Clinical Ophthalmology

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REVIEW

Strategies for improving early detection and diagnosis of neovascular age-related macular degeneration

This article was published in the following Dove Press journal:
Clinical Ophthalmology
17 February 2015
Number of times this article has been viewed

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Abstract: Treatment of the neovascular form of age-related macular degeneration (AMD) has been revolutionized by the introduction of such agents as ranibizumab, bevacizumab, and aflibercept. As a result, the incidence of legal blindness occurring secondary to AMD has fallen dramatically in recent years in many countries. While these agents have undoubtedly been successful in reducing visual impairment and blindness, patients with neovascular AMD typically lose some vision over time, and often lose the ability to read, drive, or perform other important activities of daily living. Efforts are therefore under way to develop strategies that allow for earlier detection and treatment of this disease. In this review, we begin by providing an overview of the rationale for, and the benefits of, early detection and treatment of neovascular AMD. To achieve this, we begin by providing an overview of the pathophysiology and natural history of choroidal neovascularization, before reviewing the evidence from both clinical trials and "real-world" outcome studies. We continue by highlighting an area that is often overlooked: the importance of patient education and awareness for early AMD detection. We conclude the review by reviewing an array of both established and emerging technologies for early detection of choroidal neovascularization, ranging from Amsler chart testing, to hyperacuity testing, to advanced imaging techniques, such as optical coherence tomography.

Keywords: Amsler, detection, choroidal neovascularization, hyperacuity, optical coherence tomography

Introduction

The treatment of age-related macular degeneration (AMD) has been revolutionized by the introduction of successful pharmacotherapies, such as ranibizumab, bevacizumab, and aflibercept, for the neovascular form of the disease.[1] Data from a number of countries illustrate this point. In Denmark, the incidence of legal blindness from AMD has fallen by half between 2000 and 2010, with the bulk of the reduction occurring after the introduction of ranibizumab and bevacizumab.[2] In Israel, a similar reduction in legal blindness has been reported since the introduction of these therapies.[3] In Australia, it is estimated that monthly injections with ranibizumab for patients newly diagnosed with neovascular AMD would lead to a 72% reduction in incident blindness over a 2-year period.[4] Finally, in the US it is estimated that the use of monthly ranibizumab injections would reduce the number of cases of incident blindness from 16,268 to only 4,484 individuals over a 2-year follow-up.[5] While these drugs are undoubtedly successful in reducing visual impairment and blindness, patients with neovascular AMD typically lose some vision over time, and often lose the ability to read, drive, or perform other important activities of daily living.[6] Efforts are under way to develop new pharmacotherapies and other novel approaches to treatment.[7] However, developing

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submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OPTH.S59012

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strategies to allow for earlier detection and treatment of this disease may be equally if not more effective.

In this review, we begin by providing an overview of the rationale for and the benefits of early detection and treatment of neovascular AMD (no effective treatment yet exists for the nonneovascular form of the disease). To achieve this, we begin by providing an overview of the pathophysiology and natural history of choroidal neovascularization (CNV), before reviewing the evidence from both clinical trials and "real-world" outcome studies. We continue by highlighting an area that is often overlooked: the importance of patient education and awareness for early AMD detection. We conclude the review by reviewing an array of both established and emerging technologies for early detection of CNV, ranging from Amsler chart testing, to hyperacuity testing, to advanced imaging techniques, such as optical coherence tomography (OCT) (Table 1).

Benefits of early detection and treatment

Histopathology of choroidal neovascularization

In AMD, the development and progression of CNV is responsible for more than 80% of severe visual loss.[8] In this process, new blood vessels sprout from the choroidal circulation, penetrate the overlying Bruch's membrane, and grow within the subretinal pigment epithelium space (type 1 CNV) or the subretinal space (type 2 CNV), or a combination of both.[9] In some cases, intraretinal neovascularization may also occur, leading to formation of a retinal–choroidal anastomosis; such lesions are typically referred to as retinal angiomatous proliferation or type 3 neovascularization.[10]

Development of type 1 CNV is thought to begin at multiple sites, with the penetration of Bruch's membrane by new vessels from the choroid.[9] These vessel tufts expand laterally in a horizontal fashion, utilizing the natural cleavage plane between the retinal pigment epithelium (RPE) and Bruch's membrane. This growth pattern is thought to correspond to the appearance of "occult" leakage on fundus fluorescein angiography (FA; the neovascular membrane is covered by the RPE, so its leakage is typically only seen in the late frames of the angiogram).[11,12] Patients are often relatively asymptomatic, presumably because the overlying neurosensory retina is largely intact.

In type 2 CNV, penetration of Bruch's membrane – and the RPE – occurs at a single or few ingrowth sites, with subsequent neovascular proliferation in the subretinal space.[9] As this process occurs above the RPE, the outer blood–retinal barrier does not protect the retina, and leakage from new vessels results in relatively acute visual symptoms. On angiography, this growth pattern is easily seen as a "classic" pattern of fluorescein leakage (as it lies predominantly above

Table 1 Techniques and diagnostic tools for the early detection and diagnosis of neovascular age-related macular degeneration

Test	Description	Comments
Amsler chart (classical)	Evaluates the 20° of visual field centered on fixation.[31] The complete set of Amsler charts consists of seven plates, each consisting of a 10 cm square with a central spot for fixation. Each chart is held at approximately 30 cm, and the patient is asked to fixate on the central dot, reporting any distortion, blurred areas, or blank spots anywhere on the grid.	Although widely used with patients with AMD since at least the 1960s, sensitivity and specificity for the detection of AMD is low.[31] This poor performance is related to such factors as cortical completion ("filling in") and crowding phenomena, as well as poor patient compliance.
Amsler chart (automated, threshold)	Standard Amsler chart testing is a suprathreshold stimulus, and thus relative scotomas may go undetected. In "threshold" Amsler chart testing, the subject is asked to view a white-on-black version of the chart through cross-polarizing filters.[42] An automated, computerized version of the threshold Amsler test has also been developed; patients are instructed to map any observed distortion of scotomas using a standard Amsler grid displayed on a touch-screen computer display at different contrast levels. A three-dimensional depiction of the visual field defect is then produced.[44]	High reproducibility for detection of central visual field defects on repeat testing in patients with AMD.[45] Quantitative analyses may also allow differentiation between neovascular and nonneovascular forms of AMD.[50]

(*Continued*)

Table 1 (*Continued*)

