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Using the Rate of Global and Pointwise Microperimetry Change to Predict Structural Conversion in Intermediate Age-Related Macular Degeneration

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Purpose: Studies evaluating functional change in age-related macular degeneration (AMD) using microperimetry often measure the difference in global mean sensitivity at interval time points versus baseline. We evaluate the rate of global and pointwise microperimetry change in intermediate AMD (iAMD) in the multicenter MACUSTAR (Registration NCT03349801) study and assess their prognostic value in structural conversion to late-stage AMD.

Design: Prospective study.

Subjects: Four hundred forty-seven subjects with iAMD (Beckman classification) from 20 European sites.

Methods: Subjects that underwent mesopic microperimetry on ≥3 follow-up visits were included. Two methods of assessing functional progression were evaluated: (1) global mean sensitivity regression and (2) pointwise sensitivity regression at fastest progressing N number of locations (N from 1 to 10). Rates of microperimetry progression were then evaluated in an initial series of visits prior to structural conversion to late-stage AMD.

Main Outcome Measures: Area under the receiving operating characteristic (AUC) curves and Cox proportional hazard models were used to assess risk of structural conversion based on rate of functional progression.

Results: The mean age of subjects was 72 (standard deviation 7) years. The median number of visits and duration of follow-up was 6 visits and 3 years, respectively. Structural conversion to late-stage AMD was observed in 80 (17.9%) eyes. In the visits prior to conversion, there was a greater rate of global mean sensitivity loss in eyes that eventually developed late-stage AMD compared with those that did not (−1.05 vs. −0.30 decibels/year, $P < 0.001$). The AUC for classifying structural conversion versus no conversion was 0.72 for global sensitivity progression and 0.75–0.76 for between 1 and 10 fastest progressing N pointwise locations. The rate of global (hazard ratio 1.7, confidence interval [CI] 1.4–2.0) and pointwise (hazard ratio 1.2, CI 1.2–1.3) microperimetry progression in the initial series of visits was significantly associated with structural conversion ($P < 0.0001$).

Conclusions: In the analysis of longitudinal microperimetry data from the MACUSTAR study, the rate of global and pointwise sensitivity change was significantly greater and strongly prognostic of eyes that developed structural conversion. Our findings support use of these trend-based pointwise analysis methods in assessing functional progression in iAMD.

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Interventions to stop or delay progression from intermediate age-related macular degeneration (iAMD) are required to decrease the burden of late age-related macular degeneration (AMD).[1] While change in high-contrast best-corrected visual acuity (VA) has been used as a primary end point in large multicentre landmark clinical trials in neovascular AMD in recent decades, it has limited utility to assess early functional deficits in AMD such as in iAMD, where high-contrast VA is preserved.[2] There are currently no outcome measures that are validated and accepted as clinical endpoints by regulatory agencies for drug evaluation in iAMD.[3] MACUSTAR is a prospective multicenter clinical cohort study designed to develop novel endpoints for clinical trials using functional, structural and patient-reported outcome measures in patients with iAMD.[3] The visual function tests being evaluated in MACUSTAR include best-corrected VA, low-luminance VA, Moorfields Acuity Test, Pelli-Robson

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Contrast Sensitivity, International Reading Speed Test, mesopic and scotopic microperimetry, and dark adaptation.[3]

Fundus-controlled perimetry (microperimetry) is designed to deliver visual stimuli to specific retinal locations by monitoring the fundus and compensating for eye movements; it can be done in different lighting conditions and has been shown to give useful information on functional changes in eyes with early AMD.[4,5] Global mean microperimetric sensitivity has been shown to be significantly reduced in early or iAMD compared with normal eyes, and to decline in longitudinal follow-up versus baseline.[6] Randomized clinical trials evaluating functional change in AMD using microperimetry often measure the difference in global mean sensitivity at interval time points versus baseline.[7,8] Perimetric data in location-specific points may, however, be more sensitive than global sensitivity in detecting focal structural change, and demonstrate better correlation with underlying anatomical changes. This has been observed in studies examining the use of targeted microperimetry testing of lesions in iAMD and nascent geographic atrophy (GA).[9,10] Rather than using the difference in microperimetry sensitivity between baseline and subsequent time points, we were interested in exploring if the rate of sensitivity change over time could serve as a prognostic marker for conversion to late-stage AMD. In this study, we therefore assessed the rate of functional progression using global and pointwise microperimetry sensitivity change in eyes with iAMD that displayed conversion to late-stage AMD versus no conversion in the MACUSTAR longitudinal study.

