

TOWARD EARLIER DETECTION OF CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION

Multicenter Evaluation of a Preferential Hyperacuity Perimeter Designed as a Home Device

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Purpose: The primary purpose of this study was to evaluate the ability of a home device preferential hyperacuity perimeter to discriminate between patients with choroidal neovascularization (CNV) and intermediate age-related macular degeneration (AMD), and the secondary purpose was to investigate the dependence of sensitivity on lesion characteristics.

Methods: All participants were tested with the home device in an unsupervised mode. The first part of this work was retrospective using tests performed by patients with intermediate AMD and newly diagnosed CNV. In the second part, the classifier was prospectively challenged with tests performed by patients with intermediate AMD and newly diagnosed CNV. The dependence of sensitivity on lesion characteristics was estimated with tests performed by patients with CNV of both parts.

Results: In 66 eyes with CNV and 65 eyes with intermediate AMD, both sensitivity and specificity were 0.85. In the retrospective part (34 CNV and 43 intermediate AMD), sensitivity and specificity were 0.85 ± 0.12 (95% confidence interval) and 0.84 ± 0.11 (95% confidence interval), respectively. In the prospective part (32 CNV and 22 intermediate AMD), sensitivity and specificity were 0.84 ± 0.13 (95% confidence interval) and 0.86 ± 0.14 (95% confidence interval), respectively. Chi-square analysis showed no dependence of sensitivity on type ($P = 0.44$), location ($P = 0.243$), or size ($P = 0.73$) of the CNV lesions.

Conclusion: A home device preferential hyperacuity perimeter has good sensitivity and specificity in discriminating between patients with newly diagnosed CNV and intermediate AMD. Sensitivity is not dependent on lesion characteristics.

RETINA 30:1058–1064, 2010

Although antivascular endothelial growth factor therapy prevents deterioration of vision in >90% of choroidal neovascularization (CNV) cases; visual acuity is improved in only 30% to 40%.^{1,2} These observations indicate that in a considerable number of cases, treatment is initiated after some vision has

already been compromised. Indeed, brain mechanisms that compensate for retinal malfunction often delay the typical symptoms of CNV (such as metamorphopsia, scotoma, or blurring) until the lesion is relatively large and subfoveal.³ Consequently, most patients with CNV seek medical intervention when the benefits of

treatment may already be less than optimal.⁴ A number of largescale studies have demonstrated that in terms of the absolute level of visual acuity, final outcome after long-term treatment is better when baseline visual acuity is higher^{5,6} and when CNV lesions are smaller.⁵⁻⁷ These studies emphasize the importance of earlier diagnosis for more effective treatment of CNV.^{5,8}

In principle, more frequent examinations should promote early diagnosis of CNV. High costs, limitation of human resources, and side effects make frequent fluorescein angiography, the gold standard of CNV detection, impractical. Similarly, the need for technically experienced personnel and visits to the office makes frequent optical coherence tomography imaging unrealistic. Functional changes in vision often precede anatomical and structural changes. Hence, frequent monitoring of patients with age-related macular degeneration (AMD) with sensitive psychophysical tools could advance the time of CNV detection⁹⁻¹¹ and improve the outcome of treatment. The rapidity of CNV progression (especially of the classic type) calls for weekly, or even daily, monitoring. Unfortunately, the only “tool” currently available for frequent monitoring is the Amsler grid, which has low sensitivity because of the cortical filling-in mechanisms, the difficulty of maintaining fixation, and crowding effects.¹²⁻¹⁴

Recently, a novel perimeter was specifically developed for unsupervised monitoring of patients with intermediate AMD. On the basis of preferential hyperacuity perimeter (PHP) technology, this home device uses the sensitive visual function of hyperacuity to detect and quantify the severity of visual defects associated with the development of CNV such as metamorphopsia and scotoma. Preferential hyperacuity perimeter technology has been described in detail elsewhere.^{15,16} Briefly, the test consists of a series of dotted horizontal or vertical signals successively flashed on a screen. In each signal, a few dots are

slightly misaligned. If perceived, this hyperacuity stimulus appears as a local distortion of the signal pattern (referred to an artificial distortion [AD]). The patient’s task is to mark the locations of the ADs. If a line is flashed at a retinal location that corresponds to a CNV lesion, a physical shift of the photoreceptors caused by the lesion may result in the patient perceiving a pathologic distortion instead of, or in addition to, the AD.¹⁵

