ULTRA-WIDEFIELD FUNDUS IMAGING

A Review of Clinical Applications and Future Trends

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Purpose: To review the basic principles of ultra-widefield fundus imaging and discuss its clinical utility for a variety of retinal and choroidal disorders.

Methods: A systematic review of the PubMed database was performed using the search terms Optos, optomap, panoramic, ultra-widefield, wide-angle, and ellipsoid mirror. This yielded 158 publications of which 128 were selected based on content and relevance.

Results: A total of 128 articles pertaining to ultra-widefield imaging were cited in this review.

Conclusion: Optos ultra-widefield imaging has become an essential tool for the identification of peripheral retinal and vascular pathology. The high resolution and multimodal capabilities of this device are also providing new insights into a variety of disorders, even those that primarily involve the posterior pole. Although the presence of artifact and the need for clinical validation are significant hurdles to more widespread use, ultra-widefield is evolving to become the standard-of-care imaging modality for many diseases and is finding new clinical and research applications such as for screening and telemedicine.

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Advances in retinal imaging technology over the last 50 years have enabled transformative shifts in the diagnosis and management of retinal disease. With each successive improvement in scanning laser ophthalmoscopy (SLO), angiography, autofluorescence, and optical coherence tomography (OCT), our understanding of retinal and choroidal pathology has become increasingly rich and textured with the additional information each imaging modality provides. An important supplement to this multimodal imaging paradigm has been ultra-widefield (UWF) imaging. Ultra-widefield imaging facilitates the acquisition of 200° panoramic images of the retina for a variety of modalities, including fluorescein angiography (FA), indocyanine green angiography (ICGA), pseudocolor, and fundus autofluorescence (FAF). Over the last decade, it has greatly enhanced our realization of the importance of the peripheral retina and its vasculature in a variety of conditions. With exciting new clinical applications on the horizon, UWF imaging will likely become the standard-of-care not only for diagnostic purposes but also for screening, telemedicine, and perhaps even treatment. Of course, this will require a thorough validation of the technology and its significance for clinical practice. This review will comprehensively examine the principles behind UWF imaging, illustrate its clinical utility in a variety of disorders, and then highlight emerging research trends.

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Principles of Ultra-Widefield Imaging

The traditional fundus camera uses full-field flash illumination and is capable of acquiring 30° to 60° views of the posterior pole. Lotmar[1] was the first to describe a movable fixation light to permit the acquisition of 96° fundus images using a montage of 19 photographs. In clinical practice, however, this is tedious and impractical because it requires extensive cooperation by the patient, good pupillary dilation, and a skilled photographer. In addition, for applications such as fluorescein angiography, the acquisition of a panoramic montage may take longer than the desired interval between images and the individual frames within a montage will have been taken at different times relative to dye injection.

Over the last 40 years, several innovative approaches to wide-angle fundus imaging have been introduced. These include the Pomerantzeff camera,[2] the Panoret-1000,[3] the RetCam,[4–6] and various contact and noncontact lens-based systems.[7,8] These instruments can provide 100° to 160° panoramic photographs using either traditional fundus photography or confocal SLO (cSLO). A major disadvantage of several of these approaches, including the Pomerantzeff camera, the Panoret-1000, the RetCam, and the Staurenghi lens, is the utilization of a contact lens which requires a skilled photographer to hold the camera and lens in place during image acquisition. Currently, there are two noncontact imaging technologies available that have received the designation "ultra-widefield," owing to the significantly increased viewing angle they provide: the Optos optomap and the Heidelberg Spectralis HRA ultra-widefield imaging module. Recently, the Diabetic Retinopathy Clinical Research Network (DRCRnet) has defined ultra-widefield images to be at least 100° in field of view (unpublished data).

Heidelberg Spectralis Ultra-Widefield Module

The Heidelberg UWF module uses a noncontact removable lens that attaches onto the camera head of the Heidelberg HRA cSLO (Heidelberg Engineering, Heidelberg, Germany). This greatly expands the viewing angle capabilities from a previous maximum of 55° to the UWF range for FA, ICGA, and FAF. A major advantage is that many practices already use the Heidelberg Spectralis HRA so that this lens system can easily be implemented. Although the overall coverage of the fundus is less compared with the Optos systems, the Heidelberg module is advantageous in that it provides better superior-inferior coverage, less lash artifact, and more uniform contrast.[9] The imaging of the superior and inferior periphery, however, has recently been improved on the Optos platform with the latest generation of devices. In addition, the majority of UWF imaging thus far has been performed with the Optos, and therefore the remainder of this review will refer to the Optos unless stated otherwise.

The Optos Ultra-Widefield Fundus Camera

The Optos fundus camera (Optos PLC, Dunfermline, Scotland) is a cSLO-based system with an ellipsoidal mirror that permits visualization of up to 200° of the retina. This design obviates the need for a contact lens or pupillary mydriasis, and with patient cooperation the field can be further augmented to reach the ora serrata in some cases. Other advantages include fast imaging speed, high resolution, and customizability with various laser wavelengths and filters.

The Optos camera first became commercially available in 2000 and has undergone multiple upgrades to provide additional imaging capabilities. Initially, the system was built with a 532-nm green laser and a 633-nm red laser. Since then, additional laser wavelengths have been added such as a blue 488-nm laser to allow for fluorescein angiography and, more recently, an infrared 805-nm laser for ICGA. The light path contains several optical elements including several dichroic beam-splitters and a confocal aperture. Two galvanometer mirrors provide rapid two-dimensional raster scanning onto an ellipsoidal mirror (Figure 1). The advantage of an ellipsoidal mirror is that it has

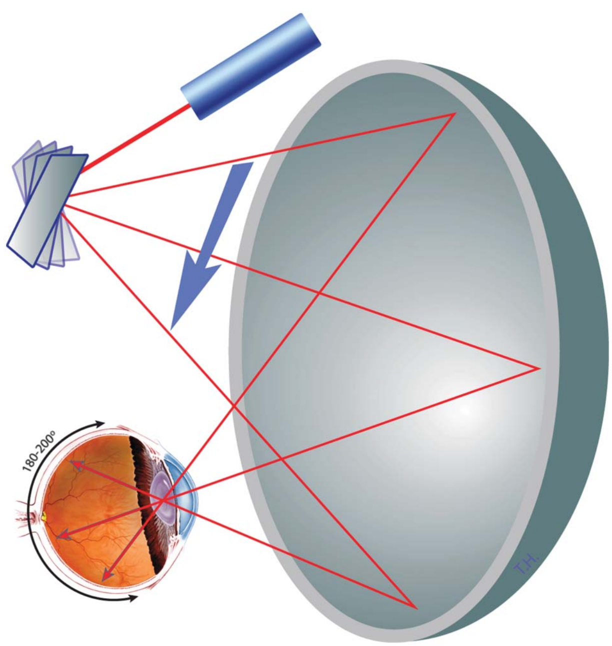

Fig. 1. Schematic illustration of ultra-widefield imaging of the retina using an ellipsoidal mirror. A laser light source is reflected off the galvanometer mirrors onto an ellipsoidal mirror. The second focal point of the mirror resides within the eye, which facilitates image acquisition anterior to the equator.

two focal points, one of which is near the mirror and the second of which lies at approximately the pupillary plane. A point source of light emitted at the first focal point will thus converge within the patient's eye and permit a wide scanning angle even without pupillary dilation. The reflected or emitted light passes back through the confocal aperture and various filters including those necessary to detect fluorescence emission wavelengths. A typical monochromatic scan can take as little as 0.25 seconds to perform and provide approximately 20-pixel resolution per degree.[10] Given the range of laser light sources and filters that can be used, the system lends itself to multimodal imaging of the fundus, including pseudocolor, FA, ICGA, and FAF. In addition, the wide depth-of-focus inherent to an ellipsoidal mirror-based cSLO readily permits in-focus imaging from the anterior retina to the posterior pole and even into deep staphylomas.[11]

However, these advantages come at a cost. The broad viewing angle that the ellipsoidal mirror provides results in significant warping of the retinal area represented by each pixel depending on its anterior-posterior location.[12] The most peripheral areas can appear magnified up to 2 times the posterior pole, and the horizontal axis seems artifactually stretched compared with the vertical axis.[13] Recently, however, Optos introduced a stereographic projection software algorithm to correct for the peripheral distortion and yield images which maintain the same angular relationship at every eccentricity. The accuracy of the measurements derived from this software has been validated in eyes containing prosthetic implants of known sizes.[14] A second limitation is that image contrast is not uniform across the fundus, especially in the nonmydriatic state.[13] Third, the very large depth-of-focus commonly results in the patient's eyelashes or nose to appear in the image. The use of a lid speculum may diminish this artifact but not entirely.[15]

Ultra-Widefield Color Imaging

The current Optos system provides a pseudocolor (two-color) image of the retina using the red and green laser wavelengths. The green (red-free) component depicts the retina and its vasculature, whereas the red component highlights deeper structures. These two laser wavelengths can be operated simultaneously allowing for rapid acquisition times. Currently, it is not possible, however, to use a blue laser to generate a blue channel for true color images. Other cSLO systems such as the Eidon (CenterVue, Padova, Italy) or F-10 (Nidek, Gamagori, Japan) can provide three-color images but they are limited to a 60° field.