Methods

The detailed methodology and the inclusion and exclusion criteria of the MACUSTAR study has been previously described (NCT03349801).[3] MACUSTAR has a cross-sectional and a longitudinal component, with the latter designed to evaluate how different clinical measures can track progression in iAMD over time, particularly from iAMD to late-stage AMD.[3] In brief, subjects with iAMD were recruited from 20 clinical centers across Europe between April 2018 and March 2020. The Beckman scale was used to determine initial AMD status of a selected study eye and was assessed by a central reading center using multimodal imaging comprising color fundus photography, confocal infrared photography, fundus autofluorescence, and spectral-domain OCT).[3] Intermediate AMD was defined as large drusen >125 μm or any AMD pigmentary abnormalities.[3] Late-stage AMD was defined as GA or choroidal neovascular membrane (CNV) formation, with specific criteria previously described.[3] In brief, GA was defined based on multimodal imaging; a retinal area with severely reduced signal by fundus autofluorescence and a minimum area size of 0.1 mm^2 correlating to loss of the outer nuclear layer and signal enhancement on spectral-domain OCT with associated changes on color fundus photography. Choroidal neovascular membrane was defined based on characteristic changes within a radius of 3000 μm of the fovea on color fundus photography, spectral-domain OCT, or fundus autofluorescence, such as serous detachment of the sensory retina, subretinal or retinal hemorrhage, pigment epithelial detachment, fibrous tissue, hard exudates, or disciform scar.[3] The features of incomplete retinal pigment epithelium (RPE) and outer retinal atrophy and complete RPE and outer retinal atrophy (cRORA) were also defined based on the Classification of Atrophy Meeting Group report 4.[11]

For each patient, 1 eye was selected as the study eye. In the event that both eyes were eligible for inclusion, the eye with better best-corrected VA was selected.[3] The study protocol included 9 visits in total, comprising a screening, baseline, and validation visit, and then follow-up visits every 6 months for 3 years. Subjects that underwent mesopic microperimetry on ≥3 follow-up visits were included. The Macular Integrity Assessment microperimeter (MAIA, iCare) uses a near-infrared line confocal scanning laser ophthalmoscopy to capture and register the fundus image and tracks each pixel at 25Hz.[5] The S-MAIA used in the MACUSTAR study allows functioning testing in the mesopic and scotopic range. An achromatic stimulus (Goldmann III) was presented for 200 milli-seconds using a 4−2 staircase strategy with a background luminance of 1.27 cd/m^2 and an initial target luminance of 2.6 ± 0.5 asb.[3,12] A stimulus grid of 33 points located at 0, 1, 3, 5, and 7 degrees from fixation was used.[13] The technician used the device to determine the optic disc center and the participant's preferred retinal locus was estimated automatically by the S-MAIA in order to correctly center the grid.[12] The standard operating procedure also instructed technicians to note if tests failed either of 2 reliability criteria (fixation losses ≥30% or if the 95% bivariate contour ellipse area >50 degrees). If the fixation errors exceeded 30%, the test was deemed unreliable and excluded.[12] Written informed consent was obtained from all subjects and MACUSTAR was approved by individual local ethics committees and conformed to the Declaration of Helsinki. We performed a retrospective analysis of the longitudinal component of the MACUSTAR cohort study, to assess the prognostic value of the rate of global and pointwise microperimetry sensitivity change in eyes with iAMD that displayed conversion versus no conversion to late-stage AMD.

Analysis 1: Population-Based Rates of Microperimetry Progression

We assessed the rate of microperimetry sensitivity change (i.e, microperimetry progression) in the study cohort using 2 methods:

1. Global mean sensitivity regression (trend-based global)

We used linear mixed-effect models (LMMs) to estimate change in mean sensitivity of the combined 33 microperimetry locations (global mean sensitivity) over time with random intercepts and slopes for each eye, as per previously published methods.[14]

2. Pointwise sensitivity regression (trend-based pointwise)

We used LMMs to calculate change in sensitivity of each microperimetry location (pointwise sensitivity) over time with random intercepts and slopes for each location, nested within eye, based on previously described methods (Fig 1).[14]

We calculated the trend-based global and pointwise rate of sensitivity change over time in the entire series, and compared the rate of sensitivity change in eyes that displayed eventual structural conversion to late-stage AMD versus eyes that did not display conversion. We then calculated the rate of sensitivity change in eyes in the visits before structural conversion to GA/CNV was documented, to test the hypothesis that eyes that later converted to GA/CNV would display a faster rate of microperimetry progression compared with eyes with no conversion. This condensed series of eyes that had ≥3 follow-up visits after excluding the final visit where GA/CNV was documented comprised 397 eyes.

