



# Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2

*Age-Related Eye Disease Study 2 Report Number 12 by the Age-Related Eye Disease Study 2 Optos PEripheral RetinA (OPERA) Study Research Group\**

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**Purpose:** To compare rates of peripheral retinal changes in Age-Related Eye Disease Study 2 (AREDS2) participants with at least intermediate age-related macular degeneration (AMD) with control subjects without intermediate age-related changes (large drusen).

**Design:** Cross-sectional evaluation of clinic-based patients enrolled in AREDS2 and a prospective study.

**Participants:** Participants from prospective studies.

**Methods:** The 200° pseudocolor and fundus autofluorescence (FAF) images were captured on the Optos 200 Tx Ultrawide-field device (Optos, Dunfermline, Scotland) by centering on the fovea and then steering superiorly and inferiorly. The montaged images were graded at a reading center with the images divided into 3 zones (zone 1 [posterior pole], zone 2 [midperiphery], and zone 3 [far periphery]) to document the presence of peripheral lesions.

**Main Outcome Measures:** Peripheral retinal lesions: drusen, hypopigmentary/hyperpigmentary changes, reticular pseudodrusen, senile reticular pigmentary changes, cobblestone degeneration, and FAF abnormalities.

**Results:** A total of 484 (951 eyes) AREDS2 participants with AMD (cases) and 89 (163 eyes) controls without AMD had gradable color and FAF images. In zones 2 and 3, neovascularization and geographic atrophy (GA) were present, ranging from 0.4% to 6% in eyes of cases, respectively, and GA was present in 1% of eyes of controls. Drusen were detected in 97%, 78%, and 64% of eyes of cases and 48%, 21%, and 9% of eyes of controls in zones 2 and 3 superior and 3 inferior, respectively ( $P < 0.001$  for all). Peripheral reticular pseudodrusen were seen in 15%. Senile reticular pigmentary change was the predominant peripheral change seen in 48% of cases and 16% of controls in zone 2 ( $P < 0.001$ ). Nonreticular pigment changes were less frequent in the periphery than in the posterior pole (46% vs. 76%) and negligible in controls.

**Conclusions:** Peripheral retinal changes are more prevalent in eyes with AMD than in control eyes. Drusen are seen in a majority of eyes with AMD in both the mid and far periphery, whereas pigment changes and features of advanced AMD are less frequent. Age-related macular degeneration may be more than a “macular” condition but one that involves the entire retina. Future longitudinal studies of peripheral changes in AMD and their impact on visual function may contribute to understanding AMD pathogenesis. *Ophthalmology* 2016;■:1–9 Published by Elsevier on behalf of the American Academy of Ophthalmology



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Age-related macular degeneration (AMD), a heterogeneous disease with complex genetic associations, is the leading cause of blindness in the developed world.<sup>1</sup> Both pathologic and clinical studies have demonstrated the presence of peripheral retinal changes, including retinal pigmentary changes and drusen in eyes with AMD.<sup>2,3</sup> Some of the

lesions of neovascular AMD in a study of autopsy eyes were located not only in the macula but also in the retinal periphery.<sup>2</sup> The clinical significance of such peripheral retinal lesions in AMD is unknown. Until recently, these peripheral retinal changes were difficult to document. However, with the development of the ultrawide-field imaging using the

Optos 200T× imaging device (Optos, Dunfermline, Scotland), changes in the retinal periphery can be reproducibly imaged. Optos is an scanning laser ophthalmoscopy–based system with an ellipsoidal mirror that permits simultaneous central pole-to-periphery visualization of up to 200° of the retina with or without mydriasis. Color images are captured in pseudocolor using 2-color laser, red (633 nm) and green (532 nm) wavelengths.<sup>4</sup> Fundus autofluorescence (FAF) also can be obtained using the green 532 nm laser for excitation and an emission filter (570–780 nm) to detect the autofluorescence. This technology has been described in previous studies evaluating the retinal periphery of persons with AMD in both a clinic-based study and a population-based study.<sup>5,6</sup>

We conducted an ancillary study of imaging the peripheral retina in persons with at least intermediate AMD enrolled in the Age-Related Eye Disease Study 2 (AREDS2) and controls from 2 AREDS2 clinical sites (Duke University and the National Eye Institute). The purpose of this ancillary study was to examine the frequency of peripheral retinal alterations and to compare with controls to determine whether these peripheral changes were due mostly to aging rather than AMD.

## Methods

### Study Population

The study design for AREDS2 is described in detail in a previous report but briefly summarized in the current article (AREDS2, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00345176) identifier NCT00345176).<sup>7</sup> Between 2006 and 2008, 4203 participants ranging from 50 to 85 years of age were enrolled at 82 retinal specialty clinics in the United States. At enrollment, participants were included if they had bilateral large drusen or unilateral advanced AMD in 1 eye and large drusen in the fellow eye. The AREDS2 participants were randomly assigned to placebo, lutein/zeaxanthin, docosahexaenoic acid plus eicosapentaenoic acid, or the combination. Although baseline and annual conventional 45° stereoscopic fundus photographs were obtained by certified photographers, we obtained at AREDS2 close-out study visits (2011–2012) additional fundus photographs using the Optos ultrawide-field imaging up to 200° in 17 AREDS2 clinics. In 2 of these AREDS2 clinics, additional studies of AMD were conducted and the participants provided the controls for this study. The controls with no evidence of posterior AMD were enrolled in another ancillary AREDS2 study of prospective spectral domain-optical coherence tomography imaging, which was conducted to evaluate the correlation of optical coherence tomography changes with progression of AMD detected on color fundus photographs and FAF (A2A SDOCT Study, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00734487) identifier NCT00734487). A study of dark adaptation using the AdaptRx dark adaptometer (MacuLogix, Atlanta, GA) in persons with varying degrees of AMD also recruited controls without posterior changes of AMD. Controls from these 2 studies were imaged with the Optos device.