Ultra-Widefield Fluorescein Angiography

The introduction of the P200A model with UWF FA capabilities was arguably the single most important breakthrough in UWF imaging. Ultra-widefield FA provides high-resolution wide-angle angiographic detail in a single capture using a 488-nm laser with a 500-nm barrier filter.[16,17] This has enabled an unprecedented direct angiographic view of peripheral retinal vascular anatomy, including perfusion abnormalities, structural features, and other angiographic findings, such as leakage and staining, in a variety of clinical settings that would have otherwise escaped notice, even with other wide-angle systems.[18,19] Future research will delineate the spectrum of normal vascular architecture and the significance of pathologic abnormalities.

Ultra-Widefield Indocyanine Green Angiography

Indocyanine green angiography is the most recent addition to the multimodal capabilities of the Optos. Indocyanine green angiography has traditionally been used to evaluate choroidal features such as occult neovascularization in the macula. In the Optos, ICGA is performed using an 805-nm excitation beam and an 835-nm barrier filter. Recent studies using UWF ICGA have demonstrated its diagnostic utility in a variety of disorders, including central serous chorioretinopathy (CSCR), uveitis, and age-related macular degeneration (AMD).[20,21] Despite providing a wide panoramic image of the fundus, the high-density raster scanning of the Optos provides enough macular detail such that it compares favorably with the traditional cSLO system such as the Heidelberg HRA for clinically relevant assessments.[20]

Ultra-Widefield Autofluorescence

Fundus autofluorescence imaging has become integral to the diagnosis and management of maculopathies. The clinical utility of panoramic FAF has recently become apparent with studies demonstrating the high prevalence of peripheral autofluorescence changes in AMD, uveitis, retinal dystrophies, and CSCR.[10,21–24] Fundus autofluorescence in the Optos camera uses the green 532-nm laser for excitation and a 570-nm to 780-nm emission filter to detect autofluorescence from lipofuscin. Of note, this differs from the short-wavelength (488-nm excitation) or the near-infrared (787-nm excitation) autofluorescence capabilities available on the Heidelberg HRA cSLO. Compared with the shorter 488-nm wavelength, the 532-nm excitation wavelength is affected less by absorbance from nuclear sclerotic cataracts and has less costimulation of collagen autofluorescence.[25] In both cSLO systems, the confocal pinhole greatly decreases out-of-focus autofluorescent signal from the crystalline lens, which can be a major contributor to image degradation commonly encountered in other systems.

Clinical Utility and Emerging Trends

Retinal Vascular Disease

The use of UWF imaging for retinal vascular disease demonstrates its potential for enhancing diagnosis and treatment. Ultra-widefield imaging, especially UWF FA, has become an invaluable tool for revealing peripheral retinal and vascular pathology that was previously difficult to realize.

Peripheral retinal perfusion abnormalities and ischemia have long been identified as major factors in diabetic retinopathy.[26,27] Fluorescein angiography is an essential tool for the management of diabetic retinopathy because it reveals retinal microvascular changes, such as microaneurysms, capillary nonperfusion, breakdown of the inner blood–retina barrier, and neovascularization. It also guides treatment decisions. However, because of its limited field of view, traditional angiography may miss major areas of peripheral nonperfusion and neovascularization that can be captured easily with UWF FA (Figure 2). A major area of study is determining the clinical significance of these peripheral findings and how they fit into diabetic retinopathy management.

Several studies have compared UWF pseudocolor images of diabetic retinopathy with the clinical examination,[28–32] two-field fundus photography,[32,33] and seven-standard field photography.[31,34–37] Friberg et al initially compared nonmydriatic UWF images with the clinical examination and found a 94% sensitivity for detecting diabetic retinopathy as a general diagnosis.[28] The follow-up interval recommendations based on imaging matched those based on the clinical examination in 86% of cases. A subsequent study comparing optomap images with the clinical examination found a sensitivity of 94% and a specificity of 100% for diagnosing retinopathy worse than mild nonproliferative diabetic retinopathy.[29] Most studies comparing UWF with traditional photographs have determined the sensitivity and specificity to be similar but with additional peripheral information provided by UWF imaging. Wilson et al found a 83.6% sensitivity for two-color UWF images versus 82.9% for two-field digital photography in identifying diabetic disease warranting referral.[32] In a study of 206 eyes encompassing all levels of diabetic retinopathy, Silva et al[31] found that UWF matched seven-standard film grading of severity in 80% of eyes and was within 1 level in 94.5% of eyes. In 10% of eyes, the additional

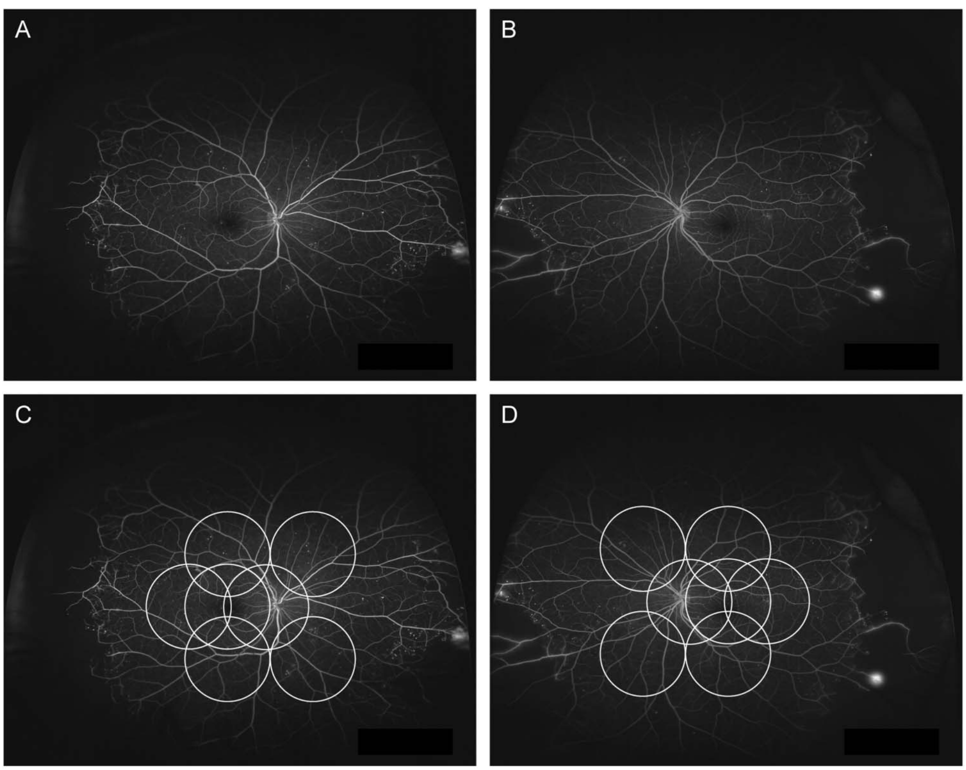

Fig. 2. Optos ultra-widefield fluorescein angiography of proliferative diabetic retinopathy. Right (**A**) and left (**B**) eyes of a patient with scattered microaneurysms, peripheral capillary nonperfusion, and focal leakage consistent with neovascularization elsewhere. The peripheral neovascularization and nonperfusion are not detectable using traditional seven-field fundus imaging (**C** and **D**).

peripheral findings identified by UWF suggested a more severe level of retinopathy than the seven-standard fields. Overall, these studies show that UWF can perform well as a screening tool for diabetic retinopathy.

Ultra-widefield FA has been found to be superior to the seven-standard fields in demonstrating angiographic abnormalities in multiple studies in eyes with diabetic retinopathy.[16,38,39] Wessel et al found that UWF FA showed 3.9 times more nonperfusion, 1.9 times more neovascularization, and 3.8 times more panretinal photocoagulation compared with a simulated seven-field overlay. Furthermore, the seven fields would have missed pathology shown on UWF FA images in 10% eyes.[39] Future studies will need to determine how UWF angiography should play into clinical guidelines that are largely based on studies that often extrapolated posterior findings to the periphery because they were performed before the broad availability of UWF imaging.

