



Agreement between image grading of conventional (45°) and ultra wide-angle (200°) digital images in the macula in the Reykjavik eye study

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Abstract

Purpose To establish the agreement between image grading of conventional (45°) and ultra wide-angle (200°) digital images in the macula.

Methods In 2008, the 12-year follow-up was conducted on 573 participants of the Reykjavik Eye Study. This study included the use of the Optos P200C AF ultra wide-angle laser scanning ophthalmoscope alongside Zeiss FF 450 conventional digital fundus camera on 121 eyes with or without age-related macular degeneration using the International Classification System. Of these eyes, detailed grading was carried out on five cases each with hard drusen, geographic atrophy and chorioretinal neovascularisation, and six cases of soft drusen. Exact agreement and κ -statistics were calculated.

Results Comparison of the conventional and ultra wide-angle images in the macula showed an overall 96.43% agreement ($\kappa = 0.93$) with no disagreement at end-stage disease; although in one eye chorioretinal neovascularisation was graded as drusenoid pigment epithelial detachment. Of patients with drusen only, the exact agreement was 96.1%. The detailed grading showed no clinically significant disagreement between the conventional 45° and 200° images.

Conclusions On the basis of our results, there is a good agreement between grading conventional and ultra wide-angle images in the macula.

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Keywords: age-related macular degeneration; image grading; geographic atrophy; choroidal neovascularisation; drusen; imaging

Introduction

Fundus imaging is frequently used to document and monitor retinal lesions. Both film and digital images are widely used and the two show good agreement.^{1–4} The 30–60° photographic field has become the standard for most studies. The magnification provided by these images is usually adequate to determine most lesions including age-related maculopathy and macular degeneration (ARM and AMD, respectively).⁵ AMD is a major cause of visual loss in the elderly⁶ that involves the retinal pigment epithelium (RPE), Bruch's membrane, choroidal vasculature and photoreceptors. Although ARM and AMD has been described for over 100 years, details of internationally accepted grading systems are relatively new and not necessarily universally used.⁷ However, determining the aetiology of ARM is important for the identification of risk factors.⁸ Validation and calibration of grading systems is difficult because clinicians, epidemiologist, and pathologist use different definitions and even different names for ARM and AMD.⁷

ARM and AMD, similar to several other retinal disorders, show distinct topographical patterns of pathology. Although diagnosis relies on changes in the macula, there are many age-related changes in the periphery that may influence the development of macular lesions or the macular pathology itself may trigger peripheral changes⁹ that could influence treatment strategies. Therefore, monitoring changes in the periphery may become an indispensable tool to fully understand ARM and AMD disease aetiology. To obtain wide-field images, standard protocols such as the seven

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field images were generated in the past. This allowed the visualisation of approximately 75° fields. Recently, the P200C AF scanning laser ophthalmoscope (OPTOS PLC) was introduced that allows the rapid (0.25 s), wide-angle (up to 200°) imaging of the retina in a single image. This image can be obtained with or without mydriasis.

The main purpose of this article was to determine the feasibility to use ultra wide-angle (200°) digital imaging to record phenotypic variation of AMD in the macula of eyes from the 12-year follow-up of Reykjavik Eye Study.

Materials and methods

The Reykjavik Eye Study includes a random sample from the Reykjavik population census 50 years and older in 1996, in which 1045 persons participated, all having an eye examination and stereo fundus photography using films.¹⁰ In 2008, the 12-year follow-up was conducted in which 573 persons participated, that is, 73% of the survivors. Participants were photographed using the P200C AF, an ultra wide-angle (200°) scanning laser ophthalmoscope that was operated by an Imaging Team provided by OPTOS and supervised by the Reading Centre of Moorfields Eye Hospital (MEHRC). The 45° fovea centred macular photographs were taken by a ZEISS FF 450 digital camera, operated by trained senior nurses of the Reykjavik Hospital Medical Retina Clinic and supervised in part by the MEHRC. Both conventional digital and ultra wide-angle images were taken through pharmacologically dilated pupils.