According to the competition principle, visual attention is attracted to the most prominent source of visual information. Hence, if the pathologic distortion is more prominent than the AD, the patient may not notice the AD. At the end of the test, the set of erroneous responses is fed to a classifier that was previously trained on known intermediate AMD and CNV tests (the normative database). The classifier calculates the probability that a patient with a CNV lesion performed the test.

Currently, PHP technology is implemented in a clinical setting, where the test is performed under supervision that ensures performance in optimal conditions: fixed distance from display, single-eye test, refraction adjusted to personal vision, low ambient light, and so on. The clinical test does not require any special technical skills, and the patient responds by pointing with a stylus at stimuli displayed on a touch screen. Previous studies have shown that a PHP test in the clinical setting can distinguish, with high sensitivity and specificity, between eyes with intermediate AMD and newly diagnosed CNV.¹⁵⁻²⁰

Adaptation of the PHP test from a clinical setting to a home device required a number of modifications toward unsupervised but still frequent use (details are given in “Patients and Methods”). This brought along the development of a different device adapted for self-training and testing by elderly patients intended for use as a home device. Therefore, the primary aim of this study was to evaluate the sensitivity and specificity of a home device test performed in an unsupervised manner. Our secondary objective was to examine the dependence of sensitivity on location, type, and size of the lesions, parameters that are associated with disease progression.

Patients and Methods

The report presented in this study consisted of a retrospective and a prospective part. Between January 2007 and September 2007, 8 clinical centers in Israel recruited patients for the retrospective part. Between April 2008 and September 2008, 15 clinical centers (8 in Israel and 7 in the United States) recruited

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patients for the prospective part. During the recruitment period, consecutive patients in each of the centers were offered participation. Except otherwise noted, all procedures and protocols were identical for the two parts.

Participant Eligibility and Enrollment

All participants signed a written informed consent before enrollment. A main inclusion criterion was evidence of intermediate AMD (as determined by definitions used in the Age-Related Eye Disease Study²¹) or recent-onset CNV within 3,000 μm of the fovea in the study eye. Additional inclusion criteria were >50 years of age, willingness and ability to sign a written informed consent, and a visual acuity with habitual correction of >20/200 on Snellen charts. In the retrospective part, experience with a computer mouse was not a prerequisite. However, candidates with no experience with a computer mouse were taught how to use the mouse. Participation in the study was conditioned on passing an in-house mouse tutorial. In the prospective part, mouse experience was part of the inclusion criteria. Exclusion criteria were macular disease other than AMD, geographic atrophy, media opacity precluding a clear view of the fundus, no or poor-quality photographs that prevented unambiguous grading, and ocular surgery in the study eye within the previous 3 months.

After self-explanatory training on the home device, eligible participants performed a test. Study ophthalmologists were masked to test results. After the test, participants underwent dilation and biomicroscopy. Eyes with evidence of advanced AMD were subject to fluorescein angiography and optical coherence tomography imaging. Color fundus photographs and fluorescein angiograms were obtained within 2 weeks of home device testing and then sent to an experienced photograph reading center that used the standard guidelines for identification of intermediate AMD and CNV.²² The results of this grading process were then used as the gold standard.