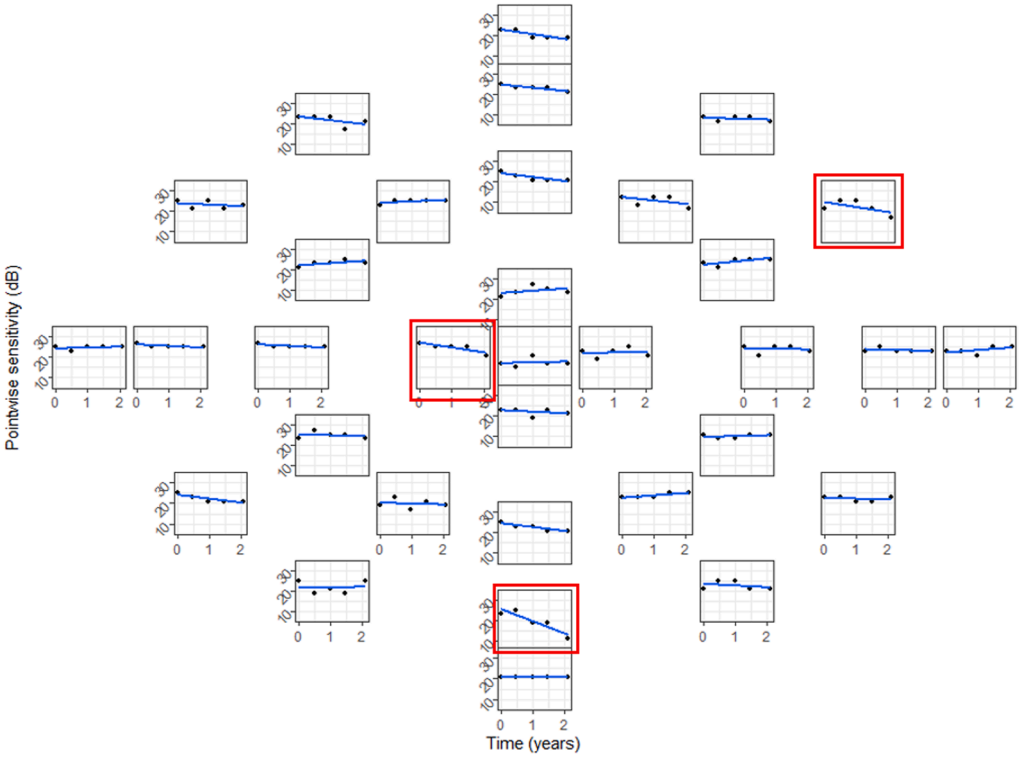

Figure 1. This shows the rate of progression at each of the 33 locations on the microperimetry grid in 1 subject of the MACUSTAR cohort with a follow-up time of 2 years. The red boxes are the 3 fastest progressing locations. dB = decibels.

Analysis 2: Eye-specific Rates of Microperimetry Progression

We then assessed whether eye-specific rates of global and pointwise microperimetry sensitivity change can be used to predict structural conversion.

1. Global mean sensitivity regression

The rate of change in global mean sensitivity in each eye was first calculated using linear regression. We then estimated receiving operating characteristic (ROC) curves and area under the ROC (AUC) to assess performance of using different levels of global rate of progression to distinguish between eyes that displayed eventual structural conversion versus eyes that did not.

2. Pointwise sensitivity regression—fastest progressing N locations

We then examined pointwise sensitivity change over time to determine if the rate of progression in a subset of locations could be used to better distinguish between eyes that displayed eventual structural conversion versus eyes that did not, as per previous work.[15,16] This is intuitive, given the focal structural change that characterizes conversion from early or intermediate AMD to late-stage AMD. We first calculated the rate of change in pointwise mean sensitivity in each of the 33 locations for each eye using linear regression and calculated what the fastest pointwise microperimetry progression was in a single location per eye. We then calculated the mean rate of pointwise progression using the 2 fastest locations and repeated this for an increasing number of locations, up to the 10 fastest locations per eye. Note that the latter number was chosen as an arbitrary threshold to study a subset of grid locations and does not represent a validated threshold for number of pointwise locations to use to assess microperimetry progression. We then estimated ROC curves adjusted by baseline covariates to assess the performance of using the fastest pointwise rate of progression over 1 to 10 locations to classify eyes that displayed eventual structural conversion versus eyes that did not. We compared the AUC against the number of pointwise locations to assess what number of locations provided the highest AUC.

