Assessment of visual distortions in age-related macular degeneration: emergence of new approaches

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Abstract

Aims: **With the arrival of effective treatments for neovascular age-related macular degeneration (nvAMD) there is a need to find improved tests that would allow early detection. Ideally, these tests would allow monitoring of vision by patients themselves from home. The aim of this review is to discuss the available evidence for two recently developed vision tests designed for this purpose: the Preferential Hyperacuity Perimeter (PHP) test and the Radial Shape Discrimination (RSD) test.**
Methods: **Articles that investigated detection of nvAMD were reviewed. The methodology of the clinical evidence, where available, was judged for bias and applicability of the results to the general population using the QUADAS-2 quality assessment tool.**
Results: **The PHP test has proved to be good at detecting nvAMD but many studies assessed in this review were biased in the selection of patients, restricting the results to only those patients who can use the test and produce reliable results. On the other hand the RSD test is a simple test, well accepted by elderly patients with AMD. However, clinical studies to determine its value in the detection of early signs of nvAMD are still required.**
Conclusions: **To date, more studies have investigated the utility of the PHP test compared with the RSD test for detection of nvAMD. Both tests show promise but further evidence is needed to determine the real generalisability of the PHP test and the sensitivity of the RSD test.**

Key words: Age-related macular degeneration, Preferential hyperacuity perimeter, Radial shape discrimination, Shape discrimination hyperacuity

Introduction

Neovascular age-related macular degeneration (nvAMD) and geographic atrophy (GA) are responsible for the majority of cases of blindness and visual impairment in developed countries.[1,2] Currently, the number of people affected by nvAMD in the UK is expected to increase from an estimated 414 561 cases in 2010 to 515 509 in 2020.[3]

Landmark clinical trials have demonstrated that ranibizumab (Lucentis),[4,5] bevacizumab (Avastin)[6,7] and aflibercept (Eylea)[8] are effective treatments for nvAMD. These drugs are capable of preventing further vision loss in most patients, and improving vision in approximately one-third of patients. It is also known that prompt treatment leads to better visual outcomes.[9]

Patients who develop nvAMD often present with central vision distortions and scotomas, which can cause them problems recognising objects, faces and text. In the UK, a rapid-access referral pathway allows general practitioners and optometrists to refer patients directly to specialised units with facilities for the investigation and treatment of nvAMD.[10] Given the availability of treatment, and the existence of an established treatment pathway in the UK,[11] early detection of nvAMD is clearly desirable.

Over the last 70 years visual distortions caused by nvAMD have mainly been assessed using the Amsler grid (AG);[12] however, there is a concern about the real utility of this test.[13] Alternative tests for the detection of distortion and scotomas have been summarised in recent reviews,[13,14] and include M-charts, the Macular Mapping Test, the Scanning Laser Entoptic Perimeter, the Preferential Hyperacuity Perimeter and the Radial Shape Discrimination test.

The aim of this review is to discuss the latter two tests: the Preferential Hyperacuity Perimeter (PHP) and the Radial Shape Discrimination test (RSD). For this purpose, an initial literature search was performed in Web of Science with the following key words: radial shape discrimination, shape discrimination hyperacuity, preferential hyperacuity perimeter, and age-related macular degeneration. Reference lists of the papers and reviews found were used to broaden the search. The methodology was assessed using the QUADAS-2 quality assessment tool[15] and conference abstracts were only included if of high relevance and the full articles could not be obtained.

Why do distortion and scotomas occur in nvAMD?

In AMD pathological changes occur in the retinal pigment epithelium (RPE) and Bruch's membrane (BM) of the macular area. The RPE is a single layer of cells that protects and provides nutrition to the neurosensory

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retina and, in combination with BM, acts as a blood–retinal barrier. The dysfunction of RPE cells contributes to a series of pathological processes that lead to the clinical features seen in AMD:[16] accumulation of lipofuscin, formation of drusen, inflammation and formation of choroidal neovascular membranes.[16] As a result, the RPE can locally detach from the underlying Bruch's membrane[17] and/or fluid can accumulate underneath the RPE, underneath the retina and/or within the retina. The photoreceptors layer is consequently disturbed and deformed, affecting its function. Deformations in the photoreceptor layer are thought to explain the central vision distortions experienced by AMD patients. Photoreceptor degeneration can result in areas of visual field loss (scotomas), which can be relative or absolute, causing partial or complete loss of vision in that area of the visual field.

