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Microperimetry to predict disease progression in eyes at high risk of age-related macular degeneration disease: The PREVISION study

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Abstract

Purpose: The aim of the present study was to determine whether microperimetric parameters could predict the progression of an eye at high risk of age-related macular degeneration (AMD) at 24 months.

Methods: We conducted a multicentric prospective non-comparative open-label study including patients with one eye in stage 4 of the Age-Related Eye Disease Study Group (AREDS) classification, and the other eye in AREDS stage 3 (study eye). A microperimetry examination (MAIA™, CenterVue, Padova, Italy) was performed at baseline and every 6 months during the 2-year follow-up. At the end of the follow-up, each study eye was classified as 'progressive' (i.e. AREDS stage 4) or 'non-progressive' (i.e. AREDS stage 3).

Results: A total of 147 patients were analysed, of which 30.6% progressed from AREDS stage 3 to stage 4. The microperimetry criterion 'mean retinal sensitivity' was significantly different at baseline between non-progressive and progressive eyes ($p = 0.022$), with lower values for the latter. With a threshold for mean retinal sensitivity set at 24.7 dB, diagnostic sensitivity was 80% [95%CI (65.4–90.4)], specificity was 30.4% [95%CI (21.7–40.3)], positive predictive value was 33.6% [95%CI (24.8–43.4)], and negative predictive value was 77.5% [95%CI (61.5–89.2)]. In the multivariate analysis including microperimetric parameters and other routine ophthalmologic examinations, mean retinal sensitivity was the only predictive parameter statistically associated with progression ($p = 0.0004$).

Conclusions: Our findings are encouraging as regards the use of microperimetry, and mean retinal sensitivity value in particular, to predict the 2-year risk of progression to AREDS stage 4 eye.

KEYWORDS
age-related macular degeneration, AREDS, biomarker, microperimetry, prediction, progression

1 | INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of visual impairment in industrialized countries (Klein et al., 2004). Using fundus retinography, the Age-Related Eye Disease Study (AREDS) simplified classification categorizes the disease in 4 stages: from the absence of AMD change (stage 1) to specific fundus alterations of the disease, including mild (stage 2), intermediate (stage 3) or advanced (stage 4) AMD changes (Age-Related Eye Disease Study Research Group, 1999; Bartlett & Eperjesi, 2007). In the most advanced stage, the patient's vision can be threatened by the progression of geographic atrophy involving the centre of the macula or the presence of macular neovascularization. Prior to stage 4, visual acuity is often not affected and cannot be used as a marker of disease progression (Narayanan et al., 2020). However, other functional tests can be performed, such as colour vision, low luminance visual acuity or contrast sensibility (Cocce et al., 2018; Pondorfer et al., 2020), but the lack of standards and reproducibility between centres limits the use of these tests in clinical practice (Hernández-Andrés et al., 2020; Patel et al., 2009). To date, only the presence of reticular pseudodrusen has been described as a predictive marker of progression (Cohen et al., 2007; Hogg et al., 2014; Pumariega et al., 2011; Zweifel et al., 2010).

Microperimetry is a promising diagnostic method, which combines measurements of light sensitivity, loss of fixation and the anatomy of the retina. It offers a new approach to the functional assessment of retinal damage in patients with AMD, as it precisely correlates anatomical and functional modifications by measuring the loss of sensitivity and macular fixation (Dinc et al., 2008; Meleth et al., 2011; Midena et al., 2007; Pilotto et al., 2011; Querques et al., 2012). We recently showed that microperimetry can be used to differentiate between the 4 AREDS stages in AMD patients (Leal et al., 2022). After confirming the accurate grading of AMD, we decided to investigate further with a longitudinal study. Our hypothesis was that there would be a change in one of the microperimetry parameters before any visible clinical modification and that this could therefore be used as a tool to predict AMD progression in patients presenting one eye at high risk of AMD. Patients with one eye at AREDS stage 3 who already have severe AMD (stage 4) in the fellow eye are considered at high risk of progression.

The availability of such a parameter would make it possible to screen eyes likely to progress from intermediate to advanced AMD at an earlier stage and subsequently provide patients who need it with earlier follow-up, preventive treatment or adapted, personalized rehabilitation as appropriate.

The main objective of present study was to determine the performance of microperimetric parameters in detecting the risk of progression at 2 years of an AREDS stage 3 eye fellow to a AREDS stage 4 eye.