This AREDS2 OPTOS PERIPHERAL RetinA (OPERA) Study was reviewed and approved by each of the institutional review boards, and written informed consent was obtained from all participants. The research was conducted according to the tenets of the Declaration of Helsinki.

### Imaging Protocol

All photographers, who were certified by Optos personnel for acquiring images according to a standardized protocol, obtained

200° images that were first centered at the fovea (on axis) and then steered superiorly and inferiorly, using the fixation light within the equipment to guide the steering. These 3 images were then montaged into 1 single image (Fig 1). This protocol was used for acquiring both the color fundus photographs and the FAF images.

### Grading Protocol

All images were assessed by trained graders using a standardized protocol at the University of Wisconsin Fundus Photograph Reading Center. A circular grid with 3 concentric circles was placed centered at a midpoint between the temporal edge of the optic nerve and center of fovea (Fig 1). The grid contains 3 zones and is adapted from the Study of Ocular Complication of AIDS, which assessed cytomegalovirus retinitis in the retinal periphery.<sup>8</sup> Zone 1 has a radius of approximately 5.4 mm (3 disc diameters) and roughly corresponds to the posterior pole. Zone 2 extends from the edge of zone 1 anteriorly with a radius of 16.2 mm (9 disc diameters) and overlaps the vortex veins. Zone 3 is the region anterior to zone 2. Zones 1 and 2 are divided into 4 quadrants: superonasal, superotemporal, inferonasal, and inferotemporal. Zone 3 is divided into superior and inferior hemispheres. A properly aligned grid fulfills 2 criteria: The center point of zone 1 corresponds to the center of the line that connects the disc and macula; the outer circle dividing zone 2 and zone 3 crosses the vortex veins at approximately 3 or more vascular landmarks. Both mounting of the grid and viewing of images were performed in proprietary software provided by Optos (V2vantage Software).

The ability to grade was assessed for the entire image initially and then for each zone separately. For the entire image to be considered gradable, the grid had to be properly aligned. A montage was considered to be the best quality if both zones 1 and 2 were gradable in all quadrants, borderline quality if 1 or more quadrants in zones 1 and 2 were ungradable, and poor quality if all subfields in both zones 1 and 2 were ungradable. For a subfield with a zone to be considered gradable, at least 50% of the subfield had to be visible.

Similar to standard color photographic grading for AREDS2, the grader first evaluated neovascular AMD characteristics.<sup>9</sup> Presence of neovascular AMD was assessed in zone 1 as a whole and for each quadrant in zone 2 and each hemisphere in zone 3. Definite presence is documented when at least 2 of the 5 features are consistent with neovascular AMD (subretinal fluid, intraretinal, subretinal, or subretinal pigment epithelium blood associated with neovascular AMD, intraretinal lipid exudates, subretinal fibrin or fibrosis, and fibrovascular or serous pigment epithelial detachment). The presence of a disciform scar by itself was considered definite neovascular AMD.

Presence of drusen, increased pigment, decreased pigment, and geographic atrophy (GA) was evaluated in each quadrant of zones 1 and 2 and each hemisphere of zone 3. Detailed assessment of drusen included a categoric count of large drusen in each subfield as 1 to 5, 6 to 20, or >20. Presence and percentage involvement of a subfield with reticular pseudodrusen were graded as <25%, 25% to 49%, 50% to 74%, and ≥75%. Peripheral abnormalities are evaluated in each subfield of zone 2 and each hemisphere of zone 3 and include reticular pigment changes, lattice, and cobblestone degeneration.

Autofluorescence montages were overlaid with a grid and assessed for image quality similar to color photographs. Both color and autofluorescence images were evaluated together by the same grader. Presence of hypoautofluorescence and hyperautofluorescence adjacent to hypoautofluorescence (halo) was graded. Any other area of hyperautofluorescence greater than drusen circle C2 (>250 μ) was noted. Presence of reticular pseudodrusen from autofluorescence images and percentage involvement of a subfield were graded as <25%, 25% to 49%, 50% to 74%, and ≥75%. Peripheral