Home Device Testing

The ForeseeHome (Notal Vision, Ltd., Tel Aviv, Israel) was specifically developed for unsupervised testing for at home use. The ForeseeHome is based on PHP technology as described in detail elsewhere.¹⁶ Adaptation of the PHP test from a supervised test suitable for a clinical setting to an unsupervised test more appropriate to home use required a number of modifications. The physical size of the device was reduced to facilitate storage and transportation. To control distance from the display, ambient light

Table 1. Demographic Information of Eligible Participants in the Retrospective Part of the Study

Parameters	Intermediate	
	AMD,* n (%)	CNV,* n (%)
Total participants	43	34
Age (years)		
50-<60	3 (7)	1 (3)
60-<70	5 (12)	5 (15)
70-<80	26 (60)	14 (41)
80-<90	8 (19)	13 (38)
Unknown	1 (2)	1 (3)
Visual acuity (Snellen equivalent)		
20/20	6 (14)	2 (6)
20/25-20/40	26 (60)	9 (26)
20/50-20/80	9 (21)	16 (47)
20/100-20/160	2 (5)	5 (15)
20/200	0	2 (6)
Sex		
Male	18 (42)	23 (68)
Female	25 (58)	10 (29)
Unknown	0	1 (3)
Study eye		
Right	20 (47)	20 (59)
Left	23 (53)	14 (41)
Computer literacy		
Yes	19 (44)	13 (38)
No	24 (56)	21 (62)

*Based on the evaluation of color fundus and angiograms by the photograph reading center.

conditions, and occlusion of the nontested eye, the screen viewer was set in a closed hood. Infrared sensors were added to the hood to ensure correct positioning of the head. In contrast to the clinical device in which the patient responded by pointing at selected locations on a touch screen, in the home device, the patient marked his or her responses with the aid of a mouse-movable cursor. To ensure fixation to the center of the display, signals were self-triggered by an operation that required full visual attention (bringing the cursor to a centered dot).

Results

Retrospective Part

A total of 109 individuals were enrolled. Of these, 14 (13%) had unreliable home device tests; 18 additional individuals were not included because of one of the following protocol violations: geographic atrophy, early AMD, or poor-quality photographs. Table 1 summarizes demographic information of eligible study eyes broken down by gold standard (intermediate AMD or CNV groups) as determined by the photograph reading center. Both groups were similar in age ($P = 0.61$, t -test) with a median age of 76 years

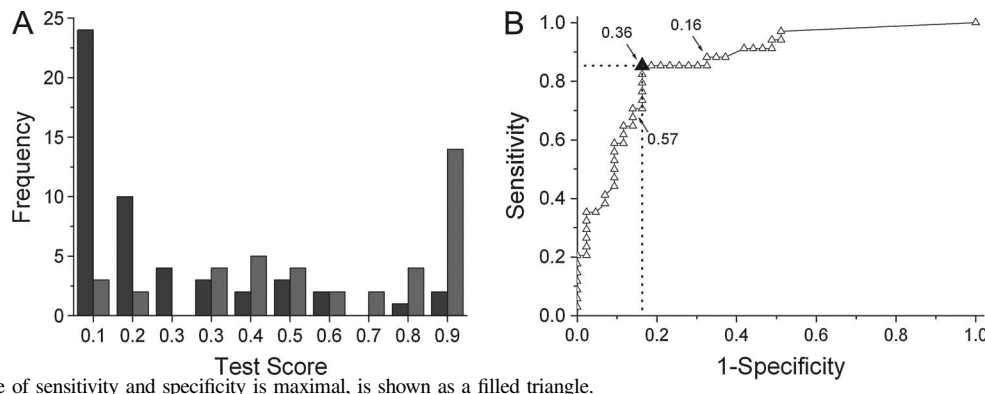


Fig. 1. Classification of test results in patients with intermediate AMD and CNV. **A.** The distributions of normalized test scores in eyes with intermediate AMD (blue bars) and CNV (red bars). **B.** Receiver operating characteristic curve plotting sensitivity and 1 - specificity for different cutoff score values. Three representative cutoff values point to the corresponding data symbols. The optimal cutoff value, for which the average of sensitivity and specificity is maximal, is shown as a filled triangle.

in both groups. Visual acuity was better in the intermediate AMD group compared with the CNV group with mean ($\mu \pm \sigma$) logarithm of the minimum angle of resolution of 0.26 ± 0.19 and 0.45 ± 0.26 , respectively ($P < 0.01$, *t*-test). The median approximate Snellen equivalents were 20/33 for the intermediate AMD group and 20/63 for the CNV group. The proportion of men was greater in the CNV group compared with the intermediate AMD group (68% vs. 42%; $P = 0.015$, chi-square). The proportion of right eyes was similar in the 2 groups ($P = 0.28$, chi-square). The proportion of computer literates was similar in the 2 groups ($P = 0.67$).