Analysis 3: Rate of Microperimetry Progression over an Initial Follow-Up

Finally, we investigated whether rates of global and pointwise microperimetry progression over an initial period were prognostic of eventual structural conversion. We calculated eye-specific rates of global and pointwise microperimetry progression as described earlier in an initial series of visits before structural conversion occurred. The number of visits in the initial series ranged from 3 to 5 visits, as not all eyes had follow-up data over the study period. Cox proportional hazard regression models were used to generate hazard ratios (HRs) of structural conversion and survival curves to compare the time to structural conversion from the last follow-up visit of the initial series. We adjusted the Cox regression models with the covariates of age at baseline, sex, and baseline global sensitivity. We used the Fine—Gray method to quantify the HRs in the presence of competing events.[17] The Harrell C index was used to assess the discriminative ability of the survival models.[18]

Results

A total of 447 eyes of 447 patients with iAMD were included in the analysis. The mean age at baseline was 71.6 years (standard deviation 7.1), and 66.7% of subjects were

female. The baseline classification of atrophy[11] was incomplete RPE and outer retinal atrophy in 9.2% of eyes, cRORA in 8.9% of eyes, and the absence of incomplete RPE and outer retinal atrophy or cRORA in the remaining 81.7% of eyes. As per the Beckman classification, eyes with cRORA were considered to have iAMD unless the atrophy involved the foveal center, in which case they were classified as having advanced AMD. The mean total follow-up duration for all eyes was 3.1 (interquartile range [IQR] 3.0−3.6, range 0.9−4.1) years. One hundred five (23.5%) eyes had follow-up microperimetry data over 7 visits, followed by eyes with microperimetry data on 9 (33; 7.4%), 8 (75; 16.8%), 6 (103; 23.0%), 5 (44; 9.8%), 4 (46; 10.3%), and 3 (39; 8.7%) visits. Structural conversion to late AMD was observed in 80 eyes (17.9%). The mean time to structural conversion in the latter was 2.1 (IQR 1.5−3.1) years, 3.0 (IQR 2.6−3.5, range 0.5−4.1) years. The median baseline global sensitivity for each eye was 24.2 (IQR 22.5 to 25.6, range 8.8−29.4) decibels (dB). The baseline demographic characteristics of the cohort are shown in Table 1, including a comparison between eyes that displayed eventual conversion to late-stage AMD and those that did not.

Rate of Global and Pointwise Sensitivity Change

The mean rate of global mean sensitivity change in eyes was significantly greater in eyes that demonstrated structural conversion versus eyes that did not convert (−1.17 dB/year vs. −0.37 dB/year, $P < 0.0001$). The mean rate of pointwise sensitivity change was also significantly greater in eyes that demonstrated structural conversion (−1.19 dB/year vs. −0.37 dB/year, $P < 0.0001$) (Fig 2).

Condensed Series Where the Visit of Structural Conversion Was Excluded

The condensed series, which excluded the visit where structural conversion was observed, comprised 397 eyes. Here we similarly observed a significantly greater rate of global (−0.99 dB/year vs. −0.34 dB/year, $P < 0.0001$) and pointwise (−1.04 dB/year vs. −0.31 dB/year, $P < 0.0001$) sensitivity loss in eyes that later developed structural conversion versus no conversion (Fig 2). We calculated the pointwise fastest rates of progression including between 1 and 10 locations. Figure S1 (available at www.ophthalmologyscience.org) shows the mean rate of progression from 1 to 10 fastest progressing locations in the condensed series.

ROC Curves of Global and Pointwise Microperimetry Progression

We estimated ROC curves for global and pointwise microperimetry progression in the condensed series—the series before structural conversion was observed. Logistic regression models were adjusted for sex, age, and baseline global sensitivity. This was for the purpose of assessing prognostic value of microperimetry progression in classifying eyes that displayed eventual structural conversion. The ROC AUC of global microperimetry progression was 0.72 (confidence interval [CI] 0.64−0.80). The ROC AUC for pointwise microperimetry progression using the first to 10 fastest progressing locations ranged from 0.75 to 0.76 (Fig S2, available at www.ophthalmologyscience.org)—for example, the ROC AUC of pointwise microperimetry progression using the mean of the 3 fastest locations was 0.75 (CI 0.68−0.83). The ROC AUC for the reference standard of difference in global sensitivity between baseline and final visit was 0.71 (CI 0.63−0.78). Figure 3 shows the ROC curves of rate of global microperimetry progression (red), pointwise rate of microperimetry progression using the 3 fastest locations (green), and difference in global sensitivity between baseline and final visit (blue, reference) as indices to predict structural conversion. The AUC was greatest for the pointwise method.