2 | METHODS

2.1 | Study design

We conducted a multicentric prospective non-comparative open-label study including patients with AMD from 5 retinal tertiary centres in France. Patients were included between September 2015 and January 2018 and were followed for 2 years. The research adhered to the Declaration of Helsinki. Patients gave written informed consent before inclusion. The study was authorized by the competent French health authority (Agence Nationale de Sécurité du Médicament et des produits de santé; ANSM), on 10 November 2014 and was approved by the research ethics committee (Comité de Protection des Personnes Sud Est IV). The study protocol was registered on the clinicaltrial.gov website (NCT02395757).

2.2 | Patients

Patients aged ≥50 years old were eligible if they were diagnosed with stage 4 AMD (according to the AREDS classification) in one eye and drusen in the fellow eye (study eye) with at least one drusen with a diameter ≥125 μm and/or extra-foveal atrophy (AREDS stage 3). The eye with AREDS stage 3 was defined as the study eye. Patients presenting another maculopathy in the study eye; patients with media alteration (cornea, lens, vitreous humour) which makes it impossible to carry out and interpret the microperimetry correctly; and patients due to undergo cataract surgery in the study eye during the 2-year study period were excluded.

2.3 | Inclusion and follow-up

Patients were followed for 24 months after inclusion, with follow-up visits scheduled every 6 months, according to standard practices. Other visits could be added at the discretion of the ophthalmologist.

When an eye progressed from AREDS stage 3 to stage 4, the data were recorded, and the patient's follow-up stopped.

2.4 | Microperimetry

Microperimetry is a non-invasive technology combining a micrometric projection of a stimulus grid onto a macular image, controlled by an eye-tracker, and correlating retinal sensitivity and fixation characteristics with the anatomical surface of the macula of each eye. As such, microperimetry allows for new approaches to the functional assessment of the retina. The MAIA™ device (CenterVue, Padova, Italy) used scanning laser ophthalmoscopy (SSLO) to obtained images of the macula. Then, a 200 ms Goldmann III stimuli size is projected over a specific area of the retina over a background luminosity of 4 asb. The MAIA™ device software quantifies and compares the retinal sensitivity to a normal patients database.

2.5 | Visits

An automatic microperimetry examination of the 10° central macular coverage 'expert test' (customized grid) had to be performed using the MAIA™ device at inclusion and then at each visit. A customized radial grid was created combining the MAIA™ 'standard' grid which covers the macular 10° and the MAIA™ macular 6° grid. The resulting customized stimuli grid had four concentric rings located at distance of 1°, 2° 3° and 5° from a central stimulus. Each stimulus ring was composed of 12 stimuli homogenously located on a clock distribution around the ring (Leal et al., 2022). This grid corresponds to the central 3 mm examination of the spectral domain optical coherence tomography (SD-OCT). There was a total of 49 stimuli in the customized grid. The duration of the test was estimated by the MAIA™ manufacturer as 7 min per eye. In each centre, all examinations were performed by the same operator on a dilated eye after 5 min in mesopic adaptation conditions. Although the MAIA™ is a non-mydriatic device (minimum pupil diameter of 2.5 mm), we chose to perform the test in the same condition to reduce variability, as described before by several authors (Dinc et al., 2008; Midena et al., 2007). However, a recent study reported no significant effect on threshold sensitivity according to pupil dilation using MAIA™ microperimetry (Han et al., 2017). The following microperimetric parameters were collected: mean retinal sensitivity; and fixation index P1 and P2. The total duration of the examination was also recorded.

All patients also underwent a complete routine ophthalmologic examination at each visit, including best-corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (ETDRS) scale, slit-lamp examination, retinography, SD-OCT, fundus autofluorescence (FAF). At baseline, the following SD-OCT parameters were recorded: 1-mm central macular thickness (CMT), presence of external limiting membrane (ELM) alterations and alterations to the ellipsoid zone/interdigitation zone (EZ/IZ). The presence of reticular pseudodrusen and extra-foveal atrophy were also recorded.

2.6 | Outcome measures

The primary outcome measure was the estimated sensitivity of baseline microperimetric parameters compared with progression (gold standard). Progression was measured by means of the AREDS grading of the study eye established from the results of the retinography, SD-OCT and FAF. Each study eye was classified as 'progressive' or 'non- progressive' according to the AREDS stage of the study eye at the end of the follow-up.