Figure 1A shows the distribution of test scores performed by the eyes with intermediate AMD and CNV in the retrospective study. On average, tests performed by intermediate AMD eyes scored lower grades: the mean score was 0.234 ± 0.246 ($\mu \pm \sigma$) and 0.649 ± 0.3 ($\mu \pm \sigma$) for eyes with intermediate AMD and CNV, respectively ($P < 0.01$, *t*-test). These scores were used to construct the receiver operating characteristic curve shown in Figure 1B. The Wilcoxon estimate of the area under the receiver operating characteristic curve was 0.87 (95% confidence interval [CI] = 0.79–0.95). Optimal accuracy (maximal sensitivity + specificity in the receiver operating characteristic curve) was found at a cutoff value of 0.356 (black triangle in Figure 1B); at this cutoff value, the device identified abnormal test results (indication of CNV) in 29 of 34 eyes with CNV and in 7 of 43 eyes with intermediate AMD. These results represent a sensitivity, specificity, and accuracy of 0.85 ± 0.12 (95% CI), 0.84 ± 0.11 (95% CI), and 0.85 ± 0.11 (95% CI), respectively.

Prospective Part

The accuracy of the device was challenged with a prospective set of patients. A total of 99 individuals were prospectively enrolled. All participants had

experience with a computer mouse. Of the 99 enrolled, 15 (15%) did not pass the home device tutorial and were excluded from the study; another 8 (8%) had unreliable home device tests; 22 additional individuals were not included because of 1 of the following protocol violations: geographic atrophy, pattern dystrophy, or no or poor-quality photographs. Table 2 summarizes the demographic information of eligible study eyes broken down by AMD stage as determined

Table 2. Demographic Information of Eligible Participants in the Prospective Part of the Study

Parameters	Intermediate	
	AMD,* n (%)	CNV,* n (%)
Total participants	22	32
Age (years)		
50-<60	2 (10)	0
60-<70	5 (25)	4 (13)
70-<80	7 (35)	13 (42)
80-90	5 (25)	14 (45)
90-<100	1 (5)	0
Unknown	2	1
Visual acuity (Snellen equivalent)		
20/20	6 (32)	1 (3.3)
20/25-20/40	11 (58)	8 (26.6)
20/50-20/80	2 (10)	10 (33.3)
20/100-20/160	0	7 (23.3)
20/200	0	4 (13.3)
Unknown	3	2
Sex		
Male	8 (40)	9 (29)
Mediate	12 (60)	22 (71)
Unknown	2	1
Study eye		
Right	12 (55)	19 (59)
Left	10 (45)	13 (41)
Computer literacy		
Yes	22 (100)	32 (100)
No	0	0

*Based on the evaluation of color fundi and angiograms by the photograph reading center.

by grading of the photograph reading center. The median age was 78 years for the CNV group and 73.5 years for the intermediate AMD group. There was a slight tendency for higher age in the CNV group, although not to a statistically significant level ($P = 0.08$). Visual acuity was better in the intermediate AMD group compared with the CNV group with average logarithm of the minimum angle of resolution of 0.17 ± 0.14 and 0.53 ± 0.26 , respectively ($P < 0.001$, t -test). Median approximate Snellen equivalents were 20/30 and 20/63 for the intermediate AMD and CNV groups, respectively. The proportion of women was slightly greater in the CNV group (71%) compared with the intermediate AMD group (60%). The proportion of right eyes was similar in the CNV and intermediate AMD groups.

