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Global Analysis of Macular Choriocapillaris Perfusion in Dry Age-Related Macular Degeneration using Swept-Source Optical Coherence Tomography Angiography

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 PURPOSE. Swept-source optical coherence tomography angiography (SS-OCTA) was used to investigate if the clinical stage of dry age-related macular degeneration (AMD) was correlated with global and regional macular choriocapillaris (CC) perfusion.

METHODS. In this retrospective, cross-sectional study, 6 × 6-mm SS-OCTA images from eyes with early, intermediate, and advanced dry AMD (56 eyes, 41 patients) were analyzed using algorithms described in the literature to assess regional flow deficit percentage (FD%) and average flow deficit size. Regions were defined by concentric areas centered on the fovea: a 1-mm-diameter area, 3-mm-diameter ring, 5-mm-diameter area, 5-mm-diameter ring, and 6 × 6-mm whole image. Data were modeled using the generalized estimating equations approach.

RESULTS. The relationship between age and CC FD% and average flow deficit size was statistically significant (P ≤ 0.05) in all regions of analysis by linear modeling. The relationship between dry AMD stage and FD% was statistically significant by linear modeling in the 5-mm ring, and between dry AMD stage and average flow deficit size in the 3-mm ring, 5-mm area, 5-mm ring, and 6 × 6-mm whole image.

CONCLUSIONS. Linear modeling suggests a statistically significant relationship between dry AMD stage and CC perfusion, most prominent in the more peripheral regions of the macula.

Keywords: OCTA, macula, choriocapillaris, retina, dry age-related macular degeneration

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4985

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limits on measurable speed of flow,\textsuperscript{5,10} offers a number of unique advantages to investigation of the CC. OCTA is currently the only modality that offers rapid, noninvasive, depth-resolved, in vivo imaging of CC flow.\textsuperscript{5,6,9,10,15,18} Features that lend great promise for both research and clinical applications. For example, it has been suggested that CC flow deficits may correlate with rate of AMD progression, thereby highlighting the potential of OCTA for risk stratification in clinical trials and possible future interventions.\textsuperscript{16,17} Its potential for CC investigation has been enhanced with the use of longer-wavelength light sources, which enables superior signal penetration through the highly scattering RPE, a particularly important feature for visualizing the CC beneath additional attenuating structures such as drusen.\textsuperscript{5,10,18–21}

There have been a number of investigations of the CC in dry AMD using OCTA. Findings have included increased flow deficits in early and intermediate dry AMD versus age-matched controls, with further focal deficits;\textsuperscript{2} flow deficits concentrated beneath drusen using swept-source (SS)-OCTA and peri-drusen areas using both spectral domain (SD) and SS-OCTA\textsuperscript{8,22}; and loss of CC beneath GA lesions and to a lesser extent in areas surrounding these lesions.\textsuperscript{15,19–23} Recently, Sacconi et al.\textsuperscript{24} Nassisi et al.,\textsuperscript{25} and Zheng et al.\textsuperscript{26} used commercially available SS-OCTA to characterize global flow characteristics of the macular CC in healthy patients. All groups found a decrease in CC perfusion associated with advancing age that preferentially affected the central macula. The current study endeavors to characterize more fully the macular CC in dry AMD, taking into consideration this improved understanding of the correlation of age with macular CC in normal eyes. In particular, the central questions of this study are (1) whether dry AMD stage has a relationship with macular CC perfusion, and (2) how this relationship (if any) varies by region.

\textbf{Methods}

This retrospective, cross-sectional study requiring informed consent was approved by the Institutional Review Board of Tufts Medical Center and adhered to the requirements of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. All patients who had been diagnosed clinically with dry AMD in at least one eye by a retinal specialist and were recorded in a database as having been imaged on an SS-OCTA instrument (PLEX Elite 9000; Carl Zeiss Meditec, Dublin, CA, USA) from December 2016 to September 2018 were considered for the study. Fellow eyes in patients with a diagnosis of wet AMD were eligible for inclusion; eyes with a diagnosis of either early or intermediate AMD, and that did not meet criteria for advanced classification, were categorized as early stage.