Test	Description	Comments
Preferential hyperacuity perimetry (PHP)	The patient is presented with a pattern of dotted lines projected for 160 ms to the central 14° of their visual field. Any geometric shift in retinal morphology occurring in the stimulated area will lead to a hyperacuity defect, and thus the perception of distortion.[37] Each dotted line also contains an artificial distortion of varying magnitude. This serves as a competitive stimulus to any pathologic distortion, if present. The point at which a test subject becomes aware of a pathologic distortion over an artificial distortion provides a measure of its magnitude.	Initial studies demonstrated that PHP can detect recent-onset choroidal neovascularization with high sensitivity (82%), and can differentiate these patients from those with intermediate AMD only with high specificity (88%).[54] The ForeseeHome device was evaluated in the HOME study, a Phase III randomized clinical trial. This study provided the first definitive evidence of efficacy for a device allowing early detection and treatment of patients with neovascular AMD.[57]
Shape-discrimination hyperacuity (SDH)	An alternative form of hyperacuity measurement involves discrimination of shapes (eg, a perfect circle compared to one that has a distorted contour).[60] Successful completion of such tests requires global shape-detection mechanisms, something that is impaired in patients with AMD but not in age-matched controls.[61]	A handheld SDH test (MyVisionTrack) has recently been implemented for use with smartphones.[63] Health Management Tool, a remote monitoring system that utilizes the MyVisionTrack app, has recently been tested in a pilot clinical trial, but the results are not yet publicly available.
Macular mapping test (MMT)	The MMT is a software program used in conjunction with a desktop computer.[66] Letters are briefly displayed in the central visual field (8° radius) on the computer display. A constant background pattern in a wagon-wheel shape aids the test subject in maintaining fixation on the center of the display area.	Designed primarily for quick assessment of residual vision in patients with maculopathies. Considerable test–retest variability may be a limitation.[67]
Entoptic perimetry	When patients with an acquired scotoma stare at images of random visual noise (eg, video static), they often perceive an inhomogeneous region corresponding to their scotoma.[68] Once the scotoma is perceived in this manner, it is often possible to map it, a procedure referred to as entoptic perimetry.	Although not very effective in eliciting scotomas from postchiasmal lesions or from the physiological blind spot, variations of this technique have been successfully used to screen for visual field defects caused by prechiasmal ocular diseases, including AMD.[70]
Optical coherence tomography (OCT)	OCT is an imaging modality that provides cross-sectional imaging of the retina in a noninvasive manner.[71] Due to its extremely high resolution, OCT may allow early detection of neovascular AMD disease features (eg, subretinal fluid) before patients become symptomatic.[73]	Initial studies with time-domain technology suggest that OCT has a greater specificity than PHP or Amsler chart testing for the detection of new-onset neovascular AMD. However, using this older technology, OCT was found to be less sensitive than conventional fundus fluorescein angiography.[74] Newer "swept source" laser-light sources may allow OCT systems to become handheld and portable. Binocular OCT designs may allow comprehensive eye examination to be performed by patients themselves without the need for skilled personnel to acquire images.[72] Commercially available OCT devices are now capable of performing retinal and choroidal angiography in a noninvasive manner.[72]

Abbreviation: AMD, age-related macular degeneration.

the RPE, the fine vessels of the neovascular membrane may be clearly seen in the early angiographic phases).[12]

In both type 1 and type 2 CNV, the growing neovascular membrane is initially capillary-like.[9] These fenestrated and friable vessels leak serous fluid, lipid, and blood into the retina and surrounding potential spaces. Vascular invasion is also accompanied by infiltration of macrophages and other inflammatory cells, which produce matrix metalloproteinases, and thus allow the growing membrane to digest through tissue planes.[13] Macrophages also produce a range of other mediators, including proinflammatory and proangiogenic factors. At some point, the balance of growth

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factors and inflammatory mediators shifts toward an anti-angiogenic, antiproteolytic, and antimigratory state, and so the invading vessels becoming arterial or venular, and the CNV lesion as a whole becoming fibrosed.[9] This process is known as disciform scar formation, and is associated with irreversible visual loss.

Natural history of choroidal neovascularization

Prior to the introduction of effective therapies for neovascular AMD (eg, anti-VEGF agents), randomized clinical trials for this condition typically included control arms where no treatment was given. The results from these studies therefore provide a unique opportunity to investigate the natural history of CNV growth (typically measured as area and diameter of the CNV lesion on FA imaging) and its effects on visual acuity in patients with AMD.

In 2008, Wong et al performed a systematic review and meta-analysis of patients with neovascular AMD enrolled in untreated control arms of clinical trials between 1980 and 2005.[14] Their work demonstrated a consistent, steady deterioration in vision in untreated patients over the first few years following CNV onset. On average, these patients experienced one line of visual acuity loss at 3 months, 2.7 lines at 12 months, and four lines lost by 24 months. By 3 years, 41.9% of eyes had experienced severe visual loss (more than six lines lost), and 75% of patients had a visual acuity of 20/200 or worse at this time point (ie, legal blindness). Of note, their review also demonstrated the development of CNV in the fellow eye in 12.2% of patients by 12 months, and in 26.8% of patients by 4 years. Another Medicare-based US study reported cumulative rates of progression to neovascular AMD were 2.6% in year 1, which increased to 20.4% over a 10-year period.[15] Of additional note, patients with retinal angiomatous proliferation lesions have a very high risk of second-eye involvement (36% within 3 years).[16]

In 2013, Liu et al conducted a retrospective meta-analysis of data from five seminal AMD clinical trials (the TAP and VIP trials of photodynamic therapy [PDT], the VISION trial of pegaptanib, and the MARINA and PIER trials evaluating ranibizumab).[17] They used untreated, control-eye data from these trials to report progression of CNV lesion size, and thus to estimate the growth rate of untreated lesions. Their results suggest that the main determinant of lesion-size progression is the duration of neovascular disease, with smaller lesions enlarging more rapidly than larger lesions. They estimate that for smaller lesions, the edge of the neovascular membrane advances at 26.0 μm per day. As a result, their data predict that by 8 days after initial formation, CNV lesions can transform from being undetectable to having a diameter of 416 μm. For longstanding lesions, they predict that the CNV edge will advance more slowly, at 7.3 μm per day. Perhaps most interestingly, from analysis of initial CNV lesion size, they estimate that even the earliest enrolled patients in these studies had had their CNV for 7.7 months prior to entry in the clinical trial.

Clinical trial outcomes

With the introduction of effective pharmacotherapies for neovascular AMD, subgroup analyses from clinical trials have provided further evidence for the benefits of early treatment.

In the TAP and VIP studies of PDT with verteporfin, the greatest benefit was seen in patients with smaller lesions at baseline (fewer than four Macular Photocoagulation Study [MPS] disk areas; each MPS disk area 2.5 mm^2).[18] For all verteporfin-treated lesions, irrespective of angiographic subtype, the amount of visual acuity loss appeared to be related to lesion size. For example, in "occult with no classic" lesions, the mean visual acuity loss for the smallest lesions was nearly four times less than for the largest lesions, while for lesions with "predominantly classic" or "minimally classic" composition, the mean visual acuity loss was nearly half that in the largest lesions.

In the MARINA study evaluating the use of ranibizumab in the treatment of minimally classic and occult CNV lesions, subgroup analysis demonstrated that larger lesion size at baseline was associated with a greater loss of letters in the sham-treatment group and less gain of letters in the two ranibizumab-treatment arms.[19] Similarly, in the ANCHOR study evaluating the use of ranibizumab for the treatment of predominantly classic CNV, smaller baseline CNV lesion size was associated with greater gain of letters in those receiving ranibizumab and less loss of letters in those receiving PDT.[20]

Finally, in the CATT study comparing the use of ranibizumab with bevacizumab, the mean baseline visual acuity score was 61 letters (Snellen equivalent 20/63), and the median total area of CNV lesion was 4.3 mm^2 (range 0.05–56.9 mm^2). A larger area of CNV at baseline was associated with worse visual acuity at 1 year, less gain in visual acuity at 1 year, and a lower proportion gaining three or more lines.[21]

Real-world outcomes

The outcomes of treatment for neovascular AMD in the real world may not always reflect those obtained in the context

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of randomized clinical trials. Traditionally, retrospective audits have been used to address this issue, although these typically involve retrospective collection of incomplete data from small numbers of patients in single centers, with considerable risk of publication bias in the event of low success rates. The increasing use of electronic medical records (EMRs) with mandatory core data sets is beginning to address this issue. Such systems allow data with a predefined structure to be collected as a by-product of routine clinical care, and allow sample sizes similar to those seen in the general population. As such, the use of EMRs has greatly improved assessment of real-world outcomes, and further emphasized the benefits of early detection and treatment of patients with neovascular AMD. Use of EMRs also allows the inclusion of second-treated eyes of patients: something that is specifically excluded from most clinical trials, and likely to be of great significance for patients, as visual outcomes in a better-seeing eye are likely to have the greatest impact on quality of life.

