

RESULTS OF A MULTICENTER CLINICAL TRIAL TO EVALUATE THE PREFERENTIAL HYPERACUITY PERIMETER FOR DETECTION OF AGE-RELATED MACULAR DEGENERATION

PREFERENTIAL HYPERACUITY PERIMETER (PHP) RESEARCH GROUP

Purpose: To compare the preferential hyperacuity perimeter (PHP) with an Amsler grid in detection of age-related macular degeneration (AMD).

Methods: Patients underwent refraction, visual acuity examination, PHP, Amsler grid examination, and macular photography.

Results: One hundred fifty patients participated in the trial. Of 19 eyes with neovascular AMD, 19 (100%) were positive on the PHP, and 10 (53%), on the Amsler grid. Of 27 eyes with geographic atrophy, 26 (96%) were positive on the PHP, and 12 (44%), on the Amsler grid. Of 20 eyes with intermediate AMD, 14 (70%) were positive on the PHP, and 4 (20%), on the Amsler grid. Of 51 eyes with early AMD, 21 (41%) were positive on the PHP, and 4 (8%), on the Amsler grid. Of 33 eyes with no AMD, 6 (18%) were positive on the PHP, and none, on the Amsler grid. Thus, 80 (68%) of 117 patients with AMD had a positive PHP, while 30 (26%) had positive results of Amsler grid examination ($P < 0.001$, McNemar test).

Conclusion: The PHP had greater sensitivity, although with a relatively high rate of false-positive results for healthy individuals, than the Amsler grid in detecting AMD-related lesions.

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The preferential hyperacuity perimeter has greater sensitivity than the Amsler grid in detecting age-related macular degeneration lesions.

Age-related macular degeneration (AMD) is a major cause of severe vision loss and of legal blindness in people 65 years of age or older in the Western world.^{1–3} It is estimated that 18% of patients with intermediate AMD in at least 1 eye and 43% of

patients with monocular advanced AMD develop choroidal neovascularization (CNV) within 5 years.⁴ CNV often results in deterioration of vision, causing 90% of all cases of severe vision loss due to AMD.⁵

Laser photocoagulation and photodynamic therapy are currently the two common methods for treating CNV.^{6–10} The need for early detection is supported by data showing that photodynamic therapy is more beneficial when the initial lesion size is smaller. If lesions that currently present as a larger size could be detected while smaller,¹¹ benefits and cost-effectiveness of treatments for CNV, such as photodynamic therapy with verteporfin, may be better.¹²

The Amsler grid is commonly used for monitoring patients at home to try to detect CNV in an eye at

A complete list of the participants in the PHP Research Group as well as the Writing Committee (whose members take authorship responsibility) is provided in the Appendix.

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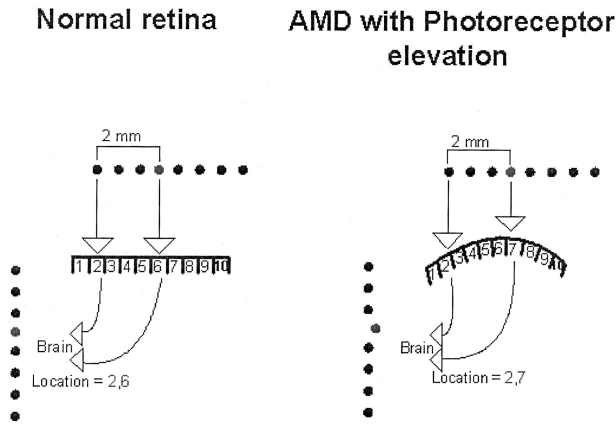


Fig. 1. When a dotted line is presented to a healthy retina, the corresponding collinear line of photoreceptor fields is stimulated, the information is processed by the visual cortex, and a straight dotted line is perceived (**left**). When there is retinal pigment epithelium elevation, there is a geometric shift in the photoreceptor location. As a result, the line stimulates a different, misaligned photoreceptor field. Thus, certain dots that are presented aligned along a straight line may be perceived at a different location from their true location in space (**right**). AMD, age-related macular degeneration.

risk.^{13,14} However, it previously has been shown to be an unreliable tool for diagnosing central visual field defects in patients with AMD, possibly due to questionable eye fixation, cortical image completion or filling in of scotoma, and visual “crowding” effect.^{15–21}

