

# Ultra-widefield Imaging in Age-Related Macular Degeneration

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## ABSTRACT

Age related macular degeneration accounts for 8.7% of all blindness worldwide and is the major cause of blindness in the developed world. The projected number of people with the disease will be 288 million in 2040, deserving the effort for early detection and treatment. In many different studies the peripheral retinal changes had been demonstrated clinically and pathologically in age related macular degeneration. Retinal imaging had a huge development within the last century and now it is easier to detect and document the peripheral retinal changes. Ultra-widefield imaging with many different commercially available devices will be one of the most important tools of retinal imaging. In this review our aim is to discuss the diagnostic, therapeutic and predictive value of ultra-widefield imaging in age related macular degeneration.

**Keywords:** Age related macular degeneration, Ultra-widefield imaging, Ultra-widefield autofluorescence.

## BACKGROUND

Age related macular degeneration (AMD) is the leading cause of visual impairment in developed countries. AMD is a heterogeneous disease with different underlying causes including genetics and environmental factors.<sup>1</sup> Peripheral retina is affected in many ophthalmic pathologies like age related macular degeneration, diabetic retinopathy, uveitis, retinopathy of prematurity, retinal vascular occlusions and should be examined in detail. In daily practice the peripheral retinal examination requires dilation and scleral indentation but this clinical examination lacks documentation and may be time consuming for the clinician and uncomfortable for the patient.

Age related macular degeneration has been graded according to the macular changes for decades, however peripheral retina shows numerous changes with age like hard and soft drusen, retinal pigment epithelial changes, pigment epithelial detachment, geographic atrophy and choroidal neovascularization. A study published by Lengyel et al. revealed that 67% of patients with age related macular degeneration had peripheral changes related to AMD.<sup>2</sup>

With every step had been taken from the color fundus pho-

tographs to angiography, scanning laser ophthalmoscopy, optical coherence tomography, autofluorescence imaging our way of understanding retinal diseases evolved incredibly. One of the exciting developments in retinal imaging is the ultra-widefield (UWF) imaging which is expected to be the future of diagnosis and screening in many retinal diseases.

## MAIN TEXT

### Evolution of retinal imaging

The journey of the retinal imaging which had started with the first fundus camera of Carl Zeiss in 1926 with a 20 degree of retinal view evolved to 200 degrees of retinal view with Optos200Tx (Optos, Dunfermline, Scotland) and non midriatic versions like Zeiss Clarus 500 and 700 (Carl Zeiss, Jena, Germany).<sup>3</sup>

The traditional fundus cameras are known to have a capability of 30-50 degrees of retinal view which has been the standard. Afterwards any camera providing imaging better than 50 degrees has been called wide field. Although Lotmar was the first person who succeeded to obtain nearly 96 degrees of retinal imaging, his technique was difficult to use.<sup>4</sup>

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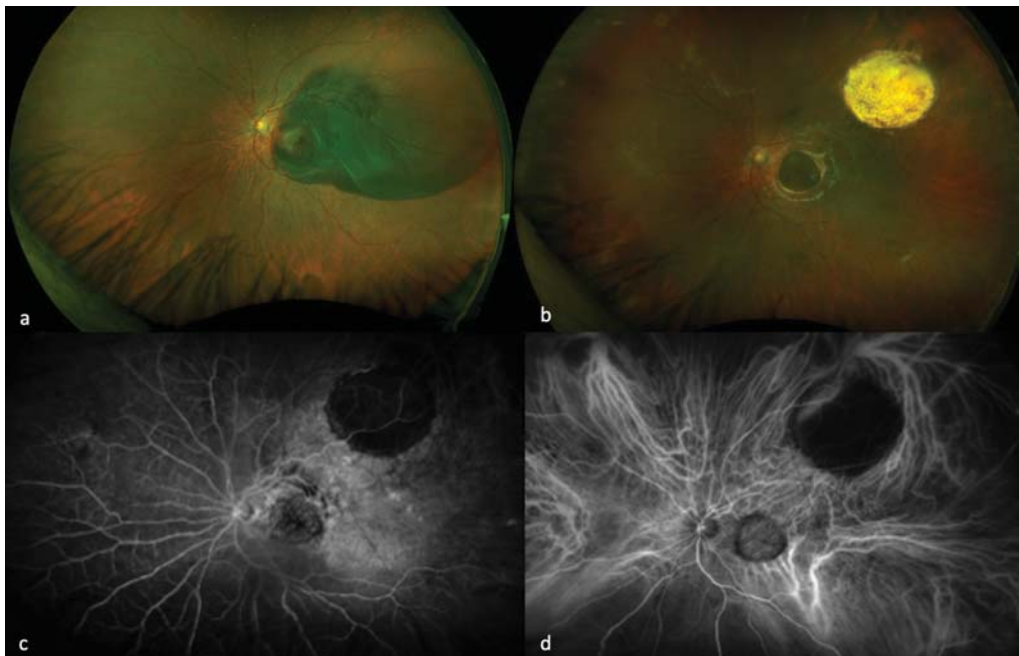
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Retcam (Clarity Medical Systems, Pleasanton, California, USA) is the very first UWF imaging system and in use since 1997. It is a contact, portable device and very useful in visualizing and monitoring the pediatric retina with 130 degrees of retinal view.<sup>5</sup> The newer version of RetCam has different lens options such as 130°, 120°, 80° and 30°. The major disadvantage of this system was the contact lens which required an experienced photographer and a compliant patient.

