Targeted High-Density Microperimetry Testing of Nascent Geographic Atrophy in Age-Related Macular Degeneration

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Purpose: To examine the effectiveness of a targeted high-density microperimetry testing strategy for detecting visual sensitivity abnormalities in eyes with nascent geographic atrophy (nGA) when compared with standard central microperimetry testing.

Design: Observational study.

Participants: Three-hundred and twenty-one eyes from 176 individuals with nonneovascular age-related macular degeneration (AMD).

Methods: Thirty-five eyes from 33 participants underwent targeted high-density microperimetry testing of atrophic lesions (either nGA or geographic atrophy [GA]) within a 1.75° radius (or approximately 1000 μm diameter) region. Another cohort of 286 eyes from 143 participants with bilateral large drusen at baseline underwent standard microperimetry testing of the central 6° radius region at 6-monthly intervals for up to 36 months and thus included eyes that developed nGA and GA over the follow-up. All eyes underwent 2 tests at each visit to evaluate intrasession measurement repeatability.

Main Outcome Measures: Magnitude of visual sensitivity abnormalities based on mean sensitivity (MS), pointwise sensitivity standard deviation (PSD), and the number of test locations with a threshold of ≤ 10 decibels (dB; or deep defects) in eyes with nGA, compared between eyes that underwent targeted high-density microperimetry testing and standard central microperimetry testing.

Results: The magnitude of visual sensitivity abnormalities based on MS, PSD and the number of deep defects were all significantly greater in eyes with nGA using targeted, high-density microperimetry testing compared with eyes with nGA using standard central microperimetry testing (all $P < 0.001$) and were all significantly less than eyes with GA using targeted, high-density microperimetry testing (all $P \leq 0.004$). The intrasession coefficient of repeatability, where 95% of the test–retest differences are expected to occur, for MS in eyes with atrophic changes was 0.9 dB with the targeted, high-density microperimetry testing, and 1.8 dB with standard central microperimetry testing.

Conclusions: Targeted, high-density microperimetry testing enabled the detection of a significantly greater magnitude of visual sensitivity abnormalities in eyes with nGA than standard microperimetry testing.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2024;4:100419 © 2023 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

One of the key challenges currently faced when evaluating novel interventions for atrophic age-related macular degeneration (AMD) is the lack of sufficiently sensitive visual function outcome measures to demonstrate their potential beneficial effects for the patients concerned. Furthermore, most of the current and recent clinical trials primarily focus on slowing the progressive growth of atrophic changes in eyes with already established geographic atrophy (GA),[1–8] where substantial photoreceptor and retinal pigment epithelium (RPE) degeneration has already occurred. However, there is a desire to intervene earlier in the disease process, before visual function is already irreversibly lost, and before it potentially becomes more challenging to slow atrophy progression.[9] To do so, there is a need to establish more sensitive visual function outcome

measures that could be used to evaluate the efficacy of such an earlier intervention.

Using OCT imaging, the distinctive features that portend the future development of atrophy, termed nascent GA (nGA), have been well described,[10] and include the subsidence of the outer plexiform layer and inner nuclear layer, and/or a hyporeflective wedge-shaped band within Henle's fiber layer.[10–12] One study reported that the presence of nGA at baseline was associated with a 56-fold increased risk of developing GA over a 9-year follow-up period.[13] We also recently reported in a prospective study that the development of nGA was associated with a 78-fold increased rate of subsequent GA development.[14] Note that the features used to define nGA represent specific features of photoreceptor degeneration and the

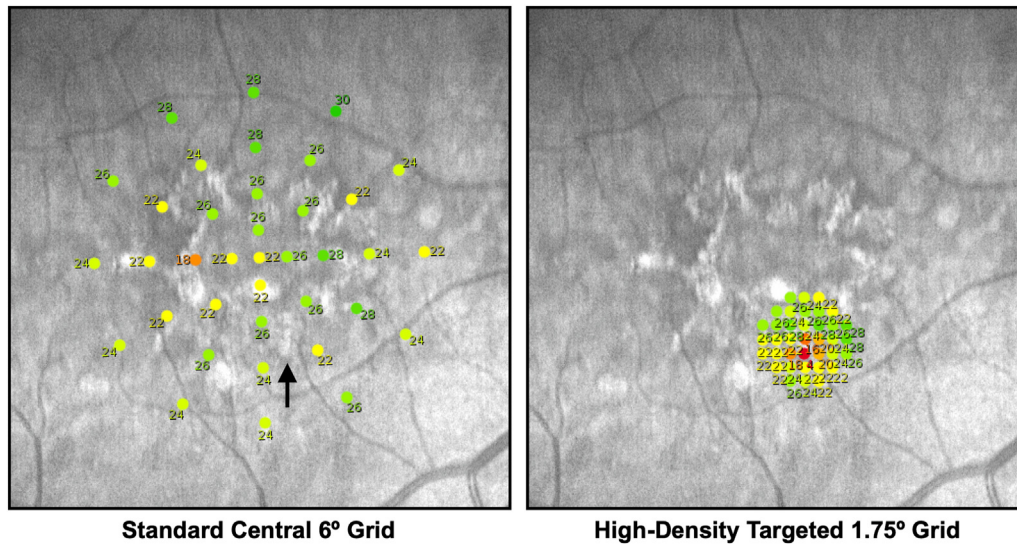**Standard Central 6º Grid**   **High-Density Targeted 1.75º Grid**