Time to Structural Conversion across Different Rates of Global and Pointwise Microperimetry Progression

Faster rates of global microperimetry progression were significantly associated with faster time to structural conversion in the Cox hazards regression model (hazard ratio [HR] 1.7, CI 1.4−2.1, $P < 0.0001$; subdistribution HR 1.7, CI 1.4−2.0, $P < 0.0001$). The Harrell C index was 0.64 for the global model. In the adjusted Cox regression model, faster global microperimetry progression (HR 1.4, CI 1.2−1.7) and lower baseline global sensitivity (HR 0.85, CI 0.79−0.92) were significantly associated with structural conversion. The rate of pointwise microperimetry progression in the 3 fastest locations was also significantly inversely associated with structural conversion in Cox hazards regression model (HR 1.2, CI 1.2−1.3, $P < 0.0001$; subdistribution HR 1.2, CI 1.1−1.4, $P < 0.0001$). The Harrell C index for the pointwise model was 0.70. In the adjusted cox regression model, pointwise microperimetry progression (HR 0.89, CI 0.80−0.99) and baseline global sensitivity (HR 1.1, CI 1.0−1.2) were significantly associated with structural conversion. We excluded eyes with cRORA at baseline and found global microperimetry progression to still be significantly associated with structural progression (HR 1.3, CI 1.0−1.7, $P = 0.03$). Finally, we compared the cox model using the rate of global microperimetry progression with a model without microperimetry (only using the variables of age at baseline, sex, and baseline global sensitivity), and the former was found to display significantly better model fit (log likelihood −281.7 vs. −287.2, $P < 0.0001$). Figure 4 shows cumulative incidence curves of structural conversion in eyes with different rates of global (panel A) and pointwise (panel B) conversion from the last follow-up visit of the initial 5 visits.

Discussion

A key objective of the MACUSTAR study is to develop novel clinical trial endpoints which assess visual function in iAMD.[3] Outcomes of interest are the ability of these measures to distinguish between AMD states and no AMD, to track functional change in AMD over time, and

Table 1. Baseline Characteristics of Patients in the Entire Series and Condensed Series

	Entire Series	Condensed Series
Number of eyes, patients	447, 447	397, 397
Age, mean (SD), yrs	71.6 (7.1)	71.3 (7.1)
Sex, n (%)		
Female	298 (66.7%)	266 (67.0%)
Male	149 (33.3%)	131 (33.0%)
BCVA, logMAR	0.02 (0.1)	0.02 (0.1)
Global microperimetry sensitivity (SD), dB	23.8 (2.8)	23.9 (2.6)
Pointwise microperimetry sensitivity (SD), dB	2.7 (1.4)	2.6 (1.3)

BCVA = best-corrected visual acuity; dB = decibels; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

to predict conversion to AMD. In this study, we found that the rates of global and pointwise sensitivity change were strongly prognostic of eyes that developed structural conversion to late-stage AMD, which support the use of trend-based pointwise analysis methods in assessing functional progression in iAMD.

Mesopic Microperimetry to Assess Functional Change in iAMD

The MACUSTAR study used mesopic microperimetry in a longitudinal cohort of subjects with iAMD. While scotopic testing is thought to be more informative in probing visual dysfunction in AMD given rods are primarily affected in AMD,[19,20] we have previously found that mesopic and scotopic S-MAIA average thresholds displayed similar test-retest variability.[12] The most widely reported microperimetry metric is mean sensitivity—the arithmetic average sensitivity across all the grid locations tested,[5] which has been shown to be significantly reduced in early or intermediate compared with normal eyes with an overall effect size of −0.9 dB across different devices.[6] Global mean sensitivity has been shown to decrease in longitudinal follow-up versus baseline with an effect size

