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# Impact of Ultra-widefield Imaging on Understanding the Pathophysiology of Peripheral Retinal Degeneration

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## ABSTRACT

Ultra-widefield imaging has revolutionized the understanding of the retinal periphery in clinical practice. Since the publication of the study “Comparison of image-assisted versus traditional fundus examination,” the practice of using fundus imaging to guide retinal examination has become ubiquitous, not only by experienced doctors in practice, but in the training of new clinicians.[1] Quick capture and review of micron-level views with various wavelengths allows clinicians to plan their fundus exam, focus their time on areas of suspicion and better understand the health of the entire retina more effectively and efficiently. Image-assisted ophthalmoscopy has excellent agreement for a variety of lesion types but confers an advantage in optic nerve assessment, review of small lesions in the mid and far periphery and in visualization of vitreous lesions. Increasing resolution, integration of new wavelengths, auto-montage, optical coherence tomography and artificial intelligence have improved the sensitivity of this tool - thus improving the overall efficiency of a fundus exam, improving outcomes and leading to more accurate assessment of risk. Advances in ultra-widefield imaging technology have allowed us to better understand the anatomy and physiology of the peripheral retina and its relation to sight threatening disease; making this an invaluable tool to educate our students in training as well as our patients with and without retinal pathology in the clinic. When an image or lesion of concern can be viewed simultaneously by student and instructor or by doctor and patient, the learning and understanding from this ultra-widefield perspective are invaluable. In this review, we explore the technological advances and the impact on detection, diagnosis and prognostic potential in a variety of retinal degenerations. In addition, we examine remaining challenges of the technology.

## Introduction

Prior to the publication of the study "Comparison of image-assisted versus traditional fundus examination," there was no peer-review work comparing image-guided exams to traditional binocular indirect ophthalmoscopy.[1] Prior to the study's initiation in 2009, there were 12 peer-reviewed PubMed indexed journal articles examining the utility of ultra-widefield (UWF) optomap imaging (Optos, Dunfermline). The first of these papers by Friberg et al. established its sufficient resolution and clarity to make accurate general diagnoses in a high percentage of cases.[2] The inclusion of panoramic ophthalmoscopy made its appearance in optometry schools with the first textbook on the subject in 2007.[3] In the ensuing years, the profession began to adopt the technology, using UWF imaging in place of traditional fundus imaging to more effectively document findings across the retina. Optometry schools began to incorporate the technology into patient care for photo documentation of retinal lesions but soon realized the value in clinical education.

## Ultra-widefield Imaging Supplementing Clinical Exams

Over the subsequent years as the technology grew in popularity, clinicians and optometric training programs began using UWF imaging as a tool to support retinal assessment prior to dilation. Like a roadmap or Global Positioning System (GPS), using an UWF image to support pathology detection can guide the doctor and the trainee in planning their approach to fundus examinations. While this became common practice, no published evidence existed on the efficacy of image-guided examinations. The "Comparison of image-assisted versus traditional fundus examination" study identified the benefits of an image-assisted examination in detecting retinal lesions and has proven to be pivotal in regards to the standard of care in the profession at that time.[1] What previously required dilation to capture small fields of view could now be captured in UWF views without dilation, all while maintaining the standard of high resolution for the central pole.

## Sensitivity of Traditional Dilated Examination vs Image-Assisted Ophthalmoscopy

It has been well documented that the sensitivity of a traditional dilated retinal examination ranges from 32% to 82%. Comparison of image-assisted versus traditional fundus examination is the first study to demonstrate the ability of UWF to enhance a traditional dilated fundus examination, concluding that non-mydriatic image-assisted fundus examination enhances detection of retinal lesions compared with traditional fundus exams alone.[1] Overall sensitivity of image-assisted ophthalmoscopy was determined to be greater than traditional ophthalmoscopy by 30%. While an improvement in the detection of peripheral lesions was anticipated, we were surprised to find that there was a higher rate of posterior pole/macula region detection of lesions with image-assisted (90.1%) versus traditional ophthalmoscopy (48.9%). By definition, traditional ophthalmoscopy included dilated fundus examination using binocular indirect ophthalmoscopy *and* slit lamp biomicroscopy with a condensing lens. When the methods disagreed there was a significant advantage for the image-assisted examination in detecting:

