Drusen Volume as a Predictor of Disease Progression in Patients With Late Age-Related Macular Degeneration in the Fellow Eye

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Purpose. Increasing drusen volume was proposed to be a predictor of disease progression in age-related macular degeneration (AMD). In patients with late AMD in one eye, the fellow eyes without neovascularization are known to be at higher risk of developing exudative AMD. We evaluated the relationship between drusen volume in these fellow eyes and their progression to late AMD.

Methods. A retrospective analysis included fellow eyes with drusen associated with nonexudative AMD. All eyes with neovascular AMD were treated with intravitreal ranibizumab, aflibercept, and/or bevacizumab and followed for 2 years. All eyes were scanned with the Cirrus HD-OCT using a 512 × 128 scan pattern. Optical coherence tomography (OCT) data at baseline, month 12, and month 24 were collected using the advanced RPE analysis tool to quantify drusen volume within 3- and 5-mm-diameter circles centered on the fovea. Optical coherence tomography scans were also evaluated for the development of geographic atrophy (GA) or macular neovascularization (MNV).

Results. Eighty-nine patients who had neovascular AMD in only one eye were studied. Optical coherence tomography drusen volume in the absence of MNV could be measured in 61 participants (68.5%). After 12 months, 4 eyes (4.5%) developed MNV and 15 eyes (16.9%) developed GA. By 24 months of follow-up, an additional 5 eyes (7.1%) developed MNV and an additional 10 eyes (14.3%) developed GA. At month 24, the eyes that developed GA or MNV had baseline drusen volumes that were significantly larger than in eyes that did not develop late AMD. Patients with a drusen volume over 0.03 mm3 had a greater than 4-fold increased risk for developing late AMD compared with those with lower drusen volumes.

Conclusions. Baseline drusen volume appears to be an important predictor for the development of late AMD within 2 years in eyes that have fellow eyes being actively treated for MNV. This suggests that OCT-derived drusen volume measurements may be a useful biomarker to identify eyes at the highest risk for progression to late AMD.

Keywords: macular degeneration, geographic atrophy, wet macular degeneration, retinal drusen, choroidal neovascularization, optical coherence tomography, drusen volume

Despite the availability of highly effective antiangiogenic therapies, age-related macular degeneration (AMD) remains a leading cause of blindness in developed nations.1,2 Multiple epidemiologic studies and clinical trials have evaluated phenotypic risk factors for the development of late AMD, defined as the development of macular neovascularization (MNV) or central geographic atrophy (GA; Refs. 3–7 and Abdelfattah NS, et al. IOVS 2015;56:ARVO E-Abstract 892). These major risk factors include the presence of large drusen, larger drusen areas, and pigmentary alterations, and these features have been incorporated into various scales used to predict the risk of developing late AMD over time.7–10 However, these features that predicted the risk of disease progression were restricted by the types of analyses that were possible using flash color film photography.10–13

Optical coherence tomography (OCT) has evolved into the dominant imaging technology that has largely supplanted flash fundus photography as the key diagnostic tool in the routine management of patients with AMD. Large drusen are well seen on OCT imaging as focal dome-shaped elevations of the retinal pigment epithelium (RPE) band, typically with a homogenous medium-reflective interior. Areas of RPE hyperpigmentation may be identified on OCT as intraretinal hyperreflective foci, and areas of RPE depigmentation can manifest as areas of subtle disruption, thinning, or irregularity of the RPE band. Due to the availability of high-density OCT scans through the macula using...
the newer spectral-domain and swept-source OCT systems, it is possible to compute the volume occupied by drusen that elevate the RPE. Recently, software for automated quantification of drusen volumes has been cleared by the Food and Drug Administration (FDA), and the natural history of drusen volume in nonneovascular AMD has been studied. Drusen volume has been demonstrated to be both highly reproducible and accurate when compared to manual segmentation of drusen by certified reading center graders. In addition, drusen volumes have been incorporated into population studies and clinical studies, and recently, genetic associations have been reported with higher drusen volumes and higher drusen growth rates.

