JOURNAL CLUB
Role of Flicker Perimetry in Predicting Onset of Late-Stage Age-Related Macular Degeneration
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Objective: To investigate the longitudinal changes in flicker perimetry in patients with age-related macular degeneration (AMD) as the condition progresses from early AMD to geographic atrophy (GA) or choroidal neovascularization (CNV).

Methods: Patients with AMD and control subjects were recruited from a longitudinal study of retinal function in early AMD consisting of 187 participants. Only those who completed at least 4 consecutive, 6-monthly flicker perimetry tests were selected for this study. Study groups consisted of everyone who went on to develop GA (n=16) or CNV (n=5), controls (n=24), and the high-risk, early-AMD participants whose eyes did not progress to GA or CNV (drusen >125 µm; n=18). The flicker sensitivity was determined, and its rate of change during the 18 months before the clinical detection of late AMD was calculated.

Results: Eyes that went on to develop GA or CNV had a significantly reduced mean (SD) flicker sensitivity in the months before clinical detection of GA (15.8[5.6] dB) or CNV (19.1[3.8] dB) (P<.001) and with eyes that did not progress to GA or CNV (21.4[3.4] dB) (P<.001). The rate of change in flicker sensitivity was significantly increased in GA eyes (−0.07 dB/mo) (P=.001) but not in CNV eyes (0.006 dB/mo) (P=.56) compared with the control eyes (−0.003 dB/mo).

Conclusions: Flicker sensitivity is reduced in eyes that go on to develop late AMD. The rate of change in flicker sensitivities over time was particularly useful in predicting eyes and areas within the eye that subsequently develop GA.


The early clinical changes seen in age-related macular degeneration (AMD) of drusen and pigmentary abnormalities in the macula are considered to be clinical markers of the risk of developing the late complications of AMD, namely, geographic atrophy (GA) and choroidal neovascularization (CNV) that threaten vision. These early changes are common in people aged 50 years and older in western communities, with approximately 15% of this age group having some signs of early AMD. However, only 1% to 2% of those aged 50 years and older develop severe visual loss from AMD.1-3 Thus, the presence of drusen and pigment change alone is not sufficient to identify those at greatest risk of vision loss. Indeed, although the morphologic changes in size, number, and confluence of drusen and the presence of pigmentary changes are used to predict risk of progression of AMD, their ability to do so is not high.4,5 It is critical that we identify, among this early disease group, those at greatest risk of developing severe visual loss.

With new interventions on the horizon, a significant impediment to their implementation is the lack of an outcome measure that can be monitored over time to determine a slowing in progression or reversal of the early AMD changes. We are in urgent need of a better marker of early disease, one that determines the risk of disease progression as well as the progression rate and the efficacy of any intervention aimed at slowing progression.

A broad range of functional abnormalities in early AMD has been well documented by our groups and others.7-10 Recently, we have shown that flicker sensitivity correlated well with clinical severity and was logistically feasible in a clinical setting.11 In a cross-sectional study,12 in early AMD, our group also has shown that compared with static perimetry, flicker pe-
Rimetry was more sensitive in detecting a reduction of retinal function. We now wish to determine whether flicker perimetry is capable of measuring change over time and of predicting those eyes that would develop GA or CNV. We used our longitudinal cohort of participants undergoing psychophysical measures of retinal function to address this question.

**METHODS**

The study was approved by the Human Research Ethics Committee of the Royal Victorian Eye and Ear Hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after explanation of the nature of the study. Participants with early AMD in at least 1 eye were recruited from the Royal Victorian Eye and Ear Hospital clinics and from private practices. Control patients were recruited from unrelated family members and friends of the patients with AMD. Patients with AMD and control participants were recruited from a large study (n = 341) of participants who underwent a range of psychophysical retinal function tests in early AMD. These participants underwent visual acuity testing, a clinical eye examination, retinal photography, and a range of psychophysical visual function tests, including perimetry. All participants had visual acuity of 20/60 or greater and no evidence of clinically detectable GA or CNV in the study eye at baseline. Any participants with a suspicion of CNV underwent fundus fluorescein angiography in the clinic and were excluded if CNV was confirmed.