- Suspicious optic nerve cupping
- Drusen in the posterior pole (macula) and mid-to-peripheral retina
- Retinal pigment epithelial changes in the posterior pole (macula)
- Nevi in the posterior pole (macula) and mid-to-peripheral retina
- Peripheral retinal degeneration
- Hemorrhage in the mid-to-peripheral retina
- Vitreous lesions

The adjudicator agreed with the image-assisted method in over 70% of cases.[1]

## The Evolving Practice of Fundus Examination

Since the publication of the study "Comparison of image-assisted versus traditional fundus examination," the practice of fundus examination has evolved fundamentally, especially post-Coronavirus-19 (COVID-19) where reducing chair time has been essential. Ultra-widefield (UWF) imaging technology has continued to advance with improvements in resolution, ease of capture and with incorporation of a variety of wavelengths into the ultra-widefield view.

Since the publication of those early clinical studies, Optos UWF technology now has over twenty-eight hundred publications demonstrating the value of the technology in a variety of diseases. Imaging prior to fundus examination is now ubiquitous. Clinicians incorporate imaging into their medical exam fee or charge patients separately, based on their needs.

## Field of View Definition and Standard Notation Developed by Consensus

As the standards for eye examinations have shifted, so did the standards for imaging the retina with increasing fields of view. Since the publication of the comparison study, the benefits of peripheral retinal imaging have been well documented. The growing popularity of wider fields of view however resulted in a disparity across the definition of widefield (WF) and ultra-widefield (UWF). The inconsistencies of the WF and UWF notation across the eyecare sphere led to confusion in incorporating this technology into clinical practice, as well as the ability to compare research results. At the time of our study, only Optos and Heidelberg with the Staurenghi lens were capturing retinal fields of view beyond the central pole. Subsequent technology providing widefield views have been developed, including the Zeiss Clarus, iCare Eidon and Nidek Mirante. The ways in which these larger fields of view are captured and presented for review vary as does the retinal area they capture. Understanding the potential of each of these technologies requires a clear understanding of method of capture and field of view.
A consensus meeting was convened in 2018 with the aim of defining and standardizing this terminology. The convergence of this international panel of retina specialists resulted in three distinct recommendations of nomenclature for future publications. The recommendation for the "ultra-widefield" definition was specific to images that show the retinal anatomy anterior

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to the vortex vein ampullae across all four quadrants. "Widefield" was defined as images capturing retinal anatomy beyond the posterior pole, but posterior to the vortex vein ampullae in all four quadrants. "Pan-retinal" imaging is defined as an image which captures the entire retina from ora to ora. The consensus group agreed that these terms should be used for retinal images of all types, including: fundus photos, Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA). Also detailed in the guidelines is the importance of specifying whether the field of view of interest is captured with one or more images and whether montaging is required.[4] These standards allow for the pooling and comparison of research findings. Our original study comparing image-assisted versus traditional ophthalmoscopy used 200 degree, single capture, red-green, Scanning Laser Ophthalmoscopy (SLO) imaging as well as 4 additional fields of view, one from each quadrant (without montaging). Today it is common in clinical practice to capture one central non-mydriatic UWF image which can include much of the nasal and temporal retina; then steer the patient to capture one superior and one inferior UWF image for views that may be blocked by the upper and lower eyelids, respectively.

## Improved Visualization with Scanning Laser Ophthalmoscopy

In many situations, imaging prior to pupil dilation has been demonstrated to be valuable to support the diagnosis of early signs of disease that may be subtle to find on exam, may not be accompanied by symptoms or require more invasive imaging like fluorescein angiography (FA).[5] Many conditions are challenging to visualize during retinal examination if there are difficulties with mydriasis, media opacity, vitreous pathology and or eye movement due to patients experiencing photophobia during traditional ophthalmoscopy. Scanning laser ophthalmoscope (SLO) imaging has advantages over white light examination when any media opacity or vitreous pathology is present. 200-degree ultra-widefield SLO imaging using two wavelengths, red (635nm) and green (532nm), optomap color RG has been reported to have benefits over white light in patients with these conditions. The addition of these two wavelengths enabled successful imaging through hazy media with up to 3+ lenticular opacity. Before these red (635 nm) and green (532 nm) wavelengths were added, it was not possible to examine the retina using traditional, white light-based methods, 85% of the time.[6] Similarly, SLO-based UWF imaging shows benefit when imaging through gas-filled eyes, eyes with silicone oil, Boston keratoprosthesis and through corneal inlays.[7-11] Non-mydriatic UWF imaging is able to capture images through 2 mm pupils with the rate of ungradable images under 2%.[12-14]