Ultra-widefield FA has emerged as an essential tool to explore the relationship between peripheral capillary dropout and the presence of neovascularization, macular edema, and macular ischemia.[18,40–42] Oliver and Schwartz first described the phenomenon of peripheral vascular leakage on UWF FA in eyes with diabetic retinopathy and found that it was present in 41% of eyes.[18] In this case series, peripheral nonperfusion and leakage were associated with neovascularization. Another retrospective study suggested a relationship between peripheral ischemia and an enlarged foveal avascular zone.[41] Neither of these two studies identified a relationship between nonperfusion and macular edema.

In contrast, two separate studies did find an association between peripheral nonperfusion and macular edema. One study in treatment-naive patients using UWF FA and OCT reported that retinal nonperfusion was significantly associated with macular edema.[42] Another study measured the "ischemic index" to represent the amount of nonperfusion in a series of patients with recalcitrant diabetic macular edema.[40] The ischemic index was the ratio of the nonperfused fundus area to the total imaged fundus area. In this study, eyes with more retinal nonperfusion were found to have the most recalcitrant macular edema. The conflicting findings with regard to the association between peripheral nonperfusion and macular edema may be related to different patient characteristics or variability in the quantification of ischemic area, which suggests an important area for further investigation. The notion of an ischemic index itself may be problematic because the retina could be ischemic despite the appearance of blood flow in neighboring capillaries—a more correct term may be "perfusion index." There is clearly a need for more accurate measures of the perfusion index that compensate for peripheral distortion,[12] perhaps using the recently introduced stereographic projection software.

Ultra-widefield FA is increasingly being used to guide the management of diabetic retinopathy. Panretinal photocoagulation has been the gold standard treatment for proliferative diabetic retinopathy and presumably works by decreasing oxygen consumption of the outer retina, increasing oxygen diffusion to the inner retina, and decreasing intraocular vascular endothelial growth factor.[43–45] There has been interest in a more targeted approach only to areas of capillary dropout if similar outcomes can be obtained without extensive macular edema, nyctalopia, and peripheral visual field loss. Reddy et al reported two cases in which UWF FA was used to guide targeted retinal photocoagulation to areas of nonperfusion with successful regression of retinal neovascularization in these two patients. A larger prospective study with 28 eyes using UWF-guided targeted retinal photocoagulation found proliferative diabetic retinopathy regression in 76% of patients after 12 weeks.[46] By 24 weeks after initial treatment 37% of eyes had complete disease regression, 33% had partial regression, and additional laser treatment was planned for the remaining 30%. These results suggest that targeted retinal photocoagulation can be as effective as panretinal photocoagulation in some instances and merits further study in a randomized trials comparing the two treatment strategies.

Vein occlusion is the most common retinal vascular occlusion and is similar to diabetic retinopathy in that it is associated with nonperfusion, macular edema, and neovascularization. And like diabetic retinopathy, UWF FA has been useful for characterizing and managing vein occlusions.[19,47–52] In eyes with central retinal vein occlusions, UWF FA seems to be a reliable modality for detecting macular leakage and ischemia in addition to peripheral nonperfusion.[47] The first study of UWF FA in eyes with branch or hemiretinal vein occlusions noted that areas of angiographic nonperfusion peripheral to the equator were significantly associated with macular edema and neovascularization.[19] Tsui et al[48] found that eyes with neovascularization after central retinal vein occlusions had a significantly higher ischemic index than those eyes without neovascularization. In eyes with branch or central retinal vein occlusion with treatment-resistant macular edema, a higher ischemic index on UWF FA images correlated with greater macular thickening and worse vision.[50] Patients with a higher ischemic index had a better gain in visual acuity and greater decrease in retinal thickness on OCT after retreatment. As demonstrated by previous multicenter randomized clinical trials,[53,54] the amount of peripheral retinal capillary nonperfusion is fundamental to evaluation, management, and prognosis. Direct visualization of almost the entire retinal capillary anatomy as seen with UWF FA after vein occlusion is thus valuable information because it excludes the extrapolation inherent in previous evaluation and management recommendations and may facilitate outcomes due to its association with macular edema and neovascularization (Figure 3). Ultra-widefield imaging may also allow for a more detailed phenotyping of vein occlusions to better characterize the effects of posterior versus anterior ischemia or progressive perfusion abnormalities. It is possible, for example, that more posterior patterns of capillary nonperfusion have a higher propensity to develop macular edema and neovascularization, or that certain angiographic features such as progression of perfusion abnormalities carry the prognostic value which could eventually be factored into an ischemic index. It should be emphasized that capillary nonperfusion is only an imperfect surrogate for retinal ischemia.

Although the majority of studies on retinal vascular disease examined the role of UWF FA in diabetic retinopathy or vein occlusion, there are a number of other disorders for which UWF has been used. In a study of six patients with sickle cell disease, UWF FA detected peripheral vascular changes in five eyes that would be missed with seven-standard field photography.[55] The UWF FA demonstrated clear borders between perfused and nonperfused retina as well as peripheral vascular remodeling in high resolution. Visualizing these peripheral vascular abnormalities is useful for monitoring response to laser treatment. It also can help with risk stratification and determining appropriate follow-up intervals.[55] Ultra-widefield FA has revealed that similar peripheral neovascular changes can also be found in patients with beta-thalassemia[56] and antiphospholipid antibody syndrome.[57] Two cases of Takayasu's arteritis imaged with UWF FA documented the delayed arm-to-retina circulation, peripheral ischemia, microaneurysm formation, and the resolution of these findings after surgical revascularization.[58,59]

Ultra-widefield FA was also used to characterize two cases of retinopathy associated with muscular dystrophy. Bass et al described a case of facioscapulohumeral muscular dystrophy with bilateral capillary dropout, arborization, and telangiectatic microaneurysms.[60] Diffuse retinopathy featuring neovascularization, capillary dropout, and venular aneurysms in a patient with Duchenne muscular dystrophy was imaged with UWF FA, prompting treatment with panretinal photocoagulation.[61]

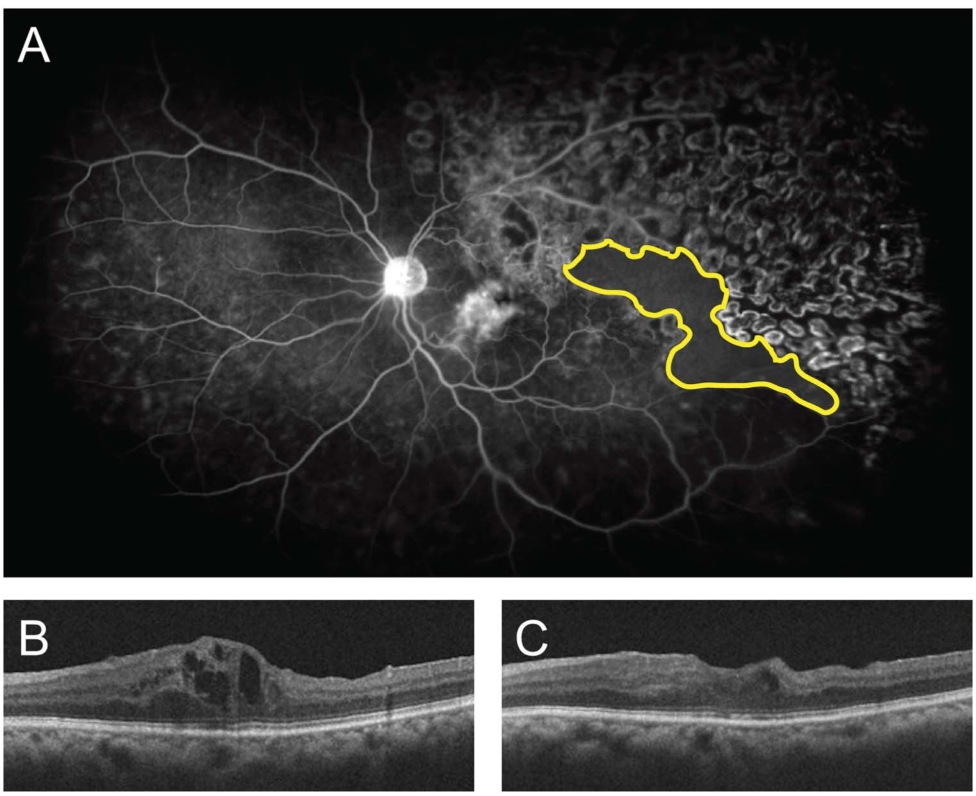

Fig. 3. Resolution of macular edema after targeted retinal photocoagulation. **A.** Ultra-widefield fluorescein angiogram of a branch vein occlusion status after scatter laser with a residual area of nonperfusion (yellow outline). **B.** The patient had recalcitrant macular edema that improved after applying laser to the nonperfused retina (**C**).