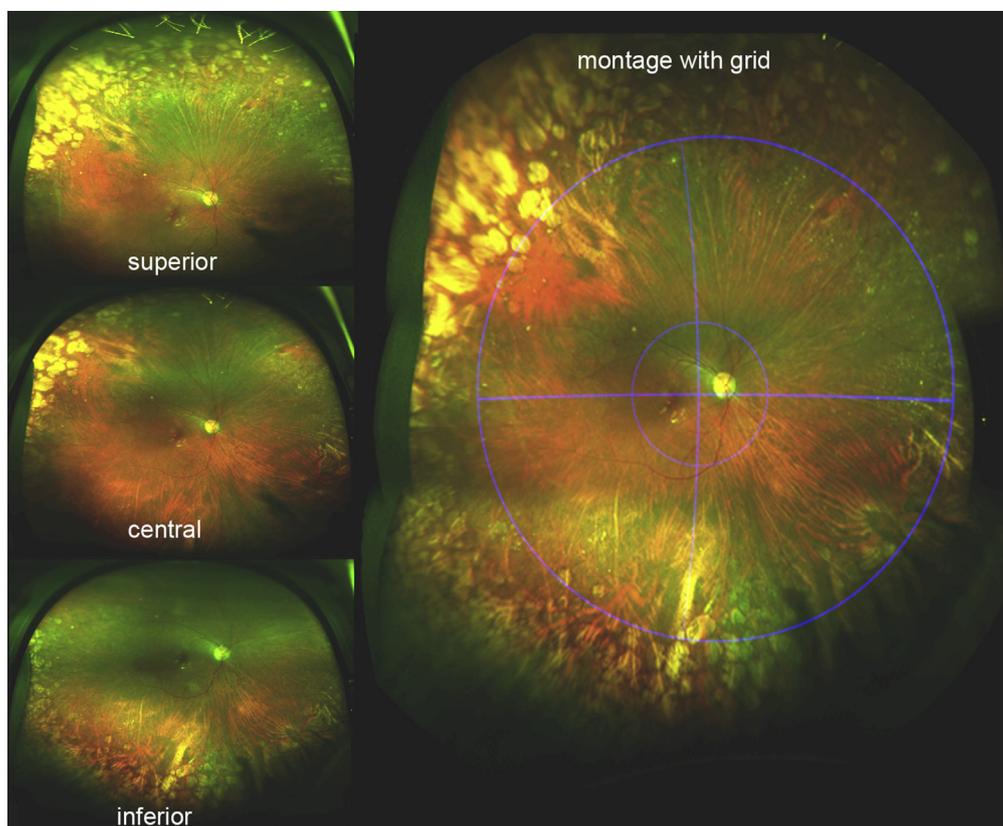


Figure 1. Central, superior, and inferior steered images are shown on the left. Montage of the 3 images with grid overlay is shown on the right.

abnormalities on autofluorescence images corresponding to cobblestone degeneration (nummular hypoautofluorescence) or reticular pigment changes were assessed. Peripheral autofluorescence changes not corresponding to any pathology on color photographs were evaluated.

## Statistical Methodology

Each characteristic of interest was categorized by the prevalence proportions among the cases and controls and were compared using generalized linear model with a logit link function for binary data and the generalized estimating equation methodology to account for clustered (eye) data. Sensitivity analyses were conducted by limiting the cohort to include cases and a subset of age-matched controls. The statistical significance level used was  $\leq 0.05$ . Data were analyzed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

## Results

Seventeen of the 82 AREDS2 clinical sites participated in this ancillary study and imaged 575 participants (1147 eyes) with AMD and 184 (358 eyes) controls. Of these, 484 (951 eyes) AREDS2 participants with AMD (cases) had gradable images and were used in this analysis. Of the controls, 89 participants (163 eyes) who had gradable ultrawide-field color and FAF images and who were found to have no evidence of large drusen were considered true controls. The mean ages were 79.0 years (71.7–83.8) and 69.5 years (64.0–74.6) for those with AMD and controls, respectively.

Some 60% and 55% of the populations were female with AMD and without AMD, respectively (Table 1).

Zone 1 (posterior pole) was gradable in 100% of cases, zone 2 (midperiphery) was gradable in 98% of cases, zone 3 (far

Table 1. Baseline Characteristics of Participants Enrolled in Age-Related Eye Disease Study 2 Ancillary Optos PEripheral RetinA Study

	Participant Demographic and Ocular Characteristics	Cases N = 484 (951 Eyes)	Controls N = 89 (163 Eyes)
Race	White	98%	95%
	African American	1%	1%
	Other/mixed race	1%	3%
	Female	60%	55%
Sex	Female	60%	55%
Age at eye examination and fundus photography	Median (IQR range) (yrs)	79.0 (71.7–83.8)	69.5 (64.0–74.6)
AMD status in zone 1 or posterior pole	Large drusen	100%	None
	Neovascular AMD	30%	None
	GA (any location in zone 1)	24%	None

AMD = age-related macular degeneration; GA = geographic atrophy; IQR = interquartile range.

periphery) superior hemisphere was gradable in 90% of cases, and inferior hemisphere was gradable in 60.5% of cases with similar distribution in the controls. Age-related macular degeneration—specific lesions (drusen, pigment changes, atrophy, or neovascular lesions) were seen in zone 2 in 100% of cases and 48% of controls. In zone 3, 78% of cases had AMD-related lesions versus 21% in controls.

### Advanced Age-Related Macular Degeneration in Peripheral Retina

Lesions of advanced AMD in both cases and controls were not frequently detected in the various zones (Table 2). Neovascularization (5%) and GA (6%) were present in cases, and GA was present in 1% of controls in zone 2 (Fig 2A and B). In cases, GA was seen in 2% in the superior zone 3 and 4% in the inferior zone 3. In controls, 0.5% was seen in the superior zone 3 and 2% was seen in the inferior zone 3.