Figure 1. Microperimetry stimulus patterns used in this study, including a standard 6° radius grid centered on the fovea (left), or a high-density 1.75° radius (or approximately 1000 μm diameter) grid manually centered on a region-of-interest (one with atrophic changes; right). Both stimulus patterns consist of 37 test locations, and the numbers shown represent visual sensitivity in decibels (dB). This example shows an eye with nascent geographic atrophy (nGA), where microperimetry testing with both stimulus patterns were performed. Note that the nGA lesion was missed with the standard central microperimetry stimulus pattern (left; lesion indicated by a black arrow), whereas high-density targeted microperimetry testing revealed a deep defect (right; 4 dB).

risk of progression to GA has been reported to be significantly greater for nGA compared with incomplete RPE and outer retinal atrophy (iRORA),[15] an OCT-defined term proposed to describe early atrophic changes.[16] The presence of iRORA is defined by evidence of overlying photoreceptor degeneration in a region with choroidal signal hypertransmission and corresponding RPE disruption or attenuation. These signs of photoreceptor degeneration can include the same features used to define nGA, but they can also include the disruption of the ellipsoid zone or external limiting membrane, or outer nuclear layer thinning. One recent study showed that the rate of progression to GA within a 24-month period was 38% and 3% for eyes with nGA and iRORA respectively, and nGA explained a significantly higher proportion of variance in the time to develop GA compared with iRORA.[15] These findings collectively demonstrate how nGA is a high-risk factor for GA development, and may thus be an ideal early stage in the atrophic AMD disease process to target for intervention trials.

Because atrophic AMD changes (including both nGA and GA) often first develop outside the foveal region,[10,17] visual acuity is an ineffective measure to capture progressive visual function decline in these eyes. Fundus-tracked perimetry, or "microperimetry," is a technique that has been increasingly used in clinical trials of retinal diseases over the past 2 decades, as it enables an assessment of visual sensitivity at specific retinal locations through the use of retinal imaging during perimetry testing.[18,19] We have previously observed that test locations on a standard microperimetry examination that sampled regions with nGA exhibited worse visual sensitivity compared with those that sampled nonatrophic regions, but showed better visual sensitivity compared with those

that sampled regions of drusen-associated atrophy seen on OCT imaging.[12]

However, standard microperimetry testing of the macula, such as with a stimulus pattern that consisted of 37 test locations within the central 6° radius region in our previous study,[12] can miss sampling regions of nGA, and might therefore be suboptimal at detecting progressive visual sensitivity decline in eyes with nGA. We thus explored in this study whether an approach based on targeted, high-density testing of nGA lesions could provide a more effective approach for capturing visual sensitivity abnormalities compared with standard central microperimetry testing when both approaches were matched for the same number of test locations (to maintain reasonable test durations). If the targeted, high-density testing approach for assessing nGA lesions can capture visual sensitivity abnormalities much more effectively, it could provide a more robust method for detecting potential beneficial functional treatment effects in trials of earlier interventions in atrophic AMD.