Longitudinal studies of drusen volume in eyes with AMD have demonstrated that drusen volumes can fluctuate, but on average, drusen volumes increase over time. A greater drusen volume, which would presumably correlate with a larger drusen area, has been suggested as a potential risk factor for developing late AMD. Drusen volume on OCT is a particularly attractive metric as it can be computed automatically, and could potentially be used as a tool to identify patients who are at the highest risk for progression and should be included in early intervention trials. The purpose of this study was to evaluate drusen volume as a risk factor for progression to late AMD in the eyes of patients who had evidence of MNV in the fellow eye.

**METHODS**

**Data Collection**

In this retrospective cohort study, subjects with neovascular AMD in one eye and early or intermediate nonneovascular AMD in the fellow eye were identified from the medical records of a private practice retina group (Retina-Vitreous Associates Medical Group) in Southern California. The study was approved by the Institutional Review Board of the David Geffen School of Medicine at the University of California in Los Angeles. The study adhered to the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki. An informed consent waiver was granted to allow retrospective analysis from the clinic. Inclusion criteria included a diagnosis of neovascular AMD in one eye and a minimum of three annual sessions of OCT imaging using the Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA), obtained between January 2008 and January 2015. A minimum of three annual OCT scans were required to ensure that all cases had at least a baseline OCT (designated as the first available visit for that patient) and an OCT at 1 and 2 years of follow-up. Optical coherence tomography imaging was restricted to the Cirrus OCT, as this is the only device for which FDA-approved drusen analysis software is available. All patients underwent macular cube scans with 512 A-scans × 128 B-scans over a 6 × 6-mm square centered on the fovea. Optical coherence tomography data for each subject were exported in a coded de-identified fashion for subsequent analysis at the Doheny Image Reading Center (DIRC). Eyes with images of insufficient quality (signal strength < 6) to permit reliable drusen analysis were included for this analysis. Medical history, including hypertension, diabetes, atherosclerosis, and smoking status (current smoker, former smoker, or never smoked), was collected for each patient. Each subject's visual acuity, refraction, and lens status (phakic, pseudophakic, or aphakic) were also noted.

**Grading Procedure**

After exportation and transmission to DIRC, OCT images of both eyes were reviewed for qualitative features and analyzed for quantitative measures by certified OCT graders using the Cirrus Advanced RPE Analysis software (Version 6.0). Automatic drusen volumes and areas within the 3- and 5-mm circles (centered on the fovea) of the Cirrus grid were recorded at baseline and at months 12 and 24.

All 128 B-scans of the volume cube were also reviewed for other pathologic features, aside from typical homogenous medium-reflective drusen. Specifically, we evaluated for “suspicious pigment epithelial detachments (PEDs),” which showed areas of internal hyperreflectivity suggestive of fluid or vascular infiltration, subretinal hyperreflective material (SHRM), subretinal fluid, intraretinal fluid, and intraretinal hyperreflective features (typically corresponding to pigment migration or lipid exudates). Presence of fluid in any compartment with an associated suspicious PED or SHRM was considered to be evidence of MNV.

In addition, OCT B-scans and the en face OCT fundus images were evaluated for the presence of atrophy. Although the Cirrus Advanced RPE Analysis software automatically identifies and quantifies atrophy, graders did not rely on the software for this determination. The software identifies atrophy based on increased transmission of signal into the choroid, which creates a well-demarcated region of hyperreflectivity on the en face OCT image obtained from a slab through the choroid. Areas of RPE depigmentation through the choroid. Areas of RPE depigmentation without RPE loss, however, can also potentially result in increased choroidal reflectivity. Thus, the graders used the reading center OCT criteria for atrophy to make this determination. These criteria include thining of the RPE band, especially with an abrupt/sharp step-down in thickness; loss of the overlying ellipsoid zone (EZ) and external limiting membrane (ELM) with thinning of the outer nuclear layer (ONL); and increased signal transmission into the choroid. If all three criteria were present, then the atrophy was deemed to be “definite,” whereas if only two were present, it was deemed to be “questionable.” Meeting only one of the criteria was insufficient to allow a diagnosis of atrophy.