Participants were invited to continue to perform the psychophysical testing in a longitudinal study every 6 months for 2 years, and 187 participants enrolled in the longitudinal study. To determine the change in flicker sensitivity over time, our selection criteria for this study were based on all participants who completed 4 consecutive, 6-monthly flicker perimetry tests.

**PARTICIPANTS**

Patients with AMD and control participants were recruited from a large study (n = 341) of participants who underwent a range of psychophysical retinal function tests in early AMD. These participants underwent visual acuity testing, a clinical eye examination, retinal photography, and a range of psychophysical visual function tests, including perimetry. All participants had visual acuity of 20/60 or greater and no evidence of clinically detectable GA or CNV in the study eye at baseline. Any participants with a suspicion of CNV underwent fundus fluorescein angiography in the clinic and were excluded if CNV was confirmed.

Participants were invited to continue to perform the psychophysical testing in a longitudinal study every 6 months for 2 years, and 187 participants enrolled in the longitudinal study. To determine the change in flicker sensitivity over time, our selection criteria for this study were based on all participants who completed 4 consecutive, 6-monthly flicker perimetry tests.
Those who went on to develop GA or CNV must have had at least 3 consecutive, 6-monthly flicker perimetry results before the study date in which they were noted to have developed late AMD. Comparison groups also required 4 consecutive, 6-monthly flicker perimetry results and were made up of either (1) normal participants at a similar age range with no evidence of AMD (no drusen or hard drusen only on the basis of formal grading of color fundus photographs) during the study or (2) participants whose baseline characteristics gave them high risk of progression (drusen >125 µm) but who neither progressed to late AMD nor progressed within early AMD, as defined in the Age-Related Eye Disease Study\textsuperscript{12} classification, during at least 2 years of follow-up.

We excluded those participants who did not successfully complete 4 consecutive, 6-monthly flicker perimetry tests. Participants with bilateral late AMD, significant cataract according to the Wilmer Grading System\textsuperscript{13} (nuclear ≥2.0, cortical ≥0.5, or posterior subcapsular of ≥1 mm\textsuperscript{2}), glaucoma, diabetes mellitus, heterotropia, amblyopia, color blindness, high blood pressure uncontrolled by medication (systolic ≥150 mm Hg and diastolic ≥90 mm Hg), or neurologic or systemic diseases, all of which could compromise vision; physical or mental impairment; medications that might affect retinal function; or inability to sign an informed consent form were also excluded from the study.

**AMD DIAGNOSIS**

All participants were examined by a qualified ophthalmologist. A dilated funduscopic examination was followed by digital fundus photography using a CR6-45NM Non-Mydriatic Retinal Camera (Canon). Detection of GA or CNV was based on clinical examination of the retina using a slitlamp microscopy and +78 diopter lens and on grading of the 45° digital color fundus images. When needed, an additional examination in the retinal clinic, including fluorescein angiography, was undertaken to verify the presence of CNV. All fundus images were graded in accordance with the International Classification and Grading System for AMD\textsuperscript{14}. The grading was conducted by 2 independent senior graders (K.-Z.A. and P.N.D.) using OptomizePro software (Digital Healthcare Image Management System; Digital Healthcare Ltd). All end-stage cases were reviewed and confirmed by a senior retinal specialist (R.H.G.). If disagreement occurred between the 2 graders, additional information was sought from clinical notes, adjudication was performed by a senior retinal specialist (R.H.G.), and consensus was reached.