## Staging and Progression of Diabetic Retinal Disease

Incorporating retinal imaging into routine, comprehensive and problem-specific examinations has long been understood as the best way for staging diseases such as diabetic retinopathy, age-related macular degeneration (AMD) and glaucoma. The adoption of UWF imaging has helped researchers understand the pathophysiology of the retinal periphery and its impact on the progression of disease. For some conditions, this has been understood in post mortem models however, being able to follow the progression of the disease over time has been challenging. In 1967, it was reported that diabetic lesions were often seen in the retinal periphery and were likely of clinical importance. The practicality of obtaining images encompassing the entire retina was near impossible with the technology of the time. As technology improved, Early Treatment Diabetic Retinopathy Study (ETDRS) 7 field imaging was developed as a standard in 1991 after rigorous study.[15] This extensive, time-consuming imaging allowed for a wider assessment of the retina, but still only evaluated about 30% of the retina (~100 degrees) at each time point. With the advent of single-capture 200 degree UWF imaging, patients can now receive a high-resolution assessment of the retina including the area defined by ETDRS, with sensitivity of 99%, and specificity of 100%, as well as the retinal periphery.[16,17] Ultra-widefield imaging has also been shown to be superior to ETDRS at identifying high-risk proliferative diabetic retinopathy.[18,19]

## Peripheral Retinal Pathophysiology in Macular Degeneration

The utility of UWF imaging has had an impact on the understanding of the pathophysiology of several other diseases such as age-related macular degeneration (AMD) and glaucoma. The first study to assess single capture, 200 degree UWF imaging in AMD, evaluated the retina using both pseudocolor, red green imaging and green autofluorescence (533 nm). That study found only 13.6% of subjects had AMD-like changes in the macula alone, 10.1% had changes in the periphery alone while a surprising 57.4% had changes in *both* the periphery and macula. This study established the idea that phenotyping the retinal periphery using the categories defined by the International Classification (75 degrees), confirmed the presence of diffuse AMD-like pathologic changes across the retina.[20] Subsequent work by the Age-Related Eye Disease Study (AREDS)-II group at 5 and ten year intervals have found that drusen is present in 97% of eyes in Zone 2 (mid-periphery), and 77% of eyes in Zone 3 (far periphery).[21] Similarly, super large drusen, choroidal neovascularization, peripheral reticular pigmentation, cobblestone degeneration and reticular pigmentation are all present in more than 50% of subjects in the mid-far periphery. Peripheral reticular pseudodrusen has been noted to be present in 15% and senile reticular pigmentary change in 48%.[22] These results underline the fact that AMD is a pan-retinal disorder, a conclusion that has been confirmed using UWF imaging.

## Resolution of Ultra-Widefield Imaging in the Central Pole

While UWF imaging is known for its ability to image the mid-far periphery, the resolution of the technology in the central pole has been validated with gold standard assessments. For example, in glaucoma, the gold standard for optic nerve head assessment is a clinical examination with dilated slit-lamp biomicroscopy carried out by a glaucoma specialist using a condensing lens through a dilated pupil. In clinical practice, as with retinal assessment, imaging of the optic nerve has played a larger role as the technologies have evolved to be more efficient and more accurate; especially with the advent of methods utilizing color, digital stereoscopic photography and OCT. In a recent study, there was almost perfect agreement between color digital stereoscopy and 200 degree UWF SLO imaging when assessed by a glaucoma specialist and could be reliably used as a replacement for digital stereo images.[23] An additional study found accuracy of glaucoma classification by fundus imaging to be 94.4% and accuracy of detecting suspicion of glaucoma in UWF SLO images to be 93.9%.[24]