Why does the Amsler grid require a successor?

The Amsler grid (AG) is commonly used to detect the metamorphopsia or distortion caused by nvAMD. It consists of a black card with a 10×10 cm white square subdivided by vertical and horizontal parallel white lines every 5 mm.[12] It has a central dot for fixation and the edges of the grid subtend 10° when held at a distance of 28–30 cm.[12] Whilst the AG is a cheap and accepted method for monitoring patients at risk of developing nvAMD, a wide range of sensitivities for detecting nvAMD has been reported including good to excellent sensitivity[18–20] as well as sensitivity as poor as chance level.[21–23] A recent meta-analysis suggested a pooled sensitivity of 78% (95% CI 64–87%) for detection of nvAMD.[24] However, the authors pointed out that many of the included studies compared patients with established nvAMD with healthy controls or other groups of patients. Moreover, in some studies the gold standard fluorescein angiography (FA) was not used to diagnose nvAMD. The implication of these limitations is that the apparent high sensitivity may not be applicable to the usual clinical situation, in which the comparison is not between healthy eyes and eyes with established disease, but between eyes with many of the age-related features known to be related to the risk of developing nvAMD and those with early, often subtle signs of nvAMD.

Perhaps a more clinically relevant design is that of Do *et al.*,[23] who evaluated the ability of the supervised AG to detect new nvAMD. Patients were identified who were at increased risk of developing nvAMD in one eye, on the basis that they already had nvAMD in the first eye, and that their second eye had changes suggestive of the eventual development of nvAMD (e.g. large drusen, focal hyperpigmentation of the RPE near the centre of the macula). These patients were then followed longitudinally until either the end of the study or they converted to nvAMD in the study eye, which was confirmed by FA. In this study the sensitivity of the AG for detecting nvAMD was 50% (95% CI 19–81%).[23]

One advantage of the AG is its apparent simplicity; clearly patients are able to take it away from the clinic and use it at home. Home surveillance with the AG was assessed in a retrospective pilot study in a population attending a UK casualty eye clinic[25] where patients were prompted to attend their emergency department in the case of sudden loss of vision. Only 29 of 100 patients who developed nvAMD attended the department because they noticed changes while using the AG.[25]

Why might the AG be ineffective? After a retinal lesion a reorganisation of cortical topography can occur as a result of strengthening of the horizontal connections around the cortical area that corresponds to the damaged area of retina.[26] This might explain why, when looking at lines and gratings, large central scotomas are perceived as a reduction in contrast and an increase in blur rather than a gap.[27] This phenomenon is called perceptual fill-in, where the filling in of the scotoma maintains the orientation of the surrounding pattern, making the grating appear uniform and complete.[27] Perceptual fill-in might explain why some scotomas caused by nvAMD are not detected by means of the AG, contributing to the low sensitivity reported in some studies.

Another limitation of the AG is that the original version of the test does not allow quantification of the visual deficit, which makes it difficult to monitor the progression of the disease or identify new distortions. A three-dimensional computer version of the AG was developed, which assesses central visual fields at different contrast levels. It was reported that the computerised AG is able to quantify the number and volume of central visual field defects present in well-established nvAMD with a sensitivity and specificity of 89.7% and 85.3%, respectively.[28] As explained above, this is not the comparison made clinically.

Overall there remains a degree of uncertainty about the ability of the AG to detect the development of nvAMD. The advent of effective treatment for nvAMD requires early and effective detection of the disease in order to improve the visual outcome. Ideally, a test that might be used to monitor patients at high risk of developing nvAMD would be inexpensive, easy to understand and easily administered, preferably by patients themselves in an unsupervised environment. A suitably high level of sensitivity is also required for such a test. Recently, two new tests have been developed which seek to quantify the visual distortions that accompany the early stages of nvAMD.