**Flicker Perimetry**

Flicker perimetry was performed with an automated perimeter (model M-700; Medmont International Pty Ltd). The M-700 is a bowl perimeter that uses light-emitting diodes (365 nm). The bowl has a background luminance of 3.2 candelas per square meter and a maximum spot luminance of 320 candelas per square meter. The light-emitting diodes subtend 0.43° (Goldmann size III) and have a background luminance of 3.2 candelas per square meter. The flicker perimetry protocol. This consisted of 48 points located at 1°, 3°, 6°, and 10° from the central fixation. However, only the data within the central 6° (a total of 24 test points) have been included in the analysis (Figure 1) because our group has previously shown that there was a greater loss in flicker sensitivity of the inner rings\textsuperscript{8} and especially within the central 6° in early AMD\textsuperscript{15}. The test uses the Zippy Estimation of Sequential Testing (ZEST) algorithm, adapted from the Bayesian method, and takes 4 to 7 minutes to complete. Flickering stimuli were presented with durations of 800 milliseconds. Participants were verbally instructed on each test to respond by button press to “flicker, twinkle, or shimmer” and allowed a 2-minute practice trial during which errors made on nonflickering presentations were pointed out and positive reinforcement given for correct responses.

### Table 1. Summary of Demographic and Clinical Findings of the Participants Who Progressed to GA and CNV

<table>
<thead>
<tr>
<th>Patient No./ End-Stage Type/ Age, y</th>
<th>Duration of Follow-up, y</th>
<th>Baseline logMAR VA\textsuperscript{b}</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study Eye</td>
<td>Fellow Eye</td>
</tr>
<tr>
<td>1/GA/74.8</td>
<td>5.0</td>
<td>-0.06 (88)</td>
<td>-0.04 (87)</td>
</tr>
<tr>
<td>2/GA/75.8</td>
<td>5.0</td>
<td>0.25 (72)</td>
<td>0.26 (72)</td>
</tr>
<tr>
<td>3/GA/77.1</td>
<td>5.0</td>
<td>0.10 (80)</td>
<td>1.02 (34)</td>
</tr>
<tr>
<td>4/GA/78.5</td>
<td>5.0</td>
<td>0.10 (80)</td>
<td>0.24 (85)</td>
</tr>
<tr>
<td>5/GA/82.3</td>
<td>2.0</td>
<td>0.22 (74)</td>
<td>0.12 (79)</td>
</tr>
<tr>
<td>6/GA/85.6</td>
<td>5.0</td>
<td>0.10 (80)</td>
<td>0.20 (75)</td>
</tr>
<tr>
<td>7/GA/82.0</td>
<td>3.0</td>
<td>0.22 (74)</td>
<td>0.24 (73)</td>
</tr>
<tr>
<td>8/GA/77.2</td>
<td>4.9</td>
<td>0.10 (80)</td>
<td>-0.02 (86)</td>
</tr>
<tr>
<td>9/GA/77.0</td>
<td>4.5</td>
<td>0.22 (74)</td>
<td>0.02 (84)</td>
</tr>
<tr>
<td>10/GA/77.7</td>
<td>3.0</td>
<td>0.29 (71)</td>
<td>0.90 (40)</td>
</tr>
<tr>
<td>11/GA/83.0</td>
<td>4.5</td>
<td>0.22 (74)</td>
<td>0.58 (56)</td>
</tr>
<tr>
<td>12/GA/89.9</td>
<td>3.9</td>
<td>0.29 (71)</td>
<td>0.52 (59)</td>
</tr>
<tr>
<td>13/GA/78.9</td>
<td>3.5</td>
<td>0.16 (77)</td>
<td>0.24 (73)</td>
</tr>
<tr>
<td>14/GA/83.4</td>
<td>2.0</td>
<td>0.16 (77)</td>
<td>1.36 (17)</td>
</tr>
<tr>
<td>15/GA/64.2</td>
<td>4.0</td>
<td>-0.02 (86)</td>
<td>0.14 (78)</td>
</tr>
<tr>
<td>16/GA/75.7</td>
<td>2.9</td>
<td>-0.08 (89)</td>
<td>1.48 (11)</td>
</tr>
<tr>
<td>17/CNV/68.9</td>
<td>4.0</td>
<td>-0.04 (87)</td>
<td>1.56 (8)</td>
</tr>
<tr>
<td>18/CNV/85.3</td>
<td>5.0</td>
<td>-0.10 (90)</td>
<td>0.16 (77)</td>
</tr>
<tr>
<td>19/CNV/70.9</td>
<td>5.0</td>
<td>-0.02 (86)</td>
<td>-0.04 (87)</td>
</tr>
<tr>
<td>20/CNV/86.5</td>
<td>3.0</td>
<td>0.16 (77)</td>
<td>0.08 (81)</td>
</tr>
<tr>
<td>21/CNV/83.2</td>
<td>3.0</td>
<td>0.10 (80)</td>
<td>0.24 (73)</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; VA, visual acuity.