## Improvement of Ultra-widefield Scanning Laser Ophthalmoscope Technology

As highlighted by the state of image-guided examinations since the publication of the comparison study, the field of retinal imaging has evolved. In conjunction with a growing expectation for accurate and efficient fundus examination, UWF technology has expanded to meet these needs. Using the principles of the technology found in the comparison study, an additional wavelength has been added to Optos' single capture UWF technology. Expanding on the device's utilization of the color red-green (RG) lasers, the addition of the 488 nm blue laser allows for a red-green-blue (RGB) imaging modality. Clinically, the complementary nature of the RG and RGB modalities has shown to be useful in practice and enhances visualization of retinal abnormalities. The addition of the blue laser results in images with more natural color, and better mimicking of the findings in dilated clinical examinations. This supplemental modality provides enhanced visualization for specific pathologies such as drusen, epiretinal membranes (ERM), the retinal nerve fiber layer (RNFL), retinal holes, lattice patterns, and details of subretinal Proliferative Vitreoretinopathy (PVR).[25]

## Stereographic Projection Improves Accuracy and Precision of Retinal Measurements

In addition to the improvements these additional modalities offer, advancements to the base technology of UWF technology have been quantified. For example, when UWF images are viewed in a 2-dimensional format, there is a level of distortion that occurs. However, there have been measures to counteract and correct these effects. The technique of stereographic projection preserves the natural retinal shape by projecting all pixelation through the equator of the eye. The dimensions of a retinal implant were measured using a prototype stereographic, projection-measurement software to accurately and precisely quantify the UWF device.[26] In this study, intragrader agreements for the independent graders were found to be 0.959 and 0.919. The intergrader agreement between the graders was found to be 0.926. The average percent difference between the graders and the implant's manufacturer specifications was 10.21%. When accounting for the subject's axial length (a parameter that is standardized in UWF image review software), this difference decreased to 1.93%. The low percent difference, the high intragrader repeatability, and the high intergrader agreement demonstrate the accuracy and precision of retinal measurements using stereographic projection technique, particularly while incorporating axial length information. The quantification of the periphery in UWF images is a significant development in retinal imaging that can support further research that requires such data.

A benefit stemming from the development of geographic projection and measurement is the precise registration of images from various imaging modalities and imaging time points. This functionality is available and allows for serial analysis with more accurate assessment of the structure-function relationship of lesions, and monitoring of specific lesion change over time.

## Combining Optical Coherence Tomography with Ultra-widefield Imaging

Another advancement of UWF technology has been the integration of optical coherence tomography (OCT) that can be planned and registered using the UWF image. The Optos Monaco and Silverstone devices utilize spectral domain and swept source OCT technology respectively, to allow for a variety of OCT scans to be collected. These combination devices allow for quick acquisition of both retinal and OCT imaging modalities, negating the need to move the patient between two separate devices - therefore improving clinic workflow and convenience for patients and clinicians. Furthermore, the improved diagnostic capabilities of using this combined technology are clear. In comparison with UWF imaging alone, the addition of OCT to UWF imaging has increased the detection of true positives for diabetic macular edema by 70% while decreasing the rate of false negatives by 58.3%. When considering macular pathology in general, the addition of OCT to UWF imaging increased the identification of macular pathology by 29.4%.[14] The increased sensitivity and specificity of these examinations has and will continue to decrease the burden on healthcare systems by unnecessary referral, while increasing patients' access to care.

In addition to diabetic macular edema (DME), the use of combined UWF and Spectral Domain (SD)-OCT devices has been studied in glaucoma. In an age-matched analysis of normal versus glaucoma subjects, it was found that the Monaco combined UWF and SD-OCT device can effectively differentiate between the normal and glaucoma suspect groups with a high level of accuracy. Specifically, the OCT measures of rim area, cup-to-disc vertical ratio, average retinal nerve fiber layer (RNFL) and average ganglion cell complex (GCC) resulted in the highest areas under the receiver operating curves (AROC).[27] The AROCs ranging from 0.92 to 0.98 support the Monaco OCT measurements as a good model for differentiating healthy eyes from glaucomatous eyes. In glaucoma screening, the visual field test has been a standard for diagnosis and management. Optical Coherence Tomography measurements with the Monaco device were shown to have moderate correlation to the Humphrey Field Analyzer 24-2 visual field test.[28] Average RNFL thickness and inferior quadrant RNFL thickness are among the highest correlated OCT measurements to mean deviation, with correlation coefficients of 0.41 and 0.42 respectively. For pattern standard deviation, the highest correlated OCT measurement was the inferior quadrant RNFL thickness with a correlation coefficient of 0.39. The moderate correlation to visual fields and the high diagnostic discernment supports the utilization of combined UWF and SD-OCT devices in the screening and management of glaucoma.