Susac syndrome is an autoimmune disorder consisting of sensorineural hearing loss, encephalopathy, and branch retinal artery occlusions. In a case report of Susac, the use of UWF FA beautifully demonstrated peripheral venous hyperfluorescence in addition to branch retinal artery occlusion. Ultra-widefield ICG demonstrated filling defects and leakage of the choroidal vasculature. This case serves as an example of how UWF imaging can be used to make key observations not made previously with traditional fundus photography.[62]

Ultra-widefield FA has also enabled the discovery of peripheral findings in various vascular diseases that have not previously been described. Ultra-widefield FA performed in a woman 2 days after emergency cesarean section for preeclampsia with HELLP syndrome revealed serous retinal detachments and late peripheral retinal vascular leakage. These findings were followed with subsequent UWF FA and found to resolve by 3 weeks postpartum. The peripheral vascular leakage suggests that a breakdown in the blood–retina barrier may accompany vasospasm in this syndrome and lead to serous retinal detachments.[63] A case of bilateral diffuse uveal melanocytic proliferation imaged with UWF FA demonstrated inferior exudative detachments that were associated with nonperfusion of the inferior periphery.[64]

Ultra-widefield FA has demonstrated peripheral vascular pathology in a wide variety of retinal vascular conditions. The significance of many of these new peripheral findings, especially as they relate to management, will be further elucidated in clinical trials. There is an ongoing DRCRnet protocol determining whether evaluation of the retinal periphery with UWF images improves our ability to assess and predict worsening of diabetic retinopathy compared with standard photography.[65] Future studies must not only ascertain the significance of peripheral vascular pathology, but also standardize and automate the calculation of an ischemic or perfusion index and outline areas of capillary dropout. It has even been proposed that subsequent iterations of the Optos device could directly incorporate an automated therapeutic laser that could be targeted to areas of retinal pathology.

Retinal Detachment

Optos UWF imaging is a useful adjunct to the clinical examination for characterizing retinal detachments. The majority of published cases have used UWF for characterizing rhegmatogenous retinal detachment (RRD), but it has also been used to document serous retinal and choroidal detachments.[66,67] In RRD, the large depth-of-field can capture the causative breaks, the entire clock hour extent of the detached retina, and the macula all in sharp focus, providing a useful way to document the preoperative state of the detachment. In comparison with indirect ophthalmoscopy, UWF imaging can in some cases provide a more precise documentation of the extent of the detachment.[68] A limitation of UWF, however, is that it is less sensitive for detecting lesions in the superior and inferior periphery.[68,69] This can theoretically be overcome by performing steered imaging in the direction of the suspected break (Figure 4). Lee et al[70] demonstrate this method with an example of an inferior RRD caused by an inferior break that was not captured in primary gaze but could be imaged by having the patient look down.

The FAF capability of the Optos provides prognostic information and a means to investigate the postoperative functional status of the previously detached retina. Witmer et al used UWF FAF to image a series

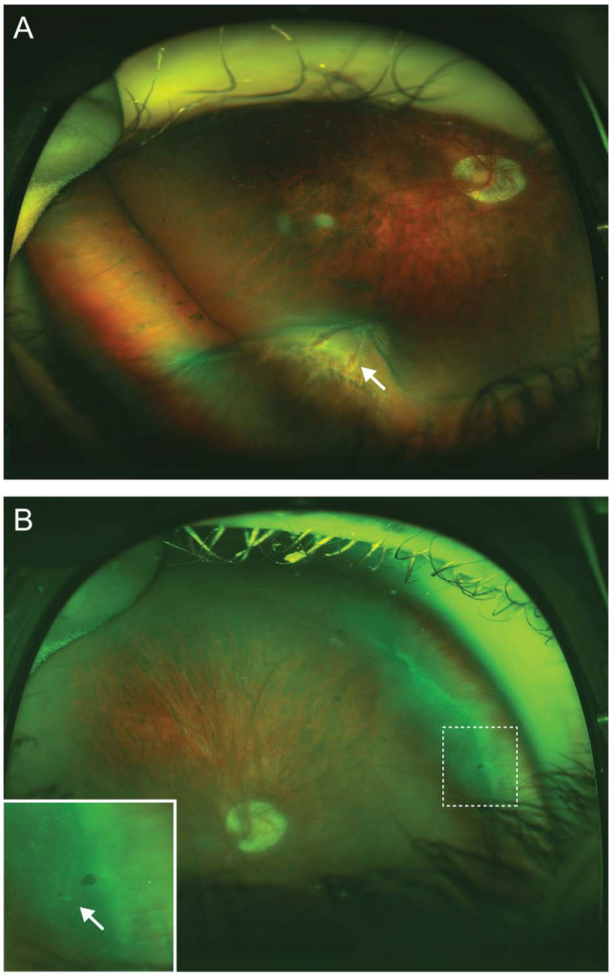

Fig. 4. Ultra-widefield documentation of peripheral retinal pathology. **A.** Inferior steering reveals a horseshoe tear that appears flat on a radial buckle element (arrow). **B.** Nasal steering at a later date revealed a new retinal detachment associated with an operculated hole (inset) at the posterior edge of the encircling band (arrow, inset).

of retinal detachment cases and found certain characteristic features including hypofluorescence over areas of bullous detachment with a sharp delineation between the attached and detached retina.[71] They also observed a hyperfluorescent leading edge in all of 12 macula-involving detachments and in three of the four macula-sparing detachments that corresponded to shallow subretinal fluid on OCT imaging and resolved postoperatively. Patients with macula-involving detachments who had persistent postoperative granular autofluorescent changes had significantly worse preoperative visual acuity and showed a trend toward worse postoperative visual acuity.

Ultra-widefield provides an efficient way for the vitreoretinal surgeon to record the outcomes of surgical interventions. Ultra-widefield can effectively image the retina even in the presence of a gas bubble and can be used to monitor the extent, absorption, and recurrence of subretinal fluid.[70,72] Salvanos et al used UWF FAF to characterize autofluorescent changes in the first postoperative days after scleral buckle with cryotherapy.[72] They found different patterns of autofluorescence in areas treated by cryotherapy corresponding to the extent of cryotherapy delivered. Their conclusion was that an ideal amount of cryotherapy causes central hypofluorescence around the break with a ring of hyperfluorescence. Another observation was an increase in hyperfluorescent streaks in the peripheral retina corresponding to an increase in indentation by the buckle element. Further studies are required to validate the significance of these findings, but UWF FAF could provide a useful way to document the immediate effects of the surgical technique. Long-term follow-up studies are needed to document FAF changes beyond the immediate postoperative period and to determine whether they can be predictive of complications such as proliferative vitreoretinopathy.

The ability of UWF to capture the full extent of retinal detachments makes it an alternative method for documenting the detachment and demonstrating the outcome of surgical interventions, as well for counseling patients regarding their condition (Figure 5). However, it is important to verify that all the important features of the examination are well imaged because they can be obscured by eyelash artifact that results from the large depth-of-field. Labriola et al[74] describe a case in which UWF and UWF FA were helpful to document neovascularization and macrocyst formation associated with a chronic retinal detachment. Ultra-widefield images have also been used to demonstrate pathology and outcomes after inferior retinectomy for recurrent RRD with proliferative vitreoretinopathy.[75]

Ultra-widefield pseudocolor images have also been used for the detection of retinal breaks but the

