Acta Diabetologica (2019) 56:981–994
https://doi.org/10.1007/s00592-019-01373-y

REVIEW ARTICLE

New imaging systems in diabetic retinopathy

Maria Vittoria Cicinelli[1] · Michele Cavalleri[1] · Maria Brambati[1] · Rosangela Lattanzio[1] · Francesco Bandello[1]

Received: 29 January 2019 / Accepted: 30 May 2019 / Published online: 15 June 2019

Abstract

Various imaging modalities are of significant utility in the screening, grading, treatment, and follow-up of the different stages of diabetic retinopathy (DR) and diabetic macular edema. Color stereographic photography, fluorescein angiography, and optical coherence tomography (OCT) have been the gold standard for DR imaging for years. Besides these tools, newer technologies are gaining validation and popularity, such as fundus autofluorescence and OCT angiography. Furthermore, widefield retinography and ultra-widefield retinography have been introduced for a more comprehensive evaluation of the medium-far and very-far retinal peripheries, which is crucial for the assessment of the diverse manifestations of the disease. The aim of this review is to illustrate the recent advancements of the imaging systems for diagnosing DR, with a focus on the newest and noninvasive diagnostic tools.

Keywords Diabetic retinopathy · Diabetic macular edema · OCT angiography · Imaging techniques · Ultra-widefield imaging

Currently, around 422 million adults are suffering from diabetes worldwide, according to data published in 2016 by the World Health Organization (WHO); the projections to 2030 predict an increase in its global prevalence up to 750 million [1]. Diabetic retinopathy (DR) is the main cause of severe visual impairment in these subjects [2–4]; specifically, proliferative DR (PDR) with its complications (vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma) and diabetic macular edema (DME) are mainly responsible for visual loss [5].

Approximately 98% of blindness from DR and DME is preventable with both public health screening programs and prompt therapeutic intervention; the aim of DR screening programs is to recognize early signs of the disease, and this can be achieved through a combination of specialized, non-invasive diagnostic tests; these include fundus examination after pharmacologic pupil dilation and fundus photography with non-mydriatic fundus camera. A prompt therapeutic approach can thus be implemented if any sign of DR is detected on screening, before the onset of advanced DR, which would dramatically lower the efficacy of currently available treatment options [6].

Both screening and fine specialized diagnostic of DR have been revolutionized in the past years with the advent of newer, less invasive retinal imaging modalities. Direct ophthalmoscopy and indirect ophthalmoscopy have been the standard of care for many years. Ophthalmoscopy allows for screening and clinical staging of the disease; despite its noninvasiveness, this technique has several drawbacks, including its subjectivity and the need for cooperation (many patients might be limited by intense photophobia). Furthermore, adequate pupil dilation is needed in order to fully explore the peripheral retina (response to mydriatic drops might be suboptimal, especially if laser or intraocular surgery has been performed).

Non-mydriatic and mydriatic stereographic fundus cameras have been demonstrated to be cost-effective, objective diagnostic tools to obtain digital photographs, which can be stored and, eventually, sent for distant grading by trained technicians/ophthalmologists. This technique allows to categorize the disease in a non-proliferative or in a proliferative stage, according to internationally accepted criteria [7]; however, despite the aforementioned techniques can provide indirect signs of the extent of capillary non-perfusion and the disruption of the blood–retinal barrier (BRB), functional perfusion-based

Managed by Massimo Federici.

✉ Francesco Bandello
bandello.francesco@hsr.it

[1] Department of Ophthalmology, Scientific Institute Ospedale San Raffaele, University Vita-Salute, via Olgettina 60, 20132 Milan, Italy

examinations are still required to recognize the extent of the impairment of the retinal microcirculation.

Fluorescein angiography (FA) is a dynamic technique in which a fluorescent dye is injected into the bloodstream to highlight the blood vessels in the back of the eye so that they can be photographed in different time points of dye transit. FA shows microaneurysms as early hyper-fluorescent dots, while capillary ischemia from non-perfused retinal areas or intraretinal/vitreous hemorrhages appear as hypo-fluorescent areas. Other pathologic findings that can be seen on FA include the enlargement of the foveal avascular zone (FAZ) and intraretinal microvascular abnormalities (IRMA). Since fluorescein is partially unbound to plasmatic proteins, the dye leaks out from vessels in case of BRB damage. This is best exemplified in DME: FA shows diffuse hyper-fluorescence in the late frames, which may assume a flower-petal pattern (cystoid macular edema), due to the disruption of the endothelial tight junctions that form the internal BRB. In eyes with PDR, retinal or optic disk neovascularization is characterized by intense late fluorescein leakage [8]. Although very useful, FA is an invasive technique and can very rarely be accompanied by serious adverse events, primarily allergic reactions up to anaphylaxis. In addition, FA only appropriately images the superficial retinal vessels, while it does not allow for good visualization of the deep retinal plexus and of the choroidal vessels.

Optical coherence tomography (OCT) aids in DR assessment by revealing pathological changes in both a qualitative manner (i.e., DME pattern, presence and aspects of cysts, fluid localization, integrity and reflectivity of retinal layers) and a quantitative (i.e., macular volume, central and sectorial retinal thickness) manner. These indices have been looked at as primary anatomical endpoints in both randomized clinical trials (RCTs) investigating either laser or intravitreal agents, and in the real-life clinical practice for treatment planning and accurate follow-up of patients with DME. Finally, OCT angiography (OCTA), a novel, dye-less, noninvasive test that combines information from both retinal morphology and perfusion, analyzes the superficial (SCP) and the deep capillary plexuses (DCP) of the inner retina. Through a combination of fundus photography, FA, OCT, and OCTA, clinicians can now gather combined data on the level of ischemia, on the chronicity of the manifestations, and on the potential response to different treatments.

The aim of this review is to illustrate the recent advancements in the imaging systems for the diagnosis of DR, with a focus on the newest noninvasive diagnostic techniques. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee of the San Raffaele Institute and with the 1964 Helsinki declaration and its later amendments. All the participants signed a written consent before using their data for scientific purposes.

Widefield and ultra-widefield fundus photography

Traditional fundus retinography and fluorangiographic photograms only include 30° of the posterior pole (i.e., the macular region and the optic nerve head); this method was at the basis of the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, which included a 13-level DR severity scale classification [9]. Despite being optimal for imaging pathologic changes of the optic nerve and of the macula, this field is inadequate for the imaging of the medium-far and very-far retinal peripheries, which is crucial to identify early signs of the disease in patients who are otherwise judged healthy by traditional methods and who are at increased risk of progression toward more severe stages of retinopathy [10, 11]. As a consequence, widefield (WF) and ultra-widefield (UWF) retinal imaging techniques have been gaining increasing importance in the scientific community.

UWF imaging allows for simultaneous evaluation of the peripheral and central retina without the requirement of eye steering. UWF images can be obtained through three methods: (1) assembling of individual smaller-field photographs, (2) adding lenses to the traditional fundus camera, and (3) using dedicated wide-angle devices.

The first attempt to gather UWF imaging was the ETDRS 7 standard fields (7SF) protocol, used by the same study group in the multicentric trial that took place starting from 1979. This method involved the acquisition of 7 retinal photographs, covering 30° each: 3 set horizontally through the macula and 4 arranged around the optic nerve head. These photographs were subsequently combined to obtain an image of about 75° [12]. This protocol has been extensively corroborated and does not require any dedicated equipment nor accessory cost. However, it has numerous disadvantages, such as the need for highly qualified technical staff, optimal mydriasis, high patient collaboration, the impossibility of acquiring pictures simultaneously, and, above all, a limited amount of information from the retinal periphery.

In order to overcome these limitations, the introduction of mountable lenses on the traditional fundus camera or on a confocal scanning laser ophthalmoscope (cSLO) (in which a near-infrared diode laser beam, coupled with a photodiode and a confocal filter, ensures that only light reflected from the narrow spot illuminated by the laser is recorded) was positively accepted in the clinical practice and in the scientific research. Among these devices, the Staurenghi lens [13] and the Heidelberg Spectralis® lens are the most commonly used ones, scanning up to 150° and 105° of the retina, respectively, in a single frame [14].

In the recent years, dedicated wide-angle cameras have been developed with the aim of obtaining the maximum visualization of the retinal periphery including: the Pomerantzeff camera [15], the Panoret-1000™ camera (Medibell Medical Vision Technologies, Haifa, Israel), and the Retcam (Clarity Medical Systems, Inc, Pleasanton, CA, USA), capturing up to 90°, 100°, and 130° of peripheral retina, respectively. Such tools were initially limited by low image resolution, the inability to penetrate opacity of ocular media (like corneal opacity, cataract, or vitreous hemorrhage), the need for pharmacological mydriasis, and difficulty in usage. Recently, these limits have been effectively resolved by the Optos Optomap® (Optos, Dunfermline, Scotland, UK) and ZEISS Clarus 500 (Zeiss, Carl Zeiss Meditech, Inc., Dublin, USA) systems, which both allow to capture up to 200° of the retina (Fig. 1).