The UK Neovascular AMD Database Study evaluated real-world outcomes in second-treated eyes receiving anti-VEGF therapy.[22,23] Regular follow-up of patients after initiating treatment in the first eye gives an opportunity to screen a high-risk population of fellow eyes using visual acuity measurements, OCT scanning, and fundus examination. The results of this study provide strong evidence that such screening leads to early detection of fellow-eye disease. Specifically, the mean baseline visual acuity of second-treated eyes was considerably better than that in first-treated eyes, suggesting earlier detection. The results from this study also suggest that earlier treatment leads to better outcomes, with better maintenance of vision in the second-treated eye over several years of follow-up.

Delays in presentation and treatment

Once CNV formation occurs, the evidence from clinical trials is clear: smaller lesions tend to respond better to treatment. A number of small studies have attempted to directly assess the effects of treatment delay, either from delays in patient presentation or from delays between diagnosis and the initiation of treatment.

In 2005, Oliver-Fernandez et al, working in the Canadian health care system, found a median time between initial diagnosis and treatment of 28 days resulted in a degree of visual loss in 44% of subjects.[24] In this pilot study of 38 consecutive patients newly diagnosed with neovascular AMD, 15% of subjects lost three or more lines of distance visual acuity, and the mean loss of visual acuity in the affected eye was 0.24 logarithm of the minimum angle of resolution units. Of note however, this study was performed prior to the introduction of ranibizumab or bevacizumab for treatment of this condition.

The effect of symptom duration has also been assessed. In 2012, Rauch et al performed a retrospective evaluation of patients receiving ranibizumab for neovascular AMD.[25] They divided a cohort of 45 subjects into three groups depending on their duration of visual symptoms: <1 month, 1–6 months, and >6 months. They found a mean time between initial symptoms and treatment of 59±62 days, and that shorter disease duration, as estimated by the prevalence of symptoms, was correlated with a better visual outcome after treatment. Similarly, in 2014 Canan et al retrospectively reviewed 104 eyes from patients undergoing intravitreal ranibizumab therapy for neovascular AMD. Again, they divided their patient cohort into groups according to their symptom duration (<1 month and 1–3 months), and demonstrated better visual outcomes in patients with shorter duration of symptoms.[26]

Patient education and awareness

Increasing awareness and knowledge of AMD in the general population may be an important first step toward aiding early detection and treatment. In the US, Australia, and Canada, between 20% and 30% of respondents to a recent survey indicated that they were "very familiar" or "somewhat familiar" with AMD.[27,28] However, much lower levels of awareness have been reported in Asian regions, such as Japan and Hong Kong,[29] and survey data are not available for many countries. With better education and awareness, older people may be more likely to have their eyesight tested regularly or participate in screening programs for ocular disease. Better disease understanding may allow at-risk populations to modify their lifestyles to reduce the impact of such factors as smoking or diet, or to pursue more frequent monitoring for the disease. In fact, the Scientific Advisory Panel of the AMD Alliance International recommends that people 55 years of age or older should have regular dilated fundus examinations performed by a qualified eye health professional every 2 years as part of an overall health package for vision. Elderly populations also need to be aware of the symptoms of AMD, so that prompt eye care can be sought should they occur.

In many countries, efforts to promote education and public awareness of AMD in the general population are under way. In particular, medical charity groups (eg, the Macular Society in the UK) provide patient support and self-help groups, as well as arranging public forums for education of the general public. Eye hospitals and clinics

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also have a role to play, particularly when they serve large populations or regions of a country. For example, in the UK, Moorfields Eye Hospital in London organizes regular patient information and support days for specific diseases, such as AMD. The AMD Awareness Week, held in conjunction with the global initiative by AMD Alliance International, seeks to generate awareness and understanding of the disease, in addition to promoting the importance of education, early detection, and knowledge of treatment and rehabilitation options.

Health campaigns have been shown to be useful in improving the utilization of eye care services. The benefits of such campaigns extend beyond AMD in isolation: eye-screening examinations present an opportunity not only to detect AMD but also other prevalent age-related eye diseases, such as cataract, glaucoma, and diabetic retinopathy. In Australia, the Vision Initiative was a public health campaign that promoted early detection of the main causes of vision loss through regular eye examinations.[30] In this initiative, target groups included those over the age of 50 years with diabetes, those who had noted changes in their vision, or those with a family history of glaucoma or AMD. This campaign was carried out in 2005, and involved a range of promotions through metropolitan and regional television, radio, and newspapers. Following the campaign, an improvement in the utilization of eye care services was noted, particularly by subjects with diabetes mellitus.

Amsler chart monitoring

Basic principles and technique

Since the 1960s, it has been widely recommended that patients at risk of CNV formation should be given an Amsler chart to detect early changes in their visual function and hence facilitate early detection and treatment.[31] Amsler charts (or "grids") were first described in 1947 by Marc Amsler, a Swiss ophthalmologist, and likely inspired by the small cards with grid patterns used by Landholt to place in the center of his perimeter when testing the macula.[32,33]

Amsler charts evaluate the 20° of the visual field centered on fixation (ie, they subtend an angle of 20° when viewed from the recommended distance of 30 cm).[31] The complete set of Amsler charts consists of seven plates, each consisting of a 10 cm square with a central spot for fixation. Chart 1 comprises a high-contrast white grid on a black background. The outer grid encloses 400 smaller 5 mm squares. When the central spot is viewed at a distance of about 30 cm, each small square subtends an angle of 1°. Chart 2 is similar to chart 1, but has diagonal lines that aid fixation on the central spot in patients with a central scotoma. Chart 3 is similar to chart 1, but has red squares instead of white. This red-on-black design aims to stimulate long-wavelength cones in the fovea, and thereby aid detection of red desaturation in toxic maculopathies, optic neuropathies, and chiasmal lesions. Chart 4 is a version with dots instead of lines, formulated to aid differentiation between scotomas and metamorphopsia. Chart 5 consists of horizontal lines only, and is particularly aimed at assessment of metamorphopsia in patients with reading difficulties. Chart 6 is similar to chart 5, but has a white background and has more closely spaced central lines, enabling more detailed evaluation. Chart 7 includes a fine central grid, with each square subtending an angle of 0.5°, theoretically allowing for greater sensitivity.

Amsler chart testing is performed with near-vision correction, if required, and with one eye covered.[31] The chart is held at approximately 30 cm, and the patient is asked to fixate on the central dot, reporting any distortion, blurred areas, or blank spots anywhere on the grid. Patients with macular disease often report that portions of the lines are "wavy", while those with optic neuropathies often note the absence of lines. The subject is also asked if all four corners and all four sides of the square are visible. Finally, the subject may be asked to trace out any detected positive or negative scotomas on a paper version of the chart. Patients are typically advised to perform this testing at least once per week, and preferably more frequently.

While the classic version of the Amsler chart consists of white lines on a black background, a black-on-white version of the chart is used far more frequently by patients.[31] This distinction is likely to have arisen due to a greater ease of printing or photocopying, and such charts are widely available through macular disease charities and pharmaceutical companies. Despite this, however, a recent comparison of these two formats found that distortion and scotomas were less obvious on the modified version of the chart that is in widespread use.[34]

An alternative and perhaps more pragmatic approach is so-called Environmental Amsler testing. In this method, patients are advised to perform vigilant observation of objects in their familiar environment – including edges of door frames, bathroom tiles, television screens, photo frames, etc – for distortion, and then to seek medical attention as appropriate. Using this approach, patients receiving anti-VEGF therapy for neovascular AMD have recently been shown to be capable of predicting disease reactivation, and thus the need for retreatment.[35]

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Evidence of diagnostic accuracy and/or screening benefit

Relatively limited evidence exists to judge the effectiveness of Amsler charts as a diagnostic test, and the evidence that does exist suggests that their diagnostic accuracy is limited.