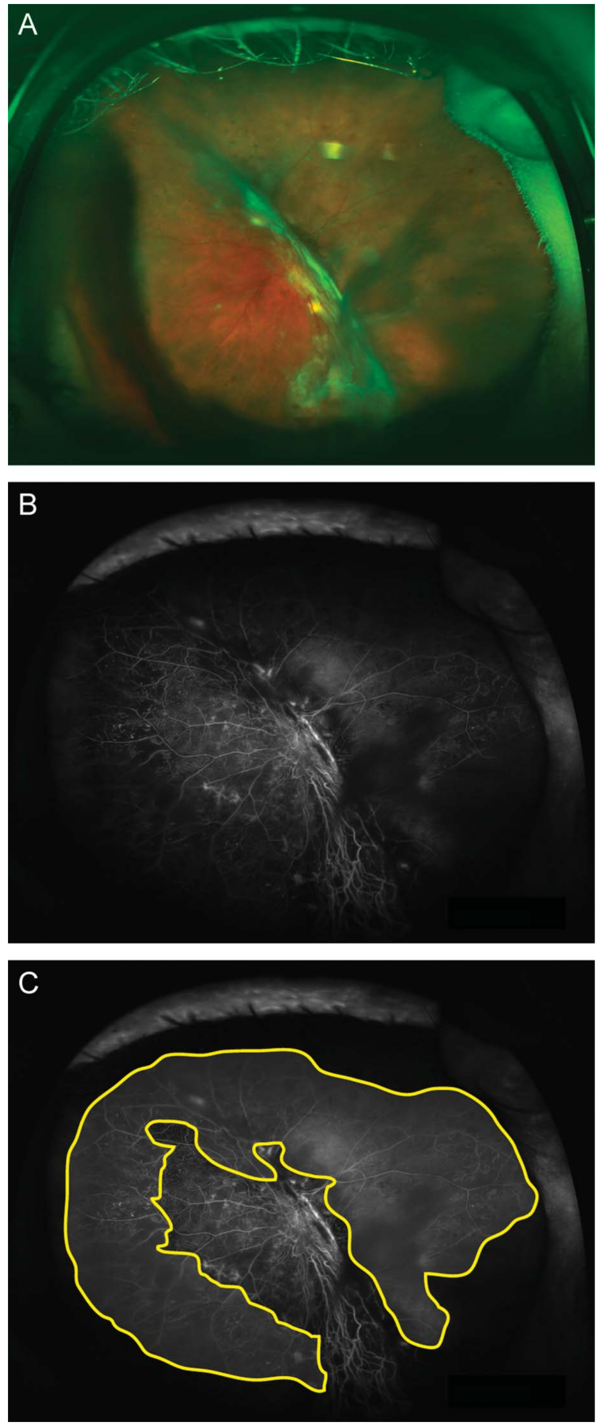

Fig. 5. Panoramic single-image capture of a large macula-involving tractional retinal detachment. **A.** Pseudocolor image of a vertically oriented tractional detachment engulfing the macula in the left eye of a patient with proliferative diabetic retinopathy. **B.** Fluorescein angiography documents severe capillary nonperfusion and areas of leakage.

sensitivity may be low to replace indirect ophthalmoloscopy.[76,77] Rather, the value of UWF imaging lies in its use as an adjunct to clinical examination to document the retinal detachment and provide functional information that is useful for postoperative monitoring. As more studies investigate postoperative UWF FAF findings in RRD and correlate them with long-term outcomes and complications, Optos imaging has the potential to take on additional importance in patient management.

Myopia

High axial myopia is an important global health issue that can be associated with degenerative changes of the fundus. In a series of 149 patients with myopia, UWF imaging had an overall 90.9% sensitivity for detecting peripheral lesions compared with clinical examination by a retina specialist. The sensitivity varied with the type of lesion and ranged from 100% for detecting white without pressure to 43.8% for detecting retinal breaks.[70]

Posterior staphylomata are a common degenerative change in highly myopic eyes and can be challenging to image with traditional fundus photography because their borders often extend beyond the 50° field of the camera. Optos UWF imaging is an advantageous modality for detecting the presence and extent of staphylomata because it has a wide enough field to capture their entire border, the depth-of-focus is large, and its multimodal capabilities maximize the sensitivity of detection. Ohno-Matsui[11] investigated the ability of Optos UWF to detect borders of staphyloma that were identified using 3-dimensional magnetic resonance imaging. Using a combination of pseudocolor, FAF, and infrared images, the sensitivity for detecting staphyloma borders was 85% with a specificity of 85.7%. Ultra-widefield FAF has also been useful for evaluating the retina immediately adjacent to staphylomata. In a series of patients with high myopia, UWF FAF demonstrated the presence of linear or leaf-like radial tracts emanating from the borders of some posterior staphylomata. These areas were further evaluated with OCT and found to correspond to areas of outer retinal and retinal pigment epithelium (RPE) loss.[78]

Ultra-widefield FA has also shed light on peripheral perfusion abnormalities in myopic eyes that were previously unrecognized.[79] Whether these have clinical significance remains to be determined, but it further illustrates that utility of multimodal UWF imaging in the evaluation of the myopic fundus.

Pediatric Retina

The pediatric patient population presents with a unique set of diagnostic and management challenges due to the limited degree of patient cooperation and a different spectrum of retinal disease than adults. The RetCam provides a wide-field view with fluorescein angiography capabilities, but this contact-based system requires a very cooperative or anesthetized patient to capture high-quality images. Optos UWF imaging represents an alternative method for documenting pediatric retinal pathology in an outpatient setting, obviating the need for an examination under anesthesia in some circumstances. In a group of 16 children with ages ranging from 5 years to 12 years, Tsui et al[80] demonstrated the utility of UWF FA for a diverse group of disorders, including uveitis, hereditary retinal dystrophies, childhood retinal vascular diseases, trauma, infection, and tumors.

Screening and fluorescein angiography of retinopathy of prematurity (ROP) have been most commonly performed using the RetCam imaging system.[81] Recent case reports and case series have described success in obtaining clinically useful images in infants with ROP and other proliferative retinopathies using the Optos system.[82–86] Fluorescein angiography in these patients can be accomplished with oral fluorescein, providing a less invasive outpatient imaging option. Intravenous fluorescein can also be used but early filling may be missed because of difficulty in positioning the patient fast enough for early frames.[80,86]

The relative ease of acquiring wide-field information is changing how pediatric diseases are classified and managed. Kang et al[87] describe several cases in which the UWF FA images were used in targeting laser therapy for patients with Coats disease and familial exudative vitreoretinopathy. Kashani et al[88] described a series of patients with familial exudative vitreoretinopathy and their relatives imaged with UWF FA. The UWF angiographic data revealed the high prevalence of peripheral changes in asymptomatic family members leading the authors to recommend screening in immediate relatives of patients with familial exudative vitreoretinopathy. They also used UWF FA to categorize peripheral angiographic findings into a disease staging system intended to guide management.[89] Optos UWF has also been used to document cases of pediatric retinal detachment.[90]

Optos has emerged as a practical option for outpatient wide-field imaging in pediatric patients. A major strength is that it can provide these images without placing the patient under anesthesia. However, it may be more prone to miss early vascular filling if the patient cannot be positioned quickly. The periphery can also be obscured by lash artifact, a problem not present with contact-based imaging systems. Providers can incorporate UWF imaging into their repertoire for cooperative children while maintaining a low threshold for examination under anesthesia. The utility of Optos UWF for ROP screening and telemedicine purposes will need to be validated with future studies.

Age-Related Macular Degeneration

It would seem counterintuitive or even counterproductive to use UWF imaging for degenerative maculopathy such as AMD. Of course, in the rare case that an AMD patient develops peripheral choroidal neovascularization, Optos widefield angiography can be an effective tool to image these neovascular lesions.[91,92] Even for the typical case of AMD, however, pseudocolor images of the macula generated with the Optos camera compare favorably with those from a traditional 45° fundus camera. In 1 study looking at eyes from the Reykjavik Eye Study, the authors found