\textsuperscript{a}When GA or CNV was detected.

\textsuperscript{b}The number of letters is shown in parentheses.

\textsuperscript{c}All study eyes had more than 125 µm drusen.
Eyes Developed CNV (n = 5)

The rate of change in flicker sensitivity for all groups was obtained using the autoclicker test. This test estimates the rate of change in flicker sensitivity over time for each tested location. In this study, we compared the mean flicker sensitivity and the rate of change in flicker sensitivity over time between patients with early AMD who went on to develop GA or CNV vs our 2 comparison groups: the control group and the high-risk, early-AMD group. The comparison groups included 24 controls and 18 participants with high-risk characteristics who progressed neither in the grade of early AMD as defined by the Age-Related Eye Disease Study severity scale nor to late AMD within at least 2 years of follow-up. The rest of the longitudinal cohort did not fit these study groups (Figure 2). The mean (SD) duration of follow-up was 4.0 (1.1) years (range, 2-5 years). Geographic atrophy and CNV were detected mostly between visits 3 to 7 (ie, 1-3 years after the initial visit). Visual acuity in the study eyes of patients with AMD at the initial visit was logMAR 0.29 (69 letters or 20/40 equivalent) or better. There was no significant difference in mean (SD) baseline visual acuity between the groups that progressed (81.7 [6.5] letters) and did not progress (85.6 [5.5] letters) (P = .06) to GA or CNV. Visual acuity in the fellow eyes of the participants who progressed to GA or CNV ranged from 20/10 to light perception. Controls had normal visual acuity of logMAR 0.0 (85 letters or 20/20 equivalent) or better. A summary of demographic characteristics and clinical findings of the participants who progressed to GA and CNV is shown in Table 1.

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AND CLINICAL FINDINGS OF THE PARTICIPANTS WHO PROGRESS TO GA AND CNV

Table 1. Flicker Visual Field Parameters of Control Eyes, High-Risk Early-AMD Eyes That Did Not Progress, and Eyes That Developed Clinically Detectable GA or CNV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 24)</th>
<th>High-Risk Early AMD (n = 18)</th>
<th>All Tested Locations</th>
<th>Only Locations That Developed GA</th>
<th>Eyes Developed GA (n = 16)</th>
<th>Eyes Developed CNV (n = 5)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.6 (6.9)</td>
<td>73.0 (5.6)</td>
<td>78.3 (5.0)</td>
<td>NA</td>
<td>78.9 (8.4)</td>
<td>NA</td>
<td>.02</td>
</tr>
<tr>
<td>Flicker sensitivity, dB&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.9 (3.0)</td>
<td>21.4 (3.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.8 (5.6)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>9.6 (2.8)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>19.1 (3.8)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>14.1 (3.2)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>22.6 to 23.3</td>
<td>21.1 to 21.8</td>
<td>15.4 to 16.2</td>
<td>7.7 to 11.5</td>
<td>18.4 to 19.8</td>
<td>10.1 to 18.1</td>
<td></td>
</tr>
<tr>
<td>Rate of change in flicker sensitivity, dB/mo</td>
<td>-0.003 (0.03)</td>
<td>-0.032 (0.015)</td>
<td>-0.07 (0.38)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.378 (0.40)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.006 (0.03)</td>
<td>-0.012 (0.40)</td>
<td>&lt;.001</td>
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<tr>
<td>95% CI</td>
<td>-0.021 to 0.015</td>
<td>-0.061 to -0.002</td>
<td>-0.124 to -0.033</td>
<td>-0.668 to -0.089</td>
<td>-0.012 to 0.025</td>
<td>-0.137 to 0.112</td>
<td>&lt;.001</td>
</tr>
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Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; NA, not applicable.

