Optical coherence tomography angiography for detection of macular neovascularization associated with atrophy in age-related macular degeneration

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Abstract

Purpose To evaluate the ability of optical coherence tomography angiography (OCTA) to detect macular neovascularization (MNV) in eyes with atrophy compared with fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT).

Methods In this prospective study, eyes with MNV and atrophy (termed macular atrophy or MA) secondary to age-related macular degeneration (AMD), and AMD eyes with geographic atrophy (GA) without MNV underwent multimodal imaging with FA, ICGA, structural OCT, and OCTA. The presence of MNV was determined using all imaging modalities by senior retina specialists and was considered the gold standard reference. Each individual imaging modality was then evaluated independently by two expert readers for the presence of MNV in a masked fashion. Morphologic characteristics of the MNV were evaluated on the custom OCTA slab.

Results Twenty-one patients with MA+MNV and 21 with GA only were enrolled. Manual segmentation on OCTA allowed detection of the MNV in 95.2% of eyes with MA+MNV and in 4.7% of eyes with GA, showing high specificity (95.2%) and sensitivity (95.2%). FA, ICGA, and OCT detected MNV in 57.1%, 52.3%, and 66.7% of eyes with MA+MNV and in 14.2%, 9.5%, and 42.8% with GA. Sensitivity and specificity were 85.7% and 57.1% for FA, 90.5% and 52.4% for ICGA, and 66.7% and 57.1% for OCT.

Conclusions OCTA appears to be superior to other imaging modalities for identification of MNV in eyes with macular atrophy. OCTA should be considered as part of the multimodal imaging evaluation of eyes with atrophy, particularly in the context of clinical trials.

Keywords Fluorescein angiography · Geographic atrophy · Indocyanine green angiography · Macular atrophy · Macular neovascularization · Optical coherence tomography · Optical coherence tomography angiography

Each of the coauthors has seen and agrees with each of the changes made to this manuscript in the revision and to the way his or her name is listed.

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Introduction

Geographic atrophy (GA) is a well-established end-stage manifestation of age-related macular degeneration (AMD) [1, 2]. It is characterized by complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA) [3]. Typically, atrophic lesions start in the perifoveal macula, sparing the foveal center, and over time expand and coalesce to include the fovea.

Although GA and macular neovascularization (MNV) are considered to be distinct manifestations of late AMD, they are not mutually exclusive and may be present in the same eye [4–6]. The development of atrophy in eyes with pre-existing MNV (termed macular atrophy or MA in this context) has

been studied extensively, but MNV may also arise in eyes with pre-existing GA [7–9]. The risk for development of MNV in eyes with atrophy whose fellow eye has MNV has been reported to be 18% at 2 years, 34% at 4 years, and 45–49% at 5 years [9–11]. However, the accurate diagnosis of MNV in an eye with atrophy may prove to be challenging. In fact, several histopathological studies have demonstrated the coexistence of atrophy and MNV in eyes, where the latter had not been clinically identified [9–11].

At present, there are no approved treatments for GA, though novel therapeutic agents are being evaluated in several randomized clinical trials [12]. In one recent phase 2 trial studying pegcetacoplan, treatment with the agent appeared to be associated with a lower GA growth rate but with an apparent increase in the development of exudation, highlighting the importance of identification of MNV in the setting of atrophy [13]. Although the presence of MNV in the study eye was an exclusion criteria, it has been speculated that some of these treated eyes may have had underlying MNV, which may not have been detected. Developing strategies and protocols for the detection of MNV in the context of atrophy would appear to be important for selecting patients for clinical trials and for interpreting the response to therapy.

At present, the gold standard imaging techniques for evaluating the presence, location, and morphology of MNV are fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) [14, 15]. However, in the presence of atrophy, detection of MNV can be challenging due to alteration of the RPE, remodeling of the outer retina, and increased visibility of the underlying choroidal vasculature, which can all impact the interpretation of these diagnostic studies.

Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique that provides high contrast for visualization of the retinal and inner choroidal microvasculature and allows for the detection of the intrinsic vasculature of MNVs [16–18]. For this reason, OCTA could be a very useful technique to improve the detection of MNV in the setting of atrophy. The purpose of this study is to evaluate the ability of different imaging modalities to detect MNV in eyes with atrophy and to describe the features for recognizing MNVs with these modalities.