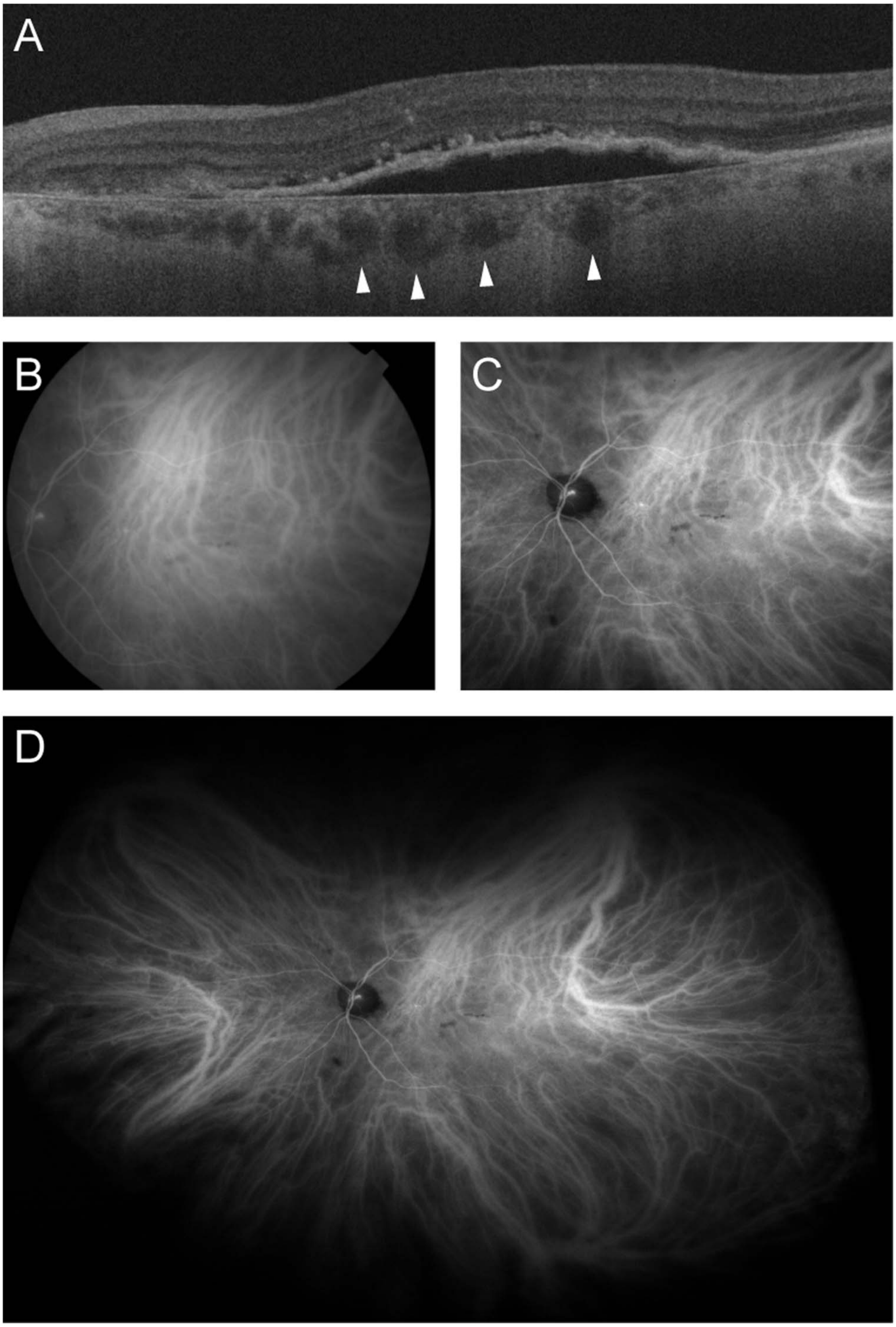

Fig. 6. Peripheral choroidal vasculature in neovascular AMD. **A.** Optical coherence tomography image demonstrating a serous pigment epithelial detachment in the left eye of an 80-year-old white woman with neovascular AMD. Note the dilated choroidal vessels coursing beneath the pigment epithelial detachment (arrowheads). **B.** Late ICGA image obtained on a standard field-of-view camera. **C.** Indocyanine green angiography on the Optos UWF platform shows comparable findings in the posterior pole. **D.** Ultra-widefield ICGA reveals dilated choroidal vessels in the superotemporal quadrant that extend into the macula.

a 96% agreement between devices when grading patients with drusen, geographic atrophy, and choroidal neovascularization.[93] The UWF ICGA capabilities have also been found to delineate the choroidal vessel anatomy of the macula and periphery at high resolution in neovascular AMD and polypoidal choroidal vasculopathy.[20] Optos ICGA images permit visualization of peripheral choroidal vascular changes that may be contributing to macular pathology (Figure 6).

A major insight into AMD phenotyping was made using the autofluorescence capabilities of the Optos. Reznicek et al demonstrated that patients with AMD have significantly increased peripheral autofluorescence and irregularity of that autofluorescence compared with healthy subjects.[94] Another retrospective study found that more than 70% of eyes with AMD have peripheral abnormalities detectable on UWF FAF and pseudocolor.[95] These studies were followed by a large prospective study of 200 eyes with AMD, which beautifully delineated distinct phenotypes of peripheral autofluorescence changes.[22] Importantly, these abnormal FAF patterns were more frequently seen in eyes with neovascular AMD compared with eyes with nonneovascular AMD. In addition, the individual FAF classifications correlated with other features such as RPE depigmentation and peripheral drusen. The strong fellow eye concordance of these findings strongly suggests that peripheral abnormalities could be used as biomarkers to grade disease severity or even predict an individual's risk of neovascular AMD. Large, long-term prospective studies using multimodal UWF imaging in conjunction with genetic testing could provide deep insights into genotype–phenotype correlations in AMD and allow for more individualized risk estimation. Ultra-widefield FAF images have also been collected in a large subset (N = 800) of subjects with AMD from the AREDS 2 study, but the results have not yet been reported.

Central Serous Chorioretinopathy

Central serous chorioretinopathy is maculopathy that causes macular detachments secondary to solitary or multifocal RPE leaks. Only recently with the use of UWF ICGA and FAF have we begun to realize the peripheral findings and the extent of choroidal vessel abnormalities. Using UWF FAF, Pang et al[21] found that 57% of eyes with CSCR had peripheral autofluorescence changes undetectable by clinical examination and 49% of eyes had gravitational tracks or gutters signaling past or present fluid movement from the macula to the inferior periphery. In addition, UWF ICGA demonstrated the presence of engorged choroidal vessels from the posterior pole to the vortex vein ampullae in over 80% of eyes. In the late angiograms, diffuse hyperfluorescence emanating from the choroid was suggestive of increased choroidal permeability, a potential contributor to CSCR pathogenesis.[20,21]

Although our management of the disease will largely be dictated by the state of the macula, the peripheral RPE and vascular changes will have important clinical implications. The presence of gravitational tracks will aid in the diagnosis of CSCR when the macula bears only nondescript RPE changes and a mixed pattern of autofluorescence (Figure 7). Dilated choroidal vessels may also serve as a diagnostic clue or even a predictor of disease course. Given that variable numbers of vortex vessel ampullae seem to be involved across eyes with CSCR, it may be possible to stratify patients at first presentation into risk categories for persistence and recurrence of fluid.

Retinal and Choroidal Dystrophies

The ability to perform multimodal imaging of the peripheral retina makes UWF the ideal platform for studying retinal and choroidal dystrophies (Figure 8). This was first demonstrated in several patients with choroideremia and gyrate atrophy.[96] The mid-phase to late-phase UWF FA reliably conveyed the full extent of choroidal degeneration and choriocapillaris loss. An added benefit was that the cSLO platform permitted a better view through cataract compared with a traditional fundus camera. Subsequent studies have taken advantage of UWF FAF for characterizing areas of

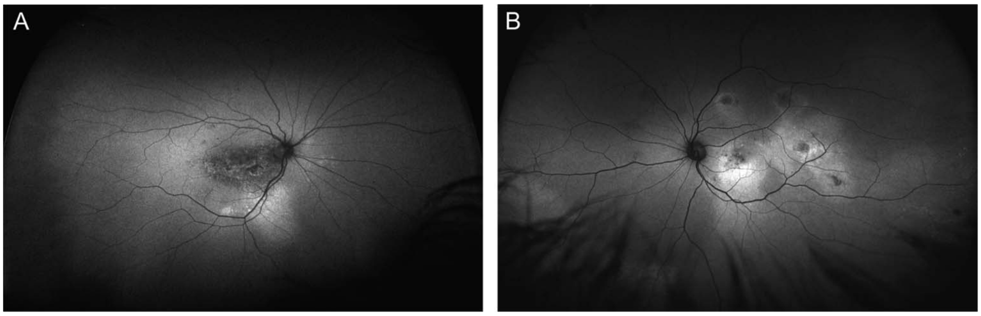

Fig. 7. Ultra-widefield autoflorescence of CSCR. **A.** The right eye contains macular autofluorescent changes and a hyperautofluorescent gravitational tract. **B.** The left eye has multiple areas of involvement with gravitational tracts.