<sup>a</sup> Estimated using general linear model.
<sup>b</sup> Significance detected against the control group (by Dunnett post hoc test).
<sup>c</sup> Significance detected against the high-risk drusen group (by Dunnett post hoc test).
<sup>d</sup> For the GA and CNV group, the flicker sensitivity of the visit immediately before the clinical detection of end-stage was used. The age-adjusted mean is presented.

RESULTS

Of the 341 participants who underwent psychophysical testing, 187 enrolled in the longitudinal study that required them to attend every 6 months for repeated testing for at least 2 years. In this cohort, 151 participants (127 patients with AMD and 24 controls) completed at least 4 consecutive 6-monthly tests of flicker perimetry (Figure 2). Of the 127 patients with AMD, 21 developed late AMD (16 with GA and 5 with CNV). The comparison groups included 24 controls and 18 participants with high-risk characteristics who progressed neither in the grade of early AMD as defined by the Age-Related Eye Disease Study severity scale nor to late AMD within at least 2 years of follow-up. The rest of the longitudinal cohort did not fit these study groups (Figure 2). The mean (SD) duration of follow-up was 4.0 (1.1) years (range, 2-5 years). Geographic atrophy and CNV were detected mostly between visits 3 to 7 (ie, 1-3 years after the initial visit). Visual acuity in the study eyes of patients with AMD at the initial visit was logMAR 0.29 (69 letters or 20/40 equivalent) or better. There was no significant difference in mean (SD) baseline visual acuity between the groups that progressed (81.7 [6.5] letters) and did not progress (85.6 [5.5] letters) (P = .06) to GA or CNV. Visual acuity in the fellow eyes of the participants who progressed to GA or CNV ranged from 20/10 to light perception. Controls had normal visual acuity of logMAR 0.0 (85 letters or 20/20 equivalent) or better. A summary of demographic characteristics and clinical findings of the participants who progressed to GA and CNV is shown in Table 1.

SUMMARY STATISTICS OF THE Flicker PERIMETRY RESULTS

Table 2. Flicker Visual Field Parameters of Control Eyes, High-Risk Early-AMD Eyes That Did Not Progress, and Eyes That Developed Clinically Detectable GA or CNV

<table>
<thead>
<tr>
<th>Variable</th>
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<sup>c</sup> Significance detected against the high-risk drusen group (by Dunnett post hoc test).
<sup>d</sup> For the GA and CNV group, the flicker sensitivity of the visit immediately before the clinical detection of end-stage was used. The age-adjusted mean is presented.
Activity was significantly reduced in all disease groups compared with the control group ($P < .001$). Eyes that went on to develop clinically detectable GA or CNV also showed greater losses in flicker sensitivity before the clinical onset compared with eyes with high-risk drusen ($P < .001$). The rate of change in flicker sensitivity over time in GA eyes, particularly in the specific areas that went on to develop GA, was significantly greater compared with that of control and high-risk drusen eyes (Table 2).

