

Preferential Hyperacuity Perimeter (PreView PHP) for Detecting Choroidal Neovascularization Study

Preferential Hyperacuity Perimetry Research Group*

Purpose: To assess the ability of the Preferential Hyperacuity Perimeter (PreView PHP; Carl Zeiss Meditec, Dublin, CA) to detect recent-onset choroidal neovascularization (CNV) resulting from age-related macular degeneration (AMD) and to differentiate it from an intermediate stage of AMD.

Design: Prospective, comparative, concurrent, nonrandomized, multicenter study.

Participants: Eligible participants' study eyes had a corrected visual acuity of 20/160 or better and either untreated CNV from AMD diagnosed within the last 60 days or an intermediate stage of AMD.

Methods: After obtaining consent, visual acuity with habitual correction, masked PHP testing, stereoscopic color fundus photography, and fluorescein angiography were performed. Photographs and angiograms were evaluated by graders masked to diagnosis and PHP results. The reading center's diagnosis determined if the patient was categorized as having intermediate AMD or neovascular AMD.

Main Outcome Measures: A successful study outcome was defined a priori as a sensitivity of at least 80% and a specificity of at least 80%.

Results: Of 185 patients who gave consent to be enrolled, 11 (6%) had PHP results judged to be unreliable. An additional 52 were not included because they did not meet all eligibility criteria. Of the remaining 122 patients, 57 had an intermediate stage of AMD and 65 had neovascular AMD. The sensitivity to detect newly diagnosed CNV using PHP testing was 82% (95% confidence interval [CI], 70%–90%). The specificity to differentiate newly diagnosed CNV from the intermediate stage of AMD using PHP testing was 88% (95% CI, 76%–95%).

Conclusions: Preferential Hyperacuity Perimeter testing can detect recent-onset CNV resulting from AMD and can differentiate it from an intermediate stage of AMD with high sensitivity and specificity. These data suggest that monitoring with PHP should detect most cases of CNV of recent onset with few false-positive results at a stage when treatment usually would be beneficial. Thus, this monitoring should be considered in the management of the intermediate stage of AMD. *Ophthalmology* 2005;112:1758–1765 © 2005 by the American Academy of Ophthalmology.

Approximately 8 million of almost 60 million people older than 55 years of age in the United States have the intermediate stage of age-related macular degeneration (AMD), of whom 1.3 million are expected to progress to the advanced stage of AMD within 5 years.¹ Current management of

these individuals includes consideration of taking a dietary supplement such as that used in the Age-Related Eye Disease Study, if there are no medical contraindications, to reduce the risk of vision loss associated with progression to advanced AMD.² Although it is estimated that 300 000 individuals on this regimen over the course of 5 years may avoid progression to advanced AMD by taking such a dietary supplement,¹ 1 million individuals are still expected to progress to the advanced stage of AMD over the same period.²

Treatment options for some people who progress to neovascular AMD include laser photocoagulation,³ photodynamic therapy with verteporfin,⁴ submacular surgery,⁵ and antiangiogenic drugs.⁶ At this time, treatments for selected cases of neovascular AMD reduce the risk of vision loss rather than improve vision.^{5–8} Therefore, for the vision to remain at a relatively good level after treatment, the choroidal neovascularization (CNV) must be identified and treated when the vision is relatively good. Furthermore, studies have shown that eyes with smaller lesions at the time of treatment have a better average visual acuity 2 years after initiation of treatment.⁹

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Management of the intermediate stage of AMD includes self-monitoring by the individual to try to detect the onset of neovascular AMD when the lesions are small and are associated with relatively good vision.¹⁰ Although some recommend use of an Amsler grid to detect progression to neovascular AMD, numerous studies have confirmed the inability of self-monitoring to detect most conversions to neovascular AMD, presumably because of such factors as difficulty with fixation and the phenomenon of cortical completion (e.g., as noted by having the brain ignore the blind spot in our visual field created by the optic nerve).^{11–13} These limitations may explain why, in part, case series document that most cases of CNV resulting from AMD at presentation to an ophthalmologist are subfoveal, relatively large, and associated with relatively poor visual acuity.¹⁴

The Preferential Hyperacuity Perimeter (PreView PHP, Carl Zeiss Meditec, Dublin, CA) was designed to detect progression from the intermediate stage of AMD to neovascular AMD. The PHP is a Food and Drug Administration-approved medical device using macular perimetry based on the human visual function of hyperacuity.¹⁵ It has the capability of detecting visual functional changes^{15–17} while addressing problems inherent to the Amsler grid, including loss of fixation and cortical completion. Hyperacuity (also termed *vernier acuity*) is defined as the ability to perceive a difference in the relative spatial localization of 2 or more visual stimuli. Retinal pigment epithelium (RPE) elevation, as that which occurs in AMD, causes a shift in the regular position of photoreceptors. Neurosensory retinal elevation also should cause a shift. It is hypothesized that such a shift causes an object to be perceived at a location different from its true location in space. This perceived shift in object location recorded by the PHP takes advantage of the human phenomenon of hyperacuity and may be the anatomical explanation for metamorphopsia.