### Drusen and Reticular Pseudodrusen

Nonadvanced AMD lesions are tabulated for each zone in Table 2. Drusen were detected more frequently in eyes of cases, 97%, 78%, and 64%, than in eyes of controls, 48%, 21%, and 9%, in zones 2 and 3 superior and inferior, respectively ( $P < 0.001$  for all 3 comparisons). Reticular pseudodrusen was present only in cases: 11%, 15%, 1%, and 0.4% in zones 1, 2, and 3 superior and inferior, respectively (Fig 3 composite).

### Pigmentary Changes

Nonreticular hyperpigmentary changes (Table 2) were seen more commonly in cases: 46% and 18% of eyes of cases and controls, respectively, in zone 2; 19% and 6% of eyes of cases and controls, respectively, in zone 3 superiorly, and 17% and 7% of eyes in cases and controls, respectively, in zone 3 inferior ( $P < 0.001$ ,  $P < 0.001$ , and  $P < 0.007$ , respectively). Hypopigmentary changes were detected mostly in cases: 27%,

10%, and 9% in zones 2, 3 superior and 3 inferior, respectively, whereas controls had 1% in zone 2 only ( $P < 0.001$  for zone 2;  $P$  values for the zone 3 areas could not be computed).

### Other Peripheral Degenerations

Other peripheral degenerations that are not traditionally associated with AMD were compared between cases and controls (Table 3). Cobblestone degeneration was seen in comparable frequency between the cases, 12%, 18%, and 30%, and controls, 11%, 11%, and 27%, in zones 2, 3 superior, and 3 inferior, respectively ( $P = 0.88$ , 0.45, and 0.83, respectively). Reticular pigmentary changes were seen in slightly greater frequency for cases, 72%, 62%, and 51%, and controls, 63%, 27%, and 36%, in zones 2, 3 superior, and 3 inferior, respectively ( $P < 0.001$  for each comparison; Fig 4A and B). In the category of other peripheral retinal changes, we included white without pressure, laser scar, diffuse depigmentation, and vitreous floaters. These were detected more frequently in the controls, with 26%, 61%, and 36% affected in zones 2, 3 superior, and 3 inferior, whereas only 24%, 20%, and 19% of the AMD cases were affected in these respective zones. However, the numbers of controls are limited in these analyses.

### Fundus Autofluorescence Images

Abnormal autofluorescence was detected more frequently in cases, 82%, 52%, and 45%, than in controls, 28%, 8%, and 12% in zones 2, 3 superior, and 3 inferior, respectively ( $P < 0.001$  for all 3 comparisons; Table 4). Hypoautofluorescence was detected in 19%, 8%, and 13% of eyes of cases and 9%, 6%, and 8% of controls in zones 2, 3 superior, and 3 inferior, respectively ( $P = 0.005$ , 0.54, and 0.18, respectively). Hyperautofluorescence was detected in 3%, 0.5%, and 1% of eyes of cases and 5%, 0%, and 1% of eyes of controls in zones 2, 3 superior, and 3 inferior, respectively ( $P = 0.19$ , not available,  $P = 0.75$ , respectively). Reticular FAF, which is considered to represent reticular pseudodrusen, was present in 6%,

Table 2. Comparison of Cases with All Controls for Presence of Neovascularization, Geographic Atrophy, or other Peripheral Retinal Features on Color Photographs on Optos

	Neovascular AMD*		GA*		Drusen <sup>†</sup>		RPE Hyperpigmentation <sup>‡</sup>		RPE Hypopigmentation <sup>§</sup>		Reticular Pseudodrusen*	
	n	%	n	%	n	%	n	%	n	%	n	%
Cases (AMD)												
Zone 1	282/951	30%	166/689	24%	669/684	98%	526/689	76%	400/689	58%	103/929	11%
Zone 2	49/933	5%	52/932	6%	903/928	97%	431/932	46%	249/932	27%	139/933	15%
Zone 3 superior	4/856	0.5%	16/854	2%	657/847	78%	165/854	19%	87/854	10%	9/852	1%
Zone 3 inferior	2/575	0.3%	21/564	4%	356/560	64%	94/565	17%	53/560	9%	2/560	0.4%
Controls												
Zone 1	0/163	—	0/162	—	32/154	21%	0	—	0	—	0	—
Zone 2	0/163	—	2/162	2%	66/136	48%	29/159	18%	2/162	1%	0	—
Zone 3 superior	0/143	—	1/143	0.7%	23/109	21%	8/141	6%	0	—	0	—
Zone 3 inferior	0/123	—	1/119	0.8%	10/117	9%	8/120	7%	0	—	0	—