The Optos Optomap® is based on a cSLO with two laser frequencies coupled with a parabolic mirror that allows sampling of the 82% of the retinal surface with a single acquisition (corresponding approximately to 200° of view) and without the need for pupil dilation. The device is able to acquire retinal photography, fundus autofluorescence (FAF), FA, and indocyanine green angiography; the color fundus relies on pseudo-colors, i.e., fake colors derived from the combination of red and green color lasers. Peripheral distortion and decreased resolution of the far temporal and nasal peripheral retina are among the most important limitations [16]. In a recent comparison between Optos Optomap® and Heidelberg Spectralis UWFA imaging, it has been found that images obtained on a single non-steered image with the Optos Optomap® cover a significantly larger total retinal surface area, compared to Heidelberg Spectralis® (Fig. 2). Furthermore, the Optos Optomap® captures an appreciably wider view of the retina temporally and nasally, notwithstanding some amount of peripheral distortion. On the other hand, the Heidelberg Spectralis® is able to image the superior and inferior retinal vasculature more peripherally [17]. The main differences between the UWF Heidelberg Spectralis® lens and UWF Optos Optomap® are listed in Table 1.

The applications of UWF imaging in DR are undoubtedly exciting, particularly in the evaluation of peripheral retinal lesions. Prospective studies comparing UWF with ETDRS 7SF images have reported a very good correlation between both imaging modalities [18]. Detection of retinal non-perfused areas and neovascularization is higher with UWF. This is particularly true for patients featuring predominantly peripheral lesions (PPLs) that have been defined as microaneurysms, hemorrhages, venous beading, IRMA, and new vessels elsewhere (NVE) in eyes with DR with more than 50% of the lesion located outside the ETDRS 7SF [19, 20]. Furthermore, the Optos Optomap® device allowed for an upgrade of the severity of DR in a significant percentage of eyes (Fig. 3) [20, 21]. The peripheral lesions detected using UWF have also potential prognostic significance: Eyes with PPLs had an increased risk of DR progression over 4 years, compared to eyes with DR lesion located more centrally [22]. Finally, the degree of peripheral ischemia assessed with Optos Optomap® has been significantly correlated with the severity of DR, with the presence of DME, and with the extent of macular ischemia [23, 24].

Besides leading to better diagnosis and staging of DR, UWF devices allowed the identification of new pathological findings such as peripheral vessel leakage (PVL), which is defined as leakage of dye by peripheral arteries and veins in the context of active DR (Fig. 4) [25]. UWF imaging can also be used to prevent adverse events related to panretinal photocoagulation (PRP), which aims to destroy ischemic areas of retinal tissue outside the temporal arcades to prevent the development of PDR. PRP has several side effects, including visual field reduction, onset/worsening of DME, choroidal detachment, and reduction in color and contrast sensitivity; thus, selective photocoagulation of the non-perfused areas identified on Optos Optomap® could represent a promising way to treat retinal ischemia and preserve unaffected retinal tissue. In the group of patients treated with UWF-“targeted” PRP,

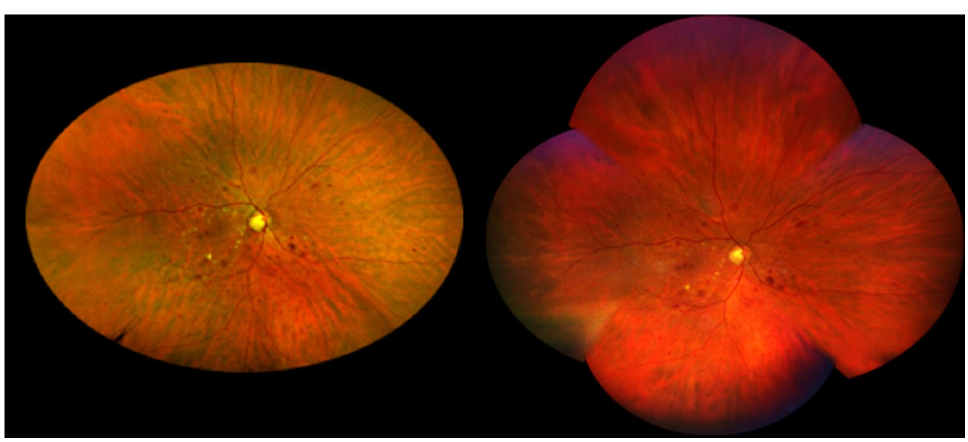

Fig. 1 Comparison of ultrawide-field color fundus photography of a patient with non-proliferative diabetic retinopathy taken on the same day. Left: Optos Optomap® (Optos, Dunfermline, Scotland, UK), based on pseudo-color. Right: ZEISS Clarus 500 (Zeiss, Carl Zeiss Meditech, Inc., Dublin, USA), relying on real color

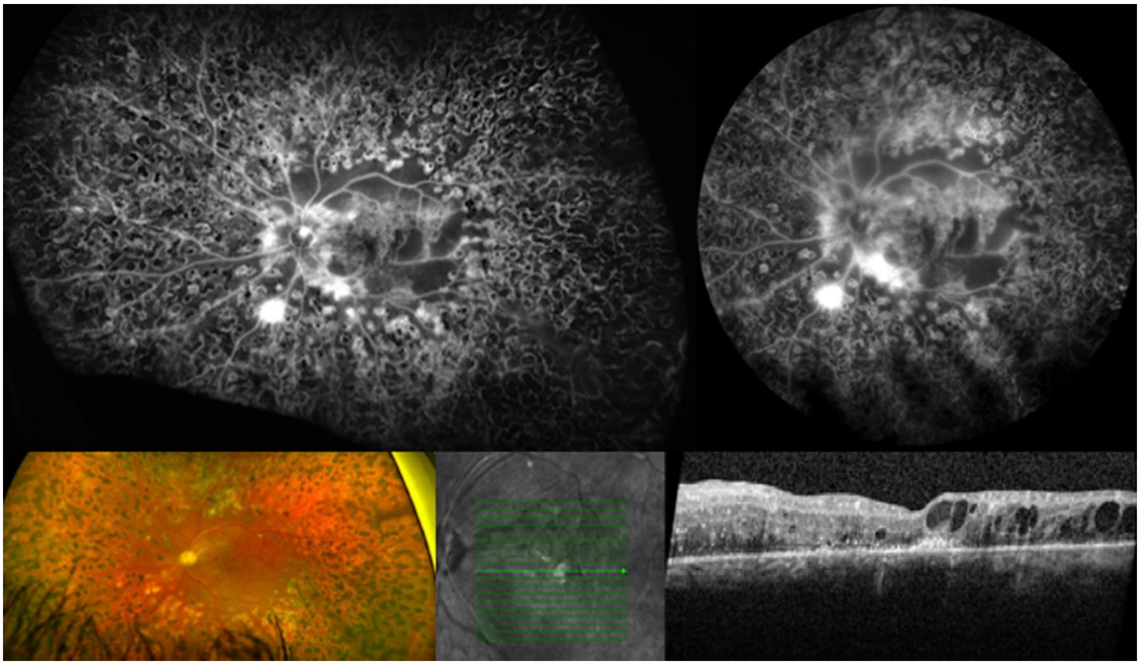

Fig. 2 Ultrawide-field fluorescein angiography (UWFA) of the same patient with proliferative diabetic retinopathy. Left: UWFA obtained with Optos Optomap® (Optos, Dunfermline, Scotland, UK). Right: UWFA obtained with the 102° lens of the Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany). Bottom: Pseudo-color fundus (left) and optical coherence tomography passing through the macula, showing diffuse macular edema

Table 1 Differences between the ultra-widefield (UWF) Heidelberg Spectralis® lens and UWF Optos Optomap®

	Heidelberg Spectralis® Lens	Optos Optomap®
Instrumentation	cSLO and interchangeable non-contact lens	cSLO and parabolic mirror
Field of acquisition (retina degrees, °)	105°	200°
Contact with eye	No	No
Need for mydriasis	Yes	No
Real-time image averaging	Yes	No
Image distortion	No distortion	Peripheral distortion
Artifacts	None	Eyelashes, vitreal opacities

cSLO confocal scanning laser ophthalmoscope

a reduction in the side effects of laser photocoagulation without sacrificing the therapeutic benefits has indeed been observed (Fig. 5) [26].

The Diabetic Retinopathy Research Network (DRCR.net) international study group has recently promoted the AA protocol with the aim of evaluating the association between peripheral lesions visible with the UWF angiography and progression of DR. The preliminary results published by Aiello et al. aimed to perform a side-by-side comparison between ETDRS images and UWF images that were masked to reveal only the ETDRS 7-field area. The study showed that PPLs were more common on UWF imaging, and UWF allowed an increase in DR severity by 2 or more steps in approximately 11.0% of eyes. An unresolved issue is the extent to which DR findings outside the area of retina visualized with ETDRS 7-field imaging can affect the risk for DR progression; the results awaited in 2020 from longitudinal data from the same study might provide a potential answer as to whether UWF images can recognize eyes at major risk for DR worsening. [27, 28].

Fundus autofluorescence

FAF relies on the phenomenon of emission of light from retinal pigments acting as natural fluorophores, which are substances that release energy when hit by a light ray with a specific wavelength.