Methods

Study participants

This prospective observational case series was approved by the Luigi Sacco Hospital Ethics Committee in Milan, and the research adhered to the tenets set forth in the Declaration of Helsinki. A written informed consent was obtained from all subjects.

Consecutive patients with MA secondary to AMD with concomitant MNV were enrolled from September 1, 2018 to November 30, 2018 at the Eye Clinic, Department of Biomedical and Clinical Sciences, Luigi Sacco Hospital, University of Milan. The major inclusion criterion was the presence of both MA and MNV in the same eye due to AMD only. In addition, a consecutive paired control cohort of patients with GA secondary to AMD without any evidence of MNV by a multimodal imaging evaluation was also recruited. In both groups, the atrophy lesions could be multifocal or unifocal, but at least 1 lesion had to be 1.27 mm² or larger (≥ 0.5 disc areas). Exclusion criteria included any previous treatment for MNV (in the group with MNV), and ocular media opacity, inadequate pupillary dilation, or poor fixation or cooperation, precluding capture of clear images.

Data collection and image analysis

Paper and electronic medical records for all enrolled cases were reviewed, and demographic data, best-corrected visual acuity (BCVA), and clinical findings were recorded. The multimodal image acquisition protocol included a combination of blue light fundus autofluorescence (FAF), spectral domain-OCT (SD-OCT, 1024 A-scans $\times$ 19 B-scans over a 6 $\times$ 6-mm area, 15 averaging; Spectralis; Heidelberg Engineering, Heidelberg, Germany), FA, ICGA (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and swept-source OCTA (SS-OCTA, Plex Elite 9000, Carl Zeiss Meditec, Dublin, CA) with both 3 $\times$ 3-mm and 6 $\times$ 6-mm acquisitions centered on the fovea.

The presence/absence of MNV in all cases was determined by a senior retinal specialist (GS) using a multimodal imaging approach based on the combination of FA, ICGA, SD-OCT, and OCTA. Eyes with MNV lesions were then further subclassified as being inactive or active, with activity defined by the presence of intraretinal or subretinal fluid on SD-OCT, or evidence of hemorrhage or leakage on FA. This multimodal image assessment by the senior retinal specialist was deemed to be the reference or gold standard for comparison of the performance of the individual modalities.

All images were then anonymized, assigned a study identifier, and presented randomly to the readers. Each imaging modality (FA, ICGA, OCT, and OCTA) was graded independently by two expert readers (FC and MC) in a masked fashion. To emphasize, the imaging modalities and cases were randomly sorted and evaluated individually. For FA and ICGA, the presence of MNV was assessed using both a dynamic video (30 s) for the transit phase and still images from the early, mid, and late phases. On OCT, MNV was detected by evaluating for the presence of various features including a) a “double-layer sign,” now termed a shallow irregular RPE elevation (SIRE)—suggestive of type 1 NB, b) subretinal hyper-reflective material (SHRM) with poorly defined

boundaries—suggestive of type 2 NV, and c) intraretinal edema with intraretinal hyper-reflective features $\pm$ characteristic pigment epithelial detachment (PED)—suggestive of type 3 NV. For OCTA, a number of automatically segmented slabs provided by the instrument software were evaluated for the presence on MNV, including outer retina-choriocapillaris (ORCC), avascular, choriocapillaris, and choroid. In addition, the graders created a custom slab by manual adjustment of the boundaries to optimize the visualization of the maximum extent of the MNV (if present). Graders also performed a qualitative analysis of the MNV to evaluate for the morphologic characteristics previously reported in the literature: shape (circular or irregular), margin (well or poorly defined), margin loop (large loop or small loop), location (subfoveal/perifoveal or extrafoveal), fine capillaries (presence/absence), peripheral anastomosis (presence/absence), and vessel arteriolization (presence/absence) [19].