The PLEX Elite 9000 has an A-scan rate of 100,000 scans per second, a central wavelength of 1060 nm, an axial resolution of approximately 6 μm in tissue, a lateral resolution of approximately 14 μm at the retinal surface, and images at a depth of 3 mm. The macula-centered 6 × 6 mm en face images used in this study are composed of 500 B-scans at 500 A-scans per B-scan. As in prior studies of the CC,\textsuperscript{17,20} segmentation of the CC slab in all eyes involved maximum projection 20 μm deep to Bruch’s membrane. For early eyes, the instrument’s “RPEt” segmentation algorithm was used, with manual adjustment as needed; intermediate and advanced eyes were manually segmented due to numerous drusen and RPE distortions. In addition, regions of GA (total RPE loss) in the advanced group were excluded from analysis as described in Figure 1. All manual segmentation and exclusion of GA were performed with a precision drawing tablet (Intuos; Wacom, Portland, OR, USA). Superficial vascular projections were addressed using the PLEX Elite software’s projection removal algorithm before image export.\textsuperscript{16,15} Exported images were processed using an algorithm written in ImageJ, version 1.52h (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) based on a previously described formula to compensate for signal attenuation beneath drusen.\textsuperscript{19,20,26} Because of this compensation algorithm, only regions of complete signal loss on both the angiography en face image and its structural correlate were excluded from analysis, as were any areas of significant structural artifact.\textsuperscript{3} Images were subsequently binarized using a Phansalkar local threshold (radius: 15 px)\textsuperscript{16,25} and inverted to highlight flow deficits. The “Analyze Particles” command (size: 1-Infinity; circularity 0–1) was then run on five different regions of analysis for each image, as described in Figure 2. Flow deficit metrics included flow deficit percentage (FD%) and average flow deficit size. In advanced eyes, regions of analysis with GA exclusions resulting in total flow deficit areas of 500 px\textsuperscript{2} or less were excluded. This is approximately equivalent to the size of a single large druse in 6 × 6-mm images or 0.05% of total 6 × 6-mm area. This was done to minimize weighting flow deficit metrics in miniscule areas equally with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Exclusion of GA lesions in advanced patients. PLEX Elite “Whole Eye” structural images were scaled appropriately, then, after validation of complete RPE loss on OCT B-scan, used to create masks that were applied to their angiographic correlates at the level of the CC. These regions were then excluded from concentric circular whole image analysis for flow deficit metrics.}
\end{figure}
much larger (often at least an order of magnitude) corresponding regions of analysis in other images.

Statistically, the object was to discern what, if any, relationship dry AMD stage had to each of the two flow deficit metrics in each of the regions of analysis. To discern the independent contributions by age, stage, and eye side (OD or OS) to FD% and average flow deficit size, the generalized estimating equations (GEE) method was used. This approach to linear modeling has particular utility for ophthalmology studies, as it can account for the correlation between fellow eyes.28 All dry AMD stages were included in a single linear model for each flow deficit metric at each region of analysis (10 models total), with each model incorporating age and eye side as covariates. A P value of 0.05 was used to determine statistical significance. Statistical analysis was performed using JMP Pro (version 13.2.1; SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 56 eyes from 41 patients were included in this study. Staging resulted in 23 early, 12 intermediate, and 21 advanced eyes (detailed characteristics in Table 1.) Before application of the 500 px² total flow deficit area threshold to advanced eyes, because of GA entirely consuming regions in some images there were 18, 20, 21, 21 and 6 × 6 mm images available for the 1-mm area, 3-mm ring, 5-mm area, 5-mm ring, and whole image regions of analysis, respectively. After applying this 500 px² threshold there were 16, 19, 21, 21, and 6 × 6 mm images available for the 1-mm area, 3-mm ring, 5-mm area, 5-mm ring, and whole image regions of analysis, respectively. Summary statistics for each dry AMD stage and each region of analysis are shown in Table 2, with example images of flow deficits at each stage and region shown in Figure 3. Mean flow deficit metrics increase with disease stage progression, with the exception of mean average flow deficit size in the 5-mm area, 5-mm ring, and whole image. Standard deviations increase with disease stage progression for both flow deficit metrics. For all stages of dry AMD, flow deficit metrics tend to decrease with increased distance from the central macula.

