quantitative measurements
Optical coherence tomography angiography	Non-invasive Short acquisition time relative to dye-based angiography Depth-resolved, allowing different capillary layers to be distinguished Lack of staining allows for visualization of vascular details Allows quantification of non-perfusion and vessel density	Good fixation needed for high-resolution images Limited field of view Susceptible to var (projection/motion/segmentation/signal loss) Not widely available Very limited velocity resolution Does not demonstrate leakage
Fundus autofluorescence	Non-invasive Short imaging time Provides an assessment of the functional status of the RPE and photoreceptors	Not broadly available Requires skill in interpretation Clear media required for high-contrast images Susceptible to artifacts related to bleaching or noise Bright flash can be uncomfortable for patients Applications in DR are still evolving; much of the information provided can also be obtained from OCT
Near-infrared reflectance imaging	Non-invasive Light is comfortable for patients Commonly available as companion images along with OCT imaging, and thus, can be useful for documentation of some features of DR	Artifacts are common and can make interpretation challenging Limited additional information provided relevant to the management of DR

DME - diabetic macular edema, DR - diabetic retinopathy, IRMA - intraretinal microvascular abnormalities, NVE - neovascularization elsewhere, OCT - optical coherence tomography, OCTA - optical coherence tomography angiography, RPE - retinal pigment epithelium

multiple spectral bands (i.e., specific blocks of wavelengths) across the electromagnetic spectrum. MSI uses sensors which detect several specific broader bands of wavelength whereas HSI detects energy in narrower and more numerous bands. The study by Li *et al.*^[74] showed that MSI had higher agreement rates with FA in grading the severity of DR compared to the dilated fundus photos. Early features of DR like microaneurysms and IRMAs were better identified with MSI. The oximetry maps of the retinal blood vessels can be obtained non-invasively based on the spectral differences between the oxygenated and deoxygenated hemoglobin.^[74] Using HSI, the difference in intravascular oxygen content and the arteriovenous oxygen gradient between the normal and diabetic eyes *in vivo* was demonstrated by Kashani *et al.*^[75]

Multicolor Imaging

In multicolor imaging (MCI) (Heidelberg Spectralis [Heidelberg Engineering, Heidelberg, Germany]), the confocal SLO captures images using the simultaneous reflectance from blue (488 nm), green (518), and infrared (820) lasers. The blue light enables the visualization of structures in the inner retina and vitreoretinal interface, the green light better delineates the deeper retinal structures, and the infrared light helps in visualizing the structures in the outer retina and choroid.^[76]

The MCI is superior to the standard fundus photo in detecting microaneurysms, epiretinal membranes, and DME.^[77,78] Small blood vessels, IRMAs, neovascularization, and diabetic proliferative membrane can be better delineated on multicolor imaging.^[77] The MCI provides clearer images than the fundus photos, especially in the eyes with media opacity and/or a small pupil.^[79]

Telemedicine in DR

Before the effective and widely available imaging technologies, clinical fundus examination by a trained ophthalmologist was the only method to diagnose DR. This led to the DR not being assessed in large segments of the population due to poor access to a specialist. With the development of technology in the form of fundus cameras and telemedicine, the retinal images of people in underserved areas can be obtained remotely. These images can then be transferred to centralized facilities and evaluated by expert readers. Patients in need of further evaluation are, thereby, identified and referred for specialized care.

The components of telemedicine include image acquisition, image transfer, image review and evaluation, patient care and referral supervision, and image and data storage.^[80] The image can be acquired by a trained optometrist or a physician non-ophthalmologist using one of the portable fundus cameras.

The desktop fundus cameras have also been made portable through mobile eye clinic vans. After the acquisition, these images are transmitted digitally through the Internet or satellite transmission. The images are then graded by a grader/reader trained in DR grading or using an automated deep-learning system. Patients requiring an in-person examination are then referred. If the images are identified as ungradable, the patients may be reimaged or referred for further evaluation.

The photography method that is used should have high sensitivity, specificity, and kappa statistics for agreement when compared with the seven-field stereo photography or ophthalmoscopy by an eye care specialist for grading the level of DR or DME.^[81] This approach of DR screening is cost-effective, reduces travel time, and expands access for patients in rural communities, and extends the geographic reach and expertise of the physicians and health care facilities.

The future of screening and grading of DR and other retinal diseases will likely rely on the retinal imaging technologies married to artificial intelligence/deep-learning algorithms.

Artificial Intelligence

Artificial intelligence (AI) is a field of computer science that refers to devices mimicking human behavior in some way. Deep learning is a technique implemented in AI that is a modern extension of the classical neural network technique. It allows computational models that are composed of multiple processing layers to learn representations of data with multiple levels of abstraction.^[82] Over the past few years, machine learning and deep learning have been widely used in image analysis, given that images are naturally complex and available in high volume. With the increasing diabetic population, there is an urgent need for automated DR screening and monitoring.

Several novel DR screening algorithms have been reported, including EyeArt, Retmarker, Google sponsored DR detection algorithms, IDx-DR system, Singapore SERI-NUS, and Bosch DR algorithms.^[83-88] Previous studies have demonstrated that some specific disease features such as microaneurysms, exudates, and hemorrhages can be successfully identified using AI technologies.^[83,89,90] More importantly, AI based on deep-learning algorithms have shown robust performance in detecting referable DR (defined as moderate and severe diabetic retinopathy, referable DME defined as any hard exudates within 1 disk diameter of the macula which is a proxy for macular edema when stereoscopic views are not available). Large data sets of images are used to train an algorithm, followed by the validation of the performance of the algorithm. The images used are fundus photos, FA, OCT, or OCT angiography images. The studies have shown sensitivity and specificity >80% and the area under receiver operating curve approaching 1.^[83-88,91]

The AI studies mentioned above suggest that AI-based algorithm can be used for DR screening with high reliability. At present, EyeArt and IDx-DR have already been cleared by the US FDA. These AI algorithms can be adopted on a large scale to relatively reduce the workload of trained specialists and graders. However, AI-based algorithms cannot completely replace human-based screening or a complete eye exam, which still requires trained specialists. Over time, with the further

development of comprehensive imaging technologies and further optimization of AI algorithms, these limitations may be overcome.

Conclusion

Multiple retinal imaging modalities are currently available for the diagnosis, classification, and management of DR. The imaging technology continues to evolve at a rapid pace. Teleophthalmology has proven to be a vital tool in screening individuals for DR in underserved areas of LMICs. The future of imaging in DR will likely incorporate AI/deep-learning systems integrated with retinal imaging in order to further streamline and optimize care. This should help in broadening the access of patients with DR to sight-saving treatment.

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Conflicts of interest

There are no conflicts of interest.

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