A performance analysis (sensitivity, specificity, positive predictive value and negative predictive value) of this parameter is proposed as the secondary outcome measure.

2.7 | Statistics

Quantitative parameters were presented as means (SD), and qualitative parameters as numbers (percentage). Comparisons between groups were performed using the Wilcoxon test for quantitative values and the chi-square test for qualitative values.

Analysis of primary outcome: The area under curve (AUC) of the receiver operating characteristic (ROC) curve was calculated for each quantitative microperimetric parameter against the gold standard. When the AUC was significantly different from 0.5, a logistic regression model was performed to predict progression (progressive /non-progressive) using this parameter. A threshold was defined which obtained a confidence interval of at least 65% and sensitivity of around 75%.

Analysis of secondary outcomes: specificity, positive predictive value (PPV) and negative predictive value (NPV) along with their confidence intervals were computed using the threshold defined for the primary outcome. The microperimetric parameters were also analysed with a multivariate logistic regression and associated with the other ophthalmic parameters (BCVA, central macular thickness, foveolar thickness, external limiting membrane, ellipsoid zone/interdigitation zone).

Lastly, a subgroup analysis according to the presence of reticular pseudodrusen at baseline was performed.

Additional analyses: the microperimetric parameter values at the final visit were compared between progressive and non-progressive eyes. The relative difference between the final microperimetry value and the baseline microperimetry value was defined as [(final value − baseline value)/baseline value].

All analyses were carried out using SAS software version 9.4 (SAS Inc, Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

A total of 182 eyes were included in the study. Two eyes presented AREDS stage 4 in the study eye at baseline and were excluded. Among the 180 eyes effectively included, 33 (18.3%) were not available for analysis for various reasons (Figure 1). Finally, 147 eyes from147 patients were analysed. The mean (SD) age was 76.4 (7.5) years, and patients were predominantly females (*n* = 95, 64.6%). At baseline, mean (SD) BCVA was 78.9 (9.5) ETDRS letters and mean (SD) CMT was 264.6 (40.3) μm. Extra-foveal atrophy was present in 31.1% (Table 1). The mean (SD) follow-up was 20.6 (7.1) months.

3.2 | Progression (gold standard)

During follow-up, 45 study eyes (30.6%) progressed from AREDS stage 3 to stage 4 and are therefore considered as 'progressive'. A neovascular form of AMD was diagnosed in 75.8% of these cases.

3.3 | Sensitivity of microperimetric parameters

The mean (SD) duration of the microperimetry examination was 6.7 (1.3) minutes. Baseline microperimetric parameters differed between non-progressive and progressive eyes; mean retinal sensitivity was the only parameter which was significantly different, with lower values for progressive eyes ($p = 0.022$, Table 2).

Considering the ROC curve of each microperimetric parameter, AUC for mean retinal sensitivity was 0.62 (0.51–0.73) and was the only parameter significantly different from the value 0.5 (hazard) ($p = 0.0283$, Figure 2).
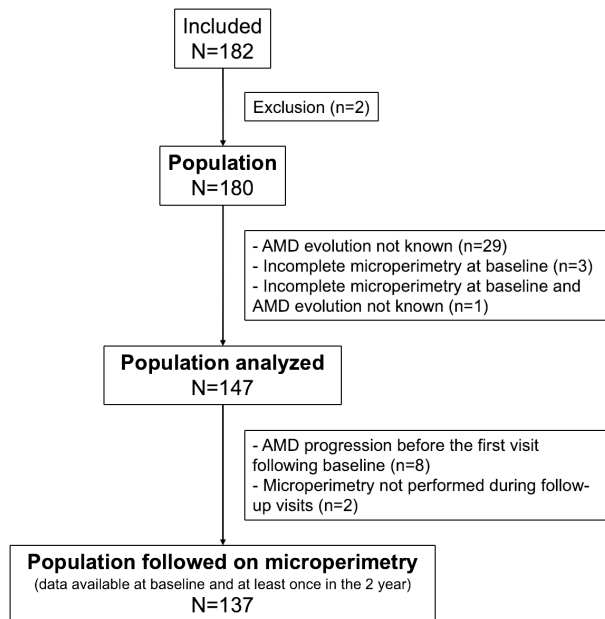