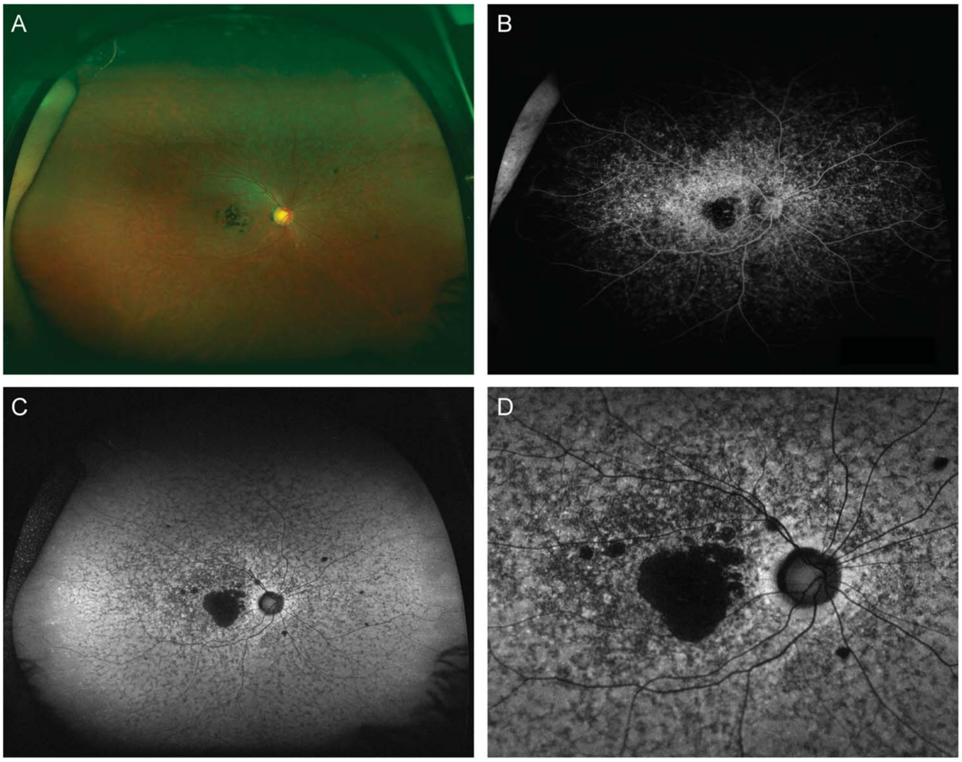

Fig. 8. Ultra-widefield imaging of Stargardt macular dystrophy. **A.** Pseudocolor panoramic imaging shows macular pigmentary changes and some peripheral stippling. **B.** The fluorescein angiogram reveals the peripheral distribution of the disease. **C.** Fundus autofluorescence illustrates even further the burden of peripheral RPE and photoreceptor changes. **D.** Cropping of the image in (**C**) demonstrates the preservation of fine detail within the image.

RPE loss. In a large family with choroideremia, UWF FAF detected the remaining islands of intact RPE in affected males and demonstrated a surprisingly high degree of phenotypic variability in carrier females.[97] Importantly, the high resolution of Optos images permitted a careful analysis of both the foveal area and the far periphery.

Three large studies of patients with retinitis pigmentosa and cone dystrophies further illustrate the power of UWF FAF for performing objective phenotyping in these patient populations. Oishi et al[98] used UWF FAF to classify retinitis pigmentosa patients based on the pattern of macular autofluorescence and found good correlations with visual acuity and mean deviation on Humphrey visual field. Furthermore, the amount of patchy hypoautofluorescence on UWF FAF was reliably correlated with the patient's age, duration of symptoms, and visual acuity. Similarly, Ogura et al[99] found a very close agreement between the spatial extent of hypoautofluorescence with the degree of visual field loss in retinitis pigmentosa patients. Another study validated the use of UWF imaging on cone and cone–rod dystrophy patients in which the posterior findings tend to predominate.[24] The area of hypoautofluorescence nevertheless correlated well with the size of the scotoma on Goldmann visual field testing and with the severity of electroretinogram dysfunction.

The association between UWF FAF and visual field deficits, electroretinography, and even visual acuity portend a future in which multimodal UWF testing will become standard-of-care for the management of these patients. It is possible that testing will shift away from visual fields and toward more objective measures of disease progression such that the total area or pattern of autofluorescence changes. The modular configuration of the Optos could permit future systems to integrate a variety of autofluorescent filter combinations to image the short-wavelength, green, and near-infrared FAF patterns.

Retinal Vasculitis and Uveitis

The use of UWF imaging for uveitis exemplifies the management dilemmas that inevitably arise when clinicians are presented with previously unavailable data. For years, the diagnosis and management of uveitis depended on clinical examination and traditional 30° to 60° fluorescein angiography. The advent of UWF FA for the first time permitted a view of capillary dropout and leakage in the far periphery. This was first demonstrated in two case series of patients with retinal vasculitis imaged with UWF FA.[100,101] The far peripheral vessels sometimes displayed leakage in the setting of an otherwise quiet-appearing fundus. A direct comparison of 9-field standard fluorescein angiography with Optos UWF FA found that Optos detected significantly more leakage even in areas captured well with standard angiography such as the posterior pole.[102] However, quantifying this area of leakage and accounting for image distortion and artifact remain a difficult issue.

Subsequent prospective studies have addressed whether UWF FA prompts a change in diagnosis and management. In two studies of patients with various underlying diagnoses, the use of UWF FA significantly increased the likelihood of a change in management based on the appearance of disease activity in the periphery.[103,104] Another study of 38 eyes with Behcet retinal vasculitis found that UWF FA detected active vasculitis not otherwise detectable in 85% of eyes, which prompted a change in management in 80% of patients.[105] The true clinical significance of peripheral vascular leakage remains unknown however; therefore, it is unclear whether peripheral vasculitis should influence management decisions.

Optos UWF imaging is also becoming more widely used in phenotyping and staging of uveitides affecting the posterior segment. An especially useful feature in this patient population is the ability to image through a secluded pupil with extensive posterior synechiae. Another is the ability to capture more peripheral pathology as was demonstrated in a study of patients with cytomegalovirus retinitis.[106] Ultra-widefield red–green pseudocolor images have also been used to create a grading system for the severity of sunset glow fundus in Vogt–Koyanagi–Harada disease, offering potential insights into disease course and prognosis.[107] A major advantage of UWF imaging for posterior uveitis lies in the multimodal imaging capabilities, especially the use of UWF FAF. A study of 20 eyes with Vogt–Koyanagi–Harada disease found a high proportion of eyes with peripheral autofluorescence changes, especially multifocal areas of hypofluorescence or hyperfluorescence.[108] Of note, however, careful comparison of the pseudocolor and FAF images demonstrated disparities, especially at sites of increased pigmentation. Depigmentation of the choroid as seen in sunset glow fundus was also poorly detected on FAF, largely because the FAF signal derives from lipofuscin in the RPE rather than melanin in the choroid. Other studies have found that UWF FAF detects a greater extent of retinal involvement in posterior uveitis than UWF pseudocolor images.[23,105,110] The extent of hypoautofluorescent changes seems to correlate with the pattern of visual field defects on Goldmann perimetry.[10] More recently, UWF ICGA was used to demonstrate peripheral changes in 60% of eyes with uveitis. In disorders such as sarcoidosis and birdshot chorioretinopathy, distinct hypofluorescent spots on the ICGA corresponded well to chorioretinal lesions.[20]

The clinical significance of peripheral autofluorescence changes in posterior uveitis, such as the presence of peripheral leakage in retinal vasculitis, remains unclear. Large prospective observational and interventional trials must be performed to assess the meaning of these findings and whether they should play a role in management decisions. Until then, however, multimodal UWF imaging will likely assume a more prominent role in the diagnosis and monitoring of patients with posterior uveitis.

Oncology

The extent and peripheral location of retinal and choroidal tumors often preclude photographic documentation using traditional fundus cameras. The Panoret-1000 was the first camera to obtain single-capture wide-field views of intraocular tumors and permit reliable assessment of tumor dimension as compared with B-scan ultrasound.[3,109] Currently, the Optos is being increasingly used for UWF imaging of retinal and choroidal lesions owing to the increased field of view and its multimodal capabilities. Panoramic pseudocolor images permit the documentation of very large choroidal lesions or metastases with extensive serous detachments in a single image.[111,112] Tumors such as RPE adenomas located in the far periphery have also been imaged with the device.[113] Measurements of choroidal lesion size on the Optos correlate reasonably well with ultrasound measurements, but the Optos overestimates size in the transverse direction.[114] The red, green, and autofluorescence imaging capabilities have also been used to compare choroidal nevi with melanomas with mixed results. In one study, there was a significantly lower UWF FAF signal from choroidal melanomas compared with that from choroidal nevi,[115] but no difference in the appearance on red or green reflectance imaging.[114]

Ultra-widefield FA is crucial for the identification and monitoring of retinal hemangioblastomas in von Hippel–Lindau disease.[116] Although there have been no published studies on the topic, we suspect the sensitivity of lesion detection to be much higher using UWF FA versus conventional FA or clinical examination (Figure 9).