Methods

This study includes individuals examined as part of a prospective observational study conducted at the Centre for Eye Research Australia who underwent high-density targeted microperimetry testing of atrophic lesions (nGA and GA). Findings from these individuals were compared with those from participants who were randomized to the sham treatment arm of the Laser Intervention in the Early Stages of AMD (LEAD) Study,[20,21] who underwent microperimetry with a standard central 6° radius grid. Both of these studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and with the tenets of the Declaration of
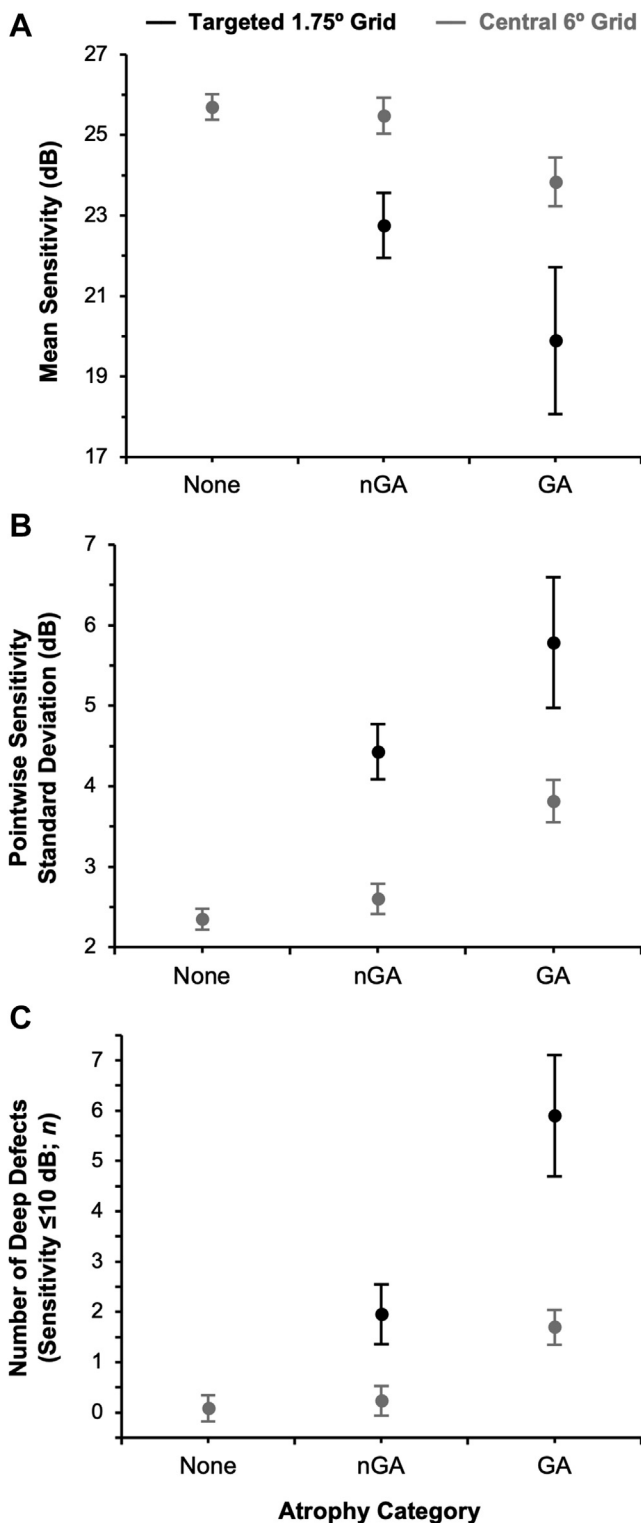
Figure 2. Comparison of the magnitude of visual sensitivity abnormalities based on the category of atrophy present in an eye (none, nascent geographic atrophy [nGA], or geographic atrophy [GA]) based separately on the microperimetry testing strategy used (high-density targeted testing with a 1.75° radius [or approximately 1000 μm diameter] grid shown in black, and a standard central 6° radius grid shown in gray). Visual sensitivity abnormalities were evaluated based on **(A)** mean sensitivity, **(B)** pointwise sensitivity standard deviation, and **(C)** number of deep defects (≤ 10 decibels [dB]). Error bars represent 95% confidence intervals of the mean.

Helsinki. Institutional review board approval at all sites was obtained for both studies, and all participants provided informed consent.

Participants

The prospective observational study included individuals aged ≥ 50 years with AMD, who had either nGA or GA and a best-corrected visual acuity of 20/100 or better in ≥ 1 eye that had not undergone any prior treatment. The LEAD Study also included individuals aged ≥ 50 years with AMD, who had ≥ 1 large drusen (> 125 μm) within the central 1500 μm radius and a best-corrected visual acuity of 20/40 or better in both eyes at baseline. Individuals with any evidence of multimodal imaging-defined late AMD (including neovascular AMD, GA, or nGA) in either eye at baseline were excluded from the LEAD Study. Individuals with any ocular, systemic, or neurologic condition(s) that could affect the assessment of the retina or visual function, or that could prohibit reliable microperimetry testing, were excluded from both studies.

Participants in the prospective observational study were seen at 1 study visit to undergo microperimetry testing of 1 eligible study eye. If both eyes met the eligibility criteria, participants were offered an opportunity to undergo microperimetry testing of both eyes across 2 different visits. In the LEAD Study, participants were seen at 6-month intervals for up to 36 months, and only visits from eyes without neovascular AMD were included in the analyses of this study. Although the prospective observational study only included eyes with atrophic changes, we included all visits from eyes of individuals in the LEAD Study that had nonneovascular AMD, with or without atrophic changes. Eyes without atrophic changes were included to serve as a reference for comparison of the extent of visual sensitivity abnormalities in eyes with nGA for standard central microperimetry testing and as a reference for measurement repeatability in eyes without atrophic changes.

Retinal Imaging

In the prospective observational study, a macular-centered OCT volume scan covering a 20° × 20° region consisting of 97 B-scans, each having 1024 A-scans and with automatic real-time averaging of 16 frames, using the Spectralis HRA + OCT device (Heidelberg Engineering GmbH). Macular-centered, nonstereoscopic color fundus photographs (CFPs) were obtained using the Canon CR6-45NM device (Canon). In the LEAD Study, a macular-centered OCT volume scan covering a 20° × 20° region consisting of 49 B-scans, each having 1024 A-scans and with 25 frames averaged, was also obtained with the Spectralis HRA + OCT device. Macular-centered, nonstereoscopic CFPs were also obtained using site-specific fundus cameras, all having a minimum resolution of 2000 × 2000 pixels. Note that CFPs were always obtained after microperimetry testing.