The device identified abnormal test results (indication of CNV) in 27 of 32 eyes with CNV and in 3 of 22 eyes with intermediate AMD. These results represent a sensitivity, specificity, and accuracy of 0.84 ± 0.13 (95% CI), 0.86 ± 0.14 (95% CI), and 0.85 ± 0.13 (95% CI), respectively.

Dependence of Sensitivity of the Home Device on Lesion Characteristics

Our secondary objective was to examine the dependence of sensitivity on location, type, and size of the lesion, because these variables are often deteriorating (from extrafoveal to subfoveal, from occult to classic, and from small to large) with the progression of the disease. For the purpose of this subanalysis, we combined the CNV cases from the retrospective and prospective parts. We divided lesions from these two parts to subfoveal and nonsubfoveal, occult (no classic component) and classic (minimally classic or predominantly classic), and small (≤ 1 -disk area) and large (> 1 -disk area). Table 3 summarizes these lesion characteristics.

In Table 4, we present the distribution of true-positive and false-negative cases broken down by type, location, and size of CNV lesions. Chi-square analysis shows no dependence of these distributions on type ($P = 0.44$, chi-square test), location ($P = 0.243$, chi-square test), and size ($P = 0.73$, chi-square test) of the CNV lesions.

The distributions of true-positive and false-negative cases are also plotted in Figure 2, which also displays the corresponding sensitivities in the bottom panels. Sensitivities were somewhat smaller for occult versus classic lesions (0.83 vs. 0.9), subfoveal versus non-subfoveal lesions (0.8 vs. 0.9), and small versus large lesions (0.81 vs. 0.86). However, as indicated by the ranges of the 95% CIs, these differences were not statistically different.

Table 3. Lesion Characteristics in the Retrospective, Prospective, and Combined Parts

	Lesion Characteristics (n = 66)		
	Retrospective, n (%)	Prospective, n (%)	Combined, n (%)
Lesion type			
Occult	25 (74)	21 (66)	46 (70)
Minimally/ predominantly classic	9 (26)	11 (34)	20 (30)
Lesion location			
Nonsubfoveal	18 (53)	17 (53)	35 (53)
Subfoveal	16 (47)	15 (47)	31 (47)
Lesion size			
Small, ≤ 1 -disk area	6 (18)	11 (34)	17 (26)
Large, > 1 -disk area	28 (82)	21 (66)	49 (74)

Discussion

In the present work, we examined the performance of the ForeseeHome, a novel PHP designed for self-testing in an unsupervised manner. To date, preferential hyperacuity perimetry was available in a clinical setting only, which allowed testing in a supervised mode. Previous studies have showed the capability of the clinical device in distinguishing between patients with newly diagnosed CNV and intermediate AMD.^{11,16,17} Several modifications were introduced to adapt this perimeter to a home device, most notably the possibility to perform the test in an unsupervised manner. The results of the current work show that a test performed with the home device can distinguish between patients with newly diagnosed CNV and intermediate AMD with an average sensitivity and specificity of 85%. This

Table 4. Contingency Tables of CNV Tests in the Combined (Retrospective + Prospective) Parts of the Study

	True-Positive	False-Negative
Type of lesion		
Occult (no classic component)	38 (39.00)	8 (6.96)
Minimally or predominantly classic	18 (16.96)	2 (3.03)
Location of lesion		
Nonsubfoveal	28 (26.30)	3 (4.69)
Subfoveal	28 (29.69)	7 (5.3)
Size of lesion		
Small (≤ 1 -disk area)	13 (13.57)	3 (2.42)
Large (> 1 -disk area)	43 (42.42)	7 (7.57)

Values outside and inside of parentheses are observed and expected, respectively.