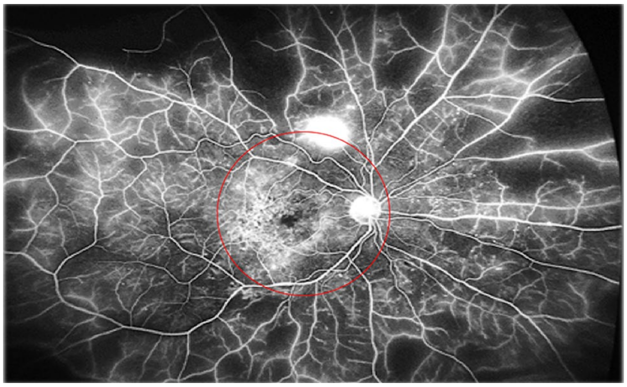

Fig. 3 Ultrawide-field fluorescein angiography (UWFA) obtained with Optos Optomap®. In red, the area virtually corresponding to the fluorescein angiogram obtained with the 55° lens of the Heidelberg Spectralis®, which fully images the posterior pole, but only a relative amount of the area outside the vascular arcades

The main fluorophores in the human retina are lipofuscin and melanin. Lipofuscin emits yellow fluorescence (480–800 nm) when stimulated with wavelengths within the blue range; melanin is excited by wavelengths within the infrared range of light spectrum. Lipofuscin is produced by retinal pigment epithelial (RPE) cells and is composed of several different molecules, the most important of which is A2E (N-retinyl-N-retinylidene ethanolamine). A2E is not recognized by lysosomal enzymes, and increased accumulation of this degraded material in the lysosomal compartment of the RPE cells is considered a hallmark of normal aging or metabolic impairment of the RPE itself. Conversely, melanin is a protective pigment found into corpuscles in the apical pole of RPE and in the choroid, protecting the RPE from excessive light scattering, radiation, oxidative stress, and light damage. Loss of RPE melanin granules has been observed with retinal aging.

In clinical practice, two types of FAF are mostly used, according to the wavelength of excitation: blue-light autofluorescence (BL-FAF), also called "short wavelength," that emits light rays at 488 nm and is specific for lipofuscin, and near-infrared autofluorescence (NIR-FAF) that emits at 787 nm and is specific for melanin (Fig. 6). Recently, a green-light autofluorescence (GAF, excitation 518 nm) has been gaining more popularity; it shows a smaller rate of absorption by the macular pigments and gives potentially useful information about the optic nerve head (Fig. 7) [29].

FAF can be obtained by a cSLO device or by a modified fundus camera; the former uses a system of mirrors to focus

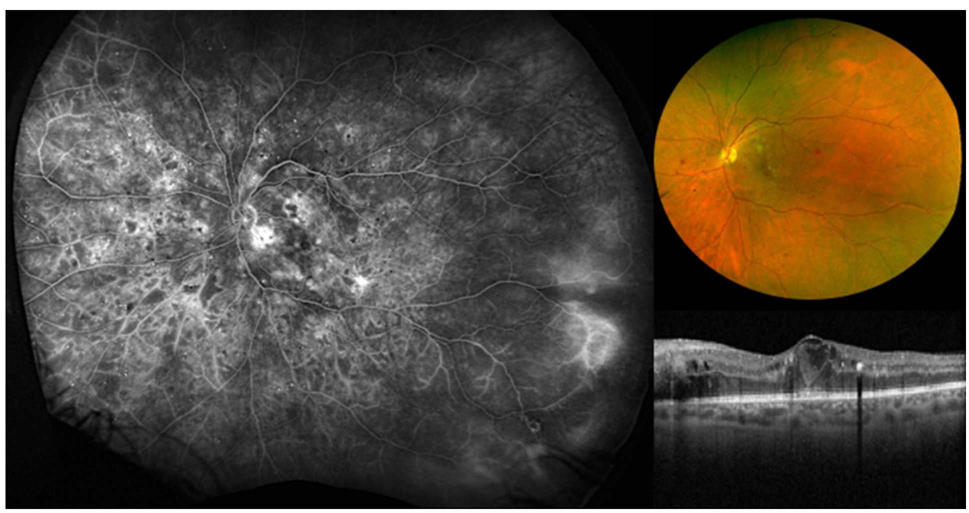

Fig. 4 Ultrawide-field fluorescein angiography (UWFA) obtained with Optos Optomap® of a patient with severe non-proliferative diabetic retinopathy. In the nasal and temporal periphery, the UWFA shows peripheral vessel leakage (PVL), which consists in the leakage of dye by peripheral arteries and veins in the context of active DR. Right: pseudo-color fundus and optical coherence tomography passing through the macula, showing cystoid macular edema

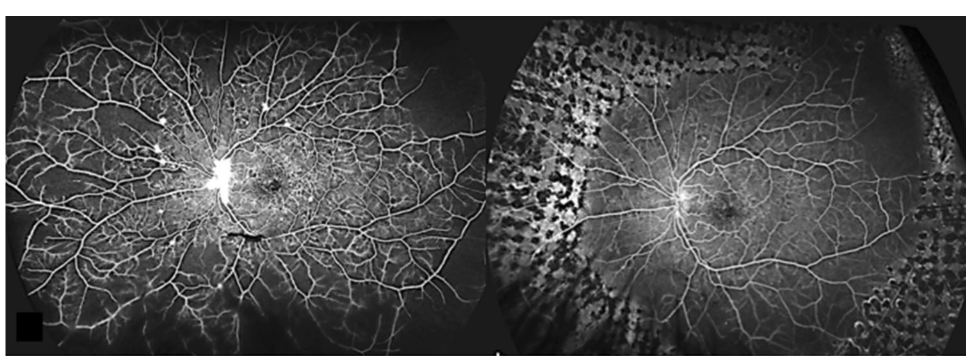

Fig. 5 Ultrawide-field fluorescein angiography (UWFA) obtained with Optos Optomap® of a patient with proliferative diabetic retinopathy before (left) and after (right) panretinal photocoagulation. UWFA helped in selecting only the ischemic areas and sparing the healthy, perfused retina

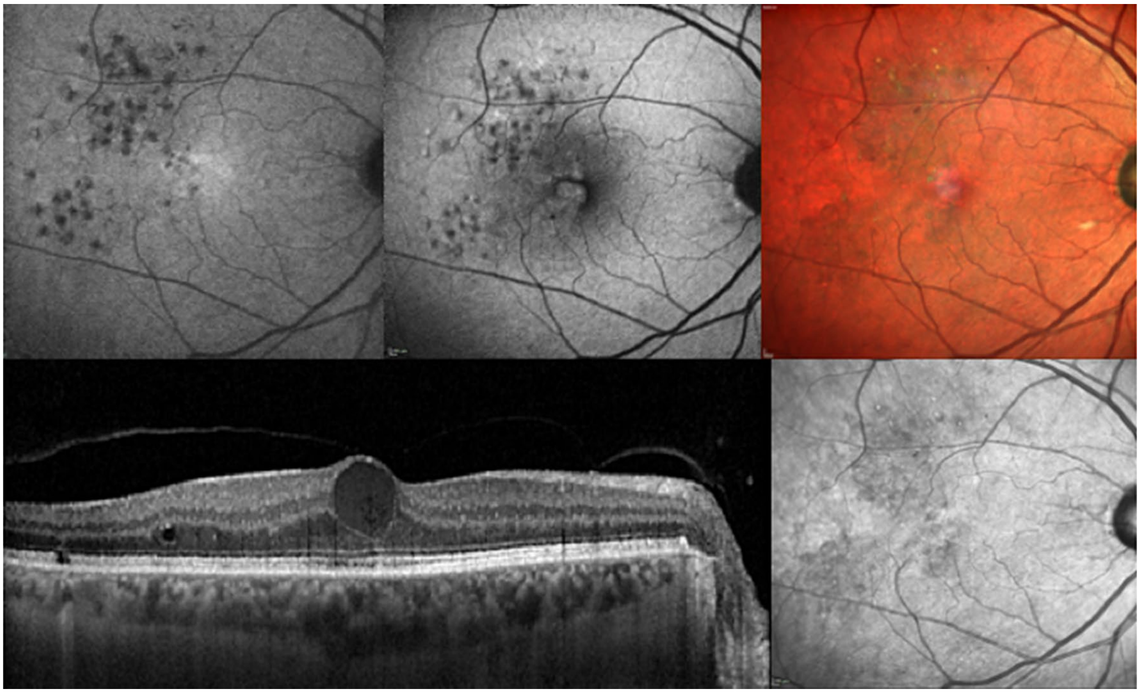

Fig. 6 Fundus autofluorescence obtained with Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany). First row, from left to right: near-infrared autofluorescence, blue autofluorescence; MultiColor® image. Bottom row: optical coherence tomography passing through the macula, showing cystoid macular edema, and infrared reflectance

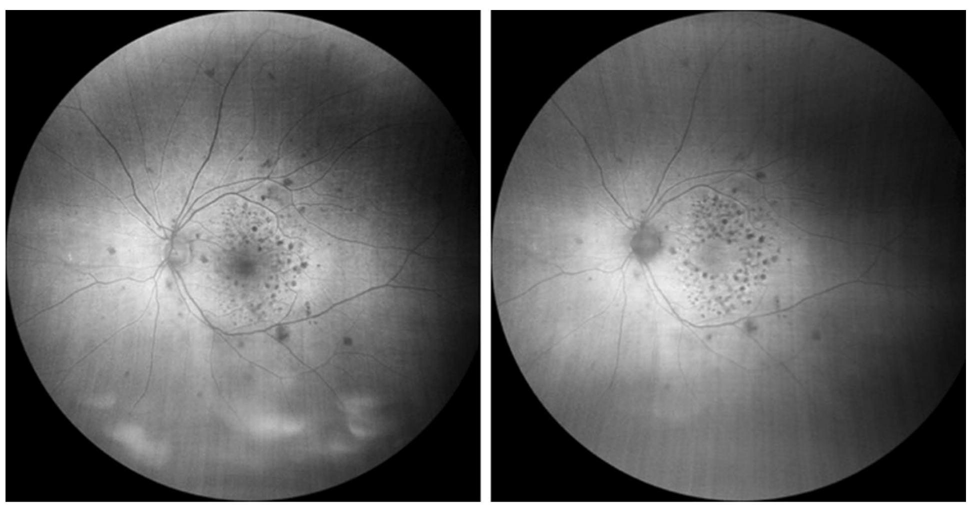

Fig. 7 Fundus autofluorescence of the same eye obtained with ZEISS Clarus 500 (Zeiss, Carl Zeiss Meditech, Inc., Dublin, USA). Left: blue autofluorescence (BL-FAF, excitation 488 nm). Right: green autofluorescence (G-FAF, excitation 518 nm), which shows a smaller rate of absorption by the macular pigments and gives potentially useful information about the optic nerve head

a low power laser in a two-dimensional raster pattern onto the fundus, while the latter relies on a digital system that captures autofluorescence using a single flash of light [30]. The cSLO system incorporated in the Heidelberg Spectralis® offers both BL-FAF and NIR-FAF, while the one built in the UWF Optos Optomap® simultaneously uses two excitation wavelengths of red (633 nm) and green (532 nm) light with an emission filter of > 540 nm.