The purpose of this study was to assess the ability of the PHP to detect recent-onset CNV resulting from AMD and to differentiate it from an intermediate stage of AMD with a high sensitivity (so as not to miss many cases of neovascular AMD) and a high specificity (so as to minimize false identification of progression to neovascular AMD that would lead to further retinal evaluations that typically include retinal imaging such as fluorescein angiography). If a high sensitivity and specificity could be demonstrated in an international, multicenter study among individuals with neovascular lesions for which treatment is most likely to be beneficial (when relatively small and associated with relatively good visual acuity),^{3–10} then monitoring with this device may be worth incorporating into the management of patients with the intermediate stage of AMD.

Patients and Methods

The Steering Committee of the PHP Research Group approved the design and methods of this study in September 2003. Seven clinical centers from Asia, Europe, and North America were selected by the Steering Committee to participate in this study. Institutional review boards or ethics committees at all participating institutions reviewed and approved the study design and the con-

Table 1. Major Eligibility Criteria

Inclusion criteria	
Age	≥ 50 years
Visual acuity with habitual correction in study eye	20/160 or better
Retina features in study eye:	
Newly diagnosed (≤60 days) nontreated neovascular lesion from AMD or	
Intermediate stage of AMD (at least 1 large druse [≥125 μm] or at least 20 medium drusen [≥63 but <125 μm]) with no geographic atrophy of the retinal pigment epithelium (≥175 μm) in the study eye	
Mental and physical ability to perform a Preferential Hyperacuity Perimeter test	
Ability to tolerate intravenous fluorescein angiography	
Subject able and willing to sign consent form and participate in study	
Exclusion criteria for study eye	
Evidence of macular disease other than AMD	
Previous surgical or laser treatment within the macular area	
Presence of any significant media opacity that precludes a clear view of the macular area as identified by biomicroscopy, fundus photography, or fluorescein angiography	
Any nonmacular-related ocular surgery performed within 3 months before the study	
AMD = age-related macular degeneration.	

sent forms to be used locally. All study participants gave signed consent before enrollment and testing with PHP.

Participant Eligibility and Enrollment

Principal eligibility criteria are summarized in Table 1. Consecutive patients were offered enrollment prospectively among the 7 clinical centers between October 15, 2003, and August 23, 2004. Participants were at least 50 years of age, judged to have the mental and physical capability to perform the PHP test, and willing and able to sign a written consent form to participate in the study after completing an informed consent process. A study eye had to have visual acuity with habitual correction of 20/160 or better on whatever standard eye chart was used routinely by the investigator. If the participant did not bring his or her glasses for refractive error, then a standardized refraction was performed before visual acuity measurements as was done in previous protocols involving patients with AMD.^{5–7,8} In addition, the study eye had to have evidence within 3000 μm of the foveal center of either one of the following: (1) an intermediate stage of AMD, modified slightly (for ease of use by investigators) from definitions used in the Age-Related Eye Disease Study² as at least 1 large druse (greatest linear diameter of at least 125 μm) or numerous (at least 20) medium drusen (greatest linear diameter at least 63 μm but smaller than 125 μm) with no evidence of either the central geographic atrophic form or neovascular form of the advanced stage of AMD; or (2) presumably recent-onset CNV (diagnosed within 60 days of enrollment as determined by all history and pertinent medical records available to the participant and clinical center personnel). The major exclusion criteria for the study eye also are listed in Table 1, including evidence of macular disease other than AMD, evidence of geographic atrophy of the RPE, previous treatment (photodynamic therapy, laser photocoagulation, or surgery) for CNV, media opacity precluding a clear view of the fundus on fundus photography and fluorescein angiography, and any ocular surgery in the study eye within the previous 3 months. If both eyes were eligible for the study, the enrolling ophthalmologist and the participant made a joint decision regarding which eye would be the study eye before undergoing PHP testing or photography.