Microperimetry Testing

Participants underwent microperimetry testing with the Macular Integrity Assessment device (CenterVue) after pupillary dilation and before any assessments that could affect the ocular surface or bleach the retina. Perimetry testing with the Macular Integrity Assessment was performed with fundus-tracking, using 36.5° × 36.5° fundus images captured with a line-scanning laser ophthalmoscope (central wavelength of 850 nm) at 25 frames per second. Goldman Size III (0.43° diameter) stimuli were used and presented against an achromatic background with a luminance of 1.27 cd/m². The luminance range of 1.35 to 318 cd/m² for the stimuli that were presented against this background thus provided a dynamic range of 36 decibels (dB) of differential contrast. All tests
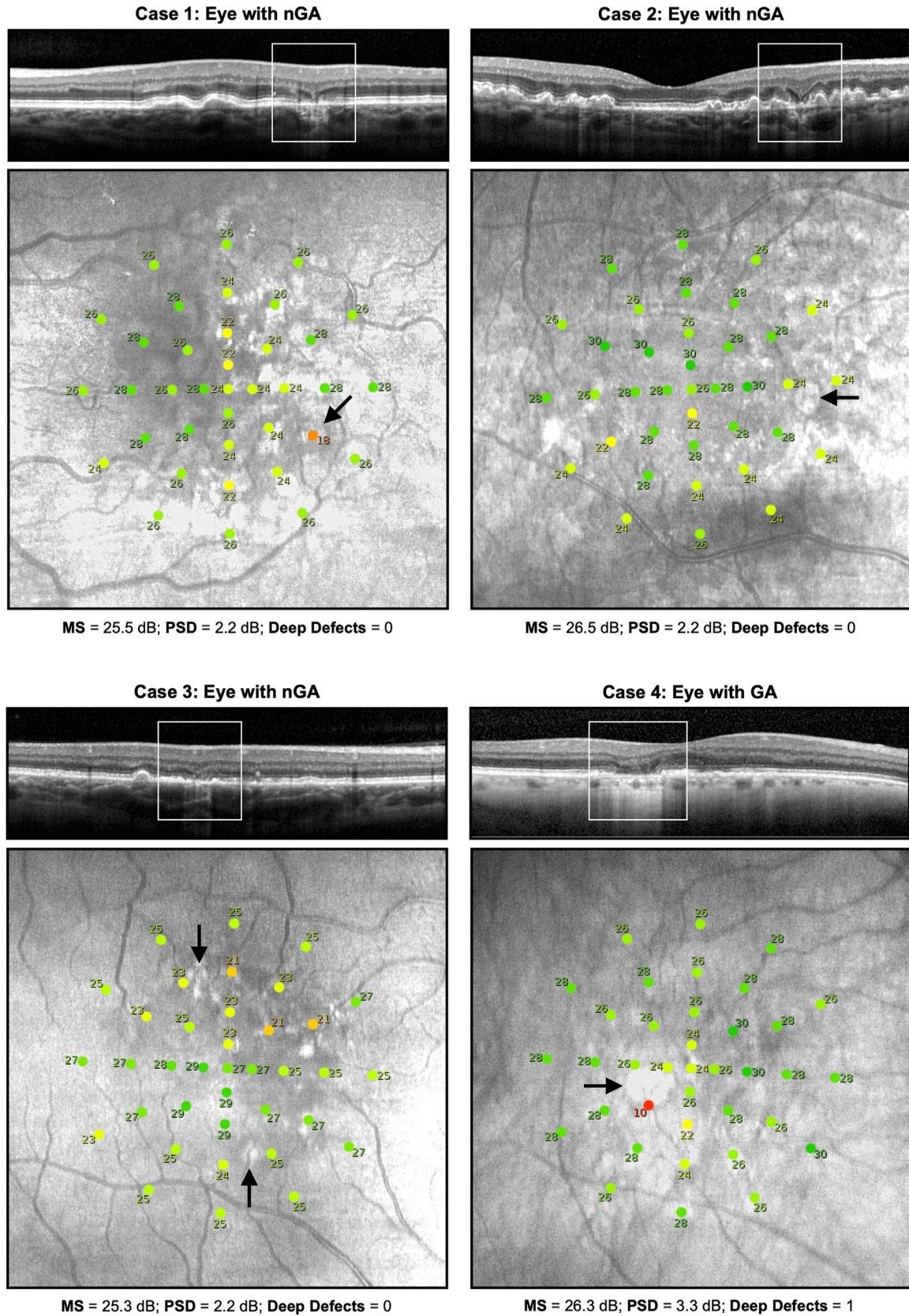
Figure 3. Exemplary cases of standard central microperimetry testing of eyes with atrophic changes (shown on the bottom of each case, with the OCT B-scan of 1 of the lesions [the superior lesion in Case 3] shown at the top of each case [the atrophic lesion is outlined with a white rectangle]), including those

were performed with a 4-2 staircase threshold strategy, using a 1° diameter red central fixation target. Test reliability was assessed based on the frequency of response to the false-positive catch trials, assessed with stimuli presented at the optic nerve head, and tests with > 25% false-positive errors were discarded and repeated where possible.

Individuals in the LEAD Study underwent microperimetry using a standard central 6° radius grid centered on the fovea (based on the preferred retinal locus determined at the start of the examination), consisting of 37 points located at 0°, 1°, 2.33°, 4° and 6° from the fovea.[22,23] This stimulus grid is shown in Figure 1, and all participants performed 2 tests in each eye at every visit. Individuals in the prospective observational study underwent high-density targeted microperimetry testing with an isotropic stimulus pattern also consisting of 37 points that sampled a 1.75° radius (or approximately 1000 μm diameter) region, with an interstimulus spacing of 0.5°. This grid was manually centered on an atrophic lesion that was identified on the OCT volume scan. The location of the lesion on the near-infrared reflectance image that was simultaneously captured during OCT imaging was used when determining where the stimulus pattern should be centered on the infrared image captured by the microperimeter, to enable targeted high-density testing of the atrophic lesion. If multiple atrophic lesions were present in an eye, only lesion(s) that were isolated from other lesions were considered eligible, so that the high-density targeted stimulus pattern only sampled 1 atrophic lesion. If multiple isolated lesions were present, the lesion that was most definite for the features of nGA was chosen for testing. This stimulus pattern is also shown in Figure 1, and each eligible study eye underwent 3 tests at a single visit.