To address some of these shortcomings, the preferential hyperacuity perimeter (PHP), based on the visual phenomenon of hyperacuity, was developed. The PHP was designed to evaluate the central macular visual field and potentially provide early detection of neovascular AMD. Hyperacuity (also termed “Vernier acuity”) is defined as the ability to perceive a minute difference in the relative spatial localization of two or more visual stimuli.^{22,23} The hyperacuity threshold may be as low as 3 to 6 seconds of arc, and hyperacuity stimuli are highly resistant to retinal image degradation and thus suitable for assessing retinal function in patients with opaque media as well.^{24,25} No systematic variation of the hyperacuity threshold was found with increasing age in a study group of patients whose ages ranged from 20 to 85 years.²⁶

When a dotted line is presented to a healthy retina, a collinear set of retinal receptive fields is stimulated. This information is processed by specialized neuronal circuits in the visual cortex, leading to perception of a straight dotted line (Fig. 1). When there is retinal pigment epithelium elevation, such as occurs in AMD, both in the case of some drusen secondary to AMD and often to a more significant degree when neovascularization develops,²⁷ a geometric shift in photoreceptor location may occur. As a result, an object

image that would stimulate certain photoreceptors when presented to a normal retina can stimulate different ones when the retinal pigment epithelium is elevated. Thus, certain dots that are presented and aligned in a straight line may be perceived at a different distorted location from their true location in space (Fig. 1). This perceived shift in object location may be the anatomic explanation for metamorphopsia and is recorded by the PHP.

Supporting this hypothesis, the PHP appeared feasible to detect AMD-related lesions with high sensitivity in a previous study,²⁷ in which the PHP had a greater positive predictive value and sensitivity than the Amsler grid in detecting AMD-related lesions. However, the previous study had several limitations, including the following: the technician was aware of the diagnosis of the tested eye, the method of diagnosis was not consistent (consisting of color photography performed only for some of the patients with nonneovascular AMD and of fluorescein angiography only in cases of neovascular AMD), and visual acuity examinations were not standardized.

To address some of these limitations, a multicenter study was designed, and the results are presented here. The aim of this study was to evaluate the PHP in a more rigorously designed multicenter study, in which the technician was masked to the diagnosis and visual acuity examinations and fundus photography were standardized.

Patients and Methods

Patients

The study was conducted at three centers between March 22, 2001, and October 25, 2001: the Department of Ophthalmology at the Tel-Aviv Medical Center (Tel-Aviv, Israel), the Department of Ophthalmology at the Kaplan Medical Center (Rehovot, Israel), and the Wilmer Ophthalmologic Institute at the Johns Hopkins University School of Medicine (Baltimore, MD). Patients were selected in a consecutive manner on the basis of medical records. A convenient group of patients (consecutive patients who met enrollment criteria when a study coordinator and other personnel necessary for the study were available) who met the inclusion criteria, agreed to participate in the study, and provided informed consent participated in the study. Principal inclusion criteria included the following: age of at least 50 years; best-corrected visual acuity letter score, using a protocol refraction with a Bailey–Lovie chart R (Lighthouse, Long Island, NY) and protocol visual acuity measurement as used in the TAP investigation⁹ with a Bailey–Lovie chart 1 (right

Table 1. Definitions of Patient Groups 1 Through 5

Group	Definition
1	No drusen or <5 small drusen of <63 μm within 3,000 μm from the FAZ center.
2	≥ 5 small drusen of <63 μm or any intermediate drusen of ≥ 63 μm but <125 μm or ≤ 5 large drusen of ≥ 125 μm within 3,000 μm from the FAZ center.
3	>5 large drusen of ≥ 125 μm within 3,000 μm from the FAZ center.
4	Geographic atrophy of ≥ 175 μm plus group 2 or 3 signs in either eye within 3,000 μm from the FAZ center.
5	CNV with fibrosis of <50% plus group 2 or 3 signs in either eye within 3,000 μm from the FAZ center.

Groups 2 through 5 had age-related macular degeneration. FAZ, foveal avascular zone; CNV, choroidal neovascularization.

eye) or 2 (left eye) of at least 38 at a 2-m distance (approximate Snellen equivalent of $\geq 20/160$); ability and agreement to sign a written informed consent form approved by the local center's institutional review board as well as the study group after participating with an investigator in an oral informed consent process; and healthy macula or AMD in the study eye.