Table 2. Determining Reliability of Preferential Hyperacuity Perimeter Results from False Positives and Negatives

False Positive/False Negative	1	2	3	None Detected
CNV reported as present				
1	Reliable	Unreliable	Unreliable	Reliable
2	Reliable	Unreliable	Unreliable	Unreliable
3	Unreliable	Unreliable	Unreliable	Unreliable
CNV reported as absent				
1	Reliable	Reliable	Unreliable	Reliable
2	Unreliable	Unreliable	Unreliable	Unreliable
3	Unreliable	Unreliable	Unreliable	Unreliable

CNV = choroidal neovascularization.

Preferential Hyperacuity Perimeter Testing

Preferential Hyperacuity Perimeter testing was completed by a study coordinator at each clinical center approved to perform the testing after a training session and before ophthalmologic examination and any evaluation of photographs by a photograph reading center. The participant sat approximately 20 inches (50 cm) from the monitor with +2.00 diopter correction added to the participant's distance correction (if a participant had no distance correction, then refraction was determined following a protocol). After a short explanatory tutorial, the examiner administered the test. After completing the test, the detection output was printed by the examiner and affixed into a sealed envelope in the case report form. The examiner also determined at the end of the first PHP test if the test was performed reliably based on the degree of false-positive and false-negative error results from the test using the criteria outlined in Table 2. In case of noncompliance or a nonreliable test result, the participant was excluded from the study and no more study procedures were performed. After pupil dilation, an additional PHP test was performed.

The PHP tests the central 14° of the visual field with approximately 500 data points sampled 3 to 5 times, each at spatial resolution of 0.75°. The stimulus is a dot deviation signal (dotted line with an artificially generated distortion, using white dots on a black background for maximal contrast) flashed in an order that may appear random to the observer, even though the order of the signals is predetermined. By using artificial distortions of different magnitudes, the algorithm determines the depth of the visual field defect. A grayscale map is generated and the intensity of the visual field defect is determined. By comparing the visual field defect intensity to a normative database, the system determines whether progression to an advanced stage of AMD is suspected. If the deviation signal is projected to a retinal lesion, then distortion, scotoma, or blurring may be perceived. The examinee is asked to touch the touch-sensitive screen at the location of any such abnormalities. By these means, any existing visual field defect detected on the signal was recorded immediately when the stimulus was positioned on a lesion. During the course of the examination, artificial distortions, imitating distortions similar to those seen by patients with neovascular AMD, are presented. These artificial distortions serve as control stimuli to quantify the extent of any presumably pathologic distortions originating from retinal lesions using preferential looking analysis. Specifically, preferential looking analysis assumes that an individual with a pathologic distortion who is presented with an artificial distortion will look at or identify whichever distortion is greater. The degree of artificial distortion is varied so that the amount of artificial distortion that is identified by preferential looking analysis instead of identifying a pathologic distortion is determined. A participant's responses are recorded and automatically analyzed by a predesigned algorithm. Following the algorithm analysis, a result is generated to indicate either "yes"

or "no" for detection of CNV as well as a numeric value indicative of the intensity of any visual field defects.

The PHP test was repeated after dilation for a secondary analysis. This second PHP was obtained only after 30 to 180 minutes had passed after pupil dilation, at least 15 minutes after any ophthalmoscopic examination, and at least 30 minutes after any fundus photographs or fluorescein angiograms were obtained.

Ocular Examination, Fundus Photographs, and Fluorescein Angiograms

After dilation, the study ophthalmologist confirmed eligibility and the presence of either the intermediate stage of AMD or recent-onset CNV resulting from AMD without knowledge of the PHP results. Stereoscopic color fundus photographs and fluorescein angiograms, following previously described protocols, were obtained within 2 weeks of obtaining the PHP results and were sent to a photograph reading center experienced in previous studies requiring identification of the intermediate stage of AMD and CNV.^{3,18,19}

Sample Size

Before initiating the study, the investigators required a sample size that, with a 95% confidence interval (CI), had a sensitivity of at least 80% and a specificity of at least 80% and that would allow them to be confident that monitoring the intermediate stage of AMD would result in identification of a high proportion of individuals with recent-onset CNV (high sensitivity) with few false positive results (high specificity). This would result in a sample size of 120 study participants (60 with the intermediate stage of AMD, 60 with recent onset CNV). However, the study group assumed that approximately 30% of those enrolled would not meet all of the eligibility criteria, either because of an inability to complete the PHP test reliably or because of diagnoses in addition to, or other than, the intermediate stage of AMD or recent-onset CNV. Thus, a final sample size of 180 was planned.

Quality Assurance and Adverse Events

In addition to training of PHP testers and use of fundus photograph graders with documented reliability for grading features of AMD,^{18,19} monitors independent of each clinical center reviewed charts to confirm that any diagnosis of CNV was recent onset (60 days previously or fewer). Additional monitoring was performed at clinical centers and the photograph reading center to confirm that information recorded on case report forms matched information in primary sources at the centers.