The use of FAF is a precious resource in all those retinal conditions where the RPE is primarily involved, like age-related macular degeneration or inherited macular dystrophies [31]. Although the role of FAF in DR and DME is yet to be fully elucidated, currently available data suggest that this imaging modality could be useful to better understand DME pathogenesis and formulate a correct prognosis. At present, FAF is not considered a screening modality for macular involvement in DR; however, it might be taken into primary consideration to choose the right treatment in the future. For instance, specific therapies aiming at RPE restoration might be more useful for subsets of patients who show RPE derangement on FAF imaging.

In detail, specific BL-FAF patterns have been observed in DME, correlating with various OCT features; a linear correlation between the amount of hyper-autofluorescence and the severity of DME has been reported [32]. Different explanations have been proposed to link the presence of intraretinal fluid to increased macular autofluorescence: It can be caused by the dispersion of macular pigments normally masking foveal fluorescence by the intraretinal cysts [33, 34], or it might be due to the activation of retinal microglial cells in eyes with DR [34]. The activation of microglia is accompanied by the oxidation of proteins and lipids, and the accumulation of the by-products of this cascade may be the source of the increased fluorescence. Vujosevic et al. described that, in case of clinically significant macular edema, BL-FAF correlates better with OCT patterns and central field microperimetry rather than with visual acuity; [35] furthermore, a reduction in abnormal BL-FAF in DME has been reported after either anti-vascular endothelial growth factor (VEGF) or steroidal therapy [36].

As far as it regards NIR-FAF, two patterns have been described in DME: a mosaic pattern, consisting of granular or patchy hyper- and hypo-autofluorescence at the fovea, and cystoid. Both the patterns were associated with worse visual acuity and more severe macular edema on OCT [37]. Finally, green-FAF has shown a poor correlation with the clinical and tomographic features of DME [38].

MultiColor® imaging

The Heidelberg Spectralis® cSLO instruments are also equipped with a MultiColor® imaging system; this tool simultaneously acquires reflectance at three different wavelengths: blue (486 nm), green (518 nm), and infrared (815 nm), which are then superimposed to gather diagnostic information from different layers of the retina [39]. In detail, each wavelength reaches different depths of penetration into the retina. Blue light, having the shortest wavelength, obtains information from the inner retina and vitreoretinal interface; green light is absorbed by hemoglobin and therefore allows for the visualization of the retinal vasculature; finally, infrared laser penetrates at the deepest level, giving insights from the outer retina, the RPE, and the choroid.

At present, MultiColor® imaging might be more costly than standard photography. A head-to-head comparison with fundus pictures has demonstrated a sensitivity and specificity superior to 90% of MCI to detect DR lesions compared to color fundus photography. MultiColor® scanning laser has shown superiority with respect to standard color fundus photography thanks to greater penetration of laser through media opacities, such as cataract, compared to visible light; it also offers minor scattering, superior spatial resolution, and better contrast (Fig. 8). An advantage of MultiColor® is that this device is embedded in the Heidelberg cSLO camera; therefore, autofluorescence, infrared imaging, OCT, and fluorescein angiography might be performed almost simultaneously, without the need for pupil dilation or multiple devices. Finally, thanks to the eye-tracking technology and the possibility of real-life image averaging, the resolution of details is excellent (Fig. 9). For these reasons, the MultiColor® imaging system has been advocated as a potential screening modality for DR [40].

Optical coherence tomography

OCT has obtained great importance in the evaluation of the macula in patients with DR. Although its main use lies in the assessment of DME, this modality provides useful information on other features, such as the vitreoretinal interface and the thickness of the nerve fiber layer, the ganglion cell layer, and the choroid [41–43]. Quantitative OCT evaluation includes the central macular thickness (CMT) and the macular volume, which are often taken into consideration as the main anatomical outcomes in many therapeutic clinical trials regarding DME.

On the other hand, OCT allows to qualitatively classify the DME in a vasogenic, non-vasogenic, or tractional subtype; [44, 45] this distinction is crucial for the correct therapeutic approach. The qualitative evaluation of the OCT also allows appreciating important factors determining the visual prognosis, such as the ellipsoid zone and the external limiting membrane, whose integrity is an indirect sign of the photoreceptors' functional health [42, 46].

Other biomarkers that can be visualized on OCT include: hyper-reflective intraretinal spots (HRS) [47, 48],

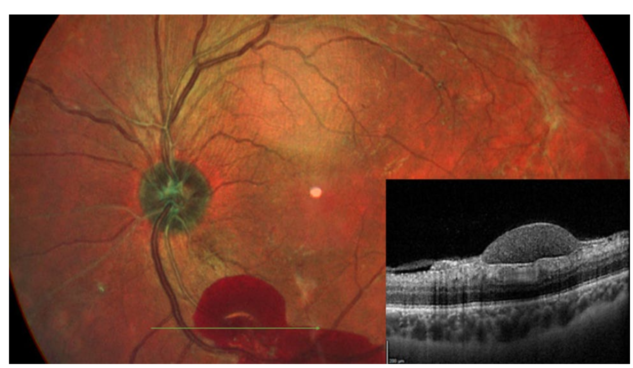

Fig. 8 MultiColor® imaging system acquired by Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany) of a patient with proliferative diabetic retinopathy and a pre-retinal hemorrhage. The green line indicates the optical coherence tomography line passing through the hemorrhage

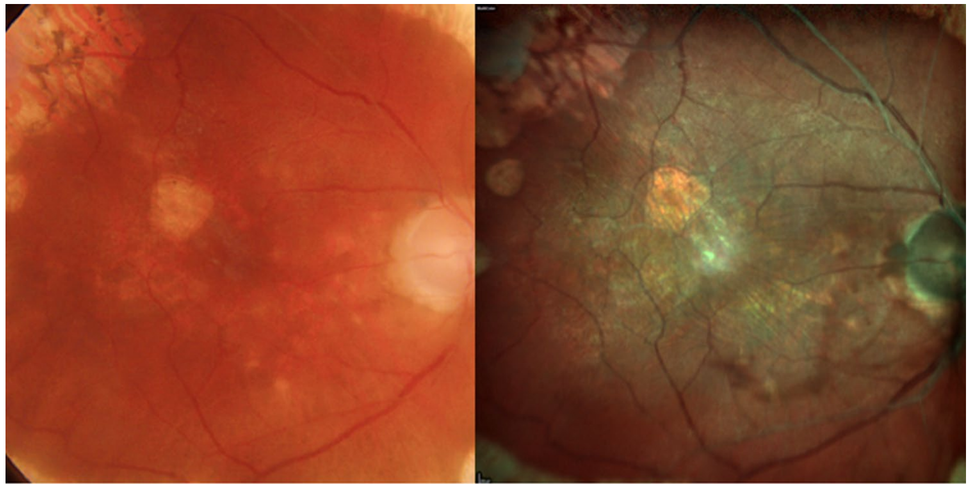

Fig. 9 Comparison of standard 45° fundus photography taken by a fundus camera (Topcon Inc., Tokyo, Japan) and MultiColor® imaging system. The MultiColor® imaging system provides better definition of the epiretinal membrane and the area of chorioretinal atrophy

the presence of vitreoretinal adhesion or epiretinal membrane [49], subfoveal neurosensory detachment [50], and disorganization of the inner retinal layers (DRIL), which is considered to be a sign of macular ischemia and therefore a negative prognostic factor [51, 52]. HRS are defined as intraretinal foci with increased reflectivity and a smaller size compared to hard exudates; their pathogenesis and functional significance are still uncertain, but it has been hypothesized that they are precursors of hard exudates, or, alternatively, a morphological sign of the hyperactivation of Müller cells. The presence of subretinal sensory detachment, the absence of HRS or DRIL, and the integrity of the ellipsoid zone have been associated with a better functional response to intravitreal therapies [53].

Limitations of OCT include the inability to distinguish the alterations in the retinal blood perfusion associated with DR, namely macular and peripheral ischemia, epiretinal neovascularization, and BRB breakdown. FA and OCT angiography are thus required to detect the retinal vasculature changes that occur in DR.

OCT angiography

OCTA evaluates the retinal and choroidal vascular layers in a noninvasive, rapid, and three-dimensional manner. The OCTA signal is generated by the comparison of consecutive cross-sectional OCT scans, which are analyzed with respect to the variation in reflected signal amplitude. By assuming that this variation is due solely to the movement of erythrocytes through retinal blood vessels, an angiogram map is ultimately rendered by the software [54]. Different angiograms can be produced according to different segmentation levels, specific for the superficial capillary plexus (SCP), the deep capillary plexus (DCP), the avascular outer retina, the choriocapillaris, and the choroid.