All gradings were performed twice by two independent graders, who were masked as to the baseline drusen volume results for these cases. In cases of disagreement, the graders met in open adjudication and discussed the case to achieve a consensus result. If consensus could not be achieved, the reading center protocol, the case was reviewed by reading center medical director (SRS), who would make the final determination.

As drusen volumes were produced by automated FDA-cleared instrument software, reproducibility between graders for this metric was not relevant. The repeatability and interscan variation for this algorithm have been reported previously. The accuracy of drusen volume measurements using this software has also been described in previous studies.

**Statistical Analysis**

The mean ± standard deviations of the drusen volumes were calculated for each circle in each case. Volume was measured...
in cubic millimeters. Change from baseline in drusen volume measurements was calculated at each available follow-up OCT image. To analyze these changes, Wilcoxon signed rank test was performed. \( P < 0.05 \) was considered statistically significant. Drusen volume at baseline was correlated with development of MNV or atrophy at 12 and 24 months of follow-up using logistic regression analysis. As a drusen volume cut-point of 0.05 mm\(^3\) has been previously suggested to be clinically relevant,\(^{15,20}\) this specific threshold was prospectively chosen to compare risk of progression to advanced AMD between individuals with high and low drusen volumes. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation, Armonk, NY, USA).

**RESULTS**

**Baseline Characteristics**

Of the 89 patients included in this analysis, 58 (65.2%) were women and 31 (34.8%) were men. The mean age of patients was 84 years (SD, 9), and the median age was 86 years (range, 46–98 years). Per the inclusion criteria, all patients carried a diagnosis of MNV in the fellow eye, and were treated with various anti-VEGF agents (bevacizumab, ranibizumab and/or aflibercept) per the treating physician’s preference. Forty-five patients had never smoked before (50.1%), while 44 patients were smokers, either current (4.3%) or former (45.6%). Sixteen patients had never smoked before (50.1%), while 44 patients were smokers, either current (4.3%) or former (45.6%). Sixteen patients were noted to have diabetes (17.8%), 48 patients had hypertension (53.9%), and 45 had a history of cardiovascular diseases (48.8%).

**Drusen Volume Analysis**

Mean drusen volumes in the study eye for the population as a whole were relatively low (mean = 0.02 mm\(^3\) in the 3-mm circle), as there were many patients with very small drusen volumes, including 28 eyes (31.5%) with drusen below the threshold of measurement by the Cirrus OCT software. Among eyes that did not progress to late AMD (GA or MNV), drusen underwent small but statistically significant average increases in volume over 2 years in this cohort as shown in Table 1.

When comparing eyes that eventually developed late AMD (GA or MNV) by 24 months of follow-up versus those that did not, drusen volumes were significantly higher at baseline among the former (Table 2). This relationship was present regardless of whether the central or larger circle grid was considered, or whether the raw volumes or the cube root volumes were analyzed.

**Progression Rates to Late AMD**

Drusen without evidence of late AMD in the fellow eye could be measured on OCT in 61 subjects (68.5%), and could yield no measurable volume (0 mm\(^3\)) in 28 eyes (31.5%). After 12 months, 4 eyes (4.5%) out of the full cohort (89 eyes) developed neovascular disease and 15 eyes (16.9%) developed GA. Among the remaining 70 eyes, at 24 months of follow-up, an additional 5 eyes (7.1%) developed MNV and an additional 10 eyes (14.3%) developed GA. The baseline drusen volume of eyes that developed GA or MNV by month 24 was significantly larger than in those that did not (Figs. 1, 2). Logistic regression analysis, assessing the importance of age, smoking status, sex, drusen volume, diabetes, hypertension, and cardiac disease, revealed that in this dataset only drusen volume was a univariate significant predictor for developing late AMD at both 1 and 2 years of follow-up (\( P < 0.001 \), Table 3), though 95% confidence intervals do not exclude sizable effects of the other variables. At 1 year of follow-up, smoking status (\( P = 0.044 \)) also entered the forward stepwise model after adjustment for 3-mm-circle volume (\( P = 0.001 \), with current smokers having a significantly higher risk of late AMD than nonsmokers. None of the other variables, including the 5-mm-circle volume, was independently significant. At 2 years of follow-up, only the 3-mm-circle volume entered the model. Figure 3 demonstrates the cohort flowchart of cases’ progression rates to late AMD.