This study included eyes with 2 reliable tests to assess the intrasession repeatability of the tests, and it required both tests to be performed with the "follow-up" function (i.e., where testing was seeded with sensitivity estimates from a prior test). This was required given our recent findings that the first test ever performed in an eye (i.e., one that was not seeded with information from a prior test) underestimates visual sensitivity losses and that over 3 tests in 1 session, the first test pair exhibits a significantly larger degree of test−retest variability than the second test pair.[24] As such, only the follow-up visits for the participants in the LEAD Study were included, as only 1 test with the "follow-up" function was performed at baseline for each eye.

Image Grading

OCT volume scans and CFPs from both studies were then graded independently for the presence of nGA and GA respectively, masked to the results of microperimetry testing. The presence of nGA was defined by subsidence of the outer plexiform layer and inner nuclear layer, and/or a hyporeflective wedge-shaped band within Henle's fiber layer.[10,14] Geographic atrophy was defined on CFP by evidence of a sharply demarcated, roughly round or oval region of complete RPE depigmentation that resulted in enhanced visibility of the underlying large choroidal vessels, which was ≥ 175 μm in diameter and located within the central 3000 μm radius. In the prospective observational study, the grading for the presence of nGA and GA was performed by 2 senior graders together, who resolved any disagreements

immediately through open adjudication. The grading methodology of nGA and GA for participants in the LEAD Study has been previously described.[14,15] In brief, 1 senior grader performed an initial grading of the OCT scans and CFPs across all visits for the presence of nGA and GA respectively, and all visits of an eye where these were deemed as being questionable or definitely present were then reviewed by 2 different senior graders together, who also resolved any disagreements immediately through open adjudication.

Statistical Analysis

Visual sensitivity abnormalities from the microperimetry tests were evaluated based on the following measures of each test: (1) mean sensitivity (MS), the arithmetic mean of pointwise sensitivities (PWS); (2) PWS standard deviation (PSD), the standard deviation of PWS; and (3) number of deep defects, based on the number of test locations with a sensitivity of ≤ 10 dB (the default stimulus intensity used for false-positive catch trials at the optic nerve head by the device, and a level of sensitivity that falls well outside the range of normal sensitivities). These parameters were compared between eyes that underwent microperimetry testing with the high-density targeted grid and the standard central grid, based on the severity of the atrophic changes of the eye or lesion tested (nGA, GA, or none). These comparisons were made using linear mixed models to account for the correlations between the 2 tests from an eye within the same visit, between tests across different visits of an eye, and between 2 eyes of each participant.

Intrasession test−retest repeatability of MS was determined based on its coefficient of repeatability (CoR), the value where 95% of the test−retest differences are expected to occur. The CoR was derived for all eyes that underwent the high-density targeted microperimetry testing and compared against the CoR from visits of eyes that underwent the standard central microperimetry tests, with and without atrophic changes separately. These comparisons were also performed using linear mixed models to account for the between-eye correlations and correlations between data across multiple visits. Comparison of the average duration of each test for all eyes that underwent targeted, high-density microperimetry testing was also compared with those that performed standard central microperimetry tests, with and without atrophic changes, using a similar linear mixed model. All analyses were conducted using Stata/IC software version 16 (StataCorp).

Results

A total of 35 eyes from 33 participants from the prospective observational study who underwent high-density targeted microperimetry testing were included in this study. These individuals were on average 73 ± 8 years old (range, 53−86 years), 30 (86%) eyes had nGA, and 5 (14%) eyes had GA. A total of 286 eyes from 143 participants from the LEAD Study who underwent standard central microperimetry testing across a total of 1556 visits where neovascular AMD was absent were also included. These individuals were on average 70 ± 8 years old (range, 51−89 years) at the first visit included in this study, and 39 (14%) eyes developed