Tenets of the Declaration of Helsinki were followed. Ethical approvals were obtained from the Data Protection Authority and the National Bio-Ethics Committee in Iceland. Signed informed consent was obtained from each participant. The digital images were sent to the MEHRC with a unique ID number displayed on all photographs. These ID numbers were used to identify patients and grading records in the Reykjavik Eye Study.

For our current protocol, 121 eyes were selected from the 12-year follow-up, and care was taken to cover the whole spectrum of ARM and AMD. Images were graded in random order without access to clinical information. Both conventional and ultra wide-angle images were graded using the Optos V2 vantage DX review software that allows the automatic fitting of a standard grid after manually defining the centres of the fovea and the optic disc. This definition of grading grid ensured that the very same macular areas were graded in both image modalities (see examples of corresponding images in Figure 1). Standard circles were used to measure the drusen and lesions sizes. Only abnormalities related to ARM and AMD were graded. Both conventional and ultra wide-angle images were phenotyped by the same person using the categories of the International

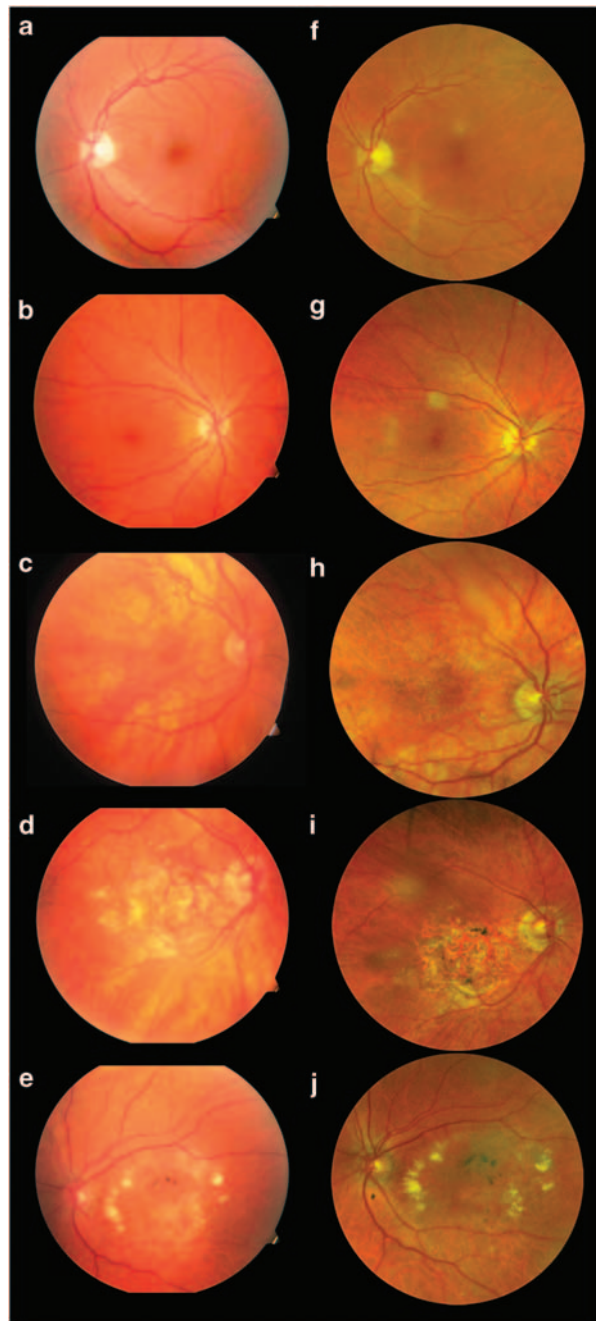


Figure 1 Corresponding images of the macula of the same eye taken by the Zeiss FF 450 conventional 45° digital fundus camera (a–e) and, after fitting landmarks on the images and cropping, Optos P200C AF ultra wide-angle laser scanning ophthalmoscope (f–j): (a–f) no pathology; (b–g) early ARM; (c–h) early AMD; (d–i) choroidal neovascularisation; (e–j) geographic atrophy.