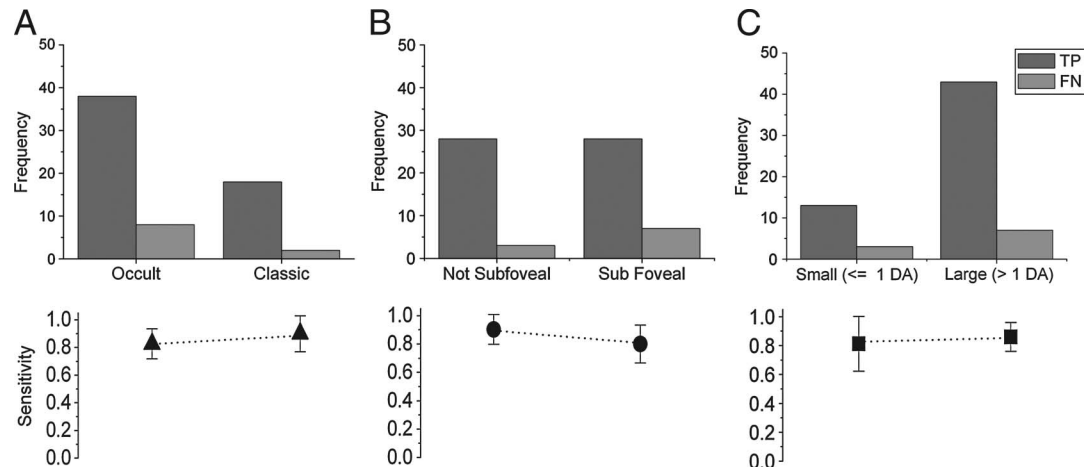


Fig. 2. Dependence of sensitivity on anatomical characteristics of the CNV lesion. In the upper panels, the number of true-positive and false-negative cases, from the population of eyes with CNV, are represented by red and green bars, respectively. In the lower panels, corresponding sensitivities are represented by symbols with error bars showing the upper and lower limits of the 95% CI. The strength of the difference effect can be estimated by the slopes of dashed lines connecting the symbols. **A.** Dependence on the type (occult vs. classic) of lesion. **B.** Dependence on the location (not subfoveal vs. subfoveal) of lesion. **C.** Dependence on the size (\leq -disk area vs. $>$ 1-disk area) of the lesion.

accuracy is comparable with that obtained with the clinical device, as shown in previous studies.

To be useful in clinical practice, useful technology for CNV detections should have high sensitivity to early CNV detection. Small lesion size is considered typical for early stages of the disease.²³ In addition, most CNV lesions start as extrafoveal and progress toward the fovea.²⁴ Regarding the type of lesion, the association is more complex, but occult disease is often considered a manifestation of early disease and, many times, is more difficult to detect.^{25,26} Because a significant proportion of CNV cases in this study were endowed with late characteristics, we performed a subanalysis to examine whether sensitivity depended on lesion type, location, and size. Although there was a slight tendency of better sensitivity for classic, large, or nonsubfoveal lesions, the differences were not statistically significant. The slightly lower sensitivity for subfoveal lesions compared with nonsubfoveal lesions was not expected. This result could be the result of cross interactions with other properties of the CNV lesions. Indeed, five of seven of the subfoveal lesions that yielded false-negative results were also occult, an observation that could have lowered sensitivity.

This study paves the way toward development of a home-based device that monitors vision of patients with AMD and promotes early detection of CNV. One limitation of the home device is the requirement of experience with a computer mouse. As exposure of the elderly to personal computers steadily increases with time, this may become less of an issue in the coming years. Another possible caveat is the 85% specificity found in this study. Although such specificity is acceptable for single-encounter tests, it may be too

high for frequent and multiple testing as is intended with a home device. If tests frequently performed by any individual were independent, a false-positive rate of 15% (85% specificity) would mean false alarms generated after a few uses of the device. Fortunately, tests performed by any individual are not independent, and individuals producing negative tests are likely to continue doing so unless vision deteriorates. Moreover, even if tests performed by an individual were independent, the rate of false-positives could be decreased by lowering sensitivity at the expense of a true-positive rate. In case of a positive event, the consequence of lowered sensitivity would merely mean an increase in detection time, which could still be acceptable if kept within a timeframe of several weeks. This could be easily obtained in individuals with high use frequency.