On GEE analysis (Table 3), the relationship between age and both flow deficit metrics was significant in all regions of analysis. Peripheral regions most consistently demonstrated a significant relationship between stage and both flow deficit metrics: FD% P ≤ 0.05 in the 5-mm ring region of analysis, and average flow deficit size P ≤ 0.05 in the 3-mm ring, 5-mm area, 5-mm ring, and whole image regions of analysis. There was no significant relationship between eye side and flow deficit metrics in any region of analysis.

DISCUSSION

Previous OCTA studies of the CC in dry AMD have focused on individual lesions and their surrounding areas, with some limited work on global analysis and staging.6,8,22 This study endeavored to investigate the CC quantitatively throughout the macula in all stages of dry AMD. GA lesions were themselves excluded from analysis because these areas are known to have extensive and often complete underlying CC loss, as well as morphological changes resulting in effective flow reduction like reduced branching and severe constriction, which could inappropriately skew quantification and

| TABLE 1. Study Patient and Eye Characteristics Stratified by Dry AMD Stage |
|-----------------------------|-------|-------|-----------------------------|-------|
| **Patients** | **Age, Mean (SD) [Range]** | **Sex** | **Eyes** | **Age, Mean (SD) [Range]** | **Sex** | **Side** |
| Stage | M | F | M | F | OD | OS |
| Early | 73 (6.1) [60–85] | 4 | 12 | 72 (6.3) [60–85] | 5 | 18 | 14 | 9 |
| Intermediate | 80 (8.9) [63–88] | 4 | 4 | 77 (9.9) [63–88] | 7 | 5 | 7 |
| Advanced | 81 (7.2) [69–97] | 5 | 12 | 81 (7.4) [69–97] | 8 | 13 | 7 | 14 |
| All patients | 78 (8.0) [60–97] | 13 | 28 | 77 (8.6) [60–97] | 20 | 36 | 26 | 30 |
thus mask the effect of subtler pathological CC changes (e.g., in nascent GA, drusen-associated GA, and peri-GA areas). GA lesion exclusion was also important to minimize detection of choroidal flow, because larger choroidal vessels tend to move inward to occupy CC space when the CC has been lost. To address the central questions posed by this study, results (1) reaffirm the conclusion of previous studies that age has a strong correlation with flow deficit metrics in the macular CC, and (2) suggest that there is a relationship between dry AMD stage and CC perfusion by linear modeling, more pronounced with increased distance from the fovea. The age-flow deficit correlation was first shown on OCTA by Alten et al. and Spaide, which agreed with histological findings. Sacconi et al., Nassisi et al., and Zheng et al. used OCTA to further specify regional differences in this correlation through topographic analyses. These three studies suggest one possible interpretation of the current study’s results, namely, that a strong effect of age on the CC toward the center of the macula may mask any dry AMD stage effects in this area, whereas toward the macular periphery, where age seems to have a reduced influence on the CC, the effects of stage become more distinguishable. Alternatively, AMD may indeed cause earlier CC alterations outside the foveal region and this may contribute to the propensity of GA to begin extrafoveally, but it is clearly beyond the scope of this cross-sectional study to answer such questions. From a histological perspective, although a corresponding study of macular topography has not been performed, results of the current study seem consistent with the findings of Seddon et al., who found CC attenuation with advancing dry AMD stage, particularly from the intermediate to the advanced (GA) stage.

It is important to note the difficulties of segmentation in OCTA studies of the CC when the RPE is distorted, as in more advanced dry AMD. Autosegmentation algorithms are currently inadequate. Irregular RPE thickening and drusen both can make segmentation of Bruch’s membrane a task that requires great care. Every aid to accurate segmentation is appropriate, from use of a drawing tablet to the ability to adjust OCT B-scan contrast for Bruch’s membrane identification. Commercial developments, including improved autosegmentation algorithms and higher axial resolution, could go some way toward enhancing CC investigation in eyes with diseased RPE. Because of the challenging nature of CC investigation using OCTA in the setting of dry AMD in particular, caution must be exercised in drawing pathophysiologic conclusions. However, in the current study, careful methodology and points of accord with known CC structure and function are encouraging toward this end.