with nascent geographic atrophy (nGA) and geographic atrophy (GA; indicated by the black arrow[s] in each case). Case 1 presents a case where 1 test location sampled the nGA lesion, which exhibited moderate visual sensitivity loss (18 decibels [dB]). Cases 2 and 3 present cases where the test locations missed sampling the nGA lesion(s). Case 4 presents a case where 1 test location sampled the GA lesion, which exhibited deep visual sensitivity loss (10 dB). Note that the numbers shown represent visual sensitivity in dB, and the mean sensitivity (MS), pointwise sensitivity standard deviation (PSD), and number of deep defects detected (or locations with ≤ 10 dB) are presented for each case.
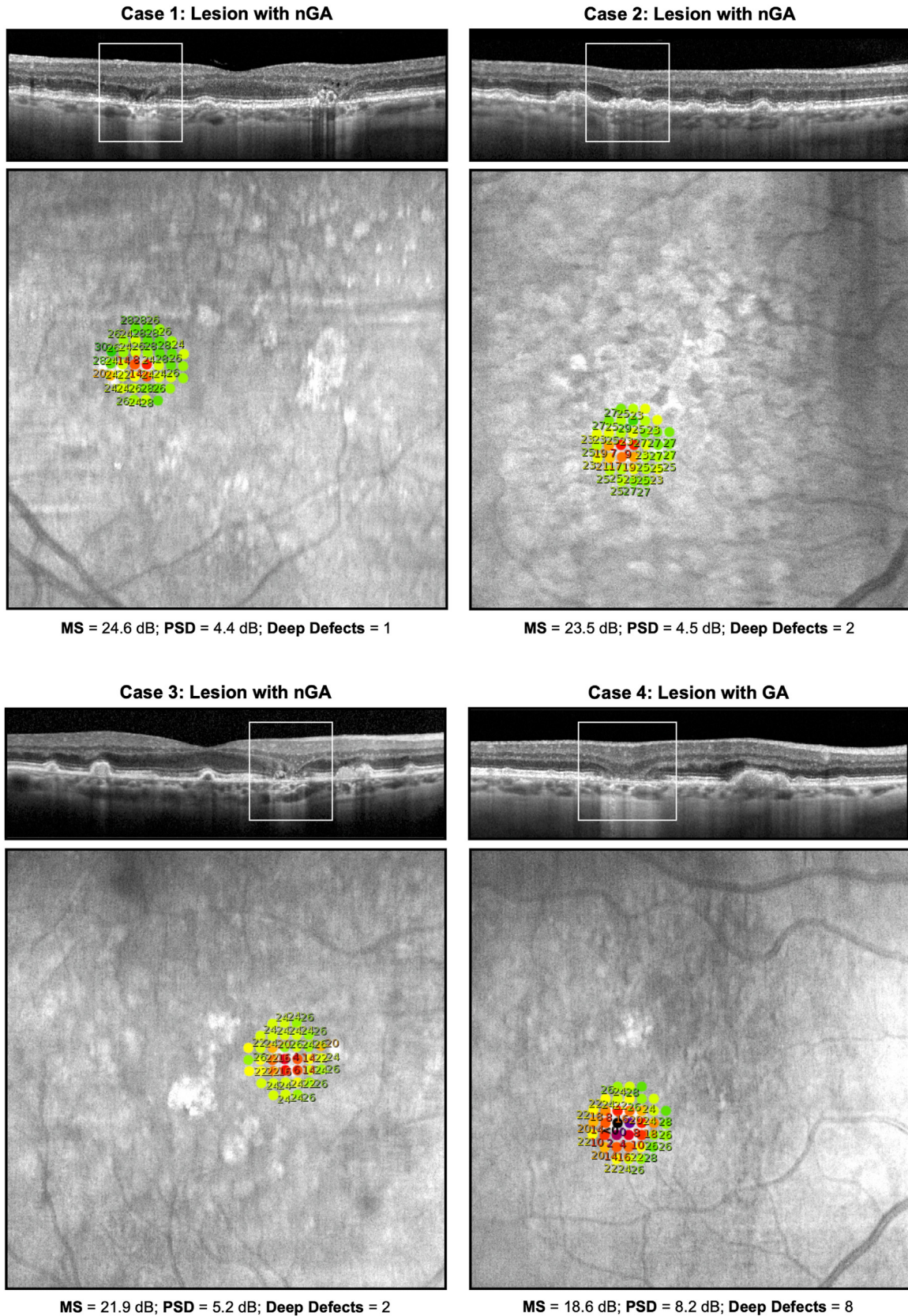
Figure 4. Exemplary cases of high-density targeted microperimetry testing of atrophic lesions (shown on the bottom of each case, with the OCT B-scan of the lesion shown at the top of each case, outlined with a white rectangle), including those with nascent geographic atrophy (nGA) and geographic atrophy

Table 1. Intrasession Coefficient of Repeatability (where 95% of the test–retest differences are expected to lie) for Mean Sensitivity (dB)

Microperimetry Testing Strategy	CoR (95% CI)	P Value*
Targeted 1.75° radius testing		
nGA or GA	0.9 (0.4–1.4)	-
Central 6° radius testing		
No atrophy	1.7 (1.6–1.8)	< 0.001
nGA or GA	1.8 (1.4–2.1)	< 0.001

CI = confidence interval; dB = decibels; GA = geographic atrophy; nGA = nascent geographic atrophy.
*Compared with targeted 1.75° radius testing of eyes with nGA or GA.

nGA and 14 (5%) eyes developed GA over the follow-up period. There was no significant difference in the age of the participants between the 2 studies considering the visits included in the analyses ($P = 0.221$).