Grading Fundus Photographs by Retina Specialists

The stereoscopic color fundus photographs of eligible participants were divided into fairly equal numbers to be graded by the principal investigators of clinical centers as either the intermediate stage of AMD or as CNV. None of the principal investigators reviewed cases that originated from his or her clinical center. Reviewing stereoscopic color fundus photographs is not entirely equivalent to biomicroscopy. However, it provides information similar to that seen on biomicroscopy with the added advantage of no eye movements, with the disadvantage of lack of a patient's history and examination results as well as lack of dynamic movement of light projected at different angles from a slit lamp onto the retina. In addition, specific to this study, graders were aware that approximately 50% of the photos they were reviewing had evidence of CNV, which could have elevated their level of suspicion and potentially their relative sensitivity compared with a real-life situation. Two cases included in the PHP analysis that had no color fundus photographs, only red-free photographs, were not used in determining the sensitivity and specificity of retina specialists' review of color fundus photographs to detect CNV.

Statistical Issues

The primary outcome was the sensitivity and specificity of the PHP to detect CNV as defined by masked photograph reading center graders from stereoscopic fundus photographs and fluorescein angiograms among study participants with either recent-onset CNV or the intermediate stage of AMD. Secondary outcomes included positive predictive value (the accuracy of a positive result; that is, the probability that an individual has CNV given that the PHP indicates CNV), negative predictive value (the accuracy of a negative result; that is, the probability that an individual does not have CNV given that the PHP indicates no CNV), accuracy (the probability that the PHP indicates CNV for individuals with CNV and indicates no CNV for individuals without CNV), and area under the receiver operating characteristics (ROC) curve. The ROC curve is a plot of sensitivity versus 1 minus the specificity at different intensities of any visual field defects detected by the PHP. The area under the ROC curve is the probability that the perceived intensity of 2 PHP tests correctly will identify individuals with CNV and individuals with no CNV. In this study, the area under the ROC curve is the probability that the intensity of individuals with CNV is larger than those without CNV. Thus, the area under the ROC curve is another measurement of accuracy of the PHP. The 95% CIs for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated by the exact method,²⁰ and the 95% CIs for the area under the ROC curve were calculated by using a normal distribution approach. SAS software version 8.02 (SAS Institute, Cary, NC) was used for all of the statistical analyses.

Results

A total of 185 individuals were enrolled. Of these, 11 (6%) had PHP results judged to be unreliable (including 2 inadvertently enrolled with visual acuity worse than 20/160). An additional 52 were not included because of at least 1 of the following protocol deviations: 12 with geographic atrophy of the RPE, 16 with other diagnoses such as retinal abnormalities consistent with a pattern dystrophy of the retina or pathologic myopia, 17 with inadequate or poor-quality photographs precluding a definitive determination as to whether any CNV was present, 4 with evidence of CNV for more than 60 days detected on quality assurance monitoring, 1 with visual acuity worse than 20/160 (not including the 2 subjects

mentioned above with unreliable PHP evaluations), 1 with the wrong eye tested with PHP, and 1 who gave consent but left the clinic before the PHP was obtained. Of the remaining 122 participants, 57 had an intermediate stage of AMD and 65 had neovascular AMD. The actual test time of the PHP (not including participant preparation, providing refractive correction for the working distance of the PHP, positioning the study participant, reviewing a tutorial on the operation of the PHP, printing results, or interpreting results) before dilation was a mean of 5.8 minutes for the participants with the intermediate stage of AMD and a mean of 6.3 minutes for those with CNV. After dilation, PHP actual test time was a mean of 5.9 minutes for the group with the intermediate stage of AMD and a mean of 5.9 minutes for the CNV group.

Demographic and Ocular Characteristics of Eligible Participants

Table 3 displays the demographic information of the eligible participants by classification of the study eye as CNV or the intermediate stage of AMD according to the photograph reading center's assessment of color fundus photographs and fluorescein angiograms. Both groups were of a similar age, with a median age of 77 years in the CNV group and 76 years in the intermediate AMD group; the proportion of women was slightly greater in the CNV group. The AMD status of the fellow eye (e.g., CNV, geographic atrophy, or the intermediate stage of AMD) had a similar distribution in both groups. The visual acuity was better in the intermediate AMD group, with a median approximate Snellen equivalent of 20/28 compared with 20/63 in the CNV group (Table 4). Nevertheless, 20 participants (31%) of the CNV group had