Main exclusion criteria included the following: macular or optic nerve disease other than AMD in the study eye; and any significant media opacity precluding a clear view of the macular area shown by biomicroscopy or fundus photography. For patients in whom both eyes were eligible, the eye was randomly selected based on the patient's medical record number (right eye for even numbers and left eye for odd numbers). After signing a written informed consent form, participants underwent protocol refraction, standardized best-corrected visual acuity examination, PHP evaluation, and a conventional, supervised Amsler grid test (in a manner described below). The PHP and Amsler grid examinations were performed in a random order by a trained technician masked to each patient's retinal condition.

Biomicroscopic examination of the fundus by a retinal specialist was followed by stereoscopic macular color photography (Kodak Ektachrome 100 plus EPP, Topcon TRC 50x, Tokyo, Japan; or Zeiss FF4 Fundus Camera, Oberkochen, Germany). Five groups of patients were selected for the study (Table 1): group 1, patients with a normal macula in the study eye (no AMD); group 2, nonneovascular AMD without a high-risk characteristic (defined as the presence of six or more large drusen); group 3, nonneovascular AMD with a high-risk characteristic; group 4, advanced AMD with geographic atrophy as well as features of

Table 2. Questions Presented To Examinees Viewing the Amsler Grid

1. Do you see the black spot in the center of the square chart?
2. Keeping your eye fixed on the black spot in the center, can you see the four corners of the big square? Can you also see the four sides of the square?
3. Keeping your eye fixed on the black spot in the center, do you see the network of small squares intact? Or are there interruptions in the network of small squares, like holes or blurry areas?
4. Keeping your eye fixed on the black spot in the center, do you see all lines, both horizontal and vertical, quite straight and parallel? In other words, is every small square equal in size and perfectly square?
5. Keeping your eye fixed on the black spot in the center, can you see anything else besides blurred areas, holes, or distortions? A vibration or waving? Anything shining? A color or tint?
6. Keeping your eye fixed on the black spot in the center, at what distance from this spot do you see any blur, hole, or distortion? How many small intact squares do you see between the central spot and the first blur, hole, or distortion (both vertical or horizontal)?

group 2 or 3 in either eye but no CNV in the study eye; and group 5, CNV with fibrosis contributing to no more than 50% of the lesion as determined on stereoscopic color fundus photographs as well as features of group 2 or 3 in either eye. Patients with CNV with fibrosis contributing to at least 50% of the lesion as determined on stereoscopic color fundus photographs as well as features of group 2 or 3 in either eye were excluded from the study.

Amsler Grid Evaluation

A black grid on white background Amsler grid was used. The Amsler grid was presented by an examiner to the patient using the patient's distance refraction measured by a protocol and adjusted to a near distance of 33 cm with an addition of +3.00 diopters. The study participant was then instructed to go through the questions outlined in Table 2, and the study participant was asked to answer yes or no or as appropriate.

PHP Evaluation

The PHP evaluation, using the test and algorithm described below, was performed with the patient's distance refraction adjusted to a near distance of 50 cm on a standard PC screen (1024 horizontal and 768 vertical).

Stages of the PHP test

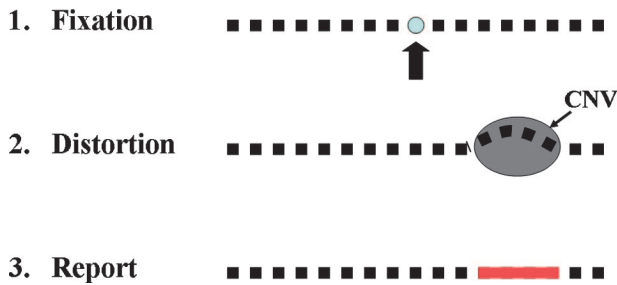


Fig. 2. The examiner initiates the stimuli by bringing the cursor to the center of the dotted line, after which the line is presented at a random location in the central visual field. Patients are instructed to fixate on the cursor at the initiation of the line movement. If the virtual line is projected onto a retinal lesion, a swift change of fixation by the patient can enable distortion, scotoma, or blurring to be perceived by the patient. The patient is instructed to report any distortion or other abnormality of the line.