### Table 1. Drusen Volume Among 55 Patients Who Never Developed Late AMD; \( P \) Values by Paired \( t \)-Test

<table>
<thead>
<tr>
<th>Drusen volume, mm(^3), ( \text{mean} \pm \text{SD} ) (range)</th>
<th>Baseline</th>
<th>12 Months</th>
<th>( P ) Value</th>
<th>24 Months</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-mm circle</td>
<td>0.006 ± 0.010 (0.00–0.05)</td>
<td>0.009 ± 0.013 (0.00–0.06)</td>
<td>0.012</td>
<td>0.015 ± 0.014 (0.00–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-mm circle</td>
<td>0.010 ± 0.015 (0.00–0.08)</td>
<td>0.012 ± 0.017 (0.00–0.07)</td>
<td>0.047</td>
<td>0.019 ± 0.020 (0.00–0.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cube root drusen volume, mm, ( \text{mean} \pm \text{SD} ) (range)</td>
<td>0.102 ± 0.124 (0.00–0.37)</td>
<td>0.127 ± 0.131 (0.00–0.39)</td>
<td>0.023</td>
<td>0.198 ± 0.120 (0.00–0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-mm circle</td>
<td>0.134 ± 0.134 (0.00–0.45)</td>
<td>0.157 ± 0.135 (0.00–0.41)</td>
<td>0.044</td>
<td>0.225 ± 0.115 (0.00–0.45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 2. Difference in Baseline Drusen Volume Between Those Who Developed and Those Who Never Developed Late AMD

<table>
<thead>
<tr>
<th>GA/MNV Developers, ( N = 34 )</th>
<th>GA/MNV Nondevelopers, ( N = 55 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline drusen volume, mm(^3), ( \text{mean} \pm \text{SD} ) (range)</td>
<td>0.049 ± 0.042 (0–0.16)</td>
<td>0.0107 ± 0.010 (0–0.05)</td>
</tr>
<tr>
<td>3-mm circle</td>
<td>0.052 ± 0.043 (0–0.16)</td>
<td>0.010 ± 0.015 (0–0.08)</td>
</tr>
<tr>
<td>5-mm circle</td>
<td>0.316 ± 0.129 (0–0.54)</td>
<td>0.102 ± 0.124 (0–0.37)</td>
</tr>
<tr>
<td>3-mm circle</td>
<td>0.3435 ± 0.128 (0–0.54)</td>
<td>0.134 ± 0.134 (0–0.43)</td>
</tr>
</tbody>
</table>

* 2-tailed unpooled variance sample \( t \)-test.
† 2-tailed pooled variance sample \( t \)-test.
Threshold Drusen Volume

At baseline, 22 eyes (25%) had drusen volume equal to or greater than 0.03 mm³ in the 3-mm circle, the threshold drusen volume selected a priori for this analysis. Of the 22 eyes with this “high” drusen volume, 19 eyes (86%) developed GA (Fig. 4) or MNV (Fig. 5) by month 24. In contrast, only 15 eyes (22%) out of the 67 eyes with “low” drusen volume developed late AMD. This difference was found to be statistically significant (P < 0.0001, Fisher exact test), and translates to relative risk of 3.86, 95% confidence interval (2.40–6.21), or odds ratio of 22.0 (95% confidence interval: 5.71–84.4). Analysis of these data with Cox proportional hazards regression, including both year 1 and year 2 outcomes, gave similar results to the logistic regression analyses: Only 3-mm drusen volume entered the model (P < 0.001), with smoking having a borderline significant P value of 0.079.