Table 3. Demographic Information of Eligible Participants

Parameters	CNV* n (%)	Intermediate AMD* n (%)
Total number of participants	64	58
Age (yrs)		
50 to <60	1 (2%)	0
60 to <70	7 (11%)	9 (16%)
70 to <80	35 (54%)	31 (54%)
80 and older	22 (34%)	17 (30%)
Median	77	76
Sex		
Women	39 (60%)	30 (57%)
Men	26 (40%)	27 (47%)
Study eye		
Right	30 (46%)	22 (39%)
Left	35 (54%)	35 (61%)
Nonstudy eye status		
CNV (includes CNV/scar or scar)	30 (46%)	22 (39%)
Geographic atrophy	2 (3%)	4 (7%)
Intermediate stage of AMD	21 (32%)	24 (42%)
Early stage of AMD or no AMD	5 (8%)	5 (9%)
Cannot grade (no photo, poor quality)	7 (11%)	2 (3%)

AMD = age-related macular degeneration; CNV = choroidal neovascularization.

*Classification of participants was based on photograph reading center's assessment of color fundus photographs and fluorescein angiograms.

Table 4. Visual Acuity (Snellen Equivalent) of Study Eyes

Visual Acuity (Snellen Equivalent)	Choroidal Neovascularization* n (%)	Intermediate Age-Related Macular Degeneration* n (%)
20/20 or better	2 (3%)	15 (26%)
20/25 to 20/40	18 (28%)	33 (58%)
20/50 to 20/80	77 (41%)	9 (16%)
20/100 to 20/160	18 (28%)	0
Median	20/63	20/28

*Classification of participants was based on photograph reading center's assessment of color fundus photographs and fluorescein angiograms.

20/40 or better visual acuity; 18 participants (28%) had visual acuity of 20/100 to 20/160.

Choroidal Neovascularization and Drusen Characteristics of Study Eyes

Of the 65 study eyes with CNV, 16 (25%) were not subfoveal, whereas in 2 additional eyes (3%), the location with respect to the foveal center and the lesion composition could not be determined. One of those lesions was no more than 1 disc area in size, whereas the size could not be graded in the other. Of the remaining 47 eyes, the area of CNV was less than 50% of the area of the entire subfoveal lesion in 5 eyes, a pattern in which it is unknown at this time if treatment with photodynamic therapy or antiangiogenic drugs can reduce the risk of vision loss. Among these 5 eyes in which the area of CNV was less than 50% of the entire lesion, 3 were no more than 3 disc areas in size and the other 2 were between 4 and 6 disc areas.

Characteristics relevant to management for the remaining 42 eyes that were subfoveal and in which the area of CNV was at least 50% of the area of the lesion are shown in Table 5. Of these, 8 eyes were predominantly classic, including 6 that had no occult CNV. For the remaining 34 eyes, the lesion composition was minimally classic in 17 eyes (with 7 having a lesion size no more than 4 disc areas, including 4 with blood associated with CNV) and was occult with no classic in 16 eyes (with 9 having a lesion size no more than 4 disc areas, including 2 with blood associated with CNV).

None of the study eyes with CNV had an area of atrophy of the RPE that was 1 or more disc areas in size. Among the 57 eyes with the intermediate stage of AMD, the area of drusen within 3000 μm of the center of the macula was at least 0.5 disc areas in 44 eyes (77%). The area of drusen could not be determined in 2 (4%) of these 57 eyes.

Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Preferential Hyperacuity Perimeter

Table 6 shows that the sensitivity to detect recent onset CNV among cases of recent-onset CNV and the intermediate stage of AMD was 82% (95% CI, 70%–90%), with a specificity of 88% (95% CI, 76%–95%). The positive predictive value (the accuracy of a positive result; that is, the probability that an individual has CNV given that the PHP indicates CNV) was 88%; the negative predictive value (the accuracy of a negative result; that is, the probability that an individual does not have CNV given that the PHP indicates no CNV) was 80%; and the accuracy of the test was

Table 5. Characteristics of Subfoveal Lesions in Study Eyes in which Area of Choroidal Neovascularization is at Least 50% of Area of Lesion

Lesion Characteristic	Total = 42 n (%)
Lesion composition	
Predominantly classic	8 (19%)
Minimally classic*	17 (41%)
Occult with no classic*	16 (38%)
Cannot determine	1 (2%)
Area of lesion (disc areas)	
≤1	5 (12%)
>1 to ≤2	6 (14%)
>2 to ≤3	10 (24%)
>3 to ≤4	1 (2%)
Cannot determine but ≤4	1 (2%)
>4 to ≤5	7 (17%)
>5 to ≤6	4 (10%)
>6 to ≤9	5 (12%)
>9 to ≤12	2 (5%)
Cannot grade	1 (2%)
Blood associated with CNV lesion	
No	22 (53%)
Questionable	0 (0%)
Yes	19 (45%)
Cannot grade	1 (2%)

CNV = choroidal neovascularization.