The signal, a virtual line composed of units (white dots on a black background, maximal contrast), was moved across different macular loci up to a perifoveal radius of 7°. Both horizontal and vertical lines were presented. A minimum of 46 signals was presented (23 horizontal and 23 vertical) and a maximum of 102 signals was presented according to patient’s responses during the test. The order of signals was random. Each signal was composed of units, where each unit was a rectangle of 0.2 × 0.2°. The gap between units was 0.6°. The signal was 11.2 cm long (on the screen), and because the patient’s eye was at 50 cm (20 in), it occupied 14° of the patient’s visual field. Thus, the total area covered by the lines was 14 × 14° in the visual field.

The examiner initiated the stimuli by bringing the cursor to the fixation target at the center of the dotted line and clicking on the mouse to initiate the appearance of the signal in its new location (Fig. 2). When lines disappear from one location and simultaneously appear at a new location, the viewer perceives a movement of the line (similar to any standard animation techniques). After the new line has been presented, the patient moves his/her gaze to that new location, and thus this new line is both the reference for pointing out the perceived defects location (if any) and the new fixation target.

The instructions to the subject were as follows: “look at the fixation point at the center of the signal, and report if there are they any distortions while the signal moves to another location.” Patients were not specifically instructed to look to the location where the line moved to, but because they were not instructed otherwise, they tended to shift their gaze to the new

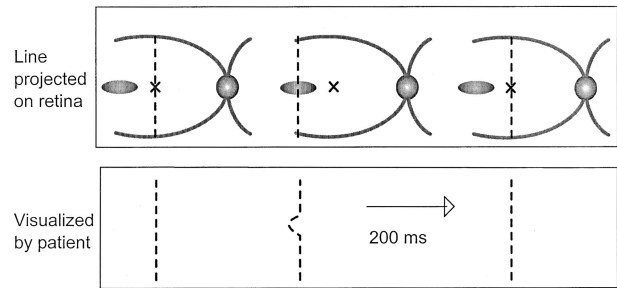


Fig. 3. Outline of stages of a specific test of a nonfoveal lesion. The x represents the fovea, while the ellipse represents an age-related macular degeneration lesion. In this case, the lesion is extrafoveal, and the vertical line that is presented to the patient (**top bar, left**) is perceived as a straight line (**bottom bar, left**). The line is then moved rapidly to different macular locations, one movement at a time covering the central 14° of the visual field. At a certain point, the line may be projected onto a lesion (**top bar, center**); some of its dots consequently will be perceived as misaligned, and the line, as wavy (**bottom bar, center**). After refixation, the line is again projected onto the fovea (**top bar, right**) and perceived as straight (**bottom bar, right**). The wavy line that became straight is eliciting an apparent motion perception of the wavy area. ms, millisecond.

location of the signal, which is the natural human tendency. Because shifting the gaze is a time-consuming process, ≈200 milliseconds long, initially, the new signal location is actually projected on a peripheral retinal location within the central 14° of the visual field. If the new signal is projected on a lesion, the patient might perceive a change from a wavy to a straight signal after shift of gaze (foveal shift).

When the patient perceived any abnormality of the dotted line, including any wavy segment within a given line, he/she was asked to indicate so by pointing to that location on the screen where it was perceived. The cursor was then brought to that location by the examiner and was recorded into the system (Fig. 2).

Adjustment was performed by calculating the distance between the fixation point and the new line presented. No modality was used to identify whether the patient fixated with his/her fovea because this technique does not aim at localizing a visual field defect relative to the fovea but rather determines if a visual field defect is present. The patient’s responses were analyzed automatically by an algorithm that was developed before the onset of the study (described below).

Presentation of the dotted line onto a retinal lesion that did not involve fixation theoretically should have been perceived as being either misaligned or partly missing for a short duration until the fixation changed. This shift in fixation could cause the apparent movement of the wavy dots from a misaligned position to an aligned one, thus giving the patient the perception of apparent movement (author’s unpublished data) (Fig. 3).