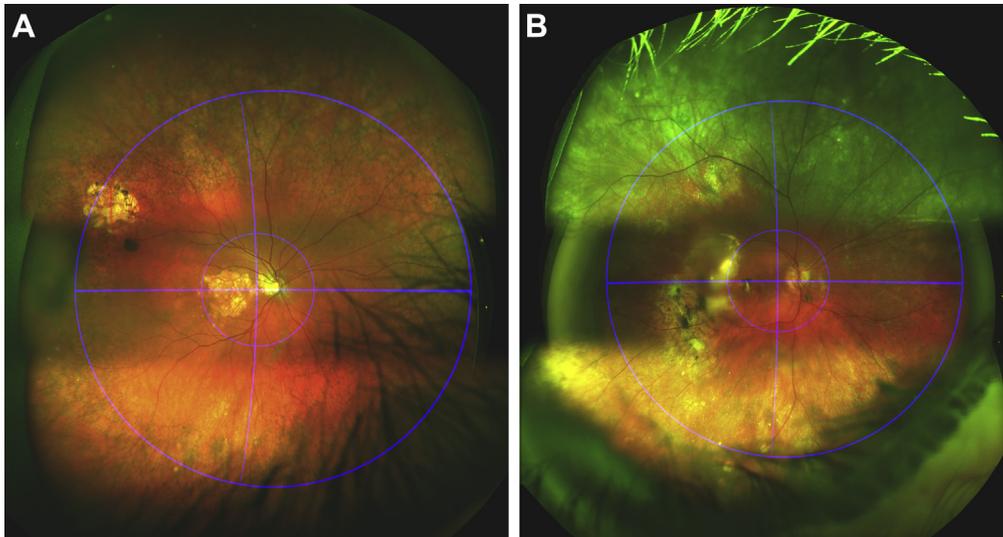
AMD = age-related macular degeneration; GA = geographic atrophy; RPE = retinal pigment epithelium.

\*No statistical analyses can be performed because of absence of or limited features in the controls.

<sup>†</sup>Drusen: defined as  $<125 \mu\text{m}$ . Controls may have small- or medium-sized drusen, whereas all AMD cases had large drusen,  $\geq 125 \mu\text{m}$ .  $P$  values: drusen:  $<0.001$  for comparisons in all zones.

<sup>‡</sup> $P$  values: RPE hyperpigmentation:  $<0.001$ ,  $<0.001$ , and 0.007, for zones 2, 3 superior, and 3 inferior, respectively.

<sup>§</sup> $P$  value: RPE hypopigmentation:  $<0.001$  for zones 2 and 3 could not be calculated.



**Figure 2.** Ultrawide-field images with advanced age-related macular degeneration (AMD) in peripheral retina. **A**, Geographic atrophy (GA) in zone 1, 2, and 3 shows an area of GA and senile reticular degeneration. **B**, Features of neovascular AMD, atrophy, and fibrosis in zone 2.

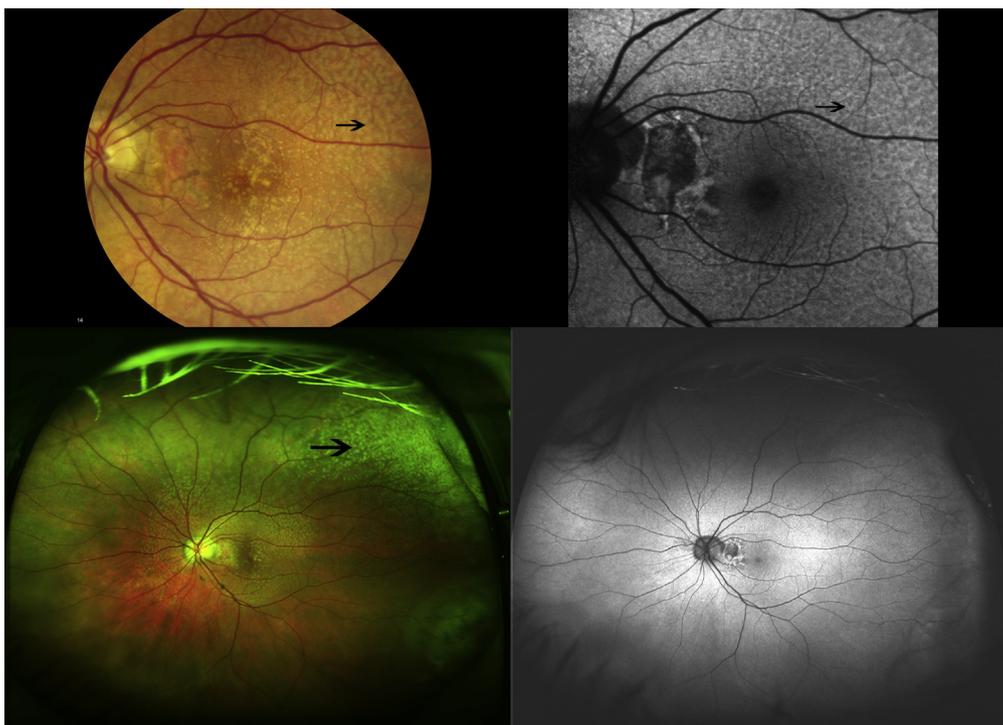
8%, 2%, and 1% in zones 1, 2, 3 superior, and 3 inferior, respectively, whereas no controls demonstrated reticular FAF.

### Intergrader Agreement

Intergrader agreement was tested by reevaluation of 30 eyes (Table 5). Percentage agreements were in the range of 73% to 100% for features of advanced AMD and 53% to 87% for nonadvanced AMD features, with decreasing agreements in zone 3 inferior.

### Sensitivity Analyses

Because of the differences in the ages between the cases and controls, additional sensitivity analyses were conducted by limiting our analyses only to controls who were age matched to our cases ( $N = 25$  [47 eyes]). The median age was 77.2 years in cases compared with 76.2 years for the age-matched controls (not statistically significant). These sensitivity analyses confirmed similar results with statistically significant differences in the peripheral lesions between the cases and age-matched controls (Table 6 and Table 7,



**Figure 3.** Top row shows standard 30° color and autofluorescence images, and arrows point to reticular pseudodrusen. Bottom row shows ultrawide-field images with arrow pointing to reticular pseudodrusen on color photograph. The pathology is not clearly visible on the autofluorescence images.