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 20.0 for Mac, IBM, Chicago, Illinois, USA) and are presented as mean $\pm$ standard deviation. Sensitivity, specificity, and positive and negative predictive values for diagnosis of MNV were computed for individual imaging modalities relative to the gold standard multimodal reference. Sensitivity was computed as the number of true positives/number of true positives + number of false negatives, specificity as the number of true negatives/number of true negatives + number of false positives, positive predictive value as the number of true positives/true positives + false positives, and negative predictive value as the true negatives/true negatives + false negatives. Cohen's Kappa coefficient was calculated to quantify the intergrader agreement for qualitative variables. The pre-specified level of statistical significance was a *P* value less than 0.05.

Results

We enrolled a total of 21 untreated eyes of 21 patients with MA associated with MNV and 21 eyes of 21 patients with GA alone. The demographic features are listed in Table 1. There was no significant difference between mean age (79.7 ± 5 years and 78.6 ± 5.5 years; $P = 0.89$), sex (7 males and 14 females, 6 males and 15 females; $P = 0.73$), BCVA (20/40 and 20/50; $P = 0.47$), and size of the atrophic area (8.42 ± 4.04 mm² and 10.76 ± 4.3 mm²; $P = 0.07$). In the MA + MNV group, 11 eyes (52.3%) were classified to have an active MNV and 10 eyes (47.7%) had an inactive lesion.

FA alone identified MNV in 12 eyes (57.1%) with MA+MNV and in 3 eyes (14.2%) with only GA, thus yielding a specificity of 85.7%, but a sensitivity of only 57.1%.

Similarly, ICGA alone identified MNV in 11 (52.3%) of the eyes with MA+MNV, but also in 2 eyes (9.5%) with only GA, thus yielding a specificity of 90.5% and a sensitivity of 52.4% (Table 2).

Structural OCT alone identified MNV in 14 eyes (66.6%) with MA+MNV and in 9 eyes (42.8%) with only GA, yielding a specificity of 66.7% and a sensitivity of 57.1%. OCTA, after applying manual segmentation, identified the MNV in 20 (95.2%) of with MA+MNV eyes and in only one (4.7%) of the eyes with only GA, yielding a specificity of 95.2% and a sensitivity of 95.2%. When the automated segmentation was used, the ORCC yielded the best results compared with the other automatically segmented slabs with identification of MNV in 18 (85.7%) of the MA+MNV eyes and in 2 (9.5%) of the GA only eyes, yielding a specificity of 90.5% and a sensitivity of 85.7%. Of note, the detection of MNV was not influenced by the activity status of the MNV (Fig. 1 and Fig. 2) (Table 3).

In all 21 cases (100%), the MNV was located at the border of the atrophy. In 4 (19%) cases, the MNVs were located subfoveally, while in the remaining 17 (81%), the MNV was extrafoveal. Fourteen lesions (66%) demonstrated a linear morphology, 4 (19%) had a circular morphology, and 3 (14%) showed an irregular morphology. The MNV margin was well defined in 21 cases (100%), and no MNV (0%) in our series had a peripheral anastomotic arcade. MNV margin loops could be distinguished in all cases and were rated as small in 7 cases (33%) and large in 14 cases (67%). For these morphologic characteristics evaluated on the custom OCTA slab, the Cohen's kappa coefficient between graders were excellent (range 0.85 to 0.92).

Discussion

In this study, we evaluated the ability of individual imaging modalities to assess for the presence of MNV in AMD eyes with associated atrophy. Overall, when compared with the gold standard of multimodal imaging assessment, OCTA appeared to show the best performance with the highest levels of sensitivity, specificity, and positive and negative predictive value, particularly when the ORCC or manual custom slabs were used. This finding would appear to emphasize the importance of OCTA in the evaluation of patients with atrophy in order to confirm the presence or the absence of MNV.

The relatively poor sensitivity of FA and ICG (both less than 60%) for detecting MNV in the setting of atrophy is an important outcome of our study. With FA in this setting, the diffusion of the fluorescein dye throughout the choriocapillaris leads to early obscuration of medium-to-large choroidal vessels, and in the presence of a PED with concomitant fibrotic material, staining of dye may make it difficult to distinguish the neovascular network. At the same

Table 1 Demographic features

	MA and MNV	GA
Number of eye	21	21
Age (years)		
Mean (range)	79.7 (71–89)	78.6 (67–84)
Race		
Caucasian	1 (100)	1 (100)
Gender		
Male	7 (33)	6 (29)
Female	14 (67)	15 (71)
Eye involved		
Right	10 (48)	11 (52)
Left	11 (52)	10 (48)
Best-corrected visual acuity, mean (range)	20/40 (20/200–20/32)	20/50 (20/200–20/32)
MNV type		
I	15 (71)	
II	6 (29)	
III	0 (0)	
Active MNV		
Yes	11 (52)	
No	10 (48)	

GA, geographic atrophy; MA, macular atrophy; MNV, macular neovascularization

time, ICGA may also not perform as well in the setting of atrophy, as it may demonstrate the medium and large choroidal vessels of the atrophic lesion but not the smaller vessels of the MNV.