Ultra-widefield imaging has become essential for monitoring suspicious or treated lesions but only plays an adjunctive role in determining the malignant potential and diagnosis of tumors, supplementing the clinical examination, OCT, and ultrasound. With the integration

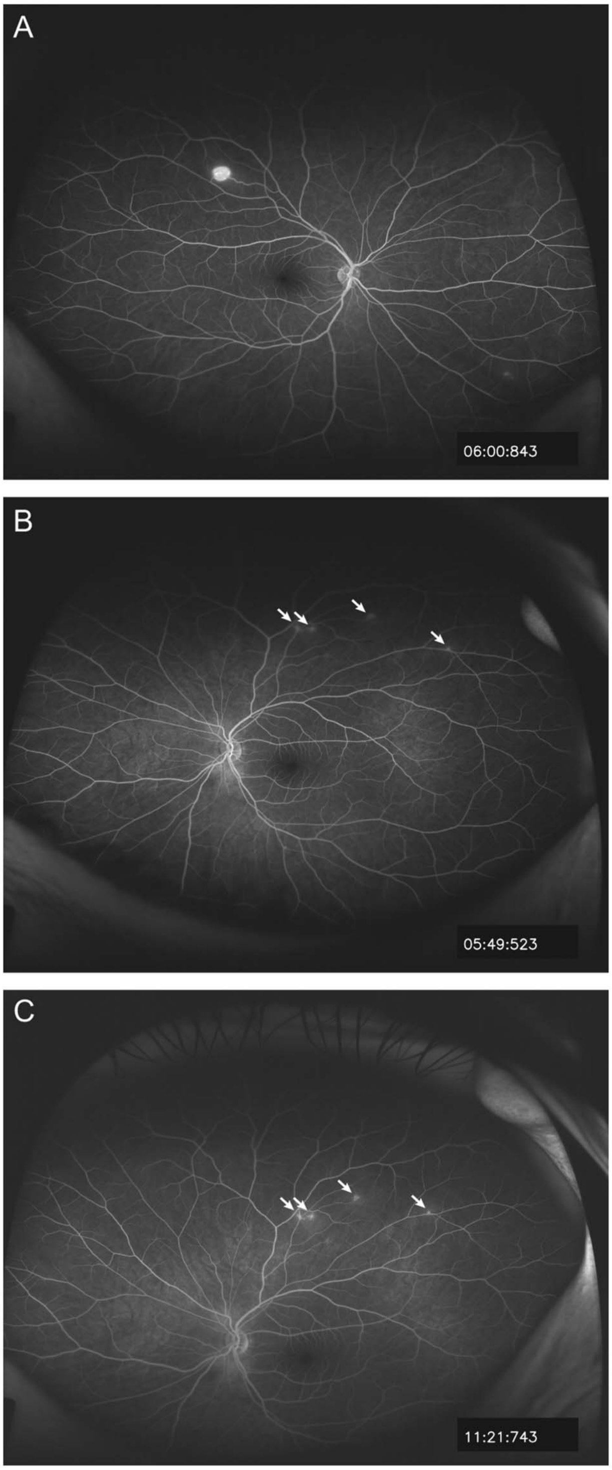

Fig. 9. Ultra-widefield fluorescein angiography of von Hippel–Lindau syndrome. **A.** A single lesion is present in the right eye. **B.** Imaging of the left eye in the primary position reveals suspicious areas superiorly (arrows) that are confirmed to be vascular lesions with superior steering (**C**, arrows).

of ICGA and even possibly OCT into the UWF imaging device, it will likely become an essential tool for all diagnostic aspects of ocular oncology.

Future Directions

Ultra-Widefield Optical Coherence Tomography

Over the last 10 years, the modular design of the Optos has facilitated a multimodal imaging approach with the successive addition of FA, FAF, and ICGA. A conceivable goal in the near future would add OCT capabilities to the device. This would permit a single-device UWF multimodal platform similar to the current configuration of the Heidelberg HRA + OCT using the ultra-widefield imaging module. Currently, however, the technology for true UWF OCT is not yet available. Most devices such as the Heidelberg Spectralis permit 30° line scans, and the latest generation of OCT devices image up to 40° of the posterior pole which includes the optic nerve and the entire macula. The next generation of OCT may use swept-source spectral-domain mode locking lasers capable of a megahertz A-scan rate.[117] These have the potential to provide up to 65° to 70° wide scans of the fundus.

It remains to be seen whether the use of an ellipsoidal mirror for OCT imaging on the Optos will permit even wider scans that go into the "ultra"-widefield range. This would undoubtedly revolutionize the identification of lesions predisposing to rhegmatogenous detachment and possibly inform the approach to retinal detachment surgery.

Screening

The use of fundus imaging for the screening of patients at risk for treatment-requiring retinal disease has become increasingly commonplace, especially for diabetic retinopathy and ROP. Diabetes mellitus is an enormous public health issue requiring the screening of many patients for diabetic retinopathy.[118] The use of UWF technology for diabetic screening has many theoretical advantages over traditional fundus photography, including its rapid acquisition time, single-photograph wide-field capture, and no need for dilation. A major downside, however, is the cost associated with the Optos device. Several studies comparing UWF pseudocolor images with clinical examination or standard seven-field fundus photography have found good agreement on the grade of retinopathy present.[29,31–37] Ultra-widefield images have also demonstrated a lower rate of ungradable image quality compared with traditional photography. In general, discrepancies in grading between Optos UWF images and standard photographs were due to upgrading by the UWF images given the increased detection of peripheral retinal pathology. One study of nonmydriatic versus mydriatic Optos images found them to be almost identical for the detection of retinopathy.[36]

Another screening paradigm for diabetic retinopathy is the use of UWF FA to detect microaneursyms, capillary nonperfusion, and neovascularization. This approach has been found in two studies to consistently reflect the retinopathy grading by clinical examination and often surpass the detection level of the seven-standard fields.[38,39] Although peripheral capillary dropout is not a standard criterion for retinopathy grade, it may be closely associated with or even predictive of neovascularization and macular edema.[40,48] These advantages may lead to its increasing use as an imaging platform for clinical trials requiring fundus imaging and angiographic data.

The use of Optos UWF imaging as a screening tool remains primarily limited to diabetic retinopathy, but some clinicians have reported good success with UWF pseudocolor and FA for evaluating ROP.[82,85] Given the overwhelming burden of ROP screening, a major emphasis has been placed on digital imaging to identify babies with treatment-requiring disease. The current gold-standard RetCam can obtain approximately 130° wide-field color images and fluorescein angiograms. A major advantage of the RetCam is that it is a handheld instrument, facilitating photography in the nursery for infants with often severe systemic comorbidities. Although Optos imaging requires "flying baby" positioning, its strength lies in the panoramic single-capture UWF imaging without the possibility of compression artifact as can be induced with the RetCam.[119,120] Until a handheld version of the Optos is developed, however, it remains unlikely to unseat the RetCam as the primary screening tool for ROP.

Telemedicine

Given the increasing popularity of the Optos for retinal screening, it appears well suited for telemedicine in underserved areas or to minimize the economic burden of ophthalmologic screening examinations. Telemedical diagnosis of retinal disease is already widely used and validated in multiple studies for ROP,[121–125] cytomegalovirus retinitis,[126,127] and diabetic retinopathy.[128] Utilization of the Optos as the retinal imaging device for these indications would carry the same advantages as its use for screening. One particular advantage of the Optos for telemedicine in underserved areas is that the operator can be less skilled than a fundus photographer. Significant downsides, however, are the higher upfront costs and that the device is not easily transportable, limiting its use to a particular screening site.

Electronic Documentation

For many ophthalmology practices, especially those at academic centers, electronic medical records have been implemented in place of paper documentation. A major source of frustration for retinal physicians has been the difficulty associated with creating fundus drawings in these electronic systems. A potential solution would be the seamless integration of an UWF color or angiographic image into the examination note that could be supplemented with annotations by the physician to note the important findings. Although this would abandon the art of color-coded retinal drawing, it would likely save time and more directly portray long-term changes in fundus appearance. For this to become a reality, however, future improvements must minimize imaging artifacts and generate true three-color fundus images.

Conclusion

Over the last 10 years, the Optos camera has undergone numerous technological improvements and been used effectively in an increasing number of clinical settings. The future of UWF imaging will undoubtedly include even wider clinical appeal and new capabilities that will extend its diagnostic power. An important task for future investigators will be to elucidate the clinical significance of far peripheral pathology and how it must inform the management decisions.

Key words: ultra-widefield, wide-angle, wide-field, Optos, optomap, fluorescein angiography, indocyanine green angiography, fundus autofluorescence, ellipsoid mirror, panoramic imaging.

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