Table 3. Peripheral Retinal Abnormalities in Cases (Age-Related Macular Degeneration) and Controls on Color Photographs on Optos

	All Peripheral Abnormalities		Cobblestone Degeneration		Senile Reticular Pigmentary Changes		Other	
	n	%	n	%	n	%	n	%
Cases (AMD)								
Zone 2*	442	48%	54	12%	319	72%	108	24%
Zone 3 superior	323	38%	59	18%	201	62%	63	20%
Zone 3 inferior	183	32%	55	30%	94	51%	34	19%
Controls								
Zone 2*	26	16%	3	11%	17	63%	7	26%
Zone 3 superior	18	13%	2	11%	5	27%	11	61%
Zone 3 inferior	11	9%	3	27%	4	36%	4	36%

AMD = age-related macular degeneration.

Other included white without pressure, laser scar, diffuse depigmentation, and vitreous floaters.

\*1 (0.2%) in zone 2 coded as lattice.

Cobblestone degeneration:  $P = 0.88, 0.45,$  and  $0.83$  for zones 2, 3 superior, and 3 inferior, respectively. Senile reticular pigmentary changes:  $P < 0.001$  for each comparison.

available at [www.aajournal.org](http://www.aajournal.org)). The AMD-associated lesions were more prevalent in the eyes of AMD. No peripheral neovascularization was seen in the periphery of age-matched controls, and only GA was seen in zone 2 of one of the age-matched controls (Table 6). In addition, drusen and retinal pigment epithelial changes were statistically significantly more common in AMD cases than in their age-matched controls (Table 6).

## Discussion

By using the AREDS2 Optos PERipheral RetinA Study grading method, AMD-associated lesions were seen in both cases with AMD and in controls, but they were more prevalent in the eyes with AMD. A major limitation is the difference in the ages of the cases and controls. How valid are such data given that the controls are younger than the cases? We believe the sensitivity analyses limited to age-matched controls showed similar results, validating our findings.

Given the prevalence in controls, is AMD an exaggeration of the normal aging process? Certainly, our controls, who are defined as those without large drusen, may have small- and medium-size drusen in zone 1. The AREDS data suggest that 50% of eyes affected with medium sized-drusen bilaterally eventually may lead to the development of large drusen in 5 years.<sup>10</sup> Therefore, such eyes may develop drusen and other lesions associated with AMD in the retinal periphery. In addition, the peripheral fundus phenotypes we describe are likely related to complex polygenetic interactions just as in AMD, yielding imperfect associations with posterior pole disease. Finally, the location of drusen and not just their presence has been described as being relevant to the risk of development of choroidal neovascularization in AMD.<sup>11</sup>

Although areas of GA and neovascularization were detected in zones 2 and 3 of cases with AMD, the rates were smaller than those suggested by Sarks<sup>2</sup> in an autopsy study of neovascularization. In a cohort of 80 patients, Sarks<sup>2</sup> found 56.6% were in the macula and 33.4% were in the periphery,

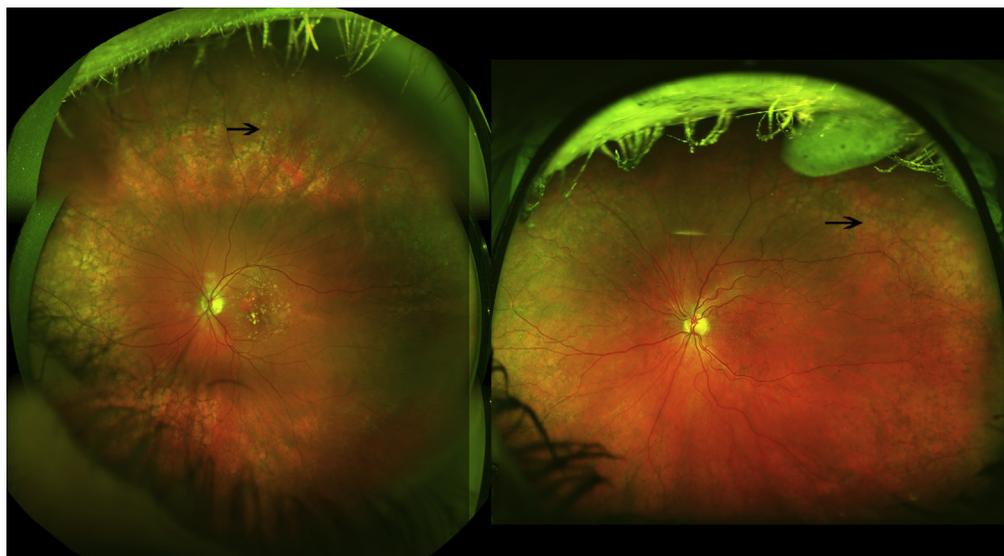


Figure 4. Reticular pigment changes in periphery (arrows) in an eye with age-related macular degeneration (AMD) (left) and a normal control eye (right).