General description of the tests

The Preferential Hyperacuity Perimeter test is based on the ability to detect a small spatial offset between targets (Vernier hyperacuity), while the Radial Shape Discrimination test is based on the ability to detect modulations on a circle (shape discrimination hyperacuity).[29] These two visual functions are considered hyperacuities because they can reach thresholds that are much smaller than those reached in a resolution acuity task (traditionally thought to be 1 arc min, or 0.00 logMAR). Hyperacuity tasks can reach down to 10 arc sec (approximately −0.78 on a logMAR scale) despite the fact that images formed on the retina are degraded by the optics of the eye.[30]

The Preferential Hyperacuity Perimeter (PHP) test

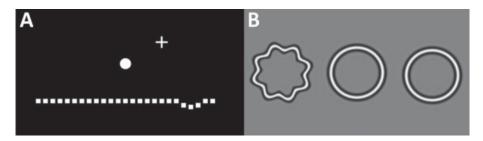The PHP test evaluates the central 14° of a patient's

Fig. 1. (*A*) Stimulus used in the PHP test: a line of dots with an artificial distortion, a central dot for fixation and a cross indicating the position of the mouse cursor. (*B*) Stimuli used in the RSD test: two circles and one RF pattern. The amplitude of the modulation is decreased or increased according to a staircase procedure.
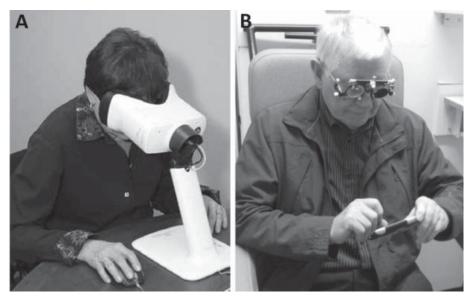

Fig. 2. (*A*) Patient using the Foresee Home PHP. The hood allows for a constant viewing distance, adequate levels of lighting and occlusion of the non-tested eye. (*B*) Patient using the handheld RSD test. The iPod is held at arm's length whilst the patient wears their usual reading correction.

visual field (macular field). The test stimulus consists of a line of dots where one of the dots is misaligned (an artificial distortion, Fig. 1A). The stimulus is presented on a display at different locations, horizontally and vertically, for a brief period of time. The participant, initially fixating on the central dot, has to indicate the location of the displaced dot on the line. If the stimulus falls on an area of retina that is elevated due to underlying pathology, it is assumed that this will create a more noticeable distortion (pathological distortion), which the patient will indicate.[21] As a result, a map of the pathological distortions is generated which can be compared with the patient's previous results or a normative database.

In the clinical versions of the device (Preview PHP by Carl Zeiss[19,23,31] and Foresee PHP by Notal Vision[21,32]) the visual stimulus is presented on a monitor viewed from a constant distance by means of a chinrest that stabilises the head. In order to facilitate unsupervised testing, a home version of the PHP (Foresee Home, Notal Vision, Fig. 2A)[33,34] was developed in which stimuli are presented on a small screen enclosed within a hood. The hood controls viewing distance, ambient light

and occlusion of the non-tested eye.[33] In both forms of the test the distortion is indicated by clicking a computer mouse[21,32–34] or by touching a touch-sensitive screen.[19,23,31]

The Radial Shape Discrimination (RSD) test

The RSD test, also called shape discrimination hyperacuity (SDH) test, uses radial frequency (RF) patterns as stimuli. A RF pattern consists of a circle with a specific number of distortions or bumps around it where the number of bumps is expressed as a frequency (Fig. 1B). For any given frequency, the amplitude of distortions can then be varied systematically. Retinal pathology, such as AMD, which disrupts the organisation of the photoreceptors, results in a reduced ability to detect the distortions on the circle leading to elevated thresholds in the test.[35]

In the laboratory version of the test, targets were displayed on a computer monitor (desktop version).[35] The stimuli were two RF patterns presented on the monitor either simultaneously or consecutively (spatial or temporal 2-alternative-forced-choice, AFC, tasks) at a

testing distance of 1 metre. The task was to identify and report which pattern was distorted. A handheld version of the test was subsequently developed[36] in which stimuli were presented on an Apple iPod Touch, a relatively inexpensive device with a sufficiently powerful operating system and graphics, and a touchscreen interface for the patient to indicate the distorted shape by simply touching it (Fig. 2B). In all versions of the test a psychophysical staircase procedure is used to determine the threshold for detecting distortion, which is reported as a logMAR value. The threshold obtained can be compared with an agreed cut-off value for the detection of disease or with the patient's previous test results.