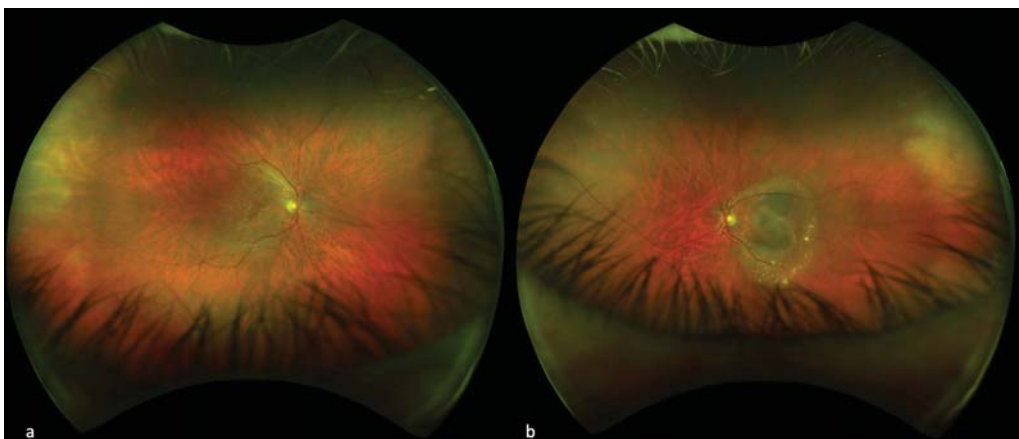
Optos camera (Optos PLC, Dunfermline, UK) provides 200° view of the retina which makes 82% of the total by using a confocal scanning laser ophthalmoscope (CSLO) technology.<sup>6-7</sup> After the retinal peripheral images are obtained by the ellipsoidal mirrors, they are corrected for

peripheral distortion. The first commercially available version has 532 nm green laser and 633 nm red laser and has been upgraded by addition of multiple lasers like 488 nm blue laser for fluorescein angiography and 805 nm infrared laser for indocyanine green angiography.<sup>6-7</sup> The device uses green laser for visualizing the retina and red laser for the deeper structures and as a result gives a pseudocolor image of the fundus. System has some disadvantages like non-uniform image contrast throughout the fundus, eye-lashes as an artifact and distortion of the horizontal axis. Optos pictures of different clinical cases are presented in figures 1-3.

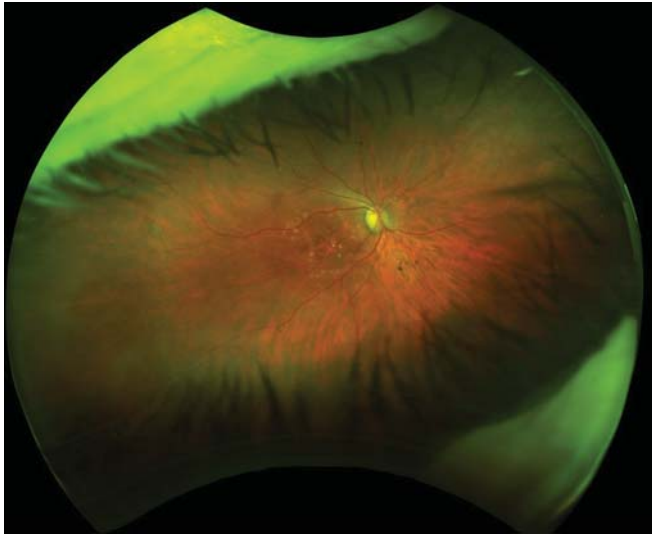
Heidelberg Spectralis Ultrawide-Widefield Module provides a detachable non-contact lens that increases the retinal



**Figure 1:** a) Submacular hemorrhage due to exudative age related macular degeneration. b) Postoperative Optos image following choroidal patch graft surgery. c-d) Postoperative FFA and ICG images. Courtesy of Professor Dr. Şengül Özdek, M.D., FEBO.