*Of the minimally classic and occult with no classic cases, 15 had blood associated with the lesion, of which 6 were no more than 4 disc areas.

84%. The area under the ROC curve, as shown in Figure 1, was 89% (95% CI, 82%–95%).

For the 16 participants in whom the CNV did not extend under the center of the foveal avascular zone, the PHP had a sensitivity of 81.3% for detecting recent-onset CNV. For the 27 cases with CNV lesions with a lesion size of 2 disc areas or less, the sensitivity was 81.4%.

Although the study was not designed to analyze outcomes within

Table 6. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Preferential Hyperacuity Perimeter

Preferential Hyperacuity Perimeter before Pupil Dilation	Gold Standard	
	CNV n (%)	Intermediate Age-Related Macular Degeneration n (%)
Total enrollment	65	57
Yes (with CNV)	53 (82%)	7 (12%)
No (without CNV)	12 (19%)	50 (88%)
		95% Confidence Interval
Sensitivity	82%	70%–90%
Specificity	88%	76%–95%
Positive predicted value	88%	77%–95%
Negative predicted value	81%	69%–90%
Accuracy (also see Fig 1)	84%	77%–90%

CNV = choroidal neovascularization.

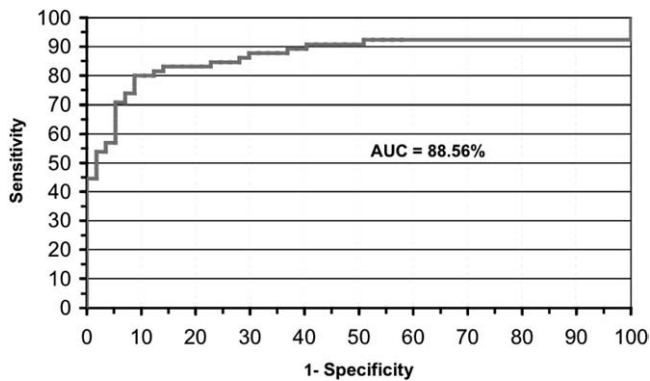


Figure 1. Receiver operating characteristic (ROC) curve shows plot of sensitivity (y axis) versus 1 minus the specificity (x axis) at different intensities of any visual field (VF) defects detected by the Preferential Hyperacuity Perimeter (PHP) as a measurement of accuracy of the PHP. The area under this ROC curve (AUC), 89%, is the probability that the intensity of VF defects in individuals with choroidal neovascularization (CNV) is larger than the intensity in those without CNV.

different visual acuity subgroups, for exploratory purposes, we retrospectively analyzed outcomes within different visual acuity subgroups, recognizing that the smaller numbers would result in larger CIs and would make judgment of statistical significance difficult. For the 104 individuals with visual acuity of 20/80 or better, 47 had CNV. Among these 104 individuals, the PHP had a sensitivity of 79% (95% CI, 64%–89%) for detecting recent-onset CNV and a specificity of 88% (95% CI, 76%–95%). Among the 68 individuals in this study with relatively good visual acuity (20/20–20/40) in this study, including 20 with recent-onset CNV and 48 with the intermediate stage of AMD, the PHP had a sensitivity of 60% (95% CI, 36%–81%) for detecting recent-onset CNV, a specificity of 90% (95% CI, 77%–97%), a positive predictive value of 71% (95% CI, 44%–90%), a negative predictive value of 84% (95% CI, 71%–93%), and an accuracy of 81% (95% CI, 70%–89%). The sensitivity to detect recent onset of CNV after dilation was higher (90%) but the specificity was worse (70%), with more false positive results.

Expert Assessment of Color Fundus Photographs Alone to Photograph Reading Center's Assessment of Color Photographs plus Fluorescein Angiograms

As a secondary planned outcome, the sensitivity and specificity of the retina specialists participating in this study to identify CNV from stereoscopic color fundus photographs among the 122 eligible participants were evaluated using the photograph reading center's assessment of color fundus photographs and fluorescein angiograms as the gold standard for classifying a participant as having CNV or the intermediate stage of AMD. For 2 participants, color fundus photographs were not available and were not included in this analysis. The retina specialists' sensitivity to detect recent onset CNV from color fundus photographs among the 120 eligible participants was 70% (95% CI, 58%–81%), whereas the specificity was 95% (95% CI, 85%–99%). The PHP's sensitivity and specificity for the 120 participants were similar to the values reported in Table 6 for all 122 eligible participants, specifically, a sensitivity of 83% and a specificity of 88%. Although the retina specialists' sensitivity might have been worse than that of the PHP ($P = 0.09$, McNemar Test), the specificity was better ($P = 0.05$, McNemar test). As an additional exploratory retrospective analysis, the retina specialists' sensitivity to detect recent-onset CNV among the 66 participants with color fundus photographs and a

visual acuity of 20/40 or better was 53% (95% CI, 30%–76%), whereas the specificity was 94% (95% CI, 83%–99%).