FIGURE 1 Flow chart

TABLE 1 Main patient and ophthalmologic characteristics at baseline ($n = 147$)

Characteristics	
Sex female, n (%)	95 (64.6)
Mean age, years (SD)	76.4 (7.5)
Laterality, right eye, n (%)	67 (45.6)
BCVA, ETDRS letters (SD)	78.9 (9.5)
Central macular thickness measured on SD-OCT, μm (SD)	264.6 (40.3)
Presence of extra-foveal atrophy, n (%)	42 (31.1)
Presence of reticular pseudodrusen, n (%)	48 (32.9)

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography.

3.4 | Performance of the selected parameters

For the mean retinal sensitivity parameter, the threshold was set at 24.7 dB to obtain a confidence interval of at least 65%. At this threshold, the diagnostic sensitivity for progression was 80.0% [95%CI (65.4–90.4)]. Other performance parameters and contingency tables are provided in Table 3.

3.5 | Multivariate analysis

In the multivariate analysis integrating other ophthalmologic parameters, mean retinal sensitivity was the only parameter statistically associated with progression ($p = 0.0004$, Table 4).

3.6 | Reticular pseudodrusen subgroup

For the subgroup of 48 eyes with reticular pseudodrusen, 19 eyes (39.6%) progressed from AREDS stage 3 to stage 4. Patients with reticular pseudodrusen therefore had a higher risk of progression [relative risk 1.9 95%CI (0.92–4.0)], but it was not statistically significant ($p = 0.0838$). Considering the threshold of 24.7 dB for the mean retinal sensitivity value, sensitivity was 63.2% [95%CI (38.4–83.7)], and specificity was 34.5% [95%CI (17.9–54.3)] in this subgroup.
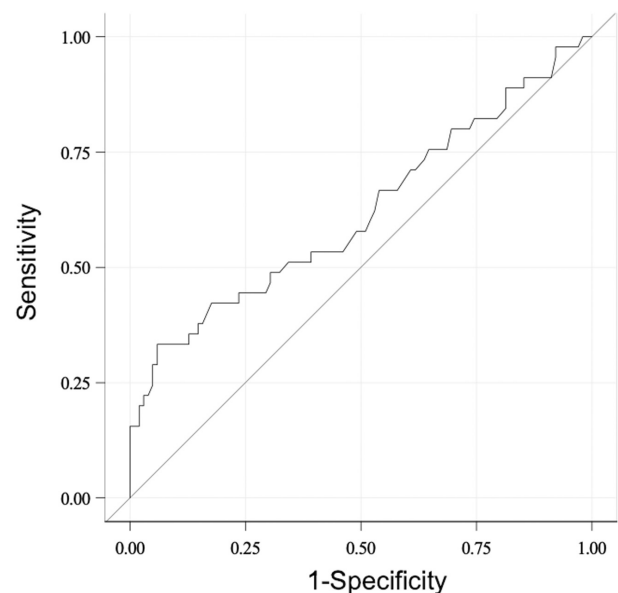
FIGURE 2 ROC curve for mean retinal sensitivity

TABLE 2 Microperimetric parameters at baseline. Values are means (SD)

Parameters	Total ($N = 147$)	Non-progressive ($N = 102$)	Progressive ($N = 45$)	p-value
Mean retinal sensitivity, dB	21.4 (5.8)	22.5 (4.1)	18.7 (7.9)	0.022
Fixation P1, %	72.9 (26.6)	75.1 (23.4)	67.8 (32.6)	0.6198
Fixation P2, %	89.2 (16.7)	90.7 (13.8)	85.8 (21.7)	0.7584

Abbreviation: SD, standard deviation.

TABLE 3 Contingency table at a mean retinal sensitivity threshold of 24.7 dB

	Non-progressive (N = 102)	Progressive (N = 45)		
≤24.7 dB, n (%)	71 (48.3)	36 (24.5)	⇒	Positive predictive value 33.6% (24.8–43.4)
>24.7 dB, n (%)	31 (21.1)	9 (6.1)	⇒	Negative predictive value 77.5% (61.5–89.2)
	⇓ Specificity 30.4% (21.7–40.3)	⇓ Sensitivity 80.0% (65.4–90.4)		

Note: % are given for the whole population (N = 147).