OCTA might potentially enable clinicians to detect pathologic changes that occur in DR in a more rapid and safer manner compared to dye angiography, which is invasive and may cause allergy-related side effects after dye injection. [55] In particular, OCTA can identify capillary abnormalities (such as microaneurysms and vascular tortuosity), alterations in the shape and size of the FAZ, and the presence of epiretinal neovascularization [56, 57]. Moreover, it is an excellent tool for evaluating areas of non-perfusion in the macular region, as it allows the different vascular plexuses to be differentiated from each other. The quantification of the fovea with OCTA is also not influenced by leakage phenomena, which sometimes complicates the assessment of FA images.

On OCTA, microaneurysms appear as focal dilation of retinal capillaries, especially nearby the FAZ area (Fig. 10) [58, 59]. There are conflicting reports on the different ability of FA and OCTA to detect microaneurysms: Some authors reported a similar detection rate between the two imaging modalities [60], while others found that the number of microaneurysms found on OCTA is significantly lower compared to FA [61]. Ishibazawa et al. reported that OCTA is able to visualize microaneurysms and retinal nonperfused areas; however, only 62% of microaneurysms seen on FA images were detected on OCTA [56]. Couturier et al. reported a lower detection rate of microaneurysms on OCTA, but noted the superiority of OCTA in identifying non-perfused areas compared to FA [61]. Finally, Parravano et al. reported that the ability to recognize microaneurysms on OCTA may be influenced by their reflectivity aspect on OCTA, with a lower detection rate for those appearing hyporeflective on structural OCT scans [62].

There is general agreement that the FAZ in eyes with DR is pathologically enlarged, with loss of symmetry and circularity in the superficial and deep vascular plexuses, even in diabetic patients without clinical signs of retinopathy [63, 64]. The increase in the FAZ area is thought to be caused

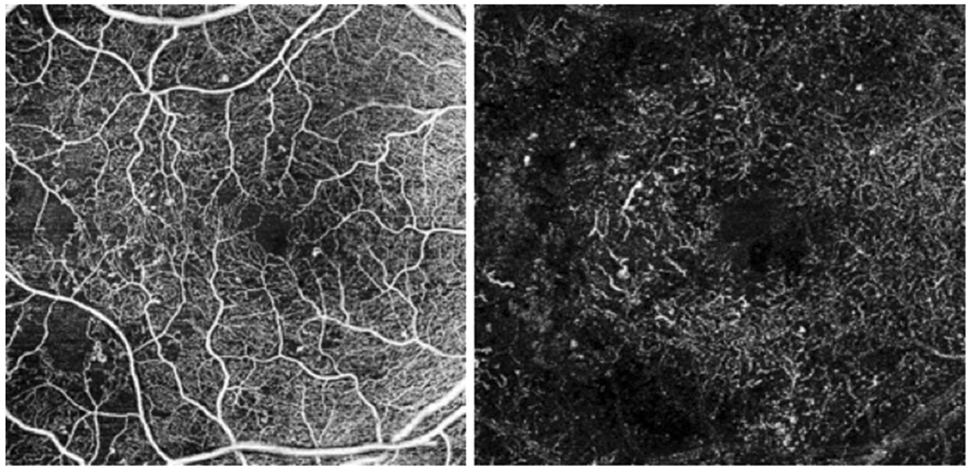

Fig. 10 Optical coherence tomography angiography (OCTA) image of the superficial capillary plexus and the deep capillary plexus of a patient with non-proliferative diabetic retinopathy imaged with AngioPlex (Carl Zeiss Meditech, Inc., Dublin, California, USA). The deep capillary plexus shows a major number of microaneurysm compared to the superficial capillary plexus slab

by micro-infarcts of the vascular capillaries delimiting the FAZ and negatively correlates with the visual acuity and the macular function. On the other hand, the FAZ area is positively correlated with the degree of DR and the extent of peripheral ischemia (Fig. 11) [10, 65].

Various quantitative OCTA indices have been developed, including vessel density (VD) and vessel perfusion density (PD). The VD value is expressed as the ratio of pixels corresponding to the vascular flow over the total number of pixels of the slab. VD is significantly lower in both the superficial and deep capillary plexuses in eyes with DR. Interestingly, the analysis of VD revealed that type 1 diabetic patients without DR or with mild non-proliferative DR already displayed a reduction in VD compared to healthy controls [66, 67]. Therefore, the rarefaction of the perifoveal capillary network has been proposed as an early marker of DR, even in the preclinical stage. OCTA has shown good reliability for VD analysis, provided that repeated measurements are obtained with the same device [68].

The main limitation of the OCTA technology is the lack of functional information on the integrity of the macula; moreover, the quality of the image can be impaired by some

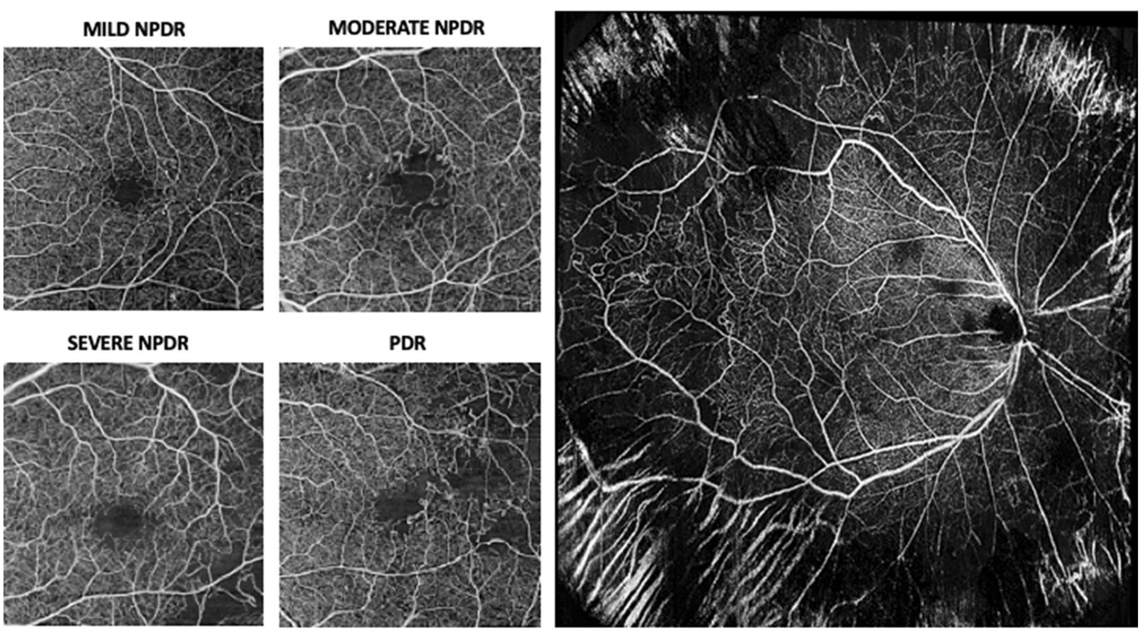

Fig. 11 Optical coherence tomography angiography (OCTA) image of different stages of diabetic retinopathy imaged with AngioPlex (Carl Zeiss Meditech, Inc., Dublin, California, USA). The images show progressive worsening of macular vascular abnormalities and capillary non-perfusion (NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy). Right: OCTA montage obtained through automatic montaging of two different 15 mmx9 mm OCTA scans of the superior and inferior halves of the retina. The area outside the vascular arcades discloses choroidal vessel due to retinal pigment epithelium atrophy consequent to laser photocoagulation

segmentation artifacts in the presence of intraretinal edema [69]. Finally, hypo-reflective intraretinal cyst on en face OCTA slab can be misinterpreted as areas of ischemia.

At present, OCTA acquisition is mainly restricted to the posterior pole; however, new scan patterns and image reconstruction methods (montage) have been developed, allowing the inclusion of wider retinal portions, beyond the posterior vascular arcades (Fig. 11). In conclusion, OCTA might become a potential screening test for early signs of disease even in the absence of manifest pathology; nevertheless, further studies are warranted to validate this method in routine practice.

Tele-ophthalmology and artificial intelligence

The latest novelties that have been introduced in noninvasive retinal imaging are pivotal for the execution of modern, cost-effective screening programs for DR, which must be able to face the recent epidemiological raise in its worldwide prevalence. In fact, the cost-effectiveness of a screening program is crucial for its success, and the choice of the preferred DR screening method should take into consideration the different availability of resources between the different countries.

The recently published guidelines for DR screening from the International Council of Ophthalmology (ICO) recommend annual DR screening to be done by means of either ophthalmoscopy (direct or indirect) or fundus photography [70]. However, since the demand for annual retinal examination is feared to exceed due to the rapidly increasing global diabetic population, a time investment of over 4.5 million hours per year is expected to be needed from every ophthalmologist by the year 2030 to evaluate all diabetics at least once a year.

Medical, psychosocial, and economic factors such as patient age, need for pupil dilation, health insurance coverage, educational status, poor awareness, costs for transportation, and limited access to primary eye care services affect the effective accomplishment of recommended screening guidelines in rural areas [71]. Even in highly urbanized settings with universal access to specialized eye care, patient and provider unawareness, long waiting times, and difficulty in booking appointments represent significative limitations of adherence to annual recommendations for eye examinations [72]. In this view, newer strategies are needed in order to realistically meet global demands.