Of the 34 eyes developing late AMD, 19 (56%) did so during the first year of follow-up, while 15 (44%) did so during the second year of follow-up. Among these 34 eyes, there was no association between baseline drusen volume and the development of late AMD at 1 or 2 years. Of those 15 eyes with small drusen (<0.03 mm³) at baseline, 8 (53%) developed late AMD during the first year, while of those 19 with large drusen (≥0.03 mm³), 11 (58%) developed late AMD during the first year (P = 1.0, Fisher exact test).

Grading Reproducibility

With respect to the OCT qualitative features and the study outcome of no progression versus developing GA versus MNV, grading reproducibility was found to be statistically significant (P < 0.0001, intraobserver and interobserver agreement).

Table 3. Logistic Regression Analysis for Potential Predictors of Development of Late AMD After 1 and (n = 19) 2 Years (n = 34); Odds Ratios Not Adjusted

| Predictor | Month 12 | | Month 24 | |
|-----------|----------|-------------------|----------|-------------------|----------|
|           | Odds Ratio | 95% CI | P       | Odds Ratio | 95% CI | P       |
| Age, 1-decade increase | 1.1 | 0.6-1.9 | 0.85 | 1.5 | 0.9-2.6 | 0.15 |
| Sex | 1.2 | 0.4-3.6 | 0.74 | 1.9 | 0.7-4.7 | 0.20 |
| Smoking | | | | | | |
| Former vs. never | 1.9 | 0.6-6.5 | | 1.3 | 0.5-3.4 | |
| Current vs. never | 13.3 | 1.0-171 | | 4.1 | 0.3-49.3 | |
| Drusen volume in 3 mm, increase in risk with a 0.01-mm³ increase in volume | 1.4 | 1.1-1.6 | <0.001 | 2.3 | 1.5-3.6 | <0.001 |
| Drusen volume in 5 mm, increase in risk with a 0.01-mm³ increase in volume | 1.3 | 1.1-1.6 | <0.001 | 1.9 | 1.4-2.6 | 0.001 |
| Diabetes | 1.9 | 0.6-6.4 | 0.29 | 1.3 | 0.4-4.0 | 0.62 |
| Hypertension | 0.9 | 0.3-2.6 | 0.90 | 0.5 | 0.2-1.3 | 0.15 |
| Heart disease | 0.4 | 0.1-1.2 | 0.11 | 0.8 | 0.3-1.8 | 0.53 |

CI, confidence interval.
developing MNV, the agreement between graders was evaluated using the unweighted $\kappa$ statistic test, as previously reported by Landis and Koch. Agreement was found to be excellent, with a $\kappa$ value of 0.93 (exact 95% confidence interval, 0.83–1.0).

**DISCUSSION**

In this study of fellow eyes from patients with neovascular AMD in one eye, drusen volume was observed to be the most important predictor for the development of advanced AMD at 12 and 24 months of follow-up. The fellow eyes of patients with late AMD in one eye (i.e., Age-Related Eye Disease Study [AREDS] category 4) are already at high risk for progressing to late AMD, with 25% and 43% developing this outcome at 2 and 5 years based on data from the AREDS.