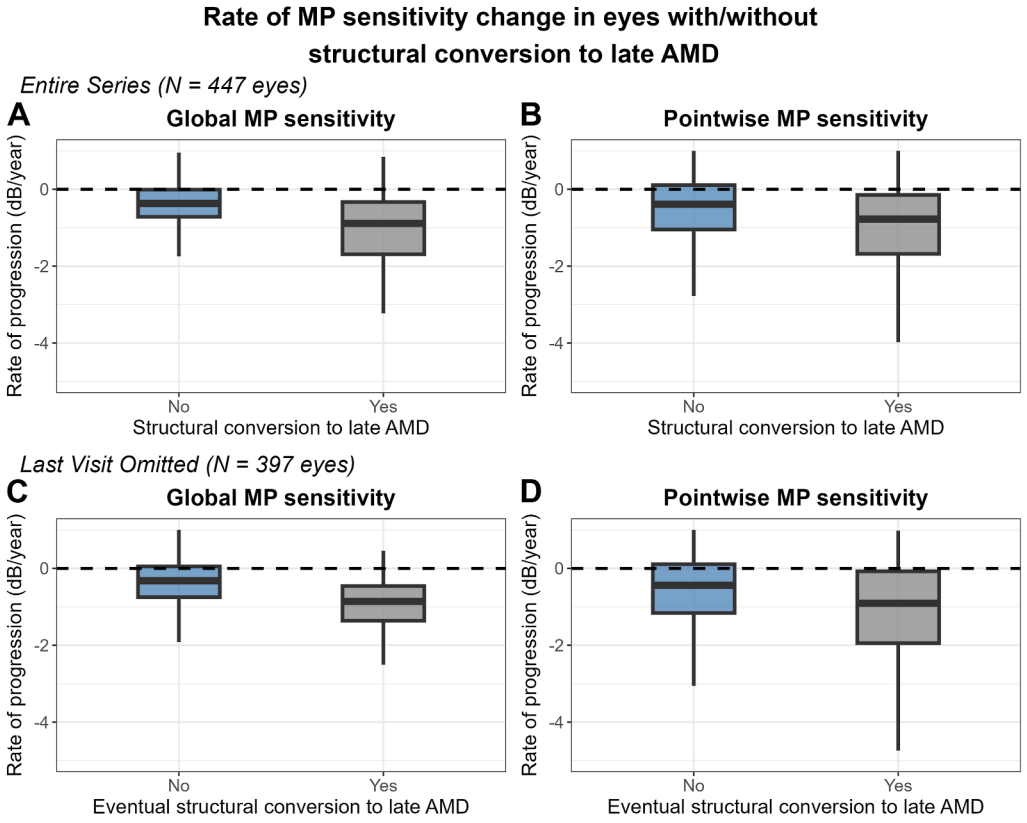

Figure 2. Boxplots of global (left) and pointwise (right) sensitivity change between eyes that displayed structural conversion vs. no conversion over entire study period (panels **A** and **B**; n = 447 eyes). Boxplots of global (left) and pointwise (right) sensitivity change between eyes that displayed structural conversion vs. no conversion in visits before structural conversion was observed (panels **C** and **D**; n = 397 eyes). AMD = age-related macular degeneration; dB = decibels; MP = microperimetry.

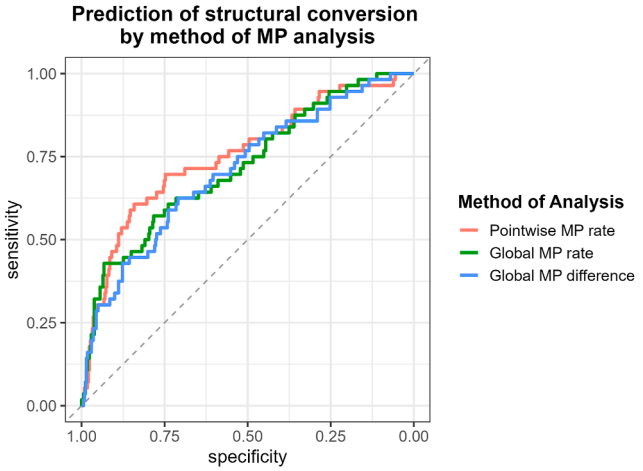

Figure 3. Receiver operating characteristic curves of global MP progression (global MP rate) and pointwise MP progression (pointwise MP rate; 3 fastest locations) as indices to predict structural conversion. The ROC of using the difference in MP between the baseline and final visit is shown as reference (global MP difference). MP = microperimetry; ROC = receiver operating characteristic.

of −1.61 MAIA dB.[6] This has been found to be more pronounced in areas with existing and new occurring anatomic changes of iAMD such as reticular pseudodrusen.[21] In our cohort of iAMD eyes, we found a significant difference in global mean sensitivity in the final visit compared with baseline in both the group of eyes that displayed structural conversion and eyes with no conversion, with a larger change observed in the former group.

Quantifying the Rate of Global Mean Sensitivity Change

Advances in analysis of standard automated perimetry may help improve endpoint development for microperimetry.[5] For instance, attempts have been made to replicate standard automated perimetry indices in microperimetry data, such as mean deviation, total deviation, and pattern standard deviation.[5] The US Food and Drug Administration currently accepts significant changes in ≥5 visual field locations in 2 consecutive visits as an endpoint defining progression in glaucoma.[22,23] Recent research has, however, highlighted the benefits of using the trend of visual field change to determine the speed of progression rather than a progression event,[24–27] which can improve the detection of treatment effects in interventional clinical trials.[25] For instance, in a natural history study of USH2A-related retinal degeneration evaluating functional and structural assessments as endpoints in clinical trials, rates of change was round to be generally more sensitive than proportions of eyes exceeding the coefficient of repeatability thresholds.[28] Similar to standard automated perimetry, the rate of change in global mean sensitivity may help quantify the speed of microperimetric progression.[29] This may potentially serve as a prognostic marker for conversion to late-stage AMD. The Laser Intervention in Early Stages of Age-related Macular Degeneration study was a randomized controlled trial of subthreshold nanosecond laser versus sham in 1 eye of 292 patients with bilateral large drusen.[30] The authors found no significant difference in the rate of global mean microperimetry sensitivity decline between subthreshold nanosecond laser and sham (−0.54 vs. −0.48 dB/year) and between study