Tele-ophthalmology and artificial intelligence-based image analysis might help in overcoming these limitations. The telemedicine approach in DR screening relies on the execution of fundus photographic examinations with non-mydriatic fundus cameras to large cohorts of diabetic patients that are subsequently interpreted by trained personnel in off-site reading centers [73]. A PubMed literature search carried out using the key terms “tele-ophthalmology” and “diabetic retinopathy” identified more than 60 papers regarding the application of this approach to diabetic patients. Reviewing the literature demonstrates that all of these approaches turned out to be successful in the identification of DR cases (including those requiring treatment) and, subsequently, the prevention of visual loss [74]. The diagnostic accuracy of this approach has been reported to be over 80% in detecting low- and high-risk PDR (Fig. 12), and over 70% in recognizing DME and mild and moderate NPDR [75]. The use of UWF imaging systems, combined with pharmacological mydriasis, has resulted in even higher sensitivity [76, 77]. Meanwhile, a study from Nathoo et al. demonstrated that over a 2-year period, tele-ophthalmology saved approximately 450 round trips to the nearest urban center, which translates to 1900 h and 180,000 km of driving [78]. According to a clinical survey performed by Boucher and colleagues, 82% of the patients screening with tele-ophthalmology indicated a preference for telemedicine DR screening over standard clinical examination, and 95% preferred to have their next screening examination in a telemedicine system, with referral to an ophthalmologist only if necessary [79].

Tele-ophthalmology has been proved to be effective in establishing interdisciplinary connections between specialists, healthcare providers, and patients, and is particularly useful in primary care setting [80, 81]. One of the most successful examples of this collaboration has been provided by the English NHS Diabetic Eye Screening Programme launched in England in 2003, where Primary Care Physician (GP), endocrinologists, public health doctors, and optometrists have worked together to ensure appropriate screening of diabetic subjects [82]. Thanks to this program, diabetic retinopathy/maculopathy is no longer the leading cause of

Fig. 12 Ultrawide-field pseudo-color fundus photography of a patient with proliferative diabetic retinopathy. The Optos Optomap® (Optos, Dunfermline, Scotland, UK) demonstrated good accuracy in visualizing epiretinal neovascularization (circle), then confirmed by fluorescein angiography

certifiable blindness among working age adults in England and Wales [83]. Another element strengthening connection between ophthalmologists and primary care providers is that most of tele-ophthalmology services in diabetic retinopathy use a store-and-forward method where a trained ocular technician, nurse, Indigenous health worker, or GP perform imaging on the patient using a non-mydriatic retinal camera and a trained reader grades it subsequently. High levels of concordance between general practitioner and ophthalmologists have been found in grading DR using universally accepted clinical classifications [84].

Finally, by visualization of their own retina, tele-ophthalmology has revealed also an educative role in increasing the patients' awareness of diabetes-related complication [85].

While the main advantages are the possibility of screening a wider share of population, especially those living in remote areas, with the concomitant alleviation of the burden for both patients and ophthalmologists, potential limitations include the need for skilled readers to interpret retinal fundus photographs and the inevitable discrepancies (both inter-reader and intrareader) that come from subjective interpretation of images [86].

On the contrary, the use of artificial intelligence-based reading programs relies on pattern recognition of common DR features, with the aim of distinguishing patients who should be referred to a complete clinical examination from those who should be kept in the screening program without the aid of the human judgment. Multiple algorithms for automated image analysis are currently available, with a reported grading performance comparable to that of trained specialists. The integration of deep learning algorithms has been linked to even higher diagnostic results [87, 88]. It must be noted, however, that these systems are still susceptible to artifacts misinterpretation, and further studies are needed to assess the feasibility of their introduction in clinical practice [89, 90].

Conclusion

In conclusion, multiple novel techniques for retinal imaging offer numerous potential advantages when applied to screening, diagnosis, and monitoring of DR. Multimodal imaging provides different complementary information on this disease, as each modality can analyze a specific structure or a specific manifestation of retinopathy. On the other hand, the noninvasiveness and the rapidity of the new diagnostic tools, as well as the possibility to explore the entire retina up to the furthest periphery in one single steering, are crucial in ensuring the good comfort and the compliance of diabetic patients for regular screening, maintaining the level of care required for appropriate DR management.

Despite multiple devices available to ophthalmologists, indirect retinal fundus examination remains the mainstay for DR screening. The detection of any sign of DR requires urgent referral to the ophthalmologist in order to appropriately stage and treat the disease. FA and OCT have the most long-standing history in the evaluation of severity and extent of DR and are of undeniable utility in clinical management of the disease. Many RCTs have validated their reproducibility and diagnostic accuracy; moreover, these techniques are cost-effective and relatively affordable. Standard FA acquires regular-field pictures that are manually combined in order to gather information on the posterior pole and the peripheral retina. Recently, ultra-widefield (UWF) devices have enabled us to acquire retinal photographs including the medium and far periphery with a single shot, without the need for eye steering. UWF seems to compare well with the ETDRS gold standard; however, further confirmations are still required to replace standard field imaging completely. UWF has shown great importance in telemedicine, which relies on the execution on large cohorts of diabetic patients of fundus photographic examinations with non-mydriatic fundus cameras, which are subsequently interpreted by trained personnel in off-site reading centers. We confidently expect this method to become a "must-have" approach in the near future.

Similarly, OCTA is a relatively new technology that provides information on vascular alterations and capillary non-perfusion without the need for fluorescein dye injection. The noninvasiveness and rapidity of OCTA make it a precious potential tool to screen patients with subclinical disease. However, few reports have been published on the role of OCTA in the management of DR, and current results are still an object of debate. Indeed, UWF and OCTA are auxiliary instruments that might become "must-have" tools in the coming years.

Strong evidence is accumulating on the role of imaging biomarkers as predictors of functional outcomes in DR, including the ellipsoid zone and the external limiting membrane integrity, the number and the location of hyper-reflective intraretinal spots, the presence of vitreoretinal adhesion or epiretinal membrane, the presence of subfoveal neurosensory detachment, and disorganization of the inner retinal layers; however, further data are needed in order to support their use as therapeutic endpoints. Imaging biomarkers could potentially be part of composite endpoints in DR trials, overcoming weaknesses that come from the use of isolated functional or structural parameters (such as best corrected visual acuity and central retinal thickness). Multicenter studies are required to validate the correlations between the information provided by novel imaging modalities and the clinical staging of DR. Furthermore, cost-effectiveness must be carefully evaluated in programming new screening programs relying on new imaging devices.

Compliance with ethical standards

Conflict of interest Maria Vittoria Cicinelli, Michele Cavalleri, Maria Brambati, Rosangela Lattanzio: declare that they have no conflict of interest. Francesco Bandello consultant for: Alcon (Fort Worth,Texas,USA), Alimera Sciences (Alpharetta, Georgia, USA), Allergan Inc (Irvine, California,USA), Farmila-Thea (Clermont-Ferrand, France), Bayer Shering-Pharma (Berlin, Germany), Bausch And Lomb (Rochester, New York, USA), Genentech (San Francisco, California, USA), Hoffmann-La-Roche (Basel, Switzerland), NovagaliPharma (Évry, France), Novartis (Basel, Switzerland), Sanofi-Aventis (Paris, France), Thrombogenics (Heverlee, Belgium), Zeiss (Dublin, USA).

Ethical standard This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study formal consent is not required.