Comparison of Visual Sensitivity Abnormalities

The magnitude of visual sensitivity abnormalities detected in eyes with nGA was significantly greater with high-density targeted microperimetry testing (black markers in Fig 2) than standard central microperimetry testing (gray markers in Fig. 2) based on MS (Fig 2A), PSD (Fig 2B), and the number of deep defects (Fig 2C; $P < 0.001$ for all). The magnitude of visual sensitivity abnormalities in eyes with nGA was significantly less than in eyes with GA when using high-density targeted microperimetry testing (black markers in Fig 2) for all 3 parameters (MS, PSD, and number of deep defects in Fig 2A, 2B and 2C respectively; $P \leq 0.004$ for all). In addition, the magnitude of visual sensitivity abnormalities based on MS (Fig 2A), PSD (Fig 2B), and number of deep defects (Fig 2C) were all significantly worse in eyes with nGA with high-density targeted microperimetry testing (black markers in Fig 2) compared with eyes without any atrophic changes (category "None" in Fig 2) with standard central microperimetry testing (gray markers in Fig 2; $P < 0.001$).

Note that with standard central microperimetry testing (gray markers in Fig 2), there were only significant differences in the magnitude of visual sensitivity abnormalities for eyes with nGA compared with eyes without atrophic changes (category "None" in Fig 2) based on PSD (Fig 2B) and number of deep defects (Fig 2C; $P \leq 0.042$), but not MS (Fig 2A; $P = 0.206$). However, the magnitude of visual sensitivity abnormalities based on MS (Fig 2A), PSD (Fig 2B), and number of deep defects (Fig 2C) were all significantly worse in eyes with GA compared with eyes with nGA with standard central microperimetry testing (gray markers in Fig 2; $P < 0.001$).

Four exemplary cases that illustrate the findings for the standard central microperimetry testing of eyes with atrophic changes are shown in Figure 3. Case 1 shows an example where only 1 of the test locations sampled the nGA lesion that developed in this eye, and this test location only exhibited a moderate degree of visual sensitivity loss. Cases 2 and 3 show examples where the test locations missed sampling the 1 and 2 nGA lesions that developed in these eyes, respectively. Case 4 also shows an example where only 1 test location sampled the GA lesion that developed in this eye, which exhibited deep visual sensitivity loss.

Four exemplary cases illustrating the findings of the high-density targeted microperimetry testing are shown in Figure 4. Cases 1 to 3 show examples where nGA lesions exhibited highly localized deep visual sensitivity losses, whereas Case 4 shows an example where a GA lesion exhibited deeper and more extensive visual sensitivity losses than the other cases with nGA.

Measurement Repeatability and Test Duration

The intrasession CoR for the high-density targeted microperimetry testing of eyes with nGA or GA (0.9 dB; 95% confidence interval [CI] = 0.4–1.4 dB) was roughly half of what was observed with conventional central microperimetry testing of both eyes also with nGA or GA (1.8 dB; 95% CI = 1.4–2.1 dB) or eyes without atrophy (1.7 dB; 95% CI = 1.6–1.8 dB); these findings are summarized in Table 1. Note also that the CoR for PSD was 1.2 dB (95% CI = 0.9–1.4 dB), 1.1 dB (95% CI = 1.0–1.3 dB), and 0.8 dB (95% CI = 0.8–0.9) for eyes with nGA or GA that underwent high-density targeted and standard central microperimetry testing, and eyes without atrophy with the latter approach, respectively. Similarly, the CoR for the number of deep defects was 1.5 locations (95% CI = 1.2–1.8 locations), 0.4 locations (95% CI = 0.2–0.6 locations), and 0.1 locations (95% CI = 0.1–0.2 locations), respectively. However, note that there was a substantially larger level of association between the repeatability and magnitude of the measurement for the number of deep defects (Kendall's $\tau = 0.74$) compared with MS and PSD (Kendall's $\tau = -0.10$ and 0.13 respectively), thus accounting for the differences in the CoR of the number of deep defects observed above (due to the marked difference seen in Fig 2 for the number of deep defects based on the eyes evaluated and the microperimetry testing strategy used).

There was also no significant difference in the average test duration for the high-density targeted microperimetry tests of eyes with nGA or GA (5.3 minutes; 95% CI = 5.2–5.5 minutes) compared with standard central microperimetry testing in eyes with nGA or GA (5.5

(GA). Cases 1 to 3 illustrate the presence of deep localized visual sensitivity losses in nGA lesions, whereas Case 4 shows even deeper and more extensive visual sensitivity losses in a GA lesion. Note that the numbers shown represent visual sensitivity in decibels (dB), and the mean sensitivity (MS), pointwise sensitivity standard deviation (PSD), and number of deep defects detected (or locations with ≤ 10 dB) are presented for each case.

minutes; 95% CI = 5.4−5.5 minutes) or eyes without atrophy (5.4 minutes; 95% CI = 5.3−5.4 minutes; $P \geq 0.133$ for both).

Discussion

This study demonstrated that the magnitude of visual sensitivity abnormalities in eyes with nGA was significantly greater based on targeted, high-density microperimetry testing of the atrophic lesion when compared with standard central microperimetry testing. The intrasession measurement variability of MS for the former was also approximately half of the latter approach. These findings collectively demonstrate the potential of a targeted, high-density microperimetry testing strategy for providing a sensitive outcome measure for evaluating novel interventions earlier in the atrophic AMD disease process.