TABLE 4 Multivariate analysis

Ophthalmologic parameters at baseline	*p*-value
Mean retinal sensitivity	0.0004
Best-corrected visual acuity	0.9270
Central macular thickness (mean of the central 1 mm)	0.5028
Foveolar thickness	0.3623
External limiting membrane integrity	0.2390
Ellipsoid zone/interdigitation zone integrity	0.1031

3.7 | Evolution of microperimetric parameters

A total of 137 patients (93.2%) underwent additional microperimetry during the follow-up period. Eight patients had AMD progression before the first visit after baseline, and for two patients, microperimetry was not performed at the follow-up visits. Mean retinal sensitivity at the final examination differed significantly between non-progressive and progressive eyes ($p = 0.0034$). Moreover, the relative difference in mean retinal sensitivity between the final examination and baseline differed significantly with a higher decrease in progressive eyes ($p = 0.0339$). The relative difference was not significantly different between non-progressive and progressive eyes for fixation P1 and fixation P2 (Table 5).

3.8 | Safety and technical considerations

A total of 678 microperimetry examinations were performed during the study; 38 serious adverse events were reported during the study period, none of which were related to the microperimetric procedure. Only four mild adverse events related to the procedure were reported and included asthenia ($n = 1$) and transient blurred vision ($n = 1$) following the microperimetry; the other two concerned difficulties carrying out the examination and uninterpretable results (presence of bone fractures not allowing to perform the examination in good conditions).

4 | DISCUSSION

The present study reports the ability of the microperimetry MAIA™ to predict disease progression in eyes at high risk of AMD, that is an AREDS stage 3 eye contralateral to a AREDS stage 4 eye. Among the 147 eyes analysed, 30.6% progressed to AREDS stage 4. Although some other studies have reported similar results regarding the progression of a AREDS stage 3 eye contralateral to an eye with AREDS stage 4, none of these studies reported any factors of progression (Ferris et al., 2005; Seddon et al., 2011; Souied et al., 2013). Given the lack of biomarkers of disease progression, we aimed to evaluate the predictive value of microperimetry. We found that the mean retinal sensitivity was significantly associated with the prediction of AMD progression. We defined a threshold at 24.7 dB which obtained sensitivity of 80% [95%CI (65.4–90.4)]: eyes with a mean retinal sensitivity ≤24.7 dB are at a higher risk of progression, and 33.6% of them will progress to stage 4 within 2 years (positive predictive value). The false positive will therefore be high but these eyes should only undergo strict follow-up. However, at this threshold, the specificity was low, at 30.4% [95%CI (21.7–40.3)], and 78% of patients above the threshold will not progress to stage 4 in the 2 years. The number of patients receiving false reassurance would therefore be 1 in 5.

Microperimetry is a safe test and appears to be predictive since it detects in at least 65% of cases (lower limit of the confidence interval for sensitivity, estimated at 80%) the risk of AMD progression from AREDS stage 3 to stage 4. In an early detection context, the sensitivity of the test is usually considered to be more important than its specificity, unlike for diagnostic tests. Our findings can be considered to encourage the use of microperimetry, and mean retinal sensitivity in particular, in standard practice to predict the risk of progression to AREDS stage 4 eye. However, the AUC for sensitivity was close to the hazard threshold and although it reached statistical significance, this result should be interpreted with caution.

The mean retinal sensitivity found in this study was close to the value previously reported by our group for AREDS stage 3 (Leal et al., 2022). We also found that the decrease in mean retinal sensitivity was significantly higher in the progressive group compared with the non-progressive group. This concurs with the significant difference in retinal sensitivity between AREDS stages found by Leal et al. (2022). The same results have been found by other groups using the same microperimetric machine (Vujosevic et al., 2017) and using a different

TABLE 5 Evolution of microperimetric parameters between baseline and final visit. Values are means of relative difference (SD)

Parameters	Total (N = 137)	Non-progressive (N = 101)	Progressive (N = 36)	p-value
Mean retinal sensitivity, dB	20.5 (6.7)	21.8 (5.4)	17.0 (8.7)	0.0034
	−0.07 (0.2)	−0.04 (0.2)	−0.1 (0.3)	0.0339
Fixation P1, %	74.0 (25.6)	75.7 (23.9)	68.9 (29.8)	0.3302
	0.2 (1.0)	0.14 (0.7)	0.4 (1.6)	0.5568
Fixation P2, %	90.5 (15.1)	91.8 (13.0)	86.9 (19.8)	0.5739
	0.06 (0.5)	0.04 (0.3)	0.1 (0.8)	0.9184