References

1. Rathmann W, Giani G (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27(10):2568–2569 **(author reply 2569)**
2. Leasher JL, Bourne RR, Flaxman SR et al (2016) Erratum. Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. Diabetes Care 39:1643–1649. https://doi.org/10.2337/dc16-er11 **(Diabetes Care 39 (11):2096)**
3. Flaxman SR, Bourne RRA, Resnikoff S et al (2017) Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Health. https://doi.org/10.1016/s2214-109x(17)30393-5
4. Bourne RRA, Flaxman SR, Braithwaite T et al (2017) Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Glob Health 5(9):e888–e897. https://doi.org/10.1016/S2214-109X(17)30293-0
5. Tong L, Vernon SA, Kiel W, Sung V, Orr GM (2001) Association of macular involvement with proliferative retinopathy in type 2 diabetes. Diabet Med 18(5):388–394
6. Stefansson E, Bek T, Porta M, Larsen N, Kristinsson JK, Agardh E (2000) Screening and prevention of diabetic blindness. Acta Ophthalmol Scand 78(4):374–385
7. Early Treatment Diabetic Retinopathy Study Research Group (1991) Classification of diabetic retinopathy from fluorescein angiograms ETDRS report number 11. Ophthalmology 98(5 Suppl):807–822
8. Abramoff MD, Fort PE, Han IC, Jayasundera KT, Sohn EH, Gardner TW (2018) Approach for a clinically useful comprehensive classification of vascular and neural aspects of diabetic retinal disease. Investig Ophthalmol Vis Sci 59(1):519–527. https://doi.org/10.1167/iovs.17-21873
9. Early Treatment Diabetic Retinopathy Study Research Group (1991) Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology 98(5 Suppl):823–833
10. Rabiolo A, Parravano M, Querques L et al (2017) Ultra-widefield fluorescein angiography in diabetic retinopathy: a narrative review. Clin Ophthalmol 11:803–807. https://doi.org/10.2147/OPTH.S133637
11. Ghasemi Falavarjani K, Tsui I, Sadda SR (2017) Ultra-wide-field imaging in diabetic retinopathy. Vis Res 139:187–190. https://doi.org/10.1016/j.visres.2017.02.009
12. Early Treatment Diabetic Retinopathy Study Research Group (1991) Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 98(5 Suppl):786–806
13. Staurenghi G, Viola F, Mainster MA, Graham RD, Harrington PG (2005) Scanning laser ophthalmoscopy and angiography with a wide-field contact lens system. Arch Ophthalmol 123(2):244–252. https://doi.org/10.1001/archopht.123.2.244
14. Reeves GM, Kumar N, Beare NA, Pearce IA (2013) Use of Staurenghi lens angiography in the management of posterior uveitis. Acta Ophthalmol 91(1):48–51. https://doi.org/10.1111/j.1755-3768.2011.02200.x
15. Pomerantzeff O (1980) Wide-angle noncontact and small-angle contact cameras. Investig Ophthalmol Vis Sci 19(8):973–979
16. Spaide RF (2011) Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. Retina 31(5):829–837. https://doi.org/10.1097/IAE.0b013e31820c841e
17. Witmer MT, Parlitsis G, Patel S, Kiss S (2013) Comparison of ultra-widefield fluorescein angiography with the Heidelberg Spectralis((R)) noncontact ultra-widefield module versus the Optos((R)) Optomap((R)). Clin Ophthalmol 7:389–394. https://doi.org/10.2147/OPTH.S41731
18. Silva PS, Cavallerano JD, Sun JK, Noble J, Aiello LM, Aiello LP (2012) Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy. Am J Ophthalmol 154(3):549–559. https://doi.org/10.1016/j.ajo.2012.03.019
19. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S (2012) Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina 32(4):785–791. https://doi.org/10.1097/IAE.0b013e3182278b64
20. Silva PS, Cavallerano JD, Tolls D et al (2014) Potential efficiency benefits of nonmydriatic ultrawide field retinal imaging in an ocular telehealth diabetic retinopathy program. Diabetes Care 37(1):50–55. https://doi.org/10.2337/dc13-1292
21. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S (2012) Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol 96(5):694–698. https://doi.org/10.1136/bjophthalmol-2011-300774
22. Silva PS, Cavallerano JD, Haddad NM et al (2015) Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. Ophthalmology 122(5):949–956. https://doi.org/10.1016/j.ophtha.2015.01.008
23. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM (2013) Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol 155(6):1038–1044. https://doi.org/10.1016/j.ajo.2013.01.007
24. Fan W, Wang K, Ghasemi Falavarjani K et al (2017) Distribution of nonperfusion area on ultra-widefield fluorescein angiography in eyes with diabetic macular edema: DAVE study. Am J Ophthalmol 180:110–116. https://doi.org/10.1016/j.ajo.2017.05.024
25. Oliver SC, Schwartz SD (2010) Peripheral vessel leakage (PVL): a new angiographic finding in diabetic retinopathy identified with ultra wide-field fluorescein angiography. Semin Ophthalmol 25(1–2):27–33. https://doi.org/10.3109/08820538.2010.481239
26. Muqit MM, Marcellino GR, Henson DB et al (2013) Optos-guided pattern scan laser (Pascal)-targeted retinal photocoagulation in proliferative diabetic retinopathy. Acta Ophthalmol 91(3):251–258. https://doi.org/10.1111/j.1755-3768.2011.02307.x
27. Baker CW, Jiang Y, Stone T (2016) Recent advancements in diabetic retinopathy treatment from the Diabetic Retinopathy Clinical

Research Network. Curr Opin Ophthalmol 27(3):210–216. https://doi.org/10.1097/ICU.0000000000000262

28. Aiello LP, Odia I, Glassman AR et al (2019) Comparison of Early Treatment Diabetic Retinopathy Study standard 7-field imaging with ultrawide-field imaging for determining severity of diabetic retinopathy. JAMA Ophthalmol 137(1):65–73. https://doi.org/10.1001/jamaophthalmol.2018.4982
29. Pfau M, Goerdt L, Schmitz-Valckenberg S et al (2017) Green-light autofluorescence versus combined blue-light autofluorescence and near-infrared reflectance imaging in geographic atrophy secondary to age-related macular degeneration. Investig Ophthalmol Vis Sci 58(6):BIO121–BIO130. https://doi.org/10.1167/iovs.17-21764
30. Sepah YJ, Akhtar A, Sadiq MA et al (2014) Fundus autofluorescence imaging: fundamentals and clinical relevance. Saudi J Ophthalmol 28(2):111–116. https://doi.org/10.1016/j.sjopt.2014.03.008
31. Pichi F, Abboud EB, Ghazi NG, Khan AO (2018) Fundus autofluorescence imaging in hereditary retinal diseases. Acta Ophthalmol 96(5):e549–e561. https://doi.org/10.1111/aos.13602
32. Pece A, Isola V, Holz F, Milani P, Brancato R (2010) Autofluorescence imaging of cystoid macular edema in diabetic retinopathy. Ophthalmologica 224(4):230–235. https://doi.org/10.1159/000260229
33. Ebrahimiadib N, Riazi-Esfahani M (2012) Autofluorescence imaging for diagnosis and follow-up of cystoid macular edema. J Ophthalmic Vis Res 7(3):261–267
34. Midena E, Bini S (2016) Multimodal retinal imaging of diabetic macular edema: toward new paradigms of pathophysiology. Graefes Arch Clin Exp Ophthalmol 254(9):1661–1668. https://doi.org/10.1007/s00417-016-3361-7
35. Vujosevic S, Casciano M, Pilotto E, Boccassini B, Varano M, Midena E (2011) Diabetic macular edema: fundus autofluorescence and functional correlations. Investig Ophthalmol Vis Sci 52(1):442–448. https://doi.org/10.1167/iovs.10-5588
36. Vujosevic S, Torresin T, Bini S et al (2017) Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema. Acta Ophthalmol 95(5):464–471. https://doi.org/10.1111/aos.13294
37. Yoshitake S, Murakami T, Horii T et al (2014) Qualitative and quantitative characteristics of near-infrared autofluorescence in diabetic macular edema. Ophthalmology 121(5):1036–1044. https://doi.org/10.1016/j.ophtha.2013.11.033
38. Reznicek L, Dabov S, Haritoglou C, Kampik A, Kernt M, Neubauer AS (2013) Green-light fundus autofluorescence in diabetic macular edema. Int J Ophthalmol 6(1):75–80. https://doi.org/10.3980/j.issn.2222-3959.2013.01.16
39. Tan AC, Fleckenstein M, Schmitz-Valckenberg S, Holz FG (2016) Clinical application of multicolor imaging technology. Ophthalmologica 236(1):8–18. https://doi.org/10.1159/000446857
40. Ahmad MSZ, Carrim ZI (2017) Multicolor scanning laser imaging in diabetic retinopathy. Optom Vis Sci 94(11):1058–1061. https://doi.org/10.1097/OPX.0000000000001128
41. Wanek J, Blair NP, Chau FY, Lim JI, Leiderman YI, Shahidi M (2016) Alterations in retinal layer thickness and reflectance at different stages of diabetic retinopathy by en face optical coherence tomography. Investig Ophthalmol Vis Sci 57(9):OCT341–OCT347. https://doi.org/10.1167/iovs.15-18715
42. Cho YJ, Lee DH, Kim M (2018) Optical coherence tomography findings predictive of response to treatment in diabetic macular edema. J Int Med Res 46(11):4455–4464. https://doi.org/10.1177/0300060518798503
43. Sala-Puigdollers A, Figueras-Roca M, Hereu M et al (2018) Repeatability and reproducibility of retinal and choroidal thickness measurements in Diabetic Macular Edema using Swept-source Optical Coherence Tomography. PLoS ONE 13(7):e0200819. https://doi.org/10.1371/journal.pone.0200819
44. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F et al (2017) Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 237(4):185–222. https://doi.org/10.1159/000458539
45. Parodi Battaglia M, Iacono P, Cascavilla M, Zucchiatti I, Bandello F (2018) A pathogenetic classification of diabetic macular edema. Ophthalmic Res 60(1):23–28. https://doi.org/10.1159/000484350
46. Zur D, Iglicki M, Busch C et al (2018) OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology 125(2):267–275. https://doi.org/10.1016/j.ophtha.2017.08.031
47. Vujosevic S, Berton M, Bini S, Casciano M, Cavarzeran F, Midena E (2016) Hyperreflective retinal spots and visual function after anti-vascular endothelial growth factor treatment in center-involving diabetic macular edema. Retina 36(7):1298–1308. https://doi.org/10.1097/IAE.0000000000000912
48. Midena E, Pilotto E, Bini S (2018) Hyperreflective intraretinal foci as an OCT biomarker of retinal inflammation in diabetic macular edema. Investig Ophthalmol Vis Sci 59(13):5366. https://doi.org/10.1167/iovs.18-25611
49. Yoon D, Rusu I, Barbazetto I (2014) Reduced effect of anti-vascular endothelial growth factor agents on diabetics with vitreomacular interface abnormalities. Int Ophthalmol 34(4):817–823. https://doi.org/10.1007/s10792-013-9884-6
50. Gupta A, Raman R, Kulothungan V, Sharma T (2014) Association of systemic and ocular risk factors with neurosensory retinal detachment in diabetic macular edema: a case-control study. BMC Ophthalmol 14:47. https://doi.org/10.1186/1471-2415-14-47
51. Radwan SH, Soliman AZ, Tokarev J, Zhang L, van Kuijk FJ, Koozekanani DD (2015) Association of disorganization of retinal inner layers with vision after resolution of center-involved diabetic macular edema. JAMA Ophthalmol 133(7):820–825. https://doi.org/10.1001/jamaophthalmol.2015.0972
52. Joltikov KA, Sesi CA, de Castro VM et al (2018) Disorganization of retinal inner layers (DRIL) and neuroretinal dysfunction in early diabetic retinopathy. Investig Ophthalmol Vis Sci 59(13):5481–5486. https://doi.org/10.1167/iovs.18-24955
53. Sophie R, Lu N, Campochiaro PA (2015) Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. Ophthalmology 122(7):1395–1401. https://doi.org/10.1016/j.ophtha.2015.02.036
54. Sambhav K, Grover S, Chalam KV (2017) The application of optical coherence tomography angiography in retinal diseases. Surv Ophthalmol 62(6):838–866. https://doi.org/10.1016/j.survophthal.2017.05.006
55. Khadamy J, Abri Aghdam K, Falavarjani KG (2018) An update on optical coherence tomography angiography in diabetic retinopathy. J Ophthalmic Vis Res 13(4):487–497. https://doi.org/10.4103/jovr.jovr_57_18
56. Ishibazawa A, Nagaoka T, Yokota H et al (2016) Characteristics of retinal neovascularization in proliferative diabetic retinopathy imaged by optical coherence tomography angiography. Investig Ophthalmol Vis Sci 57(14):6247–6255. https://doi.org/10.1167/iovs.16-20210
57. Savastano MC, Federici M, Falsini B, Caporossi A, Minnella AM (2018) Detecting papillary neovascularization in proliferative diabetic retinopathy using optical coherence tomography angiography. Acta Ophthalmol 96(3):321–323. https://doi.org/10.1111/aos.13166
58. Lee CS, Lee AY, Sim DA et al (2015) Reevaluating the definition of intraretinal microvascular abnormalities and neovascularization elsewhere in diabetic retinopathy using optical coherence tomography and fluorescein angiography. Am J Ophthalmol 159(1):101–110. https://doi.org/10.1016/j.ajo.2014.09.041
59. Nesper PL, Roberts PK, Onishi AC et al (2017) Quantifying microvascular abnormalities with increasing severity of diabetic