Classification (IC):⁷ hard and soft drusen, geographic atrophy (GA), and chorioretinal neovascularisations (CNV) were identified. Intra-observer agreement was calculated once the images were regraded after a minimum of 14 days interval.

Of the phenotyped images, detailed grading was conducted on five cases each with hard drusen, GA and CNV, and six cases of soft drusen (21 eyes in total), on both imaging modalities using the Optos V2 vantage DX review software by individually recording all drusen types and sizes for all three zones of the IC grading, together with recording RPE changes, characteristics, and size of CNV and GA. This represented the same grading protocol that was used as for the baseline and the 5-year follow-up of the Reykjavik Eye Studies to allow incidence estimates at the later date.^{10,11} Incidental findings were commented on the grading form. Intra- and inter-observer agreement was calculated once the images were regarded after 14 days by the same or by another certified grader.

Exact agreement and κ -statistics were calculated between intra- and inter-graders.¹² The κ -statistic was interpreted as follows: $\kappa < 0$, poor agreement; κ -values 0–0.2, 'slight'; 0.21–0.40, 'fair'; 0.41–0.60, 'moderate'; 0.61–0.8, 'substantial'; and $\kappa > 0.81$, 'almost perfect agreement'.¹² Statistical analysis was performed using Stata 9.0 (StataCorp LP, College Station, TX, USA).

Results

To assess the feasibility to use the P200C AF images for grading for ARM and AMD in the macula we used a two-step analysis. First, macular pathologies were graded both on ultra wide-angle and conventional digital images from 121 (10.56% of total) eyes by one grader. Of these, nine conventional digital images were not gradable. All ultra wide-angle images were sufficiently good quality for grading. After comparison of the 112 remaining eyes, there was a 96.43% agreement ($\kappa = 0.93$) in the overall diagnosis of end-stage diseases (19 eyes). The only disagreement came from one eye that was graded as CNV on the ultra wide-angle image and drusenoid pigment epithelial detachment (PED) on the conventional digital image. Seventy-seven eyes were graded as drusen only on conventional digital images and 74 on the P200C AF images. Disagreement came from three eyes that were graded as normal on the P200C AF images (exact agreement 96.1%, $\kappa = 0.00$). There were no disagreements in grading normal fundus images (16 eyes).

In the second step detailed grading was carried out by two independent graders on five cases each with hard drusen, GA and CNV, and six cases of soft drusen using the International Classification used for both the baseline and the 5-year follow-up of the Reykjavik Eye Study. Grading categories, exact agreement and κ -statistics are listed in Tables 1–3. As there was no clinically relevant difference between the two graders, their detailed

grading was collapsed and the grading of the two imaging modalities were compared. The agreement between the two imaging modalities was overall high in all categories, except grading hard ($< 63 \mu\text{m}$), intermediate soft (63–125 μm) drusen, and the area covered by drusen. In these categories the agreement ranged between moderate to low (Table 1). Inter-grader reliability for both image modalities was generally high, except for small hard drusen ($< 63 \mu\text{m}$) and for intermediate to soft drusen (63–125 μm) (Table 2). The intra-grader reliability was calculated by re-grading the images at least 14 days after the first grading. Intra-grader reliability was high in all categories (Table 3), except for some categories of drusen (Table 3). This disagreement was consistently driven by only one case, which on first grading was deemed not gradable due to image quality, but graded as normal at re-grading.

Discussion

Digital fundus photography has become a sensitive and reliable tool in grading abnormalities in ARM and AMD.⁴ Nowadays clinicians are aided by and document their diagnoses using this 'gold standard'. Therefore, it is imperative that new digital imaging systems are compared with the well accepted and characterised conventional digital fundus images. In this study, we compared the grading of macular pathologies in ultra wide-angle (200°) scanning laser ophthalmoscope-generated digital images with non-stereoscopic conventional digital fundus images (45°) of eyes of the 12-year follow-up of the Reykjavik Eye Study. The comparison showed good agreement for ARM and AMD characteristics between the two imaging modalities.