Table 4. Abnormalities on Fundus Autofluorescence Images on Optos

	Abnormal FAF*		Hypo-FAF <sup>†</sup>		Hyper-FAF <sup>‡</sup>		Reticular FAF <sup>§</sup>	
Cases (AMD)								
Zone 1	855	93%	460	50%	91	10%	53	6%
Zone 2	741	82%	169	19%	27	3%	70	8%
Zone 3 superior	404	52%	62	8%	4	0.5%	16	2%
Zone 3 inferior	234	45%	70	13%	4	1.0%	8	1%
Controls								
Zone 1	9	6%	3	2%	3	2%	0	–
Zone 2	42	28%	14	9%	8	5%	0	–
Zone 3 superior	9	8%	7	6%	0	–	0	–
Zone 3 inferior	11	12%	7	8%	1	1%	0	–

AMD = age-related macular degeneration; FAF = fundus autofluorescence.

\*Abnormal FAF  $P < 0.001$  in comparisons of all 4 zones.

<sup>†</sup>Hypo-FAF,  $P = 0.005, 0.54,$  and  $0.18,$  for zones 2, 3 superior, and 3 inferior, respectively.

<sup>‡</sup>Hyper-FAF,  $P = 0.19,$  not available,  $0.75,$  for zones 2, 3 superior, and 3 inferior, respectively.

<sup>§</sup>Reticular FAF,  $P$  values cannot be calculated with no events in the controls.

including the peripapillary area. The neovascularization found on pathologic specimens was not clinically evident. It is possible that such neovascularization is subclinical in the AREDS2 population.

Of note, for those with large drusen in the macular area, almost all of these cases also had drusen detected in the periphery, both zones 2 and 3. However, peripheral pigment changes were not as prevalent compared with the posterior pole. The corresponding areas in autofluorescence images did not show notable abnormalities in the majority of eyes. Because this is only a cross-sectional study, we do not have the natural course of these peripheral retinal changes in relationship to the development and progression in the macula. An important next step would be to evaluate participants with early and intermediate AMD to evaluate the natural course of the development and progression of drusen

in the periphery. An additional step that may be clinically relevant would be to incorporate retinal function testing, such as dark adaptation or scotopic/mesopic microperimetry, to assess the potential correlation of these peripheral retinal lesions on global retinal function.

Reticular pseudodrusen most often are detected using blue light autofluorescence or near-infrared imaging and often are not visible on color photographs. In AREDS2, an ancillary study of blue light FAF using the Heidelberg Retina Angiograph II or Spectralis (Heidelberg Engineering) was performed on a subset of participants. A preliminary analysis showed reticular pseudodrusen in 11% of eyes with autofluorescence imaging and 5% with color photographs.<sup>12</sup> This study acquired images that were approximately 45° and may miss some of the lesions that are found superior to the posterior arcades. This study that captures the ultrawide-field green light autofluorescence images yielded a lower proportion of eyes affected with reticular pseudodrusen despite the wider coverage of the retinal area. The green wavelengths may not be ideal for capturing reticular pseudodrusen. Color photography in general is considered to be an inferior modality for imaging reticular pseudodrusen.<sup>13</sup> However, the Optos ultrawide-field color photographs had a higher rate of reticular pseudodrusen (11%) compared with ultrawide-field autofluorescence (8%) and traditional 45° color photographs (5%). Infrared imaging may be superior to blue autofluorescence for imaging of reticular pseudodrusen.<sup>13</sup> We found that reticular pseudodrusen appear to involve the midperiphery more than far periphery. It may be useful to use optical coherence tomography to verify such lesions in future studies.

Peripheral retinal abnormalities were found at a higher frequency in AMD cases than in controls. Senile reticular pigmentary changes in zone 2 were the most common lesions, present in 50% to 70% of eyes with any peripheral abnormality. In comparison, zone 3 involvement of this lesion was negligible. In a clinical-pathologic study of 750 eyes approximately 30 years ago, 100 eyes were found to have reticular degeneration of the retinal pigment. These results led the investigators to conclude that these lesions

Table 5. Intergrader Agreement for Evaluation of Age-Related Macular Degeneration Features from Ultrawide-field Color and Autofluorescence Images

	Zone 1	Zone 2	Zone 3 Superior	Zone 3 Inferior
Color				
Neovascular AMD	93%	100%	87%	73%
GA	87%	87%	87%	67%
Drusen	80%	80%	53%	53%
Hyperpigmentation	79%	53%	73%	67%
Hypopigmentation	71%	67%	85%	81%
Reticular drusen	79%	73%	80%	67%
Peripheral abnormalities (non-AMD)	NA	87%	73%	80%
Autofluorescence				
Abnormal AF	100%	87%	67%	53%
Hypoautofluorescence	80%	87%	73%	60%
Halo	93%	87%	87%	60%
Hyperautofluorescence	73%	87%	87%	60%
Reticular Autofluorescence	83%	73%	87%	60%

AF = autofluorescence; AMD = age-related macular degeneration; GA = geographic atrophy; NA = not available.