The flicker visual fields from 2 representative eyes with clinically detectable GA are shown in Figure 3 and Figure 4. The flicker sensitivity was significantly reduced not only in the area imminently going on to develop GA but also in adjacent areas having no clinically apparent GA. There was a significant linear reduction in flicker sensitivity over time for 18 months preceding the development of GA (Figure 3C).

Changes in flicker sensitivity were also correlated with the progression of clinical GA. Figure 5 shows the changes in flicker sensitivity over time in a representative eye with GA. Retinal areas with abnormal flicker sensitivity but clinically nondetectable atrophy were closely matched with the areas that developed GA at a later time. This pattern of flicker sensitivity loss, in which there was significant reduction in sensitivity months to years before GA became evident, was found in 14 of the 16 eyes.

The changes in flicker sensitivity of 2 representative eyes with clinically detected CNV are shown in Figure 6 and Figure 7. Similar to GA, there was reduced flicker sensitivity before the development of clinical CNV, but unlike the widespread reductions seen in eyes that went on to develop GA, the abnormal flicker sensitivity was detected in only a few locations within the central retina. Although the mean flicker sensitivity at the visit immediately preceding the clinical onset of CNV was significantly lower than that of the control eyes or eyes with nonprogressed early AMD, the mean rate of change in flicker sensitivity during the 3 visits preceding CNV (average of 12 months’ duration) was not significantly different from either the control or nonprogressed early-AMD group (Table 2).
Currently, there is a lack of methods that can monitor progression of early AMD and predict progression from early AMD to the late complications of GA or CNV. We have shown that macular flicker sensitivity was significantly reduced in eyes with clinically detectable GA, not only in the atrophic area but also in the areas of nonclinically detectable GA. The reductions in flicker sensitivity in nonatrophic areas closely matched the areas that went on to develop GA many months later. More important, the areas that were noted to go on to develop GA had a significantly greater rate of decline in flicker sensitivity than eyes with early AMD that did not progress to atrophy in the same period. Also, even within the eye that developed atrophy, there were areas with very stable sensitivity that did not develop atrophy during the review period and areas with more rapid decline in sensitivity that went on to develop GA (Figure 3).

In the 5 participants who went on to develop clinically apparent CNV, although sensitivity was lower than controls' eyes and eyes with high-risk drusen, we did not see a significant increase in the rate of change in sensitivity over time, even when examined only in the locations that went on to develop CNV. This suggests that eyes with sudden and discrete loss of sensitivity are imminently at great risk of developing CNV and that different mechanisms may be involved in the development of CNV or GA; a more acute drop in sensitivity heralded CNV, whereas longer-term brisk demise was associated with the development of GA.

Currently, risk of progression is based on the clinical severity scale. In this scale, having late AMD in 1 eye gives the highest risk to the fellow eye of developing late AMD. However, in our study, only 5 of the 21 participants who went on to develop late AMD had late AMD in their fellow eyes. Pigmentary abnormalities are also recognized...
as a high-risk feature, yet 7 of the 21 participants whose eyes progressed to GA or CNV did not have pigmentary abnormalities at baseline (Table 1). Hence, these current criteria used to determine risk of progression were not a good predictor of progression. Flicker perimetry results would increase our ability to accurately predict risk of progression to late AMD.

Macular flicker sensitivity testing could be used to monitor early AMD and predict which eyes, and which areas of the macula within these eyes, will develop GA. A sudden drop in sensitivity could also portend imminent CNV. As such, flicker sensitivity measurements may well prove to be a useful tool in monitoring progression of early AMD in and evaluating the efficacy of new treatments aimed at stopping progression. Using flicker sensitivity results as a screening tool would enable selection of a group of participants at high risk of progression for intervention trials.