Discussion

The PHP can detect CNV among a population with recent-onset CNV (within the last 60 days) from AMD or the intermediate stage of AMD with a high sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Most cases of CNV detected either did not extend under the center of the macula or were a subfoveal lesion with features that have been shown to have the best outcomes after treatment. Specifically, the subfoveal lesions usually were small, with relatively good visual acuity, when treatment likely would result in a relatively good final visual acuity. Although the inclusion criterion that CNV was to be recent onset likely would have been expected to include lesions that either did not extend under the fovea or were relatively small with relatively good visual acuity, this study showed that such lesions can be detected by the PHP with high sensitivity and specificity among individuals who have either CNV or the intermediate stage of AMD. Few lesions had features for which treatment may not be considered with photodynamic therapy or features for which treatment may not be considered when lesions more likely would be recognizable by symptoms, visual acuity, or biomicroscopy alone. Specifically, few lesions were of a relatively large size and of a lesion composition that was minimally classic or occult with no classic, when photodynamic therapy is not likely to reduce the risk of additional vision loss and when limited data exist regarding whether antiangiogenic drugs may be considered in such lesions when presumed recent disease progression is evident. Although the average time to perform the PHP was approximately 6 minutes for an eye, either before or after pupil dilation, this time does not include participant preparation, providing refractive correction for the working distance of the PHP, positioning the study participant, reviewing instructions on the operation of the PHP, printing results, or interpreting results in light of a patient's ocular history, examination, and other past imaging information, all of which could lead to a total time of 15 to 20 minutes for each eye of a patient evaluated.

Lesions that did not extend under the center of the macula as well as lesions with a small size (≤ 2 disc areas) were detected with a sensitivity similar to what was found for the entire cohort, suggesting that the PHP results are not dependent on lesion size or location. This study could not demonstrate that review of stereoscopic color fundus photographs by experienced retina specialists had a better sensitivity or specificity than results of the PHP. Although review of stereoscopic color fundus photographs are not equivalent to biomicroscopy, review of such photographs may be more sensitive than biomicroscopy to identify retinal pathologic features.^{21,22} It should be noted that for both biomicroscopy and PHP, a patient's symptoms probably add to the sensitivity and specificity of detecting CNV among a population of individuals with CNV or the intermediate stage of AMD.

The study was not designed to evaluate only individuals with relatively good visual acuity. However, exploratory

retrospective analysis suggested that when the visual acuity was 20/80 or better, or when the visual acuity was even 20/40 or better, the sensitivity and specificity still seemed to be good. Also, the sensitivity and specificity of the PHP for those with visual acuity of 20/40 or better seemed to be similar to values calculated for review of color fundus photographs by a retina specialist of these same participants. The CIs were larger than those reported for the entire study group because of the fewer number of participants with CNV with this relatively good level of visual acuity.

The data also suggest that the PHP ideally should be performed before dilation, when fewer false-positive results for CNV will occur. Alternatively, if a dilated PHP did suggest the presence of CNV not seen on biomicroscopic examination, the PHP could be repeated in the undilated state to confirm or refute the detection of CNV before referring the participant for further evaluation and possible testing such as fluorescein angiography.

The sensitivity of retina experts' evaluation of color fundus photographs alone compared with the PHP sensitivity suggests that review of color fundus photographs alone to monitor for recent-onset CNV likely is not more sensitive than the PHP. We cannot state that the 70% sensitivity by the retina specialist's review of fundus photographs (expert's sensitivity) is significantly different from the 83% sensitivity by the PHP; the study was not designed to detect differences between these methods of identifying CNV among individuals with recent-onset CNV and the intermediate stage of AMD. Review of color fundus photographs with an ocular history and examination likely would yield fewer false-negative results by the retina specialist.