Table 6. Comparison of Cases with Age-Matched Controls for Presence of Neovascularization, Geographic Atrophy, or other Peripheral Retinal Features on Color Photographs on Optos

	Neovascular AMD*		GA*		Drusen <sup>†</sup>		RPE Hyperpigmentation <sup>‡</sup>		RPE Hypopigmentation <sup>§</sup>		Reticular Pseudodrusen*	
	n	%	n	%	n	%	n	%	n	%	n	%
Cases (AMD)												
Zone 1	282/951	30%	166/689	24%	669/684	98%	526/689	76%	400/689	58%	103/929	11%
Zone 2	49/933	5%	52/932	6%	903/928	97%	431/932	46%	249/932	27%	139/933	15%
Zone 3 superior	4/856	0.5%	16/854	2%	657/847	78%	165/854	19%	87/854	10%	9/852	1%
Zone 3 inferior	2/575	0.3%	21/564	4%	356/560	64%	94/565	17%	53/560	9%	2/560	0.4%
Controls												
Zone 1	0/47	—	0/47	—	11/46	24%	0	—	0	—	0	—
Zone 2	0/47	—	1/47	2%	20/43	46%	9/45	20%	1/47	2%	0	—
Zone 3 superior	0/42	—	0/42	—	7/37	19%	3/42	7%	0	—	0	—
Zone 3 inferior	0/35	—	0/32	—	4/31	13%	3/32	9%	0	—	0	—

AMD = age-related macular degeneration; GA = geographic atrophy; RPE = retinal pigment epithelium.

\*No statistical analyses can be performed because of the absence of features in the controls.

<sup>†</sup>Drusen: defined as <125  $\mu\text{m}$ . Controls may have small- or medium-sized drusen, whereas all AMD cases had large drusen,  $\geq 125 \mu\text{m}$ . *P* values: drusen: <0.001 for comparisons in all zones.

<sup>‡</sup>*P* values: RPE hyperpigmentation: 0.009, 0.14, and 0.28 for zones 2, 3 superior, and 3 inferior, respectively.

<sup>§</sup>*P* value: RPE hypopigmentation: 0.005 for zone 2.

were associated with AMD and to suggest that the peripheral retina should be examined in all patients with AMD.<sup>3</sup> In this study, it seems that these so-called senile reticular pigmentary changes in zone 2 are associated with AMD. In contrast, cobblestone degeneration was less frequent and of similar prevalence in both AMD cases and our controls, suggesting that this is not a peripheral retinal lesion associated with AMD. Of note, our definition of cobblestone degeneration GA is similar in that they are “small, discrete, circular or oval, yellowish white lesions with visible choroidal vessels involving a large area of the superior or inferior hemisphere.” Cobblestone degeneration is considered when multiple lesions are present, whereas GA refers to solitary or small groups of lesions. This overlapping definition may have resulted in some misclassification.

A previous study of color and FAF lesions in a prospective case series of patients with neovascular and non-neovascular AMD showed peripheral drusen (equivalent to the area outside zone 1 in our study) in 55% to 60% of eyes.<sup>5</sup> A population-based study found a high prevalence of peripheral AMD-like changes in 81%, with 57% having both macula and periphery involved. Approximately 50% of eyes with macular drusen had peripheral drusen.<sup>6</sup> Compared with both studies, our dataset had a higher rate with almost all eyes having peripheral drusen, possibly because of the more severe baseline level of AMD in the AREDS2 eyes.<sup>14</sup>

Previous studies have evaluated peripheral autofluorescence images by classification according to patterns.<sup>5,15</sup> Our current study did not use a classification, except for the nummular pattern that was graded as hypoautofluorescence corresponding to cobblestone degeneration or GA. Peripheral autofluorescence abnormalities were comparable in both studies, with a frequency of approximately 86% in those with neovascular AMD and 72.8% in those with non-neovascular AMD, whereas 18.4% were found in the controls in the previous series. The AREDS2 data appear to be similar, with 82% abnormal autofluorescence in cases and 28% in controls. Beyond these

generalizations, it is difficult to compare the results of the 2 studies because we grouped our data according to the 3 zones, which were not used in the previous study. This modality needs further research development to provide useful information from participants with and without AMD in the future.

Testing for genetic associations with the peripheral retinal lesions was the original impetus for this study (analysis in progress). Further evaluation of the burden or the extent of the peripheral drusen formation and other abnormalities may be important for genetic associations to identify specific phenotypes with varying risks of advanced AMD outcomes. It may be difficult to discriminate further because the genes that predispose to AMD may be responsible for these peripheral retinal lesions.

### Study Strengths and Limitations

The strengths of this study are in the rigorous standardization of the image acquisition and image grading. The steered view with projected and montage images along with grid overlay overcomes the frequently seen lash “artifact” to a large extent. The cases of AMD were well phenotyped with at least 5 prior annual fundus photographs available. The limitations include that this is only a cross-section evaluation of the ultrawide-field imaging and that the limited number of controls who were not age matched, as previously discussed. The sensitivity analyses with age-matched controls found in Tables 6 and 7 (available at [www.aaojournal.org](http://www.aaojournal.org)) suggest that these results are valid and robust because these results are similar to the results from the analyses using the entire group of controls.

In summary, the use of ultrawide-field imaging with both color and FAF has revealed a high number of eyes affected with peripheral retinal lesions, particularly drusen, therefore indicating a disease association more than just signs of exaggerated aging process. These data should be considered in the future classification of AMD, and longitudinal studies

using the Optos will be important in understanding the role of peripheral retina in this “macular” disease of AMD.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

**AMD** = age-related macular degeneration; **AREDS2** = Age-Related Eye Disease Study 2; **FAF** = fundus autofluorescence; **GA** = geographic atrophy.

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