Structural OCT offers the opportunity to identify early stages of the atrophic process before lesions are clinically visible or detected by fundus autofluorescence [20, 21]. Previous studies have suggested that structural OCT can be highly sensitive for identifying MNV (in the absence of atrophy), though with some loss of specificity [22]. The sensitivity of OCT for identifying MNV was considerably lower in our

study, which focused on eyes with evidence of atrophy. However, detection of MNV when atrophy is present may be impacted by RPE remodeling at the border of atrophy and by RPE detachment, which impair the visibility of the neovascularization (Fig. 3).

In contrast to some of the other imaging modalities, OCTA allows the microvasculature and capillary circulation including that of the MNV to be seen in great detail [16, 17]. However, in areas of atrophy, the loss of the RPE and choriocapillaris results in greater signal transmission to the choroid with enhanced visualization of flow and vessels in Sattler and Haller layers, which can make it difficult to appreciate small adjacent MNV. Moreover, the reference segmentation boundaries are influenced by the absence of RPE, and thus segmentation artifacts are common [3]. For these reasons, a manual adjustment of the slab is often necessary to optimally differentiate the MNV network from the underlying choroidal vessels. In fact, in our series, we found the best results in term of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using the manual custom slab. Manual adjustment, however, may not be feasible in the context of a busy clinical practice. Fortunately, we observed good performance with the ORCC slab, which also showed better performance than FA, ICG, or structural OCT.

In order to avoid any misinterpretation of choroidal vessels, Nesper et al. proposed a post-processing approach to facilitate the visualization and interpretation of OCTA in patients with neovascular AMD [23]. However, this post-processing method is time-consuming and also not feasible for use in clinical practice. Furthermore, they used a SD-OCTA system which is not as deeply penetrating as the SS-OCTA used in the study, and thus it is not clear whether their approach would have worked in this setting. Finally, Nesper and colleagues did not compare their OCTA findings with other imaging modalities.

There are several ongoing clinical trials of GA such as Beacon ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=Beacon&rank=1) Identifier: NCT02087085), Derby, and OAKS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=OAKS&rank=1) Identifier:

Table 2 Detection of macular neovascularization using fluorescein angiography, indocyanine green angiography, and optical coherence tomography angiography

	FA	ICGA	OCT	OCTA				
				ORCC	Avascular	Choriocapillaris	Choroid	Manual
Sensitivity	57.1%	52.4%	66.7%	85.7%	4.8%	28.6%	9.5%	95.2%
Specificity	85.7%	90.5%	57.1%	90.5%	100%	90.5%	100%	95.2%
PPV	80%	84.6%	60.1%	90.0%	100%	75%	100%	95.2%
NPV	66.7%	65.6%	63.1%	86.4%	51.2%	55.9%	52.5%	95.2%
Cohen's Kappa	0.95	0.94	0.90	0.95	0.95	0.92	0.94	0.95

FA, fluorescein angiography; ICGA, indocyanine green angiography; NPV, negative predictive value; OCTA, optical coherence tomography angiography; ORCC, outer retina-choriocapillaris; PPV, positive predictive value

Fig. 1 Macular atrophy complicated by macular neovascularization. Fluorescein angiography showing a well-demarcated area with hyperfluorescence as window defect corresponding to the area of atrophy with leakage in the late phase (**a, b**). Indocyanine green angiography revealing a macular neovascularization (MNV) with linear-shaped pattern (**c, d**). Optical coherence tomography (OCT) revealing the choroidal

hypertransmission, the attenuation and the disruption of the RPE band, the overlying photoreceptor degeneration, and the shallow irregular RPE elevation (**e**). OCT angiography showing the neovascular network in the outer retina to choriocapillaris (**f**), avascular (**g**), choriocapillaris (**h**), and choroid segmentations (**i**). In this case, the central core of the MNV is divided into two linear branches progressing to the borders of atrophy