The findings from this study suggest that periodic monitoring with the PHP is likely to detect recent-onset CNV for which treatment would be indicated. Furthermore, treatment of recent-onset neovascular lesions similar to those detected in this study often would have a relatively good outcome because the CNV detected in this study usually was small or not subfoveal, compared with had it grown quite large, had it been associated with fairly poor visual acuity, or both. It should be noted that most of the individuals with CNV evaluated in this study specifically came to an ophthalmologist for evaluation as a result of new signs or symptoms. The data imply that the device can detect such lesions, as evidenced by the relatively good visual acuity and relatively small size of most of the lesions in the study eye of participants with neovascular AMD.

Because an Amsler grid has not been shown to have a high sensitivity to detect recent-onset CNV,^{12,13} nor has it been shown to be as sensitive as the PHP,^{15,16} and because data from retinal practices suggest that individuals are being evaluated by a retina specialist when the lesions are usually subfoveal and quite large with relatively poor visual acuities, ophthalmologists should consider periodically monitoring individuals who have the intermediate stage of AMD with the PHP in between regular examinations to try to identify recent-onset CNV as detected in this study among individuals with either the intermediate stage of AMD or recent-onset CNV. Furthermore, individuals with the intermediate stage of AMD may benefit from PHP evaluation at the time they initially are noted to have the intermediate

stage of AMD. Such evaluation could increase the probability of detecting recent-onset CNV not suspected from the examination or could serve as a baseline test for serial monitoring using PHP testing, or both. Finally, the use of baseline and serial PHP testing may obviate the need for fluorescein angiography in some patients who have persistent symptoms suggestive of neovascular AMD, such as metamorphopsia, when the clinical examination shows no obvious features of neovascular AMD.

References

1. Age-Related Eye Disease Study Research Group. Potential public health impact of Age-Related Eye Disease Study results. AREDS report No. 11. *Arch Ophthalmol* 2003;121:1621-4.
2. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001;119:1417-36.
3. Macular Photocoagulation Study Group. Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the Macular Photocoagulation Study. *Arch Ophthalmol* 1991;109:1242-57.
4. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina* 2005;25:119-34.
5. Submacular Surgery Trials (SST) Research Group. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings. SST report no. 13. *Ophthalmology* 2004;111:1993-2006.
6. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *New Engl J Med* 2004;351:2805-16.
7. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report 2. *Arch Ophthalmol* 2001;119:198-207.
8. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult but no classic neovascularization—Verteporfin in Photodynamic Therapy report 2. *Am J Ophthalmol* 2001;131:541-60.
9. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group, Verteporfin in Photodynamic Therapy Study Group. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. *Am J Ophthalmol* 2003;136:407-18.
10. Centers for Medicare and Medicaid Services. Medicare Coverage Database. National Coverage Analyses (NCAs). Decision Memo for Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration (CAG-00066R3). Available at: <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=101>. Accessed July 15, 2004.
11. Fine AM, Elman MJ, Ebert JE, et al. Earliest symptoms

- caused by neovascular membranes in the macula. *Arch Ophthalmol* 1986;104:513–4.
12. Schuchard RA. Validity and interpretation of Amsler grid reports. *Arch Ophthalmol* 1993;111:776–80.
 13. Achard OA, Safran AB, Duret FC, Ragama E. Role of the completion phenomenon in the evaluation of Amsler grid results. *Am J Ophthalmol* 1995;120:322–9.
 14. Olsen TW, Feng X, Kasper TJ, et al. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004;111:250–5.
 15. Loewenstein A, Malach R, Goldstein M, et al. Replacing the Amsler grid: a new method for monitoring patients with age-related macular degeneration. *Ophthalmology* 2003;110:966–70.
 16. Preferential Hyperacuity Perimeter (PHP) Research Group. Results of a multicenter clinical trial to evaluate the preferential hyperacuity perimeter for detection of age-related macular degeneration. *Retina* 2005;25:296–303.
 17. Enoch JM, Williams RA, Essock EA, Barricks M. Hyperacuity perimetry: assessment of macular function through ocular opacities. *Arch Ophthalmol* 1984;102:1164–8.
 18. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group, Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report no. 2. *Arch Ophthalmol* 2003;121:1253–68.
 19. Submacular Surgery Trials Research Group. Guidelines for interpreting retinal photographs and coding findings in the Submacular Surgery Trials (SST): SST report no. 8. *Retina* 2005;25:253–68.
 20. Collett D. *Modelling Binary Data*. London: Chapman & Hall; 1991:23–5.
 21. Harding SP, Broadbent DM, Neoh C, et al. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool Diabetic Eye Study. *BMJ* 1995;311:1131–5.
 22. Maberley DA, Isbister C, MacKenzie P, Aralar A. An evaluation of photographic screening for neovascular age-related macular degeneration. *Eye* 2005;19:611–6.

Appendix: Preferential Hyperacuity Perimetry Research Group

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