In 1993, Schuchard performed Amsler chart testing using the TA-300 system (Stereo Optical, USA), and compared it to a reference standard of fundus perimetry (the latter allowed precise determination of the existence, size, and retinal location of macular scotomas).[36] Fifty-five patients with vision loss in the macular region and ten healthy volunteers without visual loss were evaluated, with testing performed under both standard and "threshold" lighting conditions (see later for a description of threshold testing). In this study, nearly half of all scotomas were not detected using the Amsler chart. For scotomas of 6° or less in diameter (ie, fewer than six small squares on the Amsler chart), 77% of standard and 87% of threshold scotomas were not detected. Also of note, in the eyes with central scotomas involving the fovea, 66% used an eccentric preferred retinal locus for fixating the center of the grid. Therefore, Schuchard argued that Amsler testing has "poor validity" and "cannot be accurately interpreted for use in clinical diagnosis of retinal defects". In a subsequent study in 2003, Lowenstein et al calculated a sensitivity of Amsler chart testing of only 9% for patients with AMD with "high-risk characteristics" for CNV formation, 7% for AMD patients with geographic atrophy (GA), and 34% for AMD patients with CNV.[37] In addition to this high rate of false negatives, they found that Amsler testing was 1 (defined as "any perception of distortion, scotoma, or blurring . . . on the Amsler grid") in 2% of the healthy controls included in their study.

The use of Amsler charts for screening of patients with AMD has not been comprehensively assessed. In 1986, Fine et al performed a survey of presenting symptoms in 103 patients with recent vision loss from neovascular AMD.[38] Of 49 patients in the cohort who said that they were performing Amsler chart testing on a regular basis, only five indicated that the Amsler chart abnormality was their first visual symptom. In 2004, Zaidi et al assessed whether the use of Amsler charts led to increased detection of CNV lesions amenable to focal laser photocoagulation (ie, of potentially earlier onset).[39] They found no difference in suitability for laser therapy in patients who presented with symptoms on Amsler versus those who presented in another manner.

Reasons for poor performance

Numerous reasons exist for the potentially poor performance of the Amsler chart. As demonstrated by Schuchard, patients with macular disease are unlikely to notice a macular visual field defect until it reaches a certain size.[36] This finding may be explained by cortical completion ("filling in"), a well-established phenomenon whereby visual features are perceived in the absence of neural input on the basis of surrounding features.[31] This is most commonly demonstrated over the physiological blind spot, where even under monocular conditions, no scotoma is visible in the visual field. Filling in has also been well demonstrated to occur across pathological scotomas, and even in healthy subjects with simulated scotomas. Other reasons for poor performance may include an inability to maintain appropriate fixation while testing the peripheral visual field (eg, in patients with central scotoma), and the crowding effect caused by the presentation of multiple, peripheral grid lines. Finally, the Amsler chart is noninteractive, potentially leading to poor compliance for long-term monitoring in a home setting and the inability to assess examination quality or reliability.

Modified Amsler chart testing

In the 1980s, Yannuzzi suggested the introduction of a credit card-size Amsler chart for increased convenience of testing, although this chart was slightly less sensitive than the conventional Amsler grid.[40] Amsler charts have also been developed consisting of blue grids on a yellow background, with the idea that most retinal and macular lesions cause blue–yellow defects, whereas optic nerve, chiasmal, and postchiasmal disorders tend to cause red–green defects.[41]

Standard Amsler chart testing is a suprathreshold stimulus, and thus relative scotomas may go undetected. In "threshold" Amsler chart testing, the subject is asked to view a white-on-black version of the chart through cross-polarizing filters.[42] This allows variation in the perceived luminance of the chart, and patients viewing the grid through these filters often notice shallow scotomas not detected during standard testing. This effect was initially reported in patients with diabetic retinopathy: in 26 patients, 22 had scotomas detected with the threshold Amsler chart, yet only four were detected using the conventional Amsler chart.[43] Of note however, this study did not employ any form of fundus perimetry as a reference standard, so it is unknown whether these patients actually had scotomas. Moreover, Schuchard noted a less impressive performance when testing was performed under more stringent conditions.[36]

An automated, computerized version of the threshold Amsler test has also been developed.[44] In this system, patients are instructed to map any observed distortion of scotomas using a standard Amsler grid displayed on a touch-screen

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computer display. The subject uses their finger to outline the margins of the defect on the touch screen at each of five contrast levels (100%, 80%, 60%, 40%, and 20%). The results are then analyzed to produce a three-dimensional depiction of visual field defects that can be analyzed in terms of slope, location, shape, and depth. This form of testing has been employed in patients with AMD, diabetic macular edema, glaucoma, and toxic optic neuropathy, with a high reproducibility for detection of central visual field defects on repeat testing.[45–48] In patients with AMD, these central defects have been shown to correspond to anatomical findings on FA imaging, and quantitative analyses have been shown to distinguish between the neovascular and nonneovascular forms of AMD.[49,50]

Smartphone visual acuity and Amsler chart testing

Visual acuity and Amsler chart testing are now possible using smartphone technology. An example of this is the Mobile Vision Assessment System (DigiSight Technologies, USA), which provides tools to support standardized and frequent vision testing. The system integrates a vision-assessment application named SightBook running on a mobile device (eg, iPhone, Apple, USA) with an Internet-based vision care network and website. Tests provided include Snellen visual acuity, Amsler chart testing, contrast sensitivity, color discrimination, and low-luminance acuity/contrast. The associated DigiSight Network is a web service that enables the results of these tests to be instantly and securely uploaded for assessment by the user's designated ophthalmologist (in cases of acute, significant reductions in visual function, the ophthalmologist may be alerted urgently and automatically).

Preferential hyperacuity perimetry

Basic principles

When a straight dotted line is presented to a healthy retina, a collinear set of retinal receptive fields is stimulated, and the information is processed in the visual cortex, leading to the perception of a straight dotted line. When changes in retinal morphology occur (eg, with RPE elevation, as occurs in AMD), a different set of photoreceptors may be stimulated, leading to perception of sections of the dotted line at a different location in space. The perceived shift in object location is the anatomic correlate for the symptom of metamorphopsia. This symptom can be assessed and recorded using preferential hyperacuity perimetry (PHP).[37]

Hyperacuity is the human ability to perceive minute differences in the relative spatial localization of two objects in space (ie, minute misalignments between the borders of objects; also termed "Vernier acuity").[51] Hyperacuity transcends by far the size limits detectable using standard visual acuity testing, with thresholds as low as 3–6 seconds of arc. Perhaps more importantly, hyperacuity thresholds do not seem to vary with increasing age, and are highly resistant to retinal image degradation as a result of ocular media opacity.[52,53]

In PHP, the patient is presented with a pattern of dotted lines projected for 160 ms to the central 14° of their visual field.[37] Any geometric shift in retinal morphology, occurring in the stimulated area, will lead to a hyperacuity defect and thus the perception of distortion. PHP devices use the phenomenon of "attention competition" to further provide for quantification of the magnitude of pathologic distortion. Each dotted line presented by the system contains an artificial distortion of varying magnitude. This serves as a competitive stimulus to any pathologic distortion, if present. In general, the brain ignores smaller distortion when an area of larger distortion is present. Therefore, the point at which a test subject becomes aware of a pathologic distortion over an artificial distortion provides a measure of its magnitude. Based on multiple responses from the subject, a visual field map can then be constructed, analyzed, and compared to normative data, and the likelihood of CNV determined. The basic principles and methods used for this test are best understood by undergoing it: this can be done online at www.foreseehome.com.