### Table 2. Summary Statistics for All Dry AMD Stages and Regions of Analysis

| Region          | Early (Mean ± SD) | Intermediate (Mean ± SD) | Advanced (Mean ± SD) | Early (Range) | Intermediate (Range) | Advanced (Range) |
|-----------------|-------------------|--------------------------|----------------------|---------------|----------------------|-----------------|
| 1-mm area       |                   |                          |                      |               |                      |                 |
| Mean (SD)       | 26.9 (3.2)        | 31.7 (7.4)               | 33.9 (8.0)           | 710.7 (230.0) | 944.1 (591.9)        | 1349.2 (834.3)  |
| [Range]         | [22.0–35.5]       | [23.9–45.0]              | [20.0–46.6]          | [381.1–1407.6]| [418.9–2053.1]       | [326.2–3457.2]  |
| 3-mm ring       |                   |                          |                      |               |                      |                 |
| Mean (SD)       | 26.4 (3.2)        | 29.8 (5.7)               | 36.6 (11.6)          | 700.4 (219.7) | 796.5 (394.8)        | 1479.7 (1023.1) |
| [Range]         | [22.1–32.7]       | [22.5–38.6]              | [18.7–58.1]          | [370.8–1119.2]| [377.7–1606.7]       | [315.9–3701.0]  |
| 5-mm area       |                   |                          |                      |               |                      |                 |
| Mean (SD)       | 25.6 (2.8)        | 27.3 (4.4)               | 32.1 (7.4)           | 676.3 (192.3) | 672.9 (291.8)        | 1259.4 (748.4)  |
| [Range]         | [20.7–31.8]       | [20.8–34.2]              | [18.4–43.4]          | [384.5–1054.0]| [353.6–1263.4]       | [309.0–2763.7]  |
| 5-mm ring       |                   |                          |                      |               |                      |                 |
| Mean (SD)       | 25.3 (2.9)        | 25.8 (3.8)               | 31.4 (7.4)           | 655.7 (192.3) | 587.1 (240.3)        | 1157.0 (676.3)  |
| [Range]         | [19.7–31.5]       | [19.6–32.1]              | [18.2–43.0]          | [381.1–1005.9]| [329.6–1060.9]       | [298.7–2396.4]  |
| Whole image     |                   |                          |                      |               |                      |                 |
| Mean (SD)       | 25.2 (2.9)        | 25.9 (3.8)               | 30.1 (6.4)           | 669.5 (192.3) | 604.2 (247.2)        | 1050.6 (535.6)  |
| [Range]         | [19.5–31.9]       | [19.5–31.8]              | [18.6–39.2]          | [394.8–1084.9]| [336.5–1091.8]       | [315.9–2087.4]  |

**FIGURE 3.** Binarized and inverted images (CC flow deficits in white) of eyes with early (A), intermediate (B), and advanced (C) dry AMD, overlaid with regions of analysis. The blue outline in (C) represents areas of GA, which were excluded from analysis.
work\textsuperscript{35,36} suggests that RPD prevalence in the current study’s cohort aligns reasonably with typical RPD prevalence in each AMD stage, and because the association between AMD and RPD is both strong and consistent, our interstage CC perfusion findings are likely to be more generalizable than if RPD were excluded. The current study did not interrogate a particular potential cause or effect of CC flow impairment (e.g., RPD versus drusen versus other), but rather global and regional flow impairment at each AMD stage, regardless of causes or manifestations of impairment. A GEE subgroup analysis also demonstrated that exclusion of eyes with RPD from the study cohort resulted in statistical significance findings almost identical to those in Table 3, in full affirmation of the central conclusions of the current study. Likewise, although it has been noted that different stages of neovascularization may be reflected in choriocapillaris flow deficit metrics in fellow eyes with dry AMD,\textsuperscript{37} any potential influence of fellow eye neovascularization has not been described for the current study’s cohort, which in any case had a reasonably tight distribution of neovascularized fellow eyes among early, intermediate, and advanced dry AMD stages.