The P200C AF imaging system (Optos, Dunfermline, UK) is a scanning laser ophthalmoscope that captures a wide-field retinal image up to 200°. Images can be captured in 250 ms allowing the rapid imaging of even the vulnerable patients often even without mydriasis. The P200C AF uses red (633 nm) and green (532 nm) lasers, which are reflected off a large concave elliptical mirror. The resulting images are displayed as red only, green only, and a combined red–green 'false colour' images. Each image has a resolution of 3000 by 3000 pixels. The P200C AF is the latest in a series of devices that use a common imaging platform to document a wide range of abnormalities in the retina. Although this is the first study with the P200C AF device, an earlier device in this series, the P200 has been used in previous studies.^{13–16}

Ultra wide-angle images had not previously been used to grade changes associated with ARM or AMD, although the presence of pathological abnormalities in the macula had been described.¹⁷ In this study, we

Table 1 Agreement between grading conventional (45) and ultra wide-angle (200) digital images

	Zone 1	Zone 2	Zone 3
Drusen <63 μm (hard drusen)	62%, κ = 0.26, P = 0.0027	60%, κ = 0.37, P = 0.0003	38%, κ = 0.15, P = 0.035
Drusen 63–125 μm (intermediate soft drusen)	79%, κ = 0.54, P < 0.0001	83%, κ = 0.75, P < 0.0001	74%, κ = 0.62, P < 0.0001
Drusen 125–250 μm (large semisolid drusen distinct, subconfluent, confluent)	95, 95, 95%, κ = 0.0, κ = 0.0, κ = 0.0, NP, NP, NP	83, 93, 98%, κ = 0.29, κ = 0.36, κ = 0.84, P = 0.015, P = 0.0079, P < 0.0001	91, 95, 100%, κ = 0.69, κ = 0.81, κ = 1.0, P < 0.0001, P < 0.0001, P < 0.0001
Drusen 250–500 μm (large semisolid drusen distinct, subconfluent, confluent)	95, 95, 95%, κ = 0.0, κ = 0.0, κ = 0.0, NP, NP, NP	100, 100, 95%, NP, NP, κ = 0.00, NP, NP, P < 0.0001	100, 98, 98%, κ = 1.0, κ = 0.00, κ = 0.00, P < 0.0001, P = 0.5, P = 0.5
Drusen > 500 μm (large semisolid drusen distinct, subconfluent, confluent)	95, 95, 93%, κ = 0.0, κ = 0.0, κ = -0.02, NP, NP, P = 0.59	100, 95, 95%, NP, κ = -0.02, κ = 0.48 NP, P = 0.56, P < 0.0001	100, 98, 98%, NP, κ < 0.01, κ = 0.66 NP, P = 0.5, P < 0.0001
Crystalline drusen	95%, κ = 0.65, P < 0.0001	90%, κ = -0.04, P = 0.61	98%, κ = 0.88, P < 0.0001
Serogranular drusen	95%, κ = 0.49, P < 0.0001		
Hyperpigmentation (presence)	95% κ = 0.84 P < 0.0001	88% κ = 0.61 P < 0.0001	91%, κ = 0.47, P < 0.0001
Hyperpigmentation (type)	95% κ = 0.83 P < 0.0001	100% NP NP	91%, κ = 0.46, P < 0.0001
Hypopigmentation (presence)	100% κ = 1.0 P < 0.0001	100% NP NP	100%, NP, NP
Geographic atrophy (presence)	100% κ = 1.0, P < 0.0001	98%, κ = 0.93, P < 0.0001	95%, κ = 0.88, P < 0.0001
Neovascular AMD (presence)	95%, κ = 1.0, P < 0.0001	86%, κ = 0.52, P < 0.0001	95%, κ = 0.65, P < 0.0001
Neovascular AMD (features)	98%, κ = 0.79, P < 0.0001	98%, κ = 0.79, P < 0.0001	100%, κ = 1.0, P < 0.0001
Neovascular AMD (scar/fibrous)	100%, κ = 1.0, P < 0.0001	91% κ = 0.56 P < 0.0001	95% κ = 0.00 NP
Neovascular AMD (retinal haemorrhage)	98%, κ = 0.00, P = 0.5000	98%, κ = 0.79, P < 0.0001	100%, κ = 1.0, P < 0.0001
Area covered by neovascular AMD		86%, κ = 0.62, P < 0.0001	
Area covered by geographic atrophy		88% κ = 0.74, P < 0.0001	
Area covered by drusen		67%, κ = 0.43, P < 0.0001	
Predominant phenotype		95%, κ = 0.94, P < 0.0001	
Image quality		59%, κ = 0.30, P = 0.0018	