Abbreviation: SD, standard deviation.

machine (Dinc et al., 2008). These studies, exploring retinal sensitivity in early (AREDS stage 2) and intermediate (AREDS stage 3) AMD, reported that retinal sensitivity decreased significantly in AREDS stage 3 compared with AREDS stage 2 and healthy controls. Regarding mean fixation P1 or P2, we did not find any difference between groups, nor any deterioration in mean fixation P1 or P2 during the study period. However, unlike the study by Vujosevic et al. (2017) which found a significant deterioration in fixation in AREDS stage 3 group over a period of 6 years, our study period was only 2 years, thus limiting our findings regarding possible changes in fixation.

The association between the higher AREDS classification stage and the decrease in retinal sensitivity is probably due to the outer retinal alteration and degeneration triggered by the disease. Previous studies have demonstrated significant and inverse correlation between retinal sensitivity and the presence of fundus autofluorescence patterns (both hypo-autofluorescence and hyper-autofluorescence), which are known to correlate with outer retinal alterations, especially retinal pigment epithelium dysfunction (Midena et al., 2007). This has been confirmed by other authors who have shown that the decrease in microperimetry retinal sensitivity correlates with alteration of the inner segment/outer segment of the photoreceptor layer on SD-OCT (Pilotto et al., 2013; Querques et al., 2012). However, we did not find any association between the different parameters showed on SD-OCT and the progression of AMD.

Our findings should be taken into consideration knowing that to date, only the presence of retinal pseudodrusen has been described as risk factor of disease progression in a AREDS stage 3 eye, contralateral to an eye with AREDS stage 4 (Schmitz-Valckenberg et al., 2021). Although many studies have investigated the association between reticular pseudodrusen and the development of geographic atrophy or neovascularization (Cohen et al., 2007; Domalpally et al., 2019; Hogg et al., 2014; Marsiglia et al., 2013), it has been shown that most patients with AMD screened specifically with SD-OCT have this specific type of drusen (De Bats et al., 2015). In the present study, we did not confirm that the presence of reticular pseudodrusen is significantly associated with the progression in AREDS stage. Moreover, when reticular pseudodrusen were identified, the sensitivity of the microperimetry examination was low and could not be used to predict disease progression.

We acknowledge the limitations of the present study. Although microperimetry is a quite rapid retinal examination which can take less than 7 minutes to perform, a certain number of patients were excluded because of the absence of microperimetry results. This examination requires a good level of patient comprehension and needs to be performed with attention. As such, some patients with unstable fixation or with neurological disorder cannot complete the whole microperimetric examination. This is for this reason that some studies excluded patients with cognitive deficit (Forshaw et al., 2021), as in addition to compliance, it is still debated in the literature how certain neurological disorder can affect the macula or are associated with an increased risk of AMD (Chen et al., 2021; Choi et al., 2020; Keenan et al., 2014; Wen et al., 2021).

Another limitation is that the performance of the model was calculated with the same individuals that were used to build it, and as such should be considered as optimistic. The mean retinal sensitivity threshold of 24.7 dB corresponds to our study population, and it is possible that this population is not fully representative of the overall AMD population, especially when considering the sample size. Finally, our follow-up period of 2 years can be considered as limited, and the findings could be changed if the study period was longer.

It will therefore be necessary to conduct further studies to confirm the promising role of microperimetry.

In conclusion, we report here the performance of microperimetry, and the mean retinal sensitivity value in particular, for predicting disease progression from AREDS stage 3 to stage 4. Given the lack of biomarkers for predicting disease progression in AMD, this result seems promising and could be used in routine practice in contralateral eyes of AREDS stage 4 eye to evaluate the risk of progression when mean retinal sensitivity is below 24.7 dB. Recognition of precursor lesions, or biomarkers of AMD progression to geographic atrophy or neovascular AMD, will be of great interest for developing future therapeutic approaches in intermediate AMD (i.e. AREDS stage 3). Identifying these biomarkers may help in selecting patients for clinical trials and defining better endpoints.

CONFLICT OF INTEREST

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