Study weaknesses included its retrospective character, failure to account for hypertension,\textsuperscript{30} lack of a control population, and a small sample size for eyes with intermediate dry AMD. As noted in related studies,\textsuperscript{6,11} residual superficial projection artifact may still have some effect on CC perfusion imaging despite the use of projection removal software, which is a challenge of imaging the CC on OCTA. There was also a sex imbalance among eyes in this study, although this has not been identified in the literature as a substantial concern. Areas for future investigation include the deployment of the models resulting from this study for CC flow deficit prediction, increasingly robust and regional histologic characterization of the macular CC, and more granular global macular analysis of CC perfusion in the phenotypically heterogeneous advanced dry AMD stage.

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### References
1. Garrity ST, Sarraf D, Freund KB, Sadda SR. Multimodal imaging of nonneovascular age-related macular degeneration. Invest Ophtalmol Vis Sci. 2018;59:AMD48–AMD64.
2. Miller JW. VEGF: from discovery to therapy: The Champalimaud Award Lecture. Truns Vis Sci Tech. 2016;5(2):9.
3. Miller JW, Bagheri S, Vavvas DG. Advances in age-related macular degeneration understanding and therapy. US Ophtalmic Rev. 2017;10:119–130.
Global Macular Choriocapillaris Perfusion in Dry AMD

IOVS | December 2019 | Vol. 60 | No. 15 | 4990

4. Brantley MA Jr, Handa JT. Foreword: dry age-related macular degeneration. Invest Ophthalmol Vis Sci. 2018;59:AMDi.

5. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1-55.

6. Waheed NK, Moult EM, Fujimoto JG, Rosenfeld PJ. Optical coherence tomography angiography of dry age-related macular degeneration. Dev Ophthalmol. 2016;56:91–100.

7. Rosenfeld PJ. Preventing the growth of geographic atrophy: an important therapeutic target in age-related macular degeneration. Ophthalmo-biology. 2018;125:794–795.

8. Borrelli E, Uji A, Sarraf D, Sadda SR. Alterations in the choriocapillaris in intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017;58:4792–4798.

9. Seddon JM, McLeod DS, Blutto IA, et al. Histopathological insights into chorioidal vascular loss in clinically documented cases of age-related macular degeneration. JAMA Ophthalmol. 2016;134:1272–1280.

10. Moult EM, Waheed NK, Novais EA, et al. Swept-source optical coherence tomography angiography reveals choriocapillaris alterations in eyes with nascent geographic atrophy and drusen-associated geographic atrophy. Retina. 2016;36(Suppl 1):S2–S11.

11. Sohn EH, Flamme-Wiese MJ, Whitmore SS, et al. Choriocapillaris degeneration in geographic atrophy. Am J Pathol. 2019;189:1473–1480.

12. Biesemeier A, Taubitz T, Julien S, Yoeruek E, Schraermeyer U. Choriocapillaris breakdown precedes retinal degeneration in age-related macular degeneration. Neurobiol Aging. 2014;35:2562–2573.

13. McLeod DS, Grebe R, Blutto I, Merges C, Baba T, Lutty GA. Relationship between RPE and choriocapillaris in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009;50:4982–4991.

14. Mullins RF, Johnson MN, Faidley EA, Skeie JM, Huang J. Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52:1606–1612.

15. Choi W, Moult EM, Waheed NK, et al. Ultrahigh-speed, swept-source optical coherence tomography angiography in non-exudative age-related macular degeneration with geographic atrophy. Ophthalmol. 2015;122:2532–2544.

16. Nassisi M, Baghdasaryan E, Borrelli E, Ip M, Sadda SR. Choriocapillaris flow impairment surrounding geographic atrophy correlates with disease progression. PLoS One. 2019;14:e0212563.

17. Thulliez M, Zhang Q, Shi Y, et al. Correlations between choriocapillaris flow deficits around geographic atrophy and enlargement rates based on swept-source OCT imaging. Ophthalmol Retina. 2019;3:478–488.

18. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence tomography angiography. Retina. 2015;35:2163–2180.

19. Nassisi M, Shi Y, Fan W, et al. Choriocapillaris impairment around the atrophic lesions in patients with geographic atrophy: a swept-source optical coherence tomography angiography study. Br J Ophthalmol. 2018;103:911–917.

20. Zhang Q, Zheng F, Motulsky EH, et al. A novel strategy for quantifying choriocapillaris flow voids using swept-source OCT angiography. Invest Ophthalmol Vis Sci. 2018;59:203–211.

21. Lane M, Moult EM, Novais EA, et al. Visualizing the choriocapillaris under drusen: comparing 1050-nm swept-source versus 840-nm spectral-domain optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2016;57:OCT585–OCT590.

22. Borrelli E, Shi Y, Uji A, et al. Topographic analysis of the choriocapillaris in intermediate age-related macular degeneration. Am J Ophthalmol. 2018;196:34–43.

23. Sacconi R, Corbelli E, Carnevali A, Querques I, Bandello F, Querques G. Optical coherence tomography angiography in geographic atrophy. Retina. 2018;38:2350–2355.

24. Sacconi R, Borrelli E, Corbelli E, et al. Quantitative changes in the ageing choriocapillaris as measured by swept source optical coherence tomography angiography. Br J Ophthalmol. 2018;103:1320–1326.

25. Nassisi M, Baghdasaryan E, Tepelus T, Asanad S, Borrelli E, Sadda SR. Topographic distribution of choriocapillaris flow deficits in healthy eyes. PLoS One. 2018;13:e0207638.

26. Zheng F, Zhang Q, Shi Y, et al. Age-dependent changes in the macular choriocapillaris of normal eyes imaged with swept-source OCT angiography. Am J Ophthalmol. 2019;200:110–122.

27. Boston Image Reading Center. Non exudative AMD imaged with SS-OCT. NLM Identifier: NCT036882432018. Available at: https://ClinicalTrials.gov/show/NCT03688243. Accessed March 21, 2019.

28. Ying GS, Maguire MG, Glynn R, Rosner B. Tutorial on biostatistics: linear regression analysis of continuous correlated eye data. Ophthalamic Epidemiol. 2017;24:130–140.

29. Alten F, Heiduschka P, Clements CR, Eter N. Exploring choriocapillaris under reticular pseudodrusen using OCT-angiography. Graefes Arch Clin Exp Ophthalmol. 2016;254:2165–2173.

30. Spaide RF. Choriocapillaris flow features follow a power law distribution: implications for characterization and mechanisms of disease progression. Am J Ophthalmol. 2016;170:58–67.

31. Ramtrattan RS, van der Schaft TL, Mooy CM, de Brujin WC, Mulder PG, de Jong PT. Morphometric analysis of Bruch’s membrane, the choriocapillaris, and the choroid in aging. Invest Ophthalmol Vis Sci 1994;35:2857–2864.

32. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. Ophthalmo-biology. 2018;125:369–390.

33. Nesper PL, Soetikno BT, Fawzi AA. Choriocapillaris non-perfusion is associated with poor visual acuity in eyes with reticular pseudodrusen. Am J Ophthalmol. 2017;174:42–55.

34. Cicinelli MV, Rabiolo A, Marchese A, et al. Choroid morphometric analysis in non-vascular age-related macular degeneration by means of optical coherence tomography angiography. Br J Ophthalmol. 2017;101:1193–1200.

35. Rabiolo A, Sacconi R, Cicinelli MV, Querques I, Bandello F, Querques G. Spotlight on reticular pseudodrusen. Clin Ophthalmol. 2017;11:1707–1718.

36. Wightman AJ, Guymer RH. Reticular pseudodrusen: current understanding. Clin Exp Optom. 2018;102:455–462.

37. Borrelli E, Souied EH, Freund KB, et al. Reduced choriocapillaris flow in eyes with type 3 neovascularization and age-related macular degeneration. Retina. 2018;38:1968–1976.