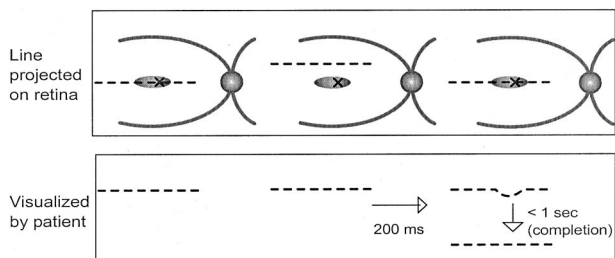


Fig. 4. Outline of stages of a specific test of a foveal lesion. The x represents the fovea, while the ellipse represents an age-related macular degeneration lesion. In this case, the lesion is subfoveal, and the horizontal line that is presented to the patient (**top bar, left**) is perceived as a straight line (**lower bar, left**) owing to relatively slow cortical completion (filling in). The line is then rapidly moved to a nonfoveal location (**top bar, center**) and is thus seen as straight (**lower bar, center**). After refixation, the line is rapidly presented onto the fovea (**top bar, upper right**). This time, because completion is a timely relatively slow process, the line is initially perceived as wavy, and only when the completion process occurs, it is perceived as straight again (**lower bar, lower right**). ms, millisecond; sec, second.

Whenever the lesion was subfoveal, two scenarios were possible. One scenario is that a new preferred retinal location might have been used during the examination, and thus the visual field defect could have appeared at a nonfoveal location. In cases in which a new preferred retinal location presumably was used, when the line was moved to a new location in the macular visual field corresponding to the location of the neovascular lesion, distortion or a scotoma could be perceived. Another scenario for subfoveal lesions in which the patient uses this area for fixation is that a relatively slow cortical completion may allow scotomata or distortions to be ignored after long exposure. Thus, a line presented for a relatively long duration to a diseased fovea might eventually be perceived as being straight (Fig. 4). If the line is then moved to a healthy retinal location, initially it should be perceived as a straight line; however, after refixation, the line would be presented rapidly to the diseased fovea and hypothetically would be perceived as distorted before the completion process occurs, allowing the line to be perceived as straight again.

An assembly of all of a patient's responses was performed followed by automated analysis, where a positive PHP was defined as the existence of at least two wavy segments that were at a proximity of at least 2° horizontally or 3° vertically (Fig. 5). Thus, a response was termed "positive" only if there was another response at a predefined proximity. Intratest analysis initiated automatic verification to areas where a single wavy segment was not supported by another marked distortion.

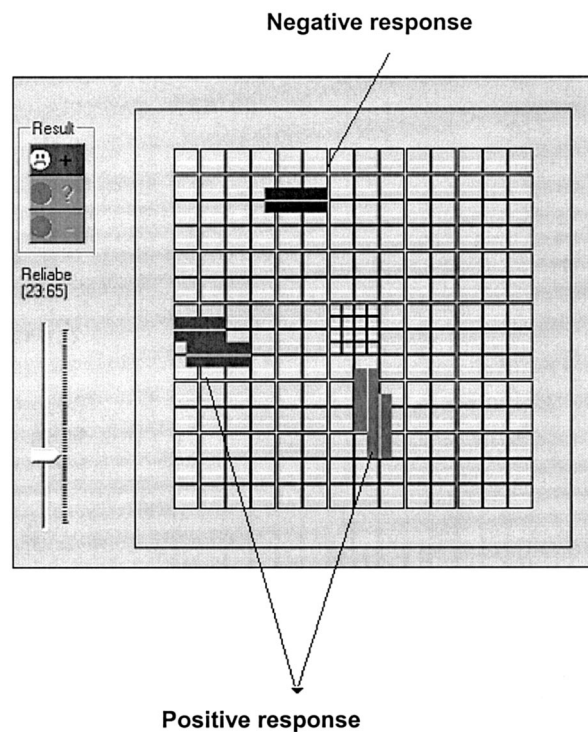


Fig. 5. Automated analysis is performed and defined as the existence of at least two wavy segments that are at a proximity of at least 2° horizontally or 3° vertically. Whenever signals that meet this definition are identified, the preferential hyperacuity perimeter is marked as positive. The darkened area represents 3° in the line (of the full 14°), which represents the area where the patient pointed to with some predefined tolerance. Intratest analysis initiated automatic verification to areas where a single wavy segment is not defined as meeting this definition.

Fundus Photograph Grading

Stereoscopic color fundus photographs were graded at the Wilmer Photograph Reading Center (Johns Hopkins University School of Medicine, Baltimore, MD) by a grader who was masked to the Amsler grid and PHP results.