Detection of age-related macular degeneration – early studies

The results of the earliest clinical study involving PHP were reported in 2003.[37] This study utilized a standard desktop computer with mouse and keyboard and software termed Macular Computerized Psychophysical Test. This testing was compared to Amsler chart testing under supervised conditions in a doctor's office. The results of this study suggested that PHP was more sensitive than the Amsler chart for each category of AMD: those with CNV, those with GA, and those with "high-risk characteristics" for CNV development. The results of this pilot study were confirmed in a subsequent multicenter international study, published in 2005.[54] A significant rate of false positives was detected from healthy control subjects, however, leading to refinements in the underlying algorithm for subsequent studies.

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PHP was further developed to differentiate between patients at high risk for developing CNV (ie, those with intermediate AMD) and patients with recent-onset CNV, to evaluate the potential role for PHP in monitoring for CNV development.[55] This study, involving multiple centers in the US, Europe, and Asia, demonstrated that PHP can detect recent-onset CNV with high sensitivity (82%), and can differentiate these patients from those with intermediate AMD only with high specificity (88%). In the same study, the diagnostic accuracy of color stereophotography was also evaluated (simulating clinical biomicroscopy), and found to be considerably less impressive than that of PHP. The device used in this study received US Food and Drug Administration (FDA) approval, and was originally marketed by Carl Zeiss Meditec as the Preview PHP, before becoming available from Notal Vision (Israel) as the Foresee PHP.

AREDS2 and the HOME study

Notal Vision subsequently developed a PHP device for use by patients within their own homes: the ForeseeHome device. This device was then evaluated in a Phase III, unmasked, randomized clinical trial: the HOME (Home Monitoring of the Eye) study.[56] The results of this seminal study provided the first definitive evidence of efficacy for a device allowing early detection and treatment of patients with neovascular AMD.[57] The study compared the use of the ForeseeHome device plus standard care, compared with standard care alone, for eyes at high risk of progression to CNV, with visual acuity at the time of CNV detection taken as an indicator of early detection. The study was conducted in 44 clinical sites of AREDS2 (Age-Related Eye Disease Study 2), a clinical trial of nutritional supplements for the treatment of AMD. Study participants were at risk for developing CNV, with either bilateral large drusen or large drusen in one eye with advanced AMD in the fellow eye. Best-corrected visual acuity of 20/60 or better was required in the study eye(s).

A total of 1,520 participants with a mean age of 72.5 years were enrolled.[56,57] Those subjects randomized to the standard care-only arm received instructions that were investigator-specific for self-monitoring of vision at home to detect progression of AMD (aids such as Amsler charts could be recommended). When participants experienced symptoms, they were instructed to call their clinical center immediately to schedule an appointment within 72 hours. In the other arm of the study, subjects received the home monitoring device, with instructions for installation and use, as well as standard care instructions. Participants were encouraged to use the device on a daily basis, and results were transmitted automatically via cellular modem to a central data-monitoring center. When the device testing suggested a change compared with the baseline measurements, an alert was sent from the monitoring center to the participant's clinical center, prompting the staff to schedule a visit with the study ophthalmologist within 72 hours. The main outcome measure was the difference in best-corrected visual acuity scores between baseline and detection of CNV. Detection of CNV was determined by investigators based on clinical examination, color fundus photography, FA, and OCT findings.

A total of 763 participants were randomized to device monitoring, and 757 participants were randomized to standard care.[56,57] Patients were followed up for a mean of 1.4 years between July 2010 and April 2013. At the prespecified interim analysis, 82 participants progressed to CNV: 51 in the device arm and 31 in the standard care arm. The primary analysis achieved statistical significance, with the participants in the device arm demonstrating a smaller decline in visual acuity with fewer letters lost from baseline to CNV detection (median −4 letters, interquartile range −11.0 to −1.0 letters) compared with standard care (median −9 letters; interquartile range −14.0 to −4.0 letters) (P=0.021), resulting in better visual acuity at CNV detection in the device arm. With these convincing results, early termination of the study was recommended.

Use of preferential hyperacuity perimetry in retreatment regimens

PHP has also been suggested as a tool for monitoring the therapeutic response to PDT and anti-VEGF treatment in neovascular AMD. In a pilot study in 2011, Querques et al investigated the ability of Foresee PHP (ie, not the ForeseeHome) in assessing responsiveness to ranibizumab therapy.[58] They examined 14 consecutive patients with newly diagnosed CNV secondary to AMD. These patients underwent PHP metamorphopsia testing before and shortly after treatment with ranibizumab. The mean PHP metamorphopsia test score improved significantly from 20.4635 at baseline to 9.2623 after a single ranibizumab injection ($P<0.05$). This improvement in metamorphopsia test scores correlated well with improvement in OCT parameters. In a follow-up study, the same authors investigated whether PHP metamorphopsia scores predicted the need for reinjection in patients receiving ranibizumab for neovascular AMD.[59] They evaluated 17 consecutive patients with newly diagnosed neovascular AMD being treated with ranibizumab over a 6-month period. At the third and sixth months, reevaluation for additional injections was done. PHP testing predicted the need for reinjection at each of these time points with an accuracy of 75% (sensitivity

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83%±12%, specificity 67%±15%). From these results, the authors suggested that home testing with a PHP device (eg, ForeseeHome) might be effective to detect disease recurrences and thus guide optimal timing of retreatment decisions, with the potential for fewer unnecessary monitoring visits. This hypothesis has recently been investigated in a randomized clinical trial (https://clinicaltrials.gov/ct2/show/NCT01336907).

Shape-discrimination hyperacuity

Basic principles

An alternative form of hyperacuity measurement involves the discrimination of shapes. Using radial frequency (RF) patterns (perfect and distorted circular contours), Wilkinson et al demonstrated a very high sensitivity (ie, <10 seconds of arc) to sinusoidal deformation from circularity in test subjects.[60] This detection threshold was not affected by contrast reduction (contrast >10%) at low RFs, and showed little change with normal aging. It has been suggested that to achieve optimal performance, a global shape-detecting mechanism is involved, and therefore such a test may be particularly suitable for patients with AMD (a limitation of conventional visual acuity testing is that patients with macular disease can use a very small healthy foveolar area to achieve near-normal performance on visual acuity tests or on other types of testing that require only local processing).

In 2002, Wang et al confirmed that patients with AMD had significant deficits in performing global shape-discrimination tasks, both spatially and temporally.[61] In each case, two RF patterns were presented, and test subjects were required to identify the deformed pattern. With spatial testing, 91% of eyes with AMD showed significant elevation of the threshold for detecting radial deformation of RF patterns when compared with normal controls. With temporal testing, 97% of eyes with AMD showed significant threshold elevations. These shape-discrimination hyperacuity (SDH) deficits were present even though the subjects had good visual acuity (≥20/32) and contrast sensitivity (≥1.50 log units).

Handheld versus desktop testing protocols

A handheld SDH (hSDH) test (MyVisionTrack; Vital Art and Science, USA) has recently been implemented for use with smartphones. Such a device is of potential importance, as it may facilitate frequent, regular home monitoring for patients with AMD, and thus earlier detection and treatment of CNV. In 2013, Wang et al reported the results of a study to 1) compare the hSDH testing protocol with an established desktop SDH testing protocol, 2) to compare hSDH with standard visual function measures, such as visual acuity and contrast sensitivity, and 3) to evaluate the effect of severity of maculopathy on hSDH.[62] They evaluated 100 subjects – 27 healthy volunteers, 37 patients with AMD, and 36 patients with DR – all with visual acuity ≥20/100. They found that handheld and desktop SDH testing were in agreement, and that measurements were higher in those with advanced AMD than in those with intermediate AMD. In an associated usability survey, test participants reported that the handheld testing was easy to use. As a result of this work, the MyVisionTrack application has recently been approved by the FDA for use by prescription only.