The convenience and clinical utility of a combination UWF and OCT enabled device has been a significant development in recent years and while it has not been studied in a systematic population study, the potential of these improvements to enhance the detection of disease is clear.

## Understanding of the Peripheral Retina

Ultra-widefield imaging has expanded the field of retinal imaging beyond the posterior pole. With the clinical significance of the periphery identified, it is important to understand what can be captured in the peripheral retina as well as the implications of these findings.

One study of over 1,000 eyes found that non-mydriatic Optos images could be captured in 99.7% of patients with peripheral retinal lesions, including retinal breaks.[29]

Ultra-widefield-based evaluation was demonstrated to have a sensitivity of 89.2% in detecting peripheral retinal lesions. In addition, the identification of peripheral retinal lesions with UWF imaging allowed for an accurate and reproducible assessment of these lesions.[30]

Myopia and progressive, degenerative myopia are a growing global problem. Recent research compared UWF imaging for the detection of peripheral lesions most associated with myopic degeneration, with and without eye steering, and found that its sensitivity rate was 75% for a single capture and 86.5% when gazes were directed into four quadrants (superior, inferior, nasal and temporal). In a population of 220 eyes, 64% (141) of eyes had peripheral degenerations imaged on UWF imaging. 52% (116) of these eyes had holes or tears, 27% (60) had lattice degeneration, 3% (7) had snail track degeneration and 2% (5) had pigmentary degeneration. 26% of eyes had more than one type of peripheral pathology and 30% had changes in more than one quadrant of the retina. Eye steering increased the detection of peripheral lesions by 30%. Neither axial length nor spherical equivalence had any impact on the rate of detection on UWF SLO imaging.[31]

New research using 200 degree UWF imaging examined the relationships among retinal structure, peripheral retinal abnormalities and epiretinal membrane, and found that idiopathic epiretinal membranes (ERM) are often associated with peripheral retinal degenerations. Ultra-widefield imaging supported the detection of 87% of all peripheral retinal lesions in patients with ERM. Lesions were identified most frequently in the temporal quadrant (49%), with 25% in the lower quadrant, 22% in the upper quadrant and 4% in the nasal quadrant. The author made note of the similarity between AMD being better understood as a pan-retinal disease - and now ERM is likely to be seen in the same context.[32]

Ultra-widefield imaging enables a better understanding of the extent of these degenerations in vivo over time. Ultra-widefield with OCT integrated imaging has been shown to change the management plans for laser, injection or surgical treatment for example, in 38% of patients, providing high-quality characterization of peripheral retinal lesions for all eyes.[13,33]

## Conclusions

While retinal imaging does not replace a thorough dilated exam, it does replace not looking at all. In a field where time and accuracy are ever important; and with the increasing burden of disease, efficient imaging tools are essential to any practice. Optometry educational programs utilize retinal imaging to help students understand the pathophysiology of the retina, choroid, optic nerve and vitreous, making these devices invaluable tools in the classroom *and* in the patient care setting. Integrating multimodal UWF imaging technology provides an efficient and effective adjunct to the clinical training of our students and examination of our patients. Screening for and quickly identifying, then discussing the findings discovered during patient encounters, provides an extremely valuable perspective for the student, the attending physician and most importantly, for the patient. Utilizing UWF with OCT offers the ability to plan dilated exam time effectively, to detect more pathology as demonstrated in our original study, and to assess the vitreous, retina and choroid in a variety of ways, all while providing the benefit of high resolution documentation of pathology.

## Disclosures:

KB: Consultancy and Equipment loan (Optos PLC, Dunfermline, Scotland, U.K.); DK: Optos employee; LT Optos employee; TP Consultancy and Equipment loan (Optos PLC, Dunfermline, Scotland, U.K.)

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