Abbreviation: NP, not possible to compute.

Table 2 Inter-observer variability

	Zone 1	Zone 2	Zone 3
Drusen <63 μm (hard drusen)	67%, κ = 0.36, P < 0.0001	64%, κ = 0.45, P < 0.0001	62%, κ = 0.46, P < 0.0001
Drusen 63–125 μm (intermediate soft drusen)	83%, κ = 0.64, P < 0.0001	74%, κ = 0.60, P < 0.0001	74%, κ = 0.62, P < 0.0001
Drusen 125–250 μm (large semisolid drusen distinct, subconfluent, confluent)	100, 100, 100%, κ = 1.0, κ = 1.0, κ = 1.0, P < 0.0001, P < 0.0001, P < 0.0001	79, 93, 98%, κ = 0.08, κ = 0.36, κ = 0.84, P = 0.257, P = 0.0079, P < 0.0001	71, 91, 95%, κ = 0.18, κ = 0.61, κ = 0.00, P = 0.02, P < 0.0001, NP
Drusen 250–500 μm (large semisolid drusen distinct, subconfluent, confluent)	100, 100, 100%, κ = 1.0, κ = 1.0, κ = 1.0, P < 0.0001, P < 0.0001, P < 0.0001	100, 100, 95%, NP, NP, κ = 0.00, NP, NP, NP	95, 98, 98%, κ = 0.0, κ = 0.00, κ = 0.00, NP, P = 0.5, P = 0.5
Drusen > 500 μm (large semisolid drusen distinct, subconfluent, confluent)	100, 100, 97%, κ = 1, κ = 1, κ = 0.66, P < 0.0001, P < 0.0001, P < 0.0001	100, 95, 91%, NP, κ = -0.024, κ = -0.018, NP, P = 0.56, P = 0.61	100, 98, 93%, NP, κ = 0.000, κ = 0.00 NP, P = 0.5, NP
Crystalline drusen	100%, κ = 1.0 P < 0.0001	95%, κ = 0.48, P < 0.0001	98%, κ = 0.87, P < 0.0001
Serogranular drusen	95%, κ = 0.49, P < 0.0001		
Hyperpigmentation (presence)	91%, κ = 0.67, P < 0.0001	93%, κ = 0.77, P < 0.0001	95%, κ = 0.73, P < 0.0001
Hyperpigmentation (type)	91%, κ = 0.67, P < 0.0001	93%, κ = 0.77, P < 0.0001	95%, κ = 0.73, P < 0.0001
Hypopigmentation (presence)	95%, NP, NP	100%, NP, NP	100%, NP, NP
Geographic atrophy (presence)	100%, κ = 1.0, P < 0.0001	98%, κ = 0.93, P < 0.0001	91%, κ = 0.77, P < 0.0001
Neovascular AMD (presence)	95%, κ = 0.87, P < 0.0001	93%, κ = 0.75, P < 0.0001	95%, κ = 0.65, P < 0.0001
Neovascular AMD (features)	98%, κ = 0.79, P < 0.0001	98%, κ = 0.79, P < 0.0001	100%, κ = 1.0, P < 0.0001
Neovascular AMD (scar/fibrous)	95%, κ = 0.84, P < 0.0001	95%, κ = 0.78, P < 0.0001	95%, κ = 0.00, NP
Neovascular AMD (retinal haemorrhage)	98%, κ = 0.000, P = 0.5	98%, κ = 0.79, P < 0.0001	100%, κ = 1.0, P < 0.0001
Area covered by neovascular AMD		93%, κ = 0.81, P < 0.0001	
Area covered by geographic atrophy		95%, κ = 0.89, P < 0.0001	
Area covered by drusen		79%, κ = 0.63 P < 0.0001	
Predominant phenotype		95% κ = 0.94, P < 0.0001	
Image quality		55%, κ = 0.23, P = 0.0103	

Abbreviation: NP, not possible to compute.