**Figure 2:** Ultra-widefield fundus photography images of a patient with non-exudative age related macular degeneration in the right eye (a) and with choroidal neovascular membrane in the left eye (b). With the courtesy of Prof. Dr. Sibel Kadayıfçılar, M.D.



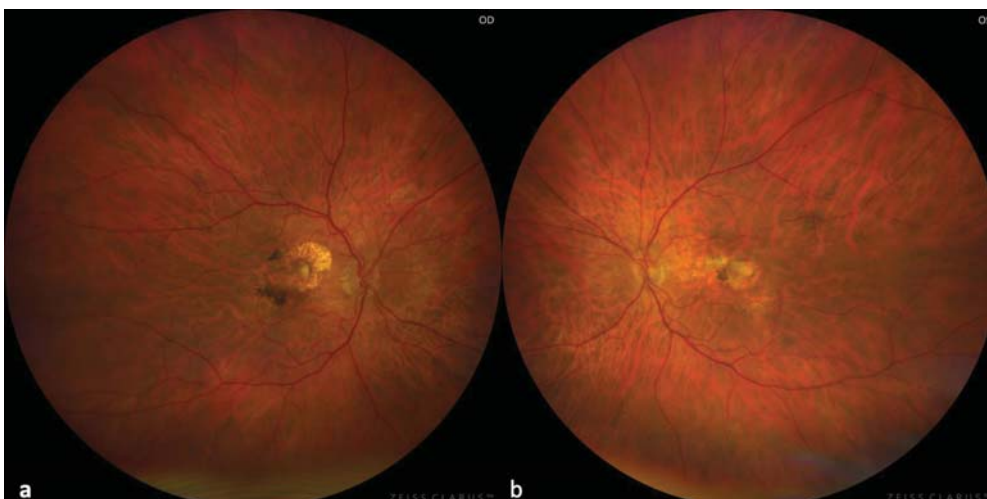
**Figure 3:** *Drusen and choroiretinal atrophy is seen in this ultra-wide field image of a patient with non-exudative age related macular degeneration, With the courtesy of Prof. Dr. Sibel Kadayıfçılar, M.D.*

view from 55 degrees to 150 degrees. The Optos shows the temporal and nasal retina better with some peripheral distortion, but ultra-widefield Heidelberg Spectralis shows the superior and inferior retinal areas better with less lash artifact.<sup>8</sup>

CLARUS 500 (Carl Zeiss Meditec, Jena, Germany) is the newest version of UWF cameras which allows 200 degrees visualization of retina under one image and 267 degrees when six images are montaged with real-like coloration. It has the capabilities of fundus autofluorescence (FAF) blue, FAF green, infrared and ocular surface imaging.<sup>9</sup> Clarus 700 provides fluorescein angiography and ICG. Macular changes of the disease can easily be documented and followed-up with regular color fundus photograph and optical coherence tomography, however it is more difficult to monitor peripheral fundus changes. At this point new commercially available devices on the market will be very helpful. Widefield fundus images obtained by Clarus 700 are presented in Figures 4 and 5. The features of commercially available devices are summarised in Table 1.



**Figure 4:** *Color fundus photographs obtained with Clarus 700 reveals drusen in the right eye (a) and choroidal neovascular membrane in the left eye (b).*



**Figure 5:** *Color fundus photographs obtained with Clarus 700 reveals choroidal neovascular membrane and accompanying pigment epithelial tear in the right eye (a) and choroidal neovascular membrane in the left eye (b).*

**Table 1:** Primary components of commercially available ultra-widefield imaging. Abbreviations: confocal scanning laser ophthalmoscope (CSLO), fluorescein angiography (FA), fundus autofluorescence (FAF), indocyanine angiography (ICGA), spectral domain optical coherence tomography (SD-OCT).