retinopathy using optical coherence tomography angiography. Investig Ophthalmol Vis Sci 58(6):BIO307–BIO315. https://doi.org/10.1167/iovs.17-21787
60. Miwa Y, Murakami T, Suzuma K et al (2016) Relationship between functional and structural changes in diabetic vessels in optical coherence tomography angiography. Sci Rep 6:29064. https://doi.org/10.1038/srep29064
61. Couturier A, Mane V, Bonnin S et al (2015) Capillary plexus anomalies in diabetic retinopathy on optical coherence tomography angiography. Retina 35(11):2384–2391. https://doi.org/10.1097/IAE.0000000000000859
62. Parravano M, De Geronimo D, Scarinci F et al (2017) Diabetic microaneurysms internal reflectivity on spectral-domain optical coherence tomography and optical coherence tomography angiography detection. Am J Ophthalmol 179:90–96. https://doi.org/10.1016/j.ajo.2017.04.021
63. Al-Sheikh M, Akil H, Pfau M, Sadda SR (2016) Swept-source OCT angiography imaging of the foveal avascular zone and macular capillary network density in diabetic retinopathy. Investig Ophthalmol Vis Sci 57(8):3907–3913. https://doi.org/10.1167/iovs.16-19570
64. Tarassoly K, Miraftabi A, Soltan Sanjari M, Parvaresh MM (2018) The relationship between foveal avascular zone area, vessel density, and cystoid changes in diabetic retinopathy: an optical coherence tomography angiography study. Retina 38(8):1613–1619. https://doi.org/10.1097/IAE.0000000000001755
65. Garcia JM, Lima TT, Louzada RN, Rassi AT, Isaac DL, Avila M (2016) Diabetic macular ischemia diagnosis: comparison between optical coherence tomography angiography and fluorescein angiography. J Ophthalmol 2016:3989310. https://doi.org/10.1155/2016/3989310
66. Scarinci F, Nesper PL, Fawzi AA (2016) Deep retinal capillary nonperfusion is associated with photoreceptor disruption in diabetic macular ischemia. Am J Ophthalmol 168:129–138. https://doi.org/10.1016/j.ajo.2016.05.002
67. Thompson IA, Durrani AK, Patel S (2018) Optical coherence tomography angiography characteristics in diabetic patients without clinical diabetic retinopathy. Eye (Lond). https://doi.org/10.1038/s41433-018-0286-x
68. Magrath GN, Say EAT, Sioufi K, Ferenczy S, Samara WA, Shields CL (2017) Variability in foveal avascular zone and capillary density using optical coherence tomography angiography machines in healthy eyes. Retina 37(11):2102–2111. https://doi.org/10.1097/IAE.0000000000001458
69. Spaide RF, Fujimoto JG, Waheed NK (2015) Image artifacts in optical coherence tomography angiography. Retina 35(11):2163–2180. https://doi.org/10.1097/IAE.0000000000000765
70. Wong TY, Sun J, Kawasaki R et al (2018) Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology 125(10):1608–1622. https://doi.org/10.1016/j.ophtha.2018.04.007
71. Liu Y, Zupan NJ, Shiyanbola OO et al (2018) Factors influencing patient adherence with diabetic eye screening in rural communities: a qualitative study. PLoS ONE 13(11):e0206742. https://doi.org/10.1371/journal.pone.0206742
72. Chin EK, Ventura BV, See KY, Seibles J, Park SS (2014) Nonmydriatic fundus photography for teleophthalmology diabetic retinopathy screening in rural and urban clinics. Telemed J E Health 20(2):102–108. https://doi.org/10.1089/tmj.2013.0042
73. DeTore J, Rizzolo D (2018) Telemedicine and diabetic retinopathy. JAAPA 31(9):1–5. https://doi.org/10.1097/01.JAA.0000544310.25116.97
74. Wilson C, Horton M, Cavallerano J, Aiello LM (2005) Addition of primary care-based retinal imaging technology to an existing eye care professional referral program increased the rate of surveillance and treatment of diabetic retinopathy. Diabetes Care 28(2):318–322
75. Shi L, Wu H, Dong J, Jiang K, Lu X, Shi J (2015) Telemedicine for detecting diabetic retinopathy: a systematic review and meta-analysis. Br J Ophthalmol 99(6):823–831. https://doi.org/10.1136/bjophthalmol-2014-305631
76. Rachapelle S, Legood R, Alavi Y et al (2013) The cost-utility of telemedicine to screen for diabetic retinopathy in India. Ophthalmology 120(3):566–573. https://doi.org/10.1016/j.ophtha.2012.09.002
77. Lee JY, Lee SWH (2018) Telemedicine cost-effectiveness for diabetes management: a systematic review. Diabetes Technol Ther 20(7):492–500. https://doi.org/10.1089/dia.2018.0098
78. Nathoo N, Ng M, Rudnisky CJ, Tennant MT (2010) The prevalence of diabetic retinopathy as identified by teleophthalmology in rural Alberta. Can J Ophthalmol 45(1):28–32. https://doi.org/10.3129/i09-220
79. Boucher MC, Nguyen QT, Angioi K (2005) Mass community screening for diabetic retinopathy using a nonmydriatic camera with telemedicine. Can J Ophthalmol 40(6):734–742. https://doi.org/10.1016/S0008-4182(05)80091-2
80. Bursell SE, Fonda SJ, Lewis DG, Horton MB (2018) Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for American Indians and Alaskan Natives. PLoS ONE 13(6):e0198551. https://doi.org/10.1371/journal.pone.0198551
81. Andonegui J, Serrano L, Eguzkiza A et al (2010) Diabetic retinopathy screening using tele-ophthalmology in a primary care setting. J Telemed Telecare 16(8):429–432. https://doi.org/10.1258/jtt.2010.091204
82. Scanlon PH (2017) The english national screening programme for diabetic retinopathy 2003–2016. Acta Diabetol 54(6):515–525. https://doi.org/10.1007/s00592-017-0974-1
83. Liew G, Michaelides M, Bunce C (2014) A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009–2010. BMJ Open 4(2):e004015. https://doi.org/10.1136/bmjopen-2013-004015
84. Kim J, Driver DD (2015) Teleophthalmology for first nations clients at risk of diabetic retinopathy: a mixed methods evaluation. JMIR Med Inform 3(1):e10. https://doi.org/10.2196/medinform.3872
85. Salongcay RP, Silva PS (2018) The role of teleophthalmology in the management of diabetic retinopathy. Asia Pac J Ophthalmol (Phila) 7(1):17–21. https://doi.org/10.22608/APO.2017479
86. Fenner BJ, Wong RLM, Lam WC, Tan GSW, Cheung GCM (2018) Advances in retinal imaging and applications in diabetic retinopathy screening: a review. Ophthalmol Ther 7(2):333–346. https://doi.org/10.1007/s40123-018-0153-7
87. Gulshan V, Peng L, Coram M et al (2016) Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 316(22):2402–2410. https://doi.org/10.1001/jama.2016.17216
88. Gargeya R, Leng T (2017) Automated identification of diabetic retinopathy using deep learning. Ophthalmology 124(7):962–969. https://doi.org/10.1016/j.ophtha.2017.02.008
89. Ting DSW, Cheung CY, Lim G et al (2017) Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA 318(22):2211–2223. https://doi.org/10.1001/jama.2017.18152
90. Krause J, Gulshan V, Rahimy E et al (2018) Grader variability and the importance of reference standards for evaluating machine learning models for diabetic retinopathy. Ophthalmology 125(8):1264–1272. https://doi.org/10.1016/j.ophtha.2018.01.034