Table 3 Intra-observer variability

	Zone 1	Zone 2	Zone 3
Drusen <63 μm (hard drusen)	76%, κ = 0.59, P < 0.0001	81%, κ = 0.71, P = 0.0001	76%, κ = 0.67, P < 0.0001
Drusen 63–125 μm (intermediate soft drusen)	95%, κ = 0.90, P < 0.0001	81%, κ = 0.73, P < 0.0001	86%, κ = 0.79, P < 0.0001
Drusen 125–250 μm (large semisolid drusen distinct, subconfluent, confluent)	100; 100; 100%, κ = 1.00; κ = 1.00; P < 0.0001; P < 0.0001; P < 0.0001	95, 90, 88%, κ = -0.01, κ = -0.02, κ = -0.02, P = 0.5628, P = 0.6105, P = 0.6287	93, 79, 83%, κ = -0.02, κ = -0.02, κ = -0.02, P = 0.5895, P = 0.6883, P = 0.6603
Drusen 250–500 μm (large semisolid drusen distinct, subconfluent, confluent)	100, 98, 100%, κ = 1.00, κ = 0.66, κ = 1.00 P < 0.0001, P < 0.0001, P < 0.0001	95, 95, 98%, κ = -0.01, κ = 0.00, κ = 0.00, P = 0.5628, P = NP, P = 0.50	95, 95, 98%, κ = -0.0120, κ = 0.00, κ = 0.00, P = 0.5628, P = NP, P = 0.5
Drusen > 500 μm (large semisolid drusen distinct, subconfluent, confluent)	100, 100, 98%, κ = 1.00, κ = 1.00, κ = 0.66, P < 0.0001, P < 0.0001, P < 0.0001	TFC, 98, 98%, NP, κ = 0.00, κ = 0.49, NP, P = 0.5, P < 0.0001	TFC, TFC, TFC, NP, κ = NP, κ = NP κ = NP, P = NP, P = NP, P = NP
Hyperpigmentation (presence)	100%, κ = 1.00, P < 0.0001	98%, κ = 0.91, P < 0.0001	100%, κ = 1.00, P < 0.0001
Hyperpigmentation (type)	100%, κ = 1.00, P < 0.0001	98%, κ = 0.91, P < 0.0001	98%, κ = 0.86, P < 0.0001
Hypopigmentation (presence)	TFC, NP, NP	TFC, NP, NP	98%, κ = 0.00, P = 0.5
Geographic atrophy (presence)	100%, κ = 1.00, P < 0.0001	100%, κ = 1.00, P < 0.0001	98%, κ = 0.93, P < 0.0001
Neovascular AMD (presence)	100%, κ = 1.00, P < 0.0001	98%, κ = 0.93, P < 0.0001	100.00%, κ = 1.00, P < 0.0001
Neovascular AMD (features)	100%, κ = 1.00, P < 0.0001	100%, κ = 1.00, P < 0.0001	98%, κ = 0.74, P < 0.0001
Neovascular AMD (scar/fibrous)	98%, κ = 0.93, P < 0.0001	98%, κ = 0.91, P < 0.0001	100%, κ = 1.00, P < 0.0001
Neovascular AMD (retinal haemorrhage)	100%, κ = 1.00, P < 0.0001	98%, κ = 0.79, P < 0.0001	98%, κ = 0.79, P < 0.0001
Area covered by neovascular AMD		100%, κ = 1.0, P < 0.0001	
Area covered by geographic atrophy		98%, κ = 0.94, P < 0.0001	
Area covered by drusen		95%, κ = 0.92, P < 0.0001	
Predominant phenotype		100%, κ = 1.00, P < 0.0001	
Image quality		52%, κ = 0.30, P = 0.0005	