Statistical Analysis

The statistical tests used for analyzing the results of this study included comparative analysis between the Amsler grid and the PHP. The McNemar test²⁸ was applied to examine differences between PHP and Amsler grid results for the dichotomous parameters (negative/positive findings). The statistical tests included 95% confidence intervals. $P < 0.05$ was considered statistically significant. No adjustments were made for multiple assessments. The sensitivity and specificity of the Amsler grid and the PHP were calculated and compared for the total population and for each group alone.

Table 3. Approximate Snellen Visual Acuity per Patient Group

Patient Group	No.	Median	Range
1	33	20/25	20/20 to 20/160
2	51	20/32	20/20 to 20/80
3	20	20/40	20/20 to 20/126
4	27	20/40	20/20 to 20/100
5	19	20/50	20/20 to 20/126
Total	150	20/32	20/20 to 20/160

Results

Of 179 patients who were enrolled in the study, 10 were excluded (2 with an inadequately dilated pupil; 4 for not meeting inclusion/exclusion criteria by either the enrolling ophthalmologist or the photograph reading center graders; 1 with loss of photographs during processing; and 1 with a computer system failure of the PHP at enrollment, 2 because of 2car stage AMD

lesion). Nineteen other patients (11%) were excluded because the quality of the photographs precluded grading by the photograph image center. Of 171 patients enrolled in the study, 93 (54.4%) were women, and 78 (46%) were men. The average age ± SD was 73.6 ± 8.6 years (range, 50–93 years). Eighty-seven patients (50.9%) had their right eye tested, while 84 patients (49.1%) had their left eye tested. Visual acuity ranged from 20/20 to 20/160 (median, 20/32). Table 3 outlines the visual acuity distribution in each group.

Figure 6 compares the Amsler grid with the PHP for detecting various categories of AMD. Table 4 provides the results of sensitivity and specificity for each group with the two methods of examination. The sensitivity of the PHP was significantly greater than that of the Amsler grid for differentiating patients with healthy retina from those with macular lesions secondary to AMD (*P* < 0.001). A similar significant difference was found when analyzing each group separately. The PHP identified six

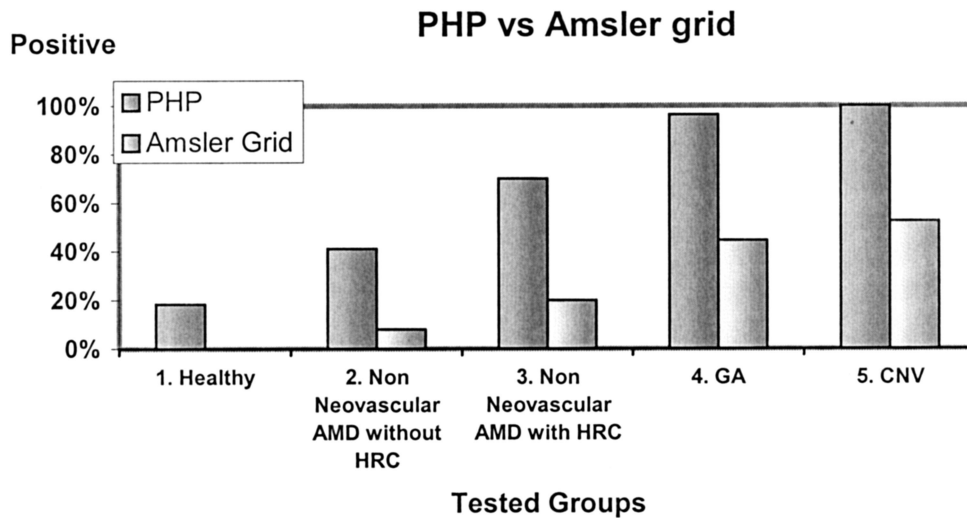


Fig. 6. Comparison of detection rate for each group by the preferential hyperacuity perimeter (PHP) and Amsler grid. The sensitivity of the PHP was significantly greater than that of the Amsler grid for differentiating patients with healthy retina from those with macular lesions secondary to age-related macular degeneration (AMD) (*P* < 0.001). HRC, high-risk characteristics; GA, geographic atrophy; CNV, choroidal neovascularization.