Imaging Device	Lens System	Field of view	Imaging Principle	Multimodal Imaging options	Image color	Disadvantages
RetCam	Contact	130°, in new models also 120°, 80° and 30°	Optical light source	FA and ICGA	True color image	Requires expert technician and patient compliance
Heidelberg Spectralis	Contact and noncontact	55° to 150°	SD-OCT with CSLO with or without Staurenhi lens	FAF, FA and ICGA	True color image	Requires expert and patient compliance
Optos	Noncontact	200°	CSLO-based	FAFA, FA and ICGA	Pseudocolor image	Non-uniform image contrast, eyelash artifact, peripheral distortion
Clarus 500 and 700	Noncontact	133°, 200° and up to 267°	Broad Line Fundus Imaging (BLFI)	FAF, FA and ICGA	True color-like image	Lacks the corroboration of true color images

### Clinical use of UWF imaging in AMD

Age related macular degeneration classification is made up on macular changes, however peripheral retina shows pathologic findings as well. Ultra-widefield imaging may be useful in detecting the peripheral changes like choroidal neovascularizations, hypopigmentary/hyperpigmentary changes, retinal pigment epithelial detachments, reticular pseudodrusen and senile reticular pigmentary changes. Reproducible documentation of the peripheral retinal changes in AMD may lead to a more comprehensive classification of the disease.

Lengyel et al. introduced the first grading system for analyzing the peripheral retinal changes lesions in AMD on UWF imaging in 2015.<sup>2</sup> These authors' system consists of three concentric rings representing the fovea, perifovea and macular zones for the central retina, a fourth zone for the mid periphery and a fifth for the far periphery. This study showed that grading peripheral lesions is possible among with the macular changes on autofluorescence and pseudocolor UWF imaging with high interobserver agreement.<sup>2</sup> Recently a new grading method with the additional zone for the perimacular area just outside the vascular arcades was described by Oellers et al.<sup>10</sup> In the mean time they used an image transformation software developed by Optos in order to overcome the peripheral retinal distortion.<sup>10</sup>

In a study by Reznicek et al. patients with AMD showed significantly increased peripheral autofluorescence when compared with the healthy subjects.<sup>11</sup> In another study by Heussen et al. nearly 70% of the patients with the diagnosis of AMD showed peripheral retinal findings on color pictures and autofluorescence.<sup>12</sup> In a following study of Tan et al. patients with neovascular AMD had been shown to have more peripheral autofluorescence abnormalities when compared to patients with non neovascular AMD.<sup>13</sup>

Peripheral autofluorescence changes and genotype relationship in retinitis pigmentosa had been studied by Trichonas et al. and a similar relationship between peripheral retinal changes and genetic subtypes had been investigated to detect an individual's risk of developing AMD.<sup>14</sup> A study of Seddon et al. showed that peripheral drusen and reticular pigment changes are related with AMD severity. Peripheral drusen were found to be associated with CFHY402H genotype and reticular pigment changes were found to be associated with CFHrs1410996 genotype in the same study.<sup>15</sup>

The OPERA study with 484 (951 eyes) AREDS2 participants with AMD and 89 (163 eyes) controls showed that AMD-associated peripheral lesions were more prevalent in eyes with AMD, by using the AREDS2 Optos Peripheral Retina (OPERA) Study grading method. In the same study 81% of the patients showed irregular FAF, while 67% showed reticular pigmentation.<sup>16-17-18</sup> These peripheral changes have been shown to be related to CFH, ARMS2, and HTRA1 single nucleotide polymorphisms (SNPs) which are known as the predictors of preneovascular AMD.<sup>19</sup>

The prospective single-blinded case-control study carried with 28 AMD patients and 11 controls of Guduru et al. also confirmed higher incidence of peripheral FAF abnormalities in patients with AMD.<sup>20</sup> Csutak et al. reported a high rate of agreement between regular 45° central fundus photography and UWF imaging for grading of abnormalities in the macula.<sup>21</sup>

A recent meta-analysis by Forshaw et al. demonstrated that peripheral lesions were more common (82.7% vs 33.3%) in eyes with AMD than healthy eyes.<sup>22</sup>

In a prospective study by Kucukiba et al., peripheral retinal changes in zone 2 and/or zone 3 were detected in 67.8%

of eyes in the AMD group, whereas 47.8% of eyes in the control group had similar peripheral changes.<sup>23</sup>

Under the light of all these studies UWF imaging appears as a promising tool in diagnosis and follow-up of age related macular degeneration.

## CONCLUSION

Age related macular degeneration is a disease which affects the whole retina instead of affecting only the macular region as thought before. As an area of probable pathology, reproducible peripheral retinal imaging is essential in screening, diagnosis and treatment of age related macular degeneration which is a sight-threatening eye disease.

Peripheral retinal changes detected by multimodal ultra-widefield imaging may be the future predictor of the patients' risk of developing neovascular age-related macular degeneration.

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