Abbreviations: NP, not possible to compute; TFC, too few rating categories.

compared grading of ultra wide-angle images and conventional digital images using the IC system developed earlier.⁷ Our first observation was that although all ultra wide-angle images were gradable, there were nine conventional images that fell short of grading standards, predominantly due to media opacities and technical difficulties with positioning the patient for long enough to take gradable images. As lasers are much less susceptible to any media opacities^{18,19} and they outperform even very high resolution digital images in terms of sharpness and contrast,²⁰ the better image quality is perhaps not surprising. However, it must be acknowledged that new graders must learn to appreciate artifacts related to the broad depth of focus of this device, such as the presence of eyelids, eyelashes, floaters (eg, see Supplementary Figure 1), the optics and the haptics of the intraocular lens or lens opacities. Also the image, as it is generated by green and red laser lights rather than the more widely used white light illumination, is unfamiliar to graders in the first instance. In our experience, most of these aspects can be overcome or minimised with practice and good imaging techniques. The camera can accommodate wheelchairs and there is no need to move the patient, a real advantage in imaging an elderly population similar to those in the Reykjavik Eye Study. In general, imaging did not require dilation, though when seeking to obtain the best quality of images in the most elderly and fragile dilation was necessary.

The phenotype of 112 eyes in this study showed a very high level of agreement between the image modalities, suggesting that the ultra wide-angle images of the P200C AF is a reliable way to identify fundus abnormalities. This was reinforced by the detailed grading of the select 21 eyes, which again showed good agreement between the grading of the two image modalities. Intra- and inter-grader variability was low (agreement was high) in both image modalities. Only one image was interpreted differently, and graded CNV by one grader and drusenoid PED by the other. This, however, is not unacceptable as to establish the correct diagnosis for PED fluorescent angiography would have been required. Despite the fact that the graders had a short learning period to understand the P200C AF images and get enough knowledge for grading small lesions and differentiate artifacts from real abnormalities the agreement was high with high κ -values, except in those instances where there were too few categories to compare. The identification of small hard drusen gave difficulties especially at the beginning of the grading. This is reflected in the somewhat lower agreement and κ -values. This might be attributed to the similarities between drusen and pixel sizes in the ultra wide-angle images. Small hyper- and hypo-pigmentation of the RPE

can be an early sign of AMD; however, grading pigment abnormalities from digital images had been shown to be difficult⁴ and our study confirmed this. Neither the conventional nor the ultra wide-angle images had good enough quality or resolution to reliably grade for small pigmentary changes.

On the basis of the concordance between the conventional (45°) and ultra wide-angle (200°) digital image grading in the macula, we were satisfied that the P200C AF images document drusen, GA, and CNV similar to those of colour digital images. This builds confidence in future peripheral retinal grading of the ultra-wide field images, which might highlight important, previously unrecognised abnormalities for the fuller understanding of the development and progression of AMD pathology. How, if at all, previously reported problems with the P200^{21,22} device in misdiagnosis and artefacts related to broad depth of field might affect far peripheral grading using P200C AF images remains to be evaluated.

Summary

What was known before

- Ultra wide-angle imaging is becoming more widely used and accepted in clinical settings. Yet information on its usability to detect and subsequently grade ARM and AMD pathologies has been lacking. As recent evidence points towards the need to analyse peripheral changes in relation to ARM and AMD, it is likely that cameras capable of peripheral imaging will become part of routine clinical care.

What this study adds

- To the best of our knowledge, this study is the first to describe the agreement between conventional and ultra wide-angle digital imaging modalities in grading ARM and AMD in the macula.
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Conflict of interest

The study and the fellowship of AC were part-funded by an unrestricted grant from OPTOS plc. The other authors declare no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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Supplementary Information accompanies the paper on Eye website (<http://www.nature.com/eye>)