Below is a discussion of the clinical evidence regarding the ability of each of these two tests to detect nvAMD. The studies included, where possible, were reviewed for the presence of bias and applicability of the results to the general population using the QUADAS-2 (quality assessment of studies of diagnostic accuracy) tool.[15]

Clinical evidence

The Preferential Hyperacuity Perimeter test

A multicentre clinical trial[21] ($n = 171$) reported that the Foresee PHP (Notal Vision) was able to detect early AMD (less than five small or intermediate drusen), intermediate AMD (more than five large drusen), geographic atrophy and nvAMD with sensitivities of 41%, 70%, 96% and 100%, respectively. The threshold sensitivity of the PHP test was set too low in this particular study to allow differentiation of different stages of AMD, leading to a high false positive rate (18%) and possibly resulting in an overestimation of the ability of the PHP to detect nvAMD. For instance, another study ($n = 65$) that assessed the ability of the Preview PHP (Carl Zeiss) to detect nvAMD found a slightly lower sensitivity of 90% (95% CI 83–97%).[19] These two studies, as with many of the studies that assessed the ability of the AG to detect distortions,[24] assessed well-established nvAMD rather than newly diagnosed disease. Both the Preview PHP (Carl Zeiss)[31] and the home-based Foresee Home PHP (Notal Vision)[33] were found to have good sensitivity for discriminating between patients with intermediate AMD (large drusen without GA at the centre of the macula) and newly diagnosed nvAMD, confirmed with FA. In these case-control studies, sensitivities were reported as 82% (95% CI 70–90%)[31] and 85% (±95% CI 12%),[33] respectively, and specificities were 88% (95%,CI 76–95%)[31] and 84% (±95% CI 11%).[33] Recent onset of nvAMD was presumed in the Preview PHP study (within 60 days) from patients' records and history.[31] It is possible, however, that significant progression had occurred over the 60-day period.[37] Similarly, it is not known how recent the diagnosis of nvAMD was in the Foresee PHP study.

These studies assessed the ability of the PHP test to detect well-established nvAMD or 'presumed' recent-onset nvAMD. A more realistic approach is to evaluate the usefulness of the test to detect the earliest signs of nvAMD before a diagnosis is made. For this Lai et al.[32] followed up two groups of patients without nvAMD, one

Table 1. Summary of the results found by Lai *et al.* (2011)[32] and Chew *et al.* (2014)[34]

	PHP monitored	Usual care
Lai *et al.* (2011)[32]		
VA in letters at conversion (mean, SD)	67.4 (12.9)	57.5 (10.6)
Change in VA in letters (mean, SD)	−11.9 (10.7)	−21.6 (9.0)
CS in letters at conversion (mean, SD)	29.1 (3.35)	22.6 (9.0)
Change in CS in letters (mean, SD)	−2.70 (2.9)	−9.89 (7.87)
Lesion area in mm² at conversion (mean, SD)	0.89 (1.1)	3.06 (3.2)
Chew *et al.* (2014)[34]		
VA in letters at conversion (mean, SD)	72.3 (13.8)	68.1 (16.1)
Change in VA in letters (mean, SD)	−7.4 (11.4)	−12.6 (16.5)
Proportion that maintained VA of 0.3 logMAR or better	87%	62%

These two longitudinal studies compared patients being monitored by the PHP with standard care alone. The visual outcome was established at conversion to nvAMD. Note that all results were inputted as mean (SD) to allow comparison between the two studies.

of which was monitored with the Foresee PHP. The group that was monitored with the PHP under clinical supervision had better visual acuity (VA; 9.7 letters, 95% CI 0.41–19.0, $p = 0.04$), better contrast sensitivity (CS; 7.2 letters, 95% CI 1.6–12.8, $p = 0.15$) and a smaller lesion area ($p = 0.023$) at conversion to nvAMD[32] (Table 1). It is not clear whether the diagnosis of nvAMD was made based on colour fundus photographs or clinical examination in this study. Colour fundus photographs could lead to under-detection of nvAMD and clinical examination was probably different in the two groups, as only the group monitored with PHP received OCT assessment, which could have aided the diagnosis of nvAMD. Despite an unclear reference standard, this study showed that monitoring of visual symptoms by means of the PHP test can lead to earlier detection and intervention.