Fig. 2 Geographic atrophy without macular neovascularization. Fluorescein angiography revealing a well-demarcated area with hyperfluorescence as window defect corresponding to the area of atrophy without leakage or pooling of the dye in the late phase (**a, b**). Indocyanine green angiography displaying the large choroidal vessels under the area of atrophy (**c, d**). Structural optical coherence tomography (OCT)

demonstrates drusen as well as regions of choroidal hypertransmission, attenuation, and the disruption of the RPE band consistent with atrophy (**e**). OCT angiography does not show the neovascular network in the outer retina to choriocapillaris (**f**) avascular (**g**), choriocapillaris (**h**), and choroid (**i**) segmentations

Table 3 Detection of macular neovascularization using fluorescein angiography, indocyanine green angiography, optical coherence tomography, and optical coherence tomography angiography

	Active MNV	Inactive MNV
FA	7/11 (63.6%)	5/10 (50%)
ICGA	6/11 (54.5%)	5/10 (50%)
OCT	8/11 (72.7%)	6/11 (54.5%)
OCTA		
ORCC	11/11 (100%)	7/10 (70%)
Avascular	1/11 (9.1%)	0/10 (0%)
Choriocapillaris	4/11 (36.3%)	2/10 (20%)
Choroid	2/11 (18.2%)	0/10 (0%)
Manual	11/11 (100%)	9/10 (90%)

FA, fluorescein angiography; ICGA, indocyanine green angiography; OCTA, optical coherence tomography angiography; OCT, optical coherence tomography

NCT03525600). However, in these studies, OCTA (as well as ICGA) was not mandatory in the clinical evaluation. In our study, we demonstrated that in order to have a high sensitivity and specificity for detecting MNV associated with MA, OCTA was an important tool. Thus, we would advise that future GA studies include OCTA to confirm the presence or absence of MNV—particularly as this may impact eligibility as well as treatment outcome.

In this study, we also evaluated the morphological features of MNV associated with MA. MNV in this setting most commonly manifested in a predominantly linear-shaped pattern (66%), as the configuration of the neovascular network tended to follow the border of atrophy with peripheral sprouting.

Based on its appearance, this structure was termed “stem-shaped,” as the neovascularization seemed to have a morphology similar to the stem of a flower. All of the MNV lesions (100%) were found at the border of atrophy, and only two cases (9%) also showed evidence of linear vessels that extended over the atrophy (Fig. 1). Five (19%) MNV demonstrated a circular shape. All of these circular lesions were located subfoveally and occurred in eyes with foveal-sparing MA lesions (Fig. 4).

Our findings are in contrast to Capuano et al. [19] who reported a quiescent MNV in MA eyes to manifest as a predominantly irregularly shaped high-flow network with no visible core [19]. However, in that study, OCTA was available for only small number of case ($N=6$ eyes). Despite initially being defined as being a quiescent MNV, 5 of these eyes developed exudation during the follow-up, and in 2 cases, OCTA revealed tiny capillaries and small inner and margin loops. In our series, the presence of margin loop or fine capillaries was not correlated with the activity status of the lesion. In fact, currently, it is not possible to use OCTA to evaluate the activity of MNV, as there are no accepted or validated criteria that define an active or inactive lesion based on the morphology of the neovascular network alone.

Our study has several limitations which need to be considered when assessing our results. First, our sample size is relatively small. On the other hand, the development of new MNV in an eye with prior atrophy may not have a very frequent occurrence. Another significant limitation of our study is that the cohort was assembled to have a 50/50 distribution of cases with and without MNV. As such, this is a “selected” population and obviously does not reflect a general clinic population of eyes with atrophy, and thus the sensitivity,