Health Management Tool

The Health Management Tool (HMT), a remote monitoring system that utilizes the MyVisionTrack app, has recently been tested in a pilot clinical trial.[63] In the HMT system, patients use a handheld device daily to test their retinal visual function between clinic visits. Data input by patients is transferred in real time to a database, which sends reminders to users regarding the test. Clinicians log in to the HMT database from an Internet-based dashboard to view results and compliance information (similar systems have been used previously for remote blood-pressure monitoring). This single-arm, prospective, open-label, 16-week, multicenter pilot study was conducted at 24 centers in the US (NCT01542866). The primary objective of this study was to determine the sensitivity and specificity of MyVisionTrack to detect disease progression in patients with neovascular AMD receiving treatment with ranibizumab.

Patients with neovascular AMD in at least one eye and eligible for ranibizumab therapy were enrolled.[63] Patients performed SHD testing daily on the HMT device (iPhone 3GS, Apple) using the MyVisionTrack application. Data entered into HMT devices were collected in the HMT database, which also sent reminders for patients to perform testing. Among 160 patients from 24 US centers enrolled in the study, 84.7% on average complied with daily MyVisionTrack testing and 98.9% complied with at least weekly MyVisionTrack testing. The HMT database successfully uploaded more than 17,000 MyVisionTrack assessment values and sent more than 9,000 reminders. At the time of writing, the actual results of the trial have yet to be published.

Macular mapping test

Basic principles

The macular mapping test (MMT) is designed primarily for quick assessment of residual vision in patients with

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maculopathies, but as it yields a quantitative score, it may also be used as a tool for monitoring disease progression.[64,65] The MMT is a software program used in conjunction with a desktop computer. Letters are briefly displayed in the central visual field (8° radius) on the computer display. A constant background pattern in a wagon-wheel shape aids the test subject in maintaining fixation at the center of the display area.

Clinical testing

In 2003, Trauzettel-Klosinski et al compared the results of MMT with those of manual kinetic perimetry in 50 patients with a variety of disorders that produce a central scotoma, including AMD, Stargardt's disease, and diabetic maculopathy.[66] They found little difference in the ability of the two tests to detect and delineate dense scotomas. In 2005, Bartlett et al investigated the test–retest variability of the MMT.[67] Thirty-one healthy eyes of 31 normal subjects underwent the test. MMT readings were also taken from 17 eyes of 17 patients with soft drusen and 12 eyes of 12 patients with GA secondary to AMD. They concluded that despite considerable variability, the MMT score could be useful for monitoring progression of AMD.

Entoptic perimetry

Basic principles

The subjective perception of scotomas is often greatly reduced by the filling-in phenomenon (see earlier).[31] In some instances, however, this phenomenon can be overcome by gazing at random visual noise, such as video static. When patients with an acquired scotoma stare at such a scene, they often perceive an inhomogeneous region corresponding to their scotoma. Once the scotoma is perceived in this manner, it is often possible to map it, a procedure referred to as entoptic perimetry.[64,65,68] Although this approach is not very effective in eliciting scotomas from postchiasmal lesions or from the physiological blind spot,[69] variations of this technique have been successfully used to screen for visual field defects caused by prechiasmal ocular diseases, including AMD.

Clinical testing

In 2004, Freeman et al demonstrated the technique of scanning laser entoptic perimetry in patients with AMD.[70] In this study, the noise field was generated by a computer-software program, and was delivered to the patient via a scanning laser virtual retinal display. Their device had an overall sensitivity of 82% and a specificity of 100% for the detection of AMD. The sensitivity for early stages of the disease is greater than 70%, and increases to above 90% for moderate-to-late stages.

Optical coherence tomography

Basic principles

OCT is a cross-sectional (tomographic) ocular imaging method, analogous to ultrasonography, but which measures reflected light waves rather than sound waves.[71] In this technique, the combination of light reflected from a tissue of interest and light reflected from a reference path produces characteristic patterns of light interference dependent on the mismatch between the reflected waves. Since the time delay and amplitude of one of the waves is known, the time delay and intensity of light returning from the sample tissue may then be extracted from the interference pattern. As the wavelength of light is so much shorter than that of sound, OCT generates image sets with considerably superior resolution to those of ultrasonography (eg, typically 3–8 μm axial resolution in commercial systems).[72,73]

In the original OCT systems, the interference patterns generated were varied as a function of time using a moving mirror in the reference pathway; such devices were commonly referred to as "time-domain" OCT. Using time-domain OCT, the AMD DOC study determined a greater specificity for OCT than Amsler chart or PHP testing in the detection of recent-onset CNV.[74] However, a significant limitation of time-domain OCT devices is their slow image-acquisition speed, which allows for only limited sampling of the macula in any given image set.[75] As a result, it is not surprising that the AMD DOC study found a lower sensitivity of OCT imaging than FA for detection of CNV.[74]

In more recent OCT devices, the interference patterns generated are measured as a function of frequency, using a spectrometer.[72] These "spectral domain" OCT devices remove the need for a moving reference mirror, and thus facilitate greatly enhanced image-acquisition speed. An alternative approach to the assessment of interference patterns in this way is through the use of a frequency-swept ("tunable") laser light source: so-called swept-source OCT.

Handheld and binocular OCT

Swept-source OCT lasers are more robust and readily portable than spectral domain-based OCT systems. This has allowed the generation of the first prototype handheld OCT systems.[76] Swept-source OCT systems employing vertical cavity surface-emission lasers have a greatly increased depth range compared to normal OCT systems (typically

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20 times greater, or 40 mm versus approximately 2 mm).[77,78] The greatly increased range of imaging for these lasers also allows simultaneous capture of the anterior and posterior segments of the eye: so-called whole-eye OCT or OCT ophthalmoscopy.

The concept of binocular OCT has recently been described.[79] In these systems, swept-source lasers are used to obtain simultaneous whole-eye images from each eye in tandem. The binocular design of such a device removes the need for additional personnel to acquire the image by enabling patients to align the optical axes of the instrument with the optical axes of their own eyes. Binocular OCT systems can also offer advanced display, input, and computing capabilities relative to conventional OCT platforms. The internal screens on a binocular OCT device can function like applications on a smartphone, presenting content (eg, letters) to the user, and registering responses with voice-recognition software or external buttons. Using this approach, "smart" binocular OCT systems can accomplish the functions of many different diagnostic devices in a single instrument. Finally, binocular OCT systems allow image capture from both eyes at the same time. This "simultaneous" ocular imaging extends the range of functional testing possible, allowing for such features as pupillometry and ocular motility. Through the rapid, automated acquisition of comprehensive ocular examination data, binocular OCT examination has the potential to transfer routine eye examinations outside the hospital setting, with comprehensive, automated assessment at distant locations, allowing patients with chronic, nonthreatening disease to visit the clinic less often, and those with recurrent disease to be detected at an earlier stage. In particular, binocular OCT may allow more frequent assessments in patients with AMD and potentially earlier detection of disease.