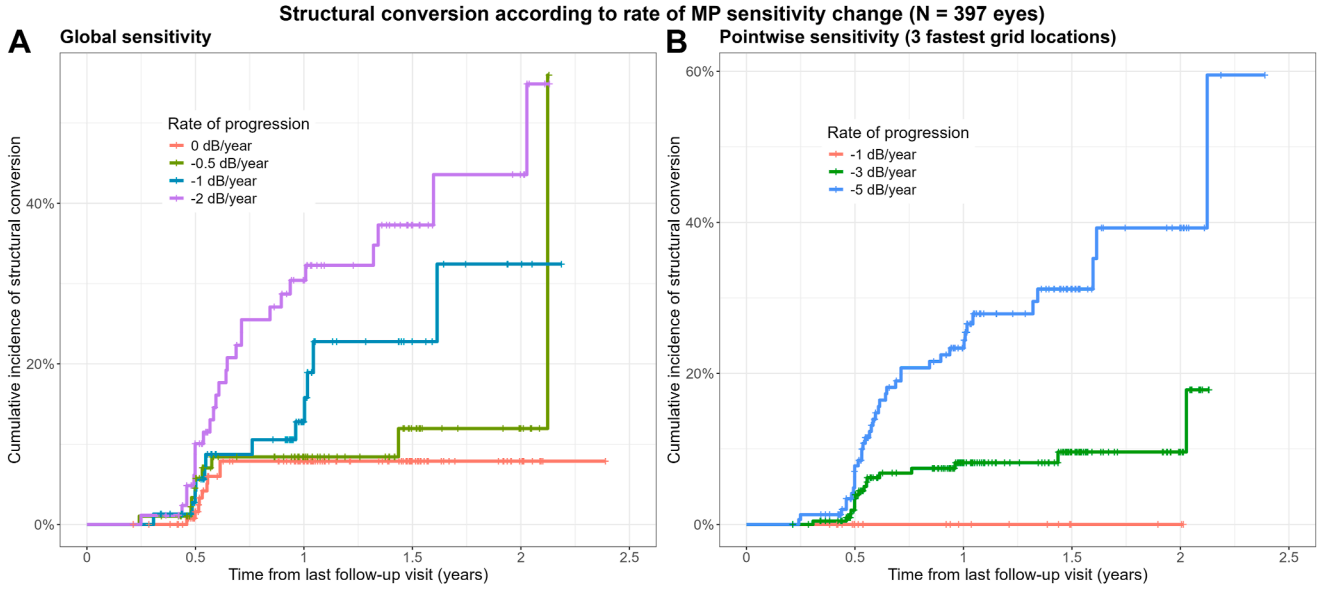

Figure 4. Cumulative incidence curves of structural conversion in eyes with different rates of global (panel **A**) and pointwise (panel **B**) progression grouped by quartiles from the last follow-up visit of the initial series. Three groups in panel B are shown to improve visualization of the curves. dB = decibels; MP = microperimetry.

and nonstudy eyes (laser: −0.54 vs. −0.56; sham: −0.48 vs. −0.50 dB/year), respectively, using LMMs. Luu et al[31] reported that eyes with early AMD that went on to develop late-stage AMD displayed reduced mean flicker sensitivity in the months prior to clinical detection of late-stage AMD compared with eyes that did not progress. The rate of change in flicker sensitivity was also significantly increased in eyes that developed GA compared with control eyes.[31] We found that the rate of change in global sensitivity loss was significantly greater in eyes that displayed structural conversion to late-stage AMD. This was also observed in the condensed series of eyes where only visits prior to where conversion were included. In this series, the rate of global sensitivity progression in distinguishing eyes that later developed structural conversion had an AUC of 0.70 and was significantly associated with an increased risk of structural conversion. The rate of global mean sensitivity progression may therefore have some value as a prognostic marker for eyes at higher risk of structural conversion, although further studies are required to validate this. Other research-driven metrics reported in the literature are more varied and include the mean sensitivity of subsections of the grid, change in mean and pointwise sensitivity over time, scotoma size, and the number of seeing versus nonseeing points.[5,8]

Analysis of Pointwise Microperimetric Sensitivity Data

In this study, we sought to apply hierarchical LMMs to pointwise sensitivity values from a standard test grid used in MACUSTAR in estimating microperimetry change over time. This may have particular relevance in capturing the variance in visual sensitivity which may occur as a result of localized regions of functional abnormalities in iAMD.[32] For example, Wu et al[4] showed that pointwise sensitivity standard deviation was significantly associated with AMD progression in a clinical cohort of 140 subjects with bilateral large drusen monitored over 3 years. Similar to global sensitivity, we found that the rate of pointwise sensitivity change using LMMs was significantly greater in eyes that displayed structural conversion to late-stage AMD versus eyes with no conversion. This was also observed in the condensed series of eyes where only visits prior to where conversion were included.