Based on the capabilities of the home device shown in this work, it is expected that multiple and frequent use of this home device will enable an algorithmically driven increase of signal-to-noise ratio and hence increase specificity without compromising much in time to detection. Long-term monitoring of patients with AMD at high risk with this home device is currently under investigation.

Key words: age-related macular degeneration, cho-roidal neovascularization, early detection, home device monitoring, preferential hyperacuity perimetry.

References

1. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-1444.

2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–1431.
3. Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial. *Ophthalmology* 2008;115:1474–1479.
4. Olsen TW, Feng X, Kasper TJ, Rath PP, Steuer ER. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004;111:250–255.
5. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007;114:246–252.
6. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. *Am J Ophthalmol* 2007;144:850–857.
7. Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1993;111:1189–1199.
8. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009;116:57–65.
9. Bedell HE, Tong J, Woo SY, House JR, Nguyen T. Orientation discrimination with macular changes associated with early AMD. *Optom Vis Sci* 2009;86:485–491.
10. Neelam K, Nolan J, Chakravarthy U, Beatty S. Psychophysical function in age-related maculopathy. *Surv Ophthalmol* 2009;54:167–210.
11. Loewenstein A. The significance of early detection of age-related macular degeneration: Richard & Hinda Rosenthal Foundation Lecture, The Macula Society 29th Annual Meeting. *Retina* 2007;27:873–878.
12. Fine AM, Elman MJ, Ebert JE, Prestia PA, Starr JS, Fine SL. Earliest symptoms caused by neovascular membranes in the macula. *Arch Ophthalmol* 1986;104:513–514.
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;120:322–329.
14. Zaidi FH, Cheong-Leen R, Gair EJ, et al. The Amsler chart is of doubtful value in retinal screening for early laser therapy of subretinal membranes. The West London Survey. *Eye (Lond)* 2004;18:503–508.
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;110:966–970.
16. Alster Y, Bressler NM, Bressler SB, et al. Preferential hyperacuity perimeter (PreView) for detecting choroidal neovascularization study. *Ophthalmology* 2005;112:1758–1765.
17. Goldstein M, Loewenstein A, Barak A, et al. Results of a multicenter clinical trial to evaluate the preferential hyperacuity perimeter for detection of age-related macular degeneration. *Retina* 2005;25:296–303.
18. Kampmeier J, Zorn MM, Lang GK, Botros YT, Lang GE. Comparison of Preferential Hyperacuity Perimeter (PHP) test and Amsler grid test in the diagnosis of different stages of age-related macular degeneration [in German]. *Klin Monatsbl Augenheilkd* 2006;223:752–756.
19. Klatt C, Sendtner P, Ponomareva L, et al. Diagnostics of metamorphopsia in retinal diseases of different origins [in German]. *Ophthalmologe* 2006;103:945–952.
20. Isaac DL, Avila MP, Cialdini AP. Comparison of the original Amsler grid with the preferential hyperacuity perimeter for detecting choroidal neovascularization in age-related macular degeneration. *Arq Bras Oftalmol* 2007;70:771–776.
21. 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;119:1417–1436.
22. Solomon SD, Bressler SB, Hawkins BS, Marsh MJ, Bressler NM. Guidelines for interpreting retinal photographs and coding findings in the Submacular Surgery Trials (SST): SST report no. 8. *Retina* 2005;25:253–268.
23. Vander JF, Morgan CM, Schatz H. Growth rate of subretinal neovascularization in age-related macular degeneration. *Ophthalmology* 1989;96:1422–1426; discussion 1426–1429.
24. Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. *Arch Ophthalmol* 1982;100:912–918.
25. Bressler NM, Frost LA, Bressler SB, Murphy RP, Fine SL. Natural course of poorly defined choroidal neovascularization associated with macular degeneration. *Arch Ophthalmol* 1988;106:1537–1542.
26. Macular Photocoagulation Study (MPS) Group. Occult choroidal neovascularization. Influence on visual outcome in patients with age-related macular degeneration. *Arch Ophthalmol* 1996;114:400–412.