With a similar design, a large, phase 3, longitudinal randomised controlled trial (RCT) compared two groups of participants at high risk of developing nvAMD.[34] One group received standard care together with the Foresee Home PHP for home monitoring and the other group received standard care alone.[34] A larger proportion of patients in the home-monitored group maintained vision of 0.3 logMAR or better at conversion to nvAMD (confirmed with a FA) compared with the standard-care group (87% vs 62%, $p = 0.014$).[34] The group monitored with the PHP lost fewer letters from baseline to conversion than the group that received standard care alone [median −4 (interquartile range, IQR −11 to −1) letters and −9 (IQR −14 to −4) letters, respectively, $p = 0.021$] (Table 1). In this RCT, the Foresee Home PHP combined with the presentation of symptoms triggered 72.5% of the visits where nvAMD was diagnosed. Fifty-one per cent of those cases were alerted by PHP alone and 21.6% of cases were alerted by patient symptoms.[34]

The sensitivities mentioned above are in agreement with those reported by Do et al.[23] where participants were followed up longitudinally ($n = 98$) and the presence or absence of nvAMD was confirmed with FA at every study visit (every 3 months). Sensitivity of the Preview PHP for detection of nvAMD for which
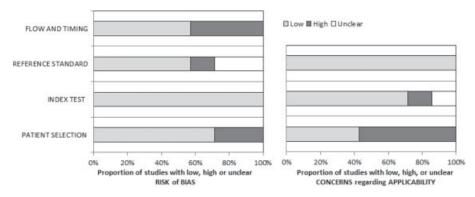
Fig. 3. QUADAS-2 results. Percentage of studies included in this review (*n* = 7) with low, high or unclear risk of internal bias (*left*) and/or concerns regarding the applicability of the results to the general population with AMD (*right*).

treatment was initiated was 70% (95% CI 35–93%) whereas the sensitivity for detection of nvAMD irrespective of treatment decision was 50% (95% CI 23–77%).[23]

The overall rate of false positives reported for all versions of the PHP test ranged from 12% to 20%.[19,21,31–33] When used for patient monitoring, a low false positive rate is desirable as it avoids unnecessary clinic visits and anxiety to the patient. Of the participants included in the Chew *et al.*[34] study, 21.1% experienced at least 1 false positive result with the PHP. Taking into account the length of the study this resulted in an acceptable rate of 0.24 false alerts per year.[34]

In the home version of the PHP (Foresee Home), the patient's task is to view the visual stimulus while manipulating a mouse that is out of their sight. For some elderly patients this can be problematic. In the study by Loewenstein *et al.*,[33] patients who did not pass a mouse tutorial were excluded. Despite this, 13% of the recruited participants had to be subsequently excluded due to unreliable results. In the prospective part of the study, where experience with a computer mouse was part of the inclusion criteria, 15% of the participants were excluded due to not passing the tutorial and another 8% had unreliable results. Similarly, Chew *et al.*[34] reported that 15% of patients screened could not do the PHP test due to pre-existing visual field defects in their study eyes. Of those who were randomised into the PHP arm, 8% could not establish a baseline measurement and 14% returned the device before the end of the study.[34] This suggests that the results of these studies might not be generalisable to the totality of the older population at risk of developing nvAMD.

The QUADAS-2 tool[15] was used to assess patient selection, adequate use of the index test, choice of reference standard and timing during conduction of the studies, where all participants receive the same reference standard and are included in the calculation of sensitivity. In many of the studies considered for this review, participants who could not operate the PHP device or produced unreliable results were either not recruited or excluded from the analysis, leading to a high risk of bias in patient selection, flow and timing, and a concern regarding the applicability of the results (Fig. 3).

To summarise, the PHP test has shown promise for the early detection of symptoms caused by nvAMD, and

when used by patients away from the clinic it seems to prompt earlier treatment promoting better visual outcomes. However, studies have excluded patients who could not perform the test or had unreliable results, potentially biasing the patient recruitment and affecting the general applicability of the test. Given that many of the studies reviewed were linked with the device manufacturer,[21,31,33,34] further evidence would be welcome.

The Radial Shape Discrimination test

Wang *et al.*[35] assessed the ability to detect radial shape deformation in eyes at high risk of developing nvAMD (i.e. eyes with large drusen, hyper- and hypopigmentation, extrafoveal geographic atrophy) in comparison with a normal-sighted control group. Results showed that eyes at high risk of nvAMD had an increased threshold for detecting radial shape deformation for both the spatial and temporal tasks performed on the desktop RSD test.[35] Similarly, thresholds obtained with the handheld RSD test, which used a spatial 3AFC task, were found to increase as severity of AMD increased.[36] These results demonstrated the potential of the test to detect functional visual loss in AMD.