Fig. 3 Macular atrophy complicated by macular neovascularization. Fluorescein angiography showing a well-demarcated area with hyperfluorescence as window defect corresponding to the area of atrophy without leakage or pooling of the dye in the late phase (a, b). Indocyanine green angiography revealing the large choroidal vessels under the area of atrophy (c, d). Structural optical coherence tomography (OCT)

demonstrates shallow irregular RPE elevation as well as regions of choroidal hypertransmission, attenuation, and the disruption of the RPE band consistent with atrophy (e). OCT angiography showing the neovascular network in the outer retina to choriocapillaris (f) and manual segmentations (g) but not in the avascular (h), choriocapillaris (i), and choroid segmentations (j)

Fig. 4 Macular atrophy complicated by macular neovascularization. Fundus autofluorescence showing sharply demarcated areas of hypoautofluorescence surrounded by an hyperautofluorescent outer border (**a, c**). Structural optical coherence tomography (OCT) demonstrates choroidal hypertransmission, attenuation, and disruption of the RPE band, and overlying photoreceptor degeneration and the shallow irregular RPE elevation (**b, d**). Indocyanine green angiography demonstrates the macular neovascularization (MNV) as well as large choroidal

vessels under the area of atrophy (**e, g**). Fluorescein angiography reveals a well-demarcated area of transmission hyperfluorescence corresponding to the area of atrophy without clear leakage from the MNV (**f, h**). OCT angiography reveals a neovascular network with a linear-shaped pattern (**i, k**). The configuration of the neovascular network followed the border of atrophy with peripheral sprouting (**j, l**). Based on its appearance, this structure was termed “stem-shaped,” as the neovascularization presented a morphology similar to the stem of a flower

specificity, PPV, and NPV results should be viewed in this context. On the other hand, the purpose of our study was really to define the best imaging modality to identify MNV in the context of associated atrophy in eyes with AMD, and so while the absolute values may not be as meaningful, the relative differences in the performance of the modalities are relevant. Another potential limitation of our study is the “gold” or reference standard. The ideal gold standard would have been histology, which is obviously not possible. In the absence of a histologic reference, we believe that our strategy to use the information from all modalities and have this evaluated by a senior expert is a reasonable option. Other studies of this type have also used a similar combined gold standard [24–27]. Finally, we used the convention of referring to atrophy in the context of MNV, as macular atrophy to highlight this may differ from GA commonly seen in non-neovascular AMD eyes. However, the merits of this distinction remain

uncertain, as eyes labeled to have GA for many years can go on to develop MNV.

Our study has several strengths including its prospective design, use of multiple graders, and a masked grading process. The use of deeper penetrating SS-OCTA is also a strength, though we would acknowledge that we do not know if our findings can be extrapolated to the SD-OCTA devices.

In conclusion, OCTA appeared to be superior to FA, ICGA, or structural OCT for identification of MNV in eyes with atrophy. OCTA should be considered in the evaluation of patients with atrophy secondary to AMD, particularly in the context of clinical trials.

Authors' contributions FC: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the manuscript. MC: conception and design, acquisition of data drafting the article, and final approval of the manuscript. AI and LP acquisition of data, revising the article critically for important intellectual content, and final approval of the manuscript. SRS: analysis and

interpretation of data, revising the manuscript critically for important intellectual content, and final approval. GS analysis and interpretation of data, acquisition of data, revising the article critically for important intellectual content, and final approval.

Data availability All data relevant to the study are included in the article or uploaded as supplementary information.

Compliance with ethical standards

Conflict of interest Disclosure of potential conflicts of interest: F.Corvi, M.Cozzi and L.Pace declare no conflict of interest. A. Invernizzi: Allergan (financial support), Novartis (consultant), and Bayer (consultant). S.R. Sadda: Allergan (consultant, financial support), Carl Zeiss Meditec (financial support), Genentech (consultant, financial support), Amgen (consultant), Novartis (consultant), Optos (consultant, financial support), Centervue (consultant), Heidelberg (consultant), Regeneron (financial support), and Oxurion (consultant). G. Staurenghi: Heidelberg Engineering (consultant), Quantel Medical (consultant), Centervue (consultant), Carl Zeiss Meditec (consultant), Alcon (consultant), Allergan (consultant), Bayer (consultant), Boehringer (consultant), Genentech (consultant), GSK (consultant), Novartis (consultant), and Roche (consultant), and has received grant support from Optos (financial support), Optovue (financial support), and Centervue (financial support).

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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