OCT angiography

An important focus of current OCT research is the generation of three-dimensional maps of the retinal and choroidal vasculature: so-called OCT angiography.[80] A number of techniques for OCT angiography are currently under development.[81,82] In essence, these all involve high-speed, sequential acquisition of OCT A-scans or B-scans at the same retinal locus, and then assessment of differences in the scans that occur as a result of blood flow. After acquisition of OCT angiography image sets, it is possible to generate three-dimensional renderings of the vasculature or two dimensional fundic images with color coding for vessel depth. The development of noninvasive OCT angiography may allow even earlier detection of CNV development than conventional OCT devices (eg, identification of the budding neovascular network prior to any exudation occurring that makes the diagnosis obvious with conventional OCT).

Conclusion

Ophthalmology is among the most technology-driven of all medical specialties. The advent of mobile-technology platforms, such as smartphones, tablet computers, and other devices, presents many unique opportunities to allow for earlier detection and treatment of patients with AMD. These changes are occurring in parallel with rapid evolution in the sophistication and utility of visual function testing; in particular, hyperacuity testing of particular efficacy in elderly populations with macular disease. The recent results of the Phase III HOME study provide robust evidence for the importance of these strategies.[57] The challenge for retina specialists in the coming years will be to build on these advances in a usable, cost-effective, and widely available manner.

Disclosure

PAK, DAS, and AT have received a proportion of their funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology. The views expressed in the publication are those of the authors, and not necessarily those of the Department of Health. PAK and DAS have received travel grants from the Allergan European Retina Panel. SG has received travel grants from Bayer and Novartis. GDS has received travel grants from Bayer and Heidelberg Engineering. RA has no conflicts of interest to report.

References

1. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014;98(9):1144–1167.
2. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am J Ophthalmol*. 2012;153(2):209–213.e2.
3. Belkin M, Kalter-Leibovici O, Chetrit A, Skaat A. Time trends in the incidence and causes of blindness in Israel. *Am J Ophthalmol*. 2013; 155(2):404.
4. Mitchell P, Bressler N, Doan QV, et al. Estimated cases of blindness and visual impairment from neovascular age-related macular degeneration avoided in Australia by ranibizumab treatment. *PLoS One*. 2014;9(6):e101072.
5. Bressler NM, Doan QV, Varma R, et al. Estimated cases of legal blindness and visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. *Arch Ophthalmol*. 2011;129(6):709–717.

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6. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013;120(11):2292–2299.
7. Holz FG, Schmitz-Valckenberg S, Fleckenstein M. Recent developments in the treatment of age-related macular degeneration. *J Clin Invest*. 2014;124(4):1430–1438.
8. Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640–1642.
9. Grossniklaus HE, Green WR. Choroidal neovascularization. *Am J Ophthalmol*. 2004;137(3):496–503.
10. Freund KB, Ho IV, Barbazetto IA, et al. Type 3 neovascularization: the expanded spectrum of retinal angiomatous proliferation. *Retina*. 2008;28(2):201–211.
11. Soubrane G, Coscas G, Français C, Koenig F. Occult subretinal new vessels in age-related macular degeneration. Natural history and early laser treatment. *Ophthalmology*. 1990;97(5):649–657.
12. Lafaut BA, Bartz-Schmidt KU, Vanden Broecke C, Aisenbrey S, De Laey JJ, Heimann K. Clinicopathological correlation in exudative age related macular degeneration: histological differentiation between classic and occult choroidal neovascularisation. *Br J Ophthalmol*. 2000;84(3):239–243.
13. Balasubramanian SA, Krishna Kumar K, Baird PN. The role of proteases and inflammatory molecules in triggering neovascular age-related macular degeneration: basic science to clinical relevance. *Transl Res*. 2014;164(3):179–192.
14. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology*. 2008; 115(1):116–126.
15. Schmier JK, Covert DW, Lau EC. Patterns and costs associated with progression of age-related macular degeneration. *Am J Ophthalmol*. 2012;154(4):675–681.e1.
16. Campa C, Harding SP, Pearce IA, Beare NA, Briggs MC, Heimann H. Incidence of neovascularization in the fellow eye of patients with unilateral retinal angiomatous proliferation. *Eye (Lond)*. 2010;24(10): 1585–1589.
17. Liu TY, Shah AR, Del Priore LV. Progression of lesion size in untreated eyes with exudative age-related macular degeneration: a meta-analysis using Lineweaver-Burk plots. *JAMA Ophthalmol*. 2013;131(3):335–340.
18. Blinder KJ, Bradley S, Bressler NM, et al. 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(3):407–418.
19. 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(2):246–252.
20. 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(6): 850–857.
21. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(1):122–129.
22. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology*. 2014;121(5):1092–1101.
23. Zarranz-Ventura J, Liew G, Johnston RL, et al. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology*. 2014; 121(10):1966–1975.
24. Oliver-Fernandez A, Bakal J, Segal S, Shah GK, Dugar A, Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration. *Can J Ophthalmol*. 2005;40(3):313–319.
25. Rauch R, Weingessel B, Maca SM, Vecsei-Marlovits PV. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. *Retina*. 2012;32(7):1260–1264.
26. Canan H, Sızmaz S, Altan-Yaycıoğlu R, Sarıtürk C, Yılmaz G. Visual outcome of intravitreal ranibizumab for exudative age-related macular degeneration: timing and prognosis. *Clin Interv Aging*. 2014;9:141–145.
27. Kandula S, Lamkin JC, Albanese T, Edward DP. Patients' knowledge and perspectives on wet age-related macular degeneration and its treatment. *Clin Ophthalmol*. 2010;4:375–381.
28. Woo JH, Au Eong KG. Don't lose sight of age-related macular degeneration: the need for increased awareness in Singapore. *Singapore Med J*. 2008;49(11):850–853.
29. Lau JT, Lee V, Fan D, Lau M, Michon J. Knowledge about cataract, glaucoma, and age related macular degeneration in the Hong Kong Chinese population. *Br J Ophthalmol*. 2002;86(10):1080–1084.
30. Müller A, Keeffe JE, Taylor HR. Changes in eye care utilization following an eye health promotion campaign. *Clin Experiment Ophthalmol*. 2007;35(4):305–309.
31. Crossland M, Rubin G. The Amsler chart: absence of evidence is not evidence of absence. *Br J Ophthalmol*. 2007;91(3):391–393.
32. Amsler M. Earliest symptoms of diseases of the macula. *Br J Ophthalmol*. 1953;37(9):521–537.
33. Marmor MF. A brief history of macular grids: from Thomas Reid to Edvard Munch and Marc Amsler. *Surv Ophthalmol*. 2000;44(4): 343–353.
34. Augustin AJ, Offermann I, Lutz J, Schmidt-Erfurth U, Tornambe P. Comparison of the original Amsler grid with the modified Amsler grid: result for patients with age-related macular degeneration. *Retina*. 2005;25(4):443–445.
35. Mathew R, Sivaprasad S. Environmental Amsler test as a monitoring tool for retreatment with ranibizumab for neovascular age-related macular degeneration. *Eye (Lond)*. 2012;26(3):389–393.
36. Schuchard RA. Validity and interpretation of Amsler grid reports. *Arch Ophthalmol*. 1993;111(6):776–780.
37. 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(5):966–970.
38. 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(4):513–514.
39. 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(5):503–508.
40. Yannuzzi LA. A modified Amsler grid. A self-assessment test for patients with macular disease. *Ophthalmology*. 1982;89(2):157–159.
41. Mutlukan E. Red dots visual field test with blue on yellow and blue on red macula test grid. *Eye (Lond)*. 2006;20(4):506–508; author reply 8–9.
42. Wall M, Sadun AA. Threshold Amsler grid testing. Cross-polarizing lenses enhance yield. *Arch Ophthalmol*. 1986;104(4):520–523.
43. Wolfe KA, Sadun AA. Threshold Amsler grid testing in diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 1991;229(3):219–223.
44. Fink W, Sadun AA. Three-dimensional computer-automated threshold Amsler grid test. *J Biomed Opt*. 2004;9(1):149–153.
45. Nazemi PP, Fink W, Lim JI, Sadun AA. Scotomas of age-related macular degeneration detected and characterized by means of a novel three-dimensional computer-automated visual field test. *Retina*. 2005;25(4):446–453.
46. Almony A, Garg S, Peters RK, et al. Threshold Amsler grid as a screening tool for asymptomatic patients on hydroxychloroquine therapy. *Br J Ophthalmol*. 2005;89(5):569–574.