Our findings are consistent with the results from previous large studies such as the Beaver Dam Eye Study and AREDS, which demonstrated that a larger drusen area was associated with a higher risk for progression to late AMD (Refs. 11, 22, and Zhang H, et al. IOVS 2015;56:ARVO E-Abstract 5149). Drusen area in these studies was estimated by semiquantitative methods (i.e., using reference circles of known sizes) from color photographs. While OCT drusen volumes are not analogous to drusen areas from color photographs, they are likely highly correlated. In addition, previous studies have suggested that drusen volumes may be more repeatable metrics compared to drusen areas. Because drusen can have poorly demarcated edges, area measurements are inherently unstable, as a small difference in the segmented diameter of a druse can lead to a large change in its area. In contrast, because of the topographic profile of drusen, the thickness of a druse at its edge is small relative to the center, and thus a small difference in the diameter or border of the drusen will have minimal effects on the volume of large drusen. The automated algorithm provides estimates of drusen volume within a 3-mm circle and a larger 5-mm circle. Regarding this algorithm, accuracy of automated segmentation was previously evaluated. In our data, the 3-mm circle preferentially entered the stepwise logistic regression model. Tall/big drusen tend to be in the central 3 mm, and these may be associated with the highest risk. Although the focus of the present paper was to use automated drusen volumes, we did evaluate the B-scans of all cases for segmentation errors and did find one case with a significant segmentation error, which was manually corrected. The fact that only one case needed correction speaks to the overall robustness of the algorithm.

There are still significant challenges when using drusen volume at a point in time to risk stratify patients for possible inclusion into clinical trials. Namely, drusen volumes can fluctuate over time as drusen appear and disappear. In longitudinal studies of drusen in patients with AMD, Yehoshua and colleagues demonstrated that while drusen volumes can fluctuate, on average, they trended to increase over time. However, in some patients, drusen volumes were shown to precipitously decrease. This precipitous decrease generally heralded or preceded the development of an adverse event such as the development of atrophy or MNV. In a longitudinal study of individual large drusen followed over years using tracked OCT scans, we also observed a tendency for drusen to grow over time, with eventual collapse of the drusen typically preceding or occurring concurrently with development of atrophy at this location. In this longitudinal study, we also observed that intraretinal hyperreflective features (corresponding to pigment migration) and the appearance of hyporeflective foci within the drusen were associated with a significantly higher risk of collapsing of the drusen and development of atrophy. These findings are consistent with retrospective analyses of incident GA in the AREDS, which demonstrated that GA was preceded years earlier by large drusen with pigment alterations.

While our analyses (Table 3) demonstrate that drusen volume, as a continuous variable, is an important predictor of AMD progression in these fellow eyes, designers of future trials may want to base inclusion criteria on a threshold value below which progression is uncommon. Prior data-driven analyses in an independent group of patients suggested that 0.03 mm$^3$ could serve this function. Our current data also suggest that it is uncommon for patients having drusen volume less than 0.03 mm$^3$ to develop late AMD. The precipitous drop in drusen volume prior to or concurrent with the development of atrophy may also explain why some patients with low drusen volume developed late AMD in this series. It is also possible that these patients with low drusen volume at baseline may have experienced an increase in drusen volume and went on to develop atrophy. Thus, important changes in drusen volume for particular cases may have been missed prior to the first visit or between the visits sampled in this study. These caveats are
important to consider when designing trials utilizing drusen volume as an inclusion criterion or outcome measure. It is important to note that other methods of drusen segmentation are also available. These methods may segment and quantify different aspects of drusen. As an example, the method reported by Stephanie Chiu and colleagues includes Bruch’s membrane thickness in their assessments. Recent previous studies examined the progression of drusen volume over time in patients with intermediate AMD in both eyes. In one study, patients had drusen volumes similar to the range in our cohort in both baseline and 2-year measurements. They also had 17.3% of their eyes developing GA and 6.7% developing MNV by month 24. However, in another study, patients had larger drusen volumes at baseline than our cohort, and they also ended up with larger drusen volumes at month 24. Although 6.7% of their eyes also developed MNV by month 24, none of the eyes developed GA over 52 weeks.

Our study is not without limitations. First, this is a retrospective collection of subjects and is potentially subject to ascertainment bias. Second, the sample size is relatively small, but our confidence in the results is strengthened by the high event rate for late AMD and the large difference in events.