The finding of this study that regions with nGA showed a lesser extent of visual sensitivity abnormalities than regions with GA on targeted, high-density microperimetry testing is consistent with our previous findings when comparing locations on a standard central microperimetry test that sampled regions with nGA and locations that sampled regions of drusen-associated atrophy on OCT imaging.[12] This finding is also consistent with the notion that nGA represents an earlier stage of the atrophic AMD disease process than GA.[10,11,14,25] The greater degree of visual sensitivity abnormalities detected in eyes with nGA with targeted, high-density microperimetry testing compared with standard central microperimetry testing in eyes with large drusen and without atrophic changes is also similar to our previous observations when comparing test locations that sampled regions with and without nGA using standard central microperimetry testing.[12] This finding is also not unexpected as nGA represents specific signs of photoreceptor degeneration associated with an increased risk of atrophy development.[13−15]

The finding of this study that the degree of visual sensitivity abnormalities detected in eyes with nGA was significantly greater with targeted, high-density microperimetry testing compared with standard central testing is unsurprising given that the sparser sampling density of the latter can miss regions with nGA (examples shown in Fig 3). However, the finding that the measurement variability of MS with targeted, high-density testing was approximately half of that seen with the standard central testing was not expected, as it may have been reasonable to expect the variability to be similar with the 2 different approaches. This observation could potentially be explained by the differences in the study protocol used for the different testing strategies, where 3 tests were performed in a single visit for targeted, high-density microperimetry testing, and the first test was used to provide initial estimates to seed the subsequent test (and excluded from the analyses). In contrast, 2 tests were performed each in both eyes with standard central microperimetry testing, and the initial estimates were obtained from the test that was performed at a visit 6 months prior. Such estimates may thus not be as precise as estimates obtained within the same visit, given that visual sensitivities

can change between visits with disease progression, and thus contribute to the larger observed variability for standard central microperimetry testing. Indeed, we observed in a previous study that the CoR for MS was 1.1 dB between the second and third tests in a cohort of eyes with AMD when 3 standard central microperimetry tests were performed within the same session using the same stimulus pattern.[22] This was comparable with the intrasession CoR of 0.9 dB between the second and third targeted, high-density microperimetry tests performed in this study. It is thus likely that the measurement variability of MS with the targeted, high-density testing approach would be more similar to those by the standard central testing if the study protocols were the same and this could be assessed in future studies. Such an evaluation in future studies could also be supported by the comparison of the measurement variability for PWS, but the observed results in this study about the repeatability of the high-density targeted microperimetry testing approach are nonetheless encouraging.

The findings of this study demonstrate the potential of targeted high-density microperimetry testing for providing a sensitive visual function outcome measure for interventional trials earlier in the atrophic AMD disease process, such as when nGA is present. This approach should be feasible in multicentered clinical trials with adequate training and if care is taken to ensure that the stimulus grid is placed appropriately over the lesion of interest. Although an important limitation of this approach is that only 1 region can be tested, this is likely outweighed by the markedly greater magnitude of visual sensitivity abnormalities that could be captured with this approach compared with standard central microperimetry testing, which could provide substantially greater power to detect a beneficial functional treatment effect. Another important limitation of this approach is that it may be more affected by floor effects, especially if the atrophic lesion that is tested is as large or larger than the stimulus pattern used, and if this approach was used to assess visual sensitivity decline over a long follow-up duration, as the entire stimulus pattern could become characterized by absolute scotomas or deep defects. It is thus important to ensure that the size of the stimulus pattern chosen is appropriate for the stage of the atrophic lesion assessed and the intended follow-up duration. For example, the size of the high-density stimulus pattern used in this study (approximately 1000 μm in diameter) would effectively capture the progression of lesions with nGA that develop GA over time, with the latter defined by the presence of a lesion that is ≥ 175 μm in diameter.

A key limitation of this study is that the comparison of the magnitude of visual sensitivity abnormalities in eyes with nGA between the 2 microperimetry testing strategies was performed using different cohorts, rather than a single cohort of individuals that underwent testing with both strategies. There may thus be slight differences in the "severity" of nGA (such as the degree of photoreceptor degeneration) of the eyes between the 2 cohorts, as the cohort that underwent standard central testing included 6-monthly visits from eyes where nGA first developed. However, the magnitude of visual sensitivity abnormalities was still significantly greater in regions with nGA on

targeted, high-density microperimetry testing than in eyes with nGA at the latest visit (either before GA development or at the last visit) with standard central testing ($P < 0.001$ for MS, PSD, and number of deep defects). The above limitation is also applicable for the eyes with GA, which is why we limited the comparison of visual sensitivities between eyes with GA and nGA to those in the same cohort that underwent the same testing strategies. Another limitation of this study is the relatively small number of eyes with nGA and GA that underwent targeted, high-density microperimetry testing. However, the precision of the estimates of the magnitude of visual sensitivity abnormalities of these eyes was enhanced with the inclusion of the 2 tests performed at each visit. These estimates were also compared with a relatively large number of standard central microperimetry tests from eyes with nGA and GA, consisting of a total of 2 tests at each of the 81 visits from 39 eyes with nGA and 66 visits from 14 eyes with GA.

In conclusion, this study showed that a targeted, high-density microperimetry testing approach enables the detection of a markedly greater magnitude of visual sensitivity abnormalities in eyes with nGA than standard central microperimetry testing. This approach could substantially improve the detection of potential beneficial treatment effects of novel interventions on visual function when evaluated earlier in the atrophic AMD disease process.

Footnotes and Disclosures

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