Our findings confirm the results of previous studies that visual field sensitivity was reduced in patients with AMD,9,15,19-23 However, to our knowledge, none of the previous studies have examined the longitudinal changes in flicker sensitivity in eyes that proceed to GA or CNV. Although other researchers have suggested that flicker sensitivities could be used to evaluate deterioration in AMD, no one to date has considered this important question prospectively. The novel findings of longitudinal changes in flicker sensitivity before the development of clinically detectable GA or CNV shown in this study have important clinical implications, including a potential role in predicting the type of late disease that might develop in a given patient and the location of GA as well as predicting its progression and providing an outcome measure for evaluating treatment efficacy.

The strength of this study is that by selecting cases from our large longitudinal study, we were able to use information gained over many years to identify those who progressed to late AMD. These longitudinal data provide more convincing evidence of the utility of flicker perimetry than cross-sectional data reported in the previous studies.9,15

The limitation of our study was that the presence or absence of GA at baseline and the onset of GA could be determined only on the basis of digital color fundus images. Our longitudinal study commenced before autofluorescence was readily available and used to confirm areas of atrophy. Even with the use of fundus fluorescein angiography, GA is still currently defined on the basis of color fundus photography. As such, it might have been possible to detect very small patches of GA on autofluorescence before they were clinically detected, but the missing patches on fundus fluorescein angiography would still need to be validated as patches of GA on the color fundus appearance. The underlying observations are still valid for predicting which eyes and which areas within eyes will go on to develop GA. Even if a small patch of unrecognized atrophy was present to explain a small patch of reduced sensitivity, the fact that adjacent regions also showed reduced sensitivity and subsequently went on to develop atrophy validate our conclusion. It is not possible that we missed these larger areas of atrophy. Second, the lack of image stabilization and a fixation tracking system in visual field testing when using the Medmont perimeter means that we had to repeat un-
reliable tests because of poor fixation. However, all the participants had good visual acuity (>20/40) before the development of late AMD so that they had no problem seeing the central fixation spot. None of the tests had more than 20% fixation loss, false-positive responses, or false-negative responses after retest, and the time for the test was 4 to 7 minutes, making this a fast procedure. Although it has been suggested that fixation instability is associated with the progression of late-stage AMD, we did not find this in our cohort of patients. In addition, our group has previously shown that flicker perimetry in our laboratory is highly repeatable.9 It is encouraging that new microperimetry models, such as the macular integrity assessment device, have a fundus tracking system to provide image stabilization, which should improve the test-retest reliability and enhance the accuracy of detecting and locating the retinal changes during disease progression. To our knowledge, however, no pe-

Figure 6. Color fundus photograph and the flicker sensitivity of a representative eye with choroidal neovascularization (CNV). A reduction in flicker sensitivity was observed 6 months before clinical detection of CNV (A). Further reduction in flicker sensitivity was seen when CNV was detected (B). The rate of change in flicker sensitivity during the 18 months before CNV detection showed a small decline in flicker sensitivity over a few locations.
rimeter incorporates these features with a flickering target, which has been shown to be more sensitive than a static target.25

In conclusion, we found that eyes with early high-risk AMD had reduced flicker sensitivity compared with control eyes. Eyes that went on to develop clinically detectable GA and CNV had even lower mean sensitivity levels than high-risk eyes that did not progress to late AMD. Eyes about to develop clinically apparent GA appear to have widespread losses of flicker sensitivity. The rate of change in sensitivity before clinical detection of GA was rapid and occurred over several testing intervals before the clinical detection of GA, and the area in that eye of greatest rate of change in sensitivity predicted the area where the atrophy developed. In eyes with CNV, the loss of flicker sensitivity was not as great as that seen in GA nor as widespread in the macula, and the rate of change over several visits before CNV detection was...
not as great. A sudden drop in sensitivity may portend the development of clinically significant CNV. These findings suggest that flicker perimetry, in particular monitoring the rate of change in sensitivity, could provide the important functional outcome measure of early disease progression that is urgently needed for predicting GA development, monitoring disease progression, determining targeted selection for clinical intervention studies, and determining the efficacy of treatments aimed at slowing progression of disease.

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