![Figure 4](image1.png)

**Figure 4.** (A, B, C) Central OCT scans of a fellow eye at baseline, month 12, and month 24 of follow-up. (A) OCT at baseline; drusen volume was 0.13 mm³. (B) At month 12, GA started developing. (C) At month 24, enlarged GA. (D, E, F) Central OCT scans of another fellow eye at baseline, month 12, and month 24 of follow-up. (D) OCT at baseline; drusen volume was 0.08 mm³. (E) At month 12, drusen volume became 0.11 mm³. (F) At month 24, GA developed. Red arrows highlight areas of choroidal hypertransmission due to developing atrophy.

![Figure 5](image2.png)

**Figure 5.** (A, B, C) Central OCT scans of a fellow eye at baseline, month 12, and month 24 of follow-up. (A) OCT at baseline; drusen volume was 0.01 mm³. (B) At month 12, GA started developing. (C) At month 24, multiple foci of GA. (D, E, F) Central OCT scans of another fellow eye at baseline, month 12, and month 24 of follow-up. (D) OCT at baseline; drusen volume was 0.08 mm³. (E) At month 12, MNV developed. (F) At month 24, MNV. Red arrows highlight areas of choroidal hypertransmission due to developing atrophy.
between the high and low drusen groups. Third, we included only subjects with MNV in the fellow eye, so we are uncertain whether our results can be extrapolated to patients with only drusen in both eyes or only GA in the fellow eye, though it seems likely that the association between drusen volume and an increased risk of late AMD would apply regardless of fellow eye status. In addition, it is remotely possible that anti-VEGF therapy in one eye could suppress the formation of MNV in a fellow eye due to presence of these drugs in the systemic circulation. While such fellow eye effects have rarely been reported, it is possible that our results represent an underestimate of MNV formation in eyes with a drusen burden of at least 0.03 mm³. Finally, our study was based exclusively on OCT imaging to identify both potential imaging risk factors and the development of late AMD. Other imaging modalities such as fundus angiography (FA) or color photography (CP) were not assessed at the reading center to confirm the presence of late AMD based on these other modalities. However, these other modalities were reviewed by the examining physician, who indicated their interpretation in the available clinical record. In any event, it is important to note that the sensitivity and specificity of OCT for detection of MNV have varied from study to study, with some studies reporting a very high sensitivity and others reporting either a poor specificity or low sensitivity.26,27 However, the sensitivity and specificity would be expected to vary depending on the type of OCT (spectral versus time domain), scanning protocol (dense cube versus sparse scans), and grading criteria (e.g., inclusion of sub-RPE fluid and/or evidence of sub-RPE “vascular” infiltration) used in the study. Ideally, we would have wanted concurrent OCT angiography or fluorescein angiography in all cases to confirm the diagnosis, but that was not available in this retrospective study. On the other hand, the assessment for MNV was based on dense OCT scanning and reading center OCT criteria for MNV, and was shown to be highly reproducible. A similar concern exists for the assessment of GA, as color and fundus autofluorescence (FAF) images were not available for most visits. In addition, consensus OCT criteria for atrophy have yet to be developed despite the availability of FDA-cleared algorithms for measuring atrophy by OCT. However, correlative studies have shown good agreement between OCT and FAF assessments of atrophy, and determination of the presence of atrophy using our reading center criteria was highly reproducible.28,29 Our study also has several strengths that should be considered, including the use of masked, independent, certified, experienced reading center OCT graders; a standardized grading protocol and definition for atrophy; and the demonstration of high levels of grading reproducibility.28,29

In summary, drusen volume appears to be a significant risk factor for progression to late AMD in the fellow eye of patients with neovascular AMD in one eye. A drusen volume threshold of 0.03 mm³ appeared to have particular relevance as it confers a 4-fold higher risk for developing late AMD compared with eyes with lower drusen volumes. These findings may be of value in the design of future AMD clinical trials, particularly those targeting earlier stages for therapeutic intervention.

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