Using the handheld RSD (hRSD) test, Wang *et al.*[38] compared a small group of eyes with nvAMD (*n* = 9) with a group of eyes at high risk of developing nvAMD (i.e. eyes with large drusen but no geographic atrophy, *n* = 24). In this study, where a 2-interval forced choice (2IFC) paradigm was used, the test had a sensitivity and specificity of 88.9% (95% CI 56.5–98.0%) and 79.2% (95% CI 59.5–90.8%) for detecting nvAMD.[38] While promising, the patient numbers in this case-control study were small, patients had well-established nvAMD rather than newly diagnosed nvAMD, and the diagnosis of nvAMD did not seem to be confirmed with the gold standard FA which means that some subtle cases of nvAMD could have been missed. The corresponding sensitivities for detecting nvAMD found for visual acuity, contrast sensitivity and the Amsler grid were 44.4% (95% CI 18.9–73.3%), 33.3% (95% CI 12.1–64.6%) and 66.7% (95% CI 35.4–87.9%),[38] respectively, which suggests a superiority of the hRSD test for detection of nvAMD despite the limitations of the study.

Given the portability and the apparent ease of use of

the hRSD test, in which the stimuli are presented on the screen of an Apple iPod Touch, the hRSD test has also been assessed as a mean of self-monitoring visual function by patients.[39] The test was embedded in a system (called the Health Management Tool) which sent daily audio and sound notifications to remind the patient to do the hRSD test. One hundred and sixty patients were provided with the test to use at home for a period of 16 weeks. It was reported that 85% of elderly patients with AMD complied with the self-testing protocol on a daily basis during the 16-week period, while 99% completed the test at least once a week.[39] This was, however, a relatively short period of time over which patients were monitored compared with the usual follow-up pattern in AMD patients, in which they might be monitored for many months or years. The compliance with the test over longer periods of time remains unknown. This study reported no test failures due to inability to perform the test. This could be because, as with other studies of this type, patient selection at recruitment was biased towards motivated participants who had an interest and/or knowledge of using handheld electronic devices.[39]

Usability is a key property of any test, particularly if it is to be used by older patients away from the clinic. The hRSD test is held at a comfortable arm's length. Moreover, in a spatial AFC task the stimuli are presented simultaneously and they stay on the screen until the participant decides which circle has the modulations and touches it. A flexible testing distance and unrestricted testing time facilitates unsupervised testing. In fact, results from questionnaires given to patients using the hRSD test showed that more than 90% of patients thought that the device and the test were easy to use.[36,39]

In summary, there is some evidence to suggest that the hRSD test has the potential to detect the presence of AMD, and that test performance is correlated with AMD severity. Currently the evidence base is weaker than for the PHP test, with only one small study assessing the hRSD test for detection of nvAMD. The QUADAS-2 tool was therefore not used. Similarly to the PHP test, the authors of the papers included in this review are also the designers of the hRSD test, highlighting the need for independent evaluation. Larger clinical studies are required to confirm the test sensitivity and specificity for detecting new nvAMD and to compare it with existing methods of detecting nvAMD. One clear limitation of this test is that only 3° of visual field is assessed. Future studies should establish whether the test is able to detect lesions located outside the centre of the fovea.[36] Provided that larger clinical studies confirm an adequate level of sensitivity and specificity, this test could have a role in AMD clinics, patient self-monitoring strategies and perhaps also in screening for nvAMD due to its affordability (available as an Apple App) and ease of use.

Conclusion

The emergence of new, effective treatments for nvAMD mean that identifying patients as early as possible is now more important than ever. On the one hand this puts more pressure on the health system to provide assessments, but it also provides an impetus for the development of alternative approaches, including those which might be used away from formal clinical settings or in patients' own homes. Detection and measurement of the visual distortions that accompany the development of nvAMD remains a promising approach. Historically, the Amsler grid has fulfilled this role despite its limitations, which include its variable sensitivity for the detection of nvAMD, its provision of an all-or-nothing result (not a measurement), and the uncertainty about its ability to detect scotomas due to the cortical fill-in phenomenon. Both the PHP and the hRSD tests reviewed have shown promise in terms of sensitivity for detecting nvAMD and for use in home monitoring. But clinical data, in real clinical populations, are still required for determining the ability of these tests, particularly the hRSD test, to identify the earliest signs of nvAMD. Given the age of the target population, the usability of these tests, particularly if they are to be used unsupervised over long periods of time, needs to be investigated thoroughly.

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