Prognostic Value of Global and Pointwise Microperimetry Change

Both the global and pointwise rates of microperimetry progression were prognostic of structural conversion in the condensed series and were superior to the interval change in global sensitivity compared with baseline. These metrics may, therefore, be helpful in distinguishing eyes with rapid functional progression and at higher risk of structural conversion. The prediction value of global and pointwise rate of progression was, however, still poor, especially with high specificity; the fastest progressing pointwise locations improved the AUC of structural conversion from 0.70 to 0.75 to 0.76. While the improvement in AUC with pointwise analysis over global progression is modest, it may be used to more precisely stratify patients at higher risk of progression. This may support more efficient trial designs by enriching for likely converters, thereby reducing sample sizes or follow-up durations. Importantly, these trend-based microperimetry progression metrics could be improved with tests targeted to high-risk or diseased locations, such as targeted test grids,[9,10] and improved testing strategies, such as performing 2 tests per visit[33–35] to yield better quality data. For instance, targeted microperimetry testing has been shown to enable the detection of a significantly greater magnitude of visual sensitivity abnormalities in eyes with nascent GA.[10] Longitudinal studies have demonstrated a correlation between changes in outer retinal microstructure and mesopic retinal sensitivity in patients with iAMD.[21,29] Overall, targeted testing and identification of fast progressing locations may be more effective than using standard grids and global sensitivity change in detecting progressing functional decline in eyes with iAMD.

Limitations

Firstly, a single microperimetry test was performed at each visit. The Laser Intervention in Early Stages of Age-related Macular Degeneration study administered 2 MAIA microperimetry tests at each visit,[30] as the second test has been previously shown to display substantially less measurement variability.[33] Specifically, this was observed in eyes with an average mean sensitivity $\leq$24 dB and average pointwise sensitivity of $\leq$18 dB.[33] Secondly, the number of visits was not the same for all subjects (median 6 visits, ranging from 3 to 9). We therefore analyzed if rate of change over an earlier defined time period from the first 3 to 5 visits for all subjects was prognostic of structural conversion. We performed an analysis where the number of earlier visits were fixed at 3, 4, or 5 visits, and similarly found a significant prognostic value of pointwise and global rate of progression and structural conversion. Our adopted approach was intended to maximize the number of eyes captured in the initial follow-up period. Thirdly, we did not perform any structure-function correlations in the fastest progressing pointwise locations; we did not correlate the sensitivity and rate of sensitivity change at each pointwise location with underlying structural changes at these corresponding grid locations. As Heier[8] had found, improvements on microperimetry were observed for scotomatous points within the junctional zone of GA in patients on pegcetacoplan. Contextualizing the fastest-progressing locations with structural information may, therefore, improve how this metric may be used more effectively (i.e., how many and which locations to use) and is the subject of a future study.[36] An additional limitation is the lack of data on smoking history and use of Age-Related Eye Disease Study 2 supplementation, both of which are known risk factors for AMD progression. Their absence may limit the ability to account for important confounders in our analyses. Finally, as multiple analyses were

performed within the same cohort and across varying follow-up subsets without formal correction for multiple testing, some findings—particularly from pointwise analyses—should be interpreted with caution.

Conclusion

In the analysis of longitudinal microperimetry data from the MACUSTAR study, the rate of global and pointwise sensitivity change was significantly greater in eyes that developed structural conversion. Rates of global and pointwise sensitivity change in an initial series of follow-ups were also strongly prognostic of eyes that later developed structural conversion, with pointwise rate having greater prognostic value. Our findings support the use of the rate of microperimetry change methods in assessing functional progression in iAMD.

Footnotes

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Author Contributions:

Conception and design: Tan, Montesano, Behning, Dunbar, Finger, Tufail, Terheyden, Holz, Luhmann, Crabb

Data collection: Tan, Montesano, Behning, Dunbar, Finger, Tufail, Terheyden, Holz, Luhmann, Crabb

Analysis and interpretation: Tan, Montesano, Behning, Dunbar, Finger, Tufail, Terheyden, Holz, Luhmann, Crabb

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AUC** = area under the receiving operating characteristic; **CI** = confidence interval; **CNV** = choroidal neovascular membrane; **cRORA** = complete retinal pigment epithelium and outer retinal atrophy; **dB** = decibels; **GA** = geographic atrophy; **HR** = hazard ratio; **iAMD** = intermediate age-related macular degeneration; **IQR** = interquartile range; **LMM** = linear mixed-effect model; **ROC** = receiving operating characteristic; **RPE** = retinal pigment epithelium; **VA** = visual acuity.

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