Clinical Ophthalmology downloaded from https://www.dovepress.com/ by 137.108.70.14 on 20-Jan-2020
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47. Nazemi PP, Fink W, Sadun AA, Francis B, Minckler D. Early detection of glaucoma by means of a novel 3D computer-automated visual field test. *Br J Ophthalmol*. 2007;91(10):1331–1336.
48. Kim JK, Fahimi A, Fink W, Nazemi PP, Nguyen D, Sadun AA. Characterizing ethambutol-induced optic neuropathy with a 3D computer-automated threshold Amsler grid test. *Clin Experiment Ophthalmol*. 2008;36(5):484–488.
49. Jivrajka RV, Kim JK, Fink W, Sadun AA, Sebag J. Quantitative analysis of central visual field defects in macular edema using three-dimensional computer-automated threshold Amsler grid testing. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(2):165–170.
50. Robison CD, Jivrajka RV, Bababeygy SR, Fink W, Sadun AA, Sebag J. Distinguishing wet from dry age-related macular degeneration using three-dimensional computer-automated threshold Amsler grid testing. *Br J Ophthalmol*. 2011;95(10):1419–1423.
51. Westheimer G. The spatial sense of the eye. Proctor lecture. *Invest Ophthalmol Vis Sci*. 1979;18(9):893–912.
52. Enoch JM, Williams RA, Essock EA, Barricks M. Hyperacuity perimetry. Assessment of macular function through ocular opacities. *Arch Ophthalmol*. 1984;102(8):1164–1168.
53. Lakshminarayanan V, Aziz S, Enoch JM. Variation of the hyperacuity gap function with age. *Optom Vis Sci*. 1992;69(6):423–426.
54. 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(3): 296–303.
55. Alster Y, Bressler NM, Bressler SB, et al. Preferential hyperacuity perimeter (PreView PHP) for detecting choroidal neovascularization study. *Ophthalmology*. 2005;112(10):1758–1765.
56. Chew EY, Clemons TE, Bressler SB, et al. Randomized trial of the ForeseeHome monitoring device for early detection of neovascular age-related macular degeneration. The HOme Monitoring of the Eye (HOME) study design – HOME Study report number 1. *Contemp Clin Trials*. 2014;37(2):294–300.
57. Chew EY, Clemons TE, Bressler SB, et al. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. *Ophthalmology*. 2014;121(2):535–544.
58. Querques G, Berboucha E, Leveziel N, Pece A, Souied EH. Preferential hyperacuity perimeter in assessing responsiveness to ranibizumab therapy for exudative age-related macular degeneration. *Br J Ophthalmol*. 2011;95(7):986–991.
59. Querques G, Querques L, Rafaeli O, Canoui-Poitrine F, Bandello F, Souied EH. Preferential hyperacuity perimeter as a functional tool for monitoring exudative age-related macular degeneration in patients treated by intravitreal ranibizumab. *Invest Ophthalmol Vis Sci*. 2011; 52(9):7012–7018.
60. Wilkinson F, Wilson HR, Habak C. Detection and recognition of radial frequency patterns. *Vision Res*. 1998;38(22):3555–3568.
61. Wang YZ, Wilson E, Locke KG, Edwards AO. Shape discrimination in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2002;43(6):2055–2062.
62. Wang YZ, He YG, Mitzel G, Zhang S, Bartlett M. Handheld shape discrimination hyperacuity test on a mobile device for remote monitoring of visual function in maculopathy. *Invest Ophthalmol Vis Sci*. 2013;54(8):5497–5505.
63. Kaiser PK, Wang YZ, He YG, Weisberger A, Wolf S, Smith CH. Feasibility of a novel remote daily monitoring system for age-related macular degeneration using mobile handheld devices: results of a pilot study. *Retina*. 2013;33(9):1863–1870.
64. Trevino R, Kynn MG. Macular function surveillance revisited. *Optometry*. 2008;79(7):397–403.
65. Trevino R. Recent progress in macular function self-assessment. *Ophthalmic Physiol Opt*. 2008;28(3):183–192.
66. Trauzettel-Klosinski S, Biermann P, Hahn G, Weismann M. Assessment of parafoveal function in maculopathy: a comparison between the macular mapping test and kinetic manual perimetry. *Graefes Arch Clin Exp Ophthalmol*. 2003;241(12):988–995.
67. Bartlett H, Davies LN, Eperjesi F. The macular mapping test: a reliability study. *BMC Ophthalmol*. 2005;5:18.
68. Aulhorn E, Köst G. [White noise field campimetry. A new form of perimetric examination]. *Klin Monbl Augenheilkd*. 1988;192(4):284–288.
69. Schiefer U, Skalej M, Kolb M, et al. Lesion location influences perception of homonymous scotomata during flickering random dot pattern stimulation. *Vision Res*. 1998;38(9):1303–1312.
70. Freeman WR, El-Bradey M, Plummer DJ. Scanning laser entoptic perimetry for the detection of age-related macular degeneration. *Arch Ophthalmol*. 2004;122(11):1647–1651.
71. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178–1181.
72. Keane PA, Sadda SR. Retinal imaging in the twenty-first century: state of the art and future directions. *Ophthalmology*. 2014;121(12): 2489–2500.
73. Keane PA, Patel PJ, Liakopoulos S, Heussen FM, Sadda SR, Tufail A. Evaluation of age-related macular degeneration with optical coherence tomography. *Surv Ophthalmol*. 2012;57(5):389–414.
74. Do DV, Gower EW, Cassard SD, et al. Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC study. *Ophthalmology*. 2012;119(4):771–778.
75. Keane PA, Bhatti RA, Brubaker JW, Liakopoulos S, Sadda SR, Walsh AC. Comparison of clinically relevant findings from high-speed Fourier-domain and conventional time-domain optical coherence tomography. *Am J Ophthalmol*. 2009;148(2):242–248.e1.
76. Lu CD, Kraus MF, Potsaid B, et al. Handheld ultrahigh speed swept source optical coherence tomography instrument using a MEMS scanning mirror. *Biomed Opt Express*. 2013;5(1):293–311.
77. Grulkowski I, Liu JJ, Potsaid B, et al. Retinal, anterior segment and full eye imaging using ultrahigh speed swept source OCT with vertical-cavity surface emitting lasers. *Biomed Opt Express*. 2012;3(11):2733–2751.
78. Grulkowski I, Liu JJ, Zhang JY, et al. Reproducibility of a long-range swept-source optical coherence tomography ocular biometry system and comparison with clinical biometers. *Ophthalmology*. 2013; 120(11):2184–2190.
79. Walsh AC. Binocular optical coherence tomography. *Ophthalmic Surg Lasers Imaging*. 2011;42(4):S95–S105.
80. Puliafito CA. OCT angiography: the next era of OCT technology emerges. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45(5):360.
81. Schwartz DM, Fingler J, Kim DY, et al. Phase-variance optical coherence tomography: a technique for noninvasive angiography. *Ophthalmology*. 2014;121(1):180–187.
82. Jia Y, Bailey ST, Wilson DJ, et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology*. 2014;121(7):1435–1444.

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