Table 4. Summary of PHP and Amsler Grid Results per Patient Group

Patient Group	PHP				Amsler Grid				<i>P</i>
	Negative	Positive	Sensitivity	Specificity	Negative	Positive	Sensitivity	Specificity	
1	27	6	—	0.818	33	0	—	1	0.031
2	30	21	0.412	—	47	4	0.078	—	<0.001
3	6	14	0.70	—	16	4	0.20	—	0.002
4	1	26	0.963	—	15	12	0.444	—	<0.001
5	0	19	1	—	9	10	0.526	—	0.004
Total*	27	80	0.684	0.818	33	30	0.256	1	<0.001

* Reflects the number of patients included for sensitivity and specificity calculations. PHP, preferential hyperacuity perimeter.

subjects with no AMD as positive; Amsler grid testing identified no such cases. The *P* value for this difference in specificity was 0.031.

Discussion

This study demonstrated that the PHP had a greater sensitivity than the Amsler grid in detecting AMD-related lesions after a standardized protocol. The study also verified the ability of the specifically developed algorithm to produce real-time automatic analysis and objective, standardized interpretation according to a patient's responses. Moreover, the results confirmed the observations of other researchers regarding the poor validity of the Amsler grid in detecting the neovascular form of AMD.^{12,13}

A few limitations of the study were noted. The Amsler grid consisted of black lines over a white background, while the PHP consisted of white lines over a black background. It is unknown at this time how the PHP would compare if the Amsler grid consisted of dashed lines or was altered in other ways; the standard Amsler grid was chosen for initial comparisons because it was perceived to be the most widely used type of test to detect AMD-related lesions. The high sensitivity of the test likely contributed to the relatively high rate of false-positive results for individuals with healthy retina. In addition, the threshold sensitivity used in this study likely was set too low (i.e., was too sensitive) to allow differentiation among the different stages of AMD, diagnosing as positive both patients with neovascular AMD and patients with features of nonneovascular AMD who were at high risk for developing neovascular AMD. Although the results currently indicate differences among the tested groups, studies of validation of the ability of the PHP to differentiate among groups with both high sensitivity and high specificity are under way using revised algorithms and testing strategies. In addition, because fluorescein angiography is the gold standard for diagnosing CNV and in this study only color fundus photos were used, it is possible that subtle CNV might have been missed. It should be mentioned, however, that even if indeed some CNVs were missed, it was with an identical bias for the PHP and for the Amsler grid.

Although the PHP could be used in a home setting as well as in the clinic, this trial did not demonstrate the ability of people with AMD to operate the PHP in an unsupervised manner from their home. Validation of our results is currently under way with the patient performing the study at home.

The high sensitivity of the PHP in this study also likely contributed to its limited specificity, probably con-

tributing to the six cases with false-positive results. Although the PHP was shown to be highly sensitive, its specificity is somewhat less satisfactory. As a tool to detect progression to an intermediate or an advanced stage of AMD in a large population, higher specificity is desired to address the need for an efficient tool as well as to prevent an overload of false-positive results on the medical system. Altering test settings might allow better differentiation between the different subgroups; this hypothesis is under investigation.

The average visual acuity was relatively good in all study groups and did not limit the sensitivity of the PHP in detecting the advanced stages of AMD (CNV and geographic atrophy). Thus, the PHP may be one of the best methods for early detection of advanced AMD without ophthalmoscopy. If a device based on the PHP could be used to screen for intermediate AMD where reliable and valid ophthalmoscopic examination is not available, those patients identified could be referred for definitive diagnosis. This is an important consideration because the Age-Related Eye Disease Study Research Group reported a reduced rate of visual loss from advanced AMD for patients with intermediate AMD who were assigned to antioxidant and zinc supplements.⁴ The PHP may be able to contribute to reducing the magnitude of vision loss from AMD if further studies confirm its usefulness in identifying intermediate AMD or monitoring eyes with the intermediate stage of AMD for the development of CNV.

Appendix

PHP Research Group

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Authors with an asterisk take authorship responsibility for the article and had complete access to the data for this report. Financial disclosures: Anat Loewenstein, MD, is paid as a consultant to Notal Vision, Ltd., and has stock options in Notal Vision, Ltd. Neil

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Key words: age-related macular degeneration, choroidal neovascularization, drusen.

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