Multifocal multi-channel objective perimetry for the diagnosis of visual field defects

August 2004

MSAC application 1078

Assessment report

ISBN 0 642 82731 1

ISSN (Print) 1443-7120

ISSN (Online) 1443-7139

First printed December 2005

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Ornella Clavisi, Ms Elena Gospodarevskaya, Dr Emma Bryan, A/Professor Anthony Harris, Dr Omar Abdulwadud, Jillian Broadbear, Ms Sharon King and Ms Anne Parkhill from the Monash Evaluation Group. The report was edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Minister for Health and Ageing on 31 August 2004.

Publication approval number: 3695

Contents

Tables

Figures

Executive summary

The procedure

The measurement of visually evoked potentials (VEPs) is an objective electrophysiological technique used to detect visual field defects. It examines the response of the occipital cortex to light, allowing the clinician to examine components of the visual field. Multifocal VEPs (mVEPs) are recorded from scalp electrodes on the occipital region while the patient views a screen displaying a rapidly alternating checkerboard pattern with multiple zones each changing according to a different sequence in time. Multifocal multichannel objective perimetry (MMOP) is a modification of the technique that involves the use of a bipolar electrode which straddles the inion and a four-channel system with an occipital cross electrode holder to record a signal simultaneously on multiple channels.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Australian Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from Monash University was engaged to conduct a systematic review of literature on MMOP for the diagnosis of visual field defects. An Advisory Committee with expertise in this area then evaluated the evidence and provided advice to the MSAC.

MSAC's assessment of Multifocal Multichannel Objective Perimetry for the Diagnosis of Visual Field Defects

Clinical need

Data for glaucoma and overall visual impairment were identified. Limited data are available regarding the burden of disease of patients with visual field defects secondary to ocular diseases or suspected pathology of the visual pathway or brain. According to the Australian Institute of Health and Welfare, the prevalence of visual impairment and blindness in Australia is approximately 1 per cent, with the burden of disease estimated for glaucoma calculated at 1,850 disability adjusted life years. The overall annual direct costs to the Australian government associated with glaucoma have been estimated at $320 million.

Australian prevalence data for glaucoma have also been reported for an urban New South Wales population aged over 49 years (The Blue Mountains Eye Study, BMES) and

a random sample of Victorians aged over 40 years (Melbourne Visual Impairment Project, MVIP). Based on the results of these studies the prevalence of glaucoma was between 3 per cent (BMES) and 1.8 per cent (MVIP). The BMES also found an exponential rise in glaucoma prevalence with increasing age. It was eg 0.4 per cent for people younger than 60 years, 1.3 per cent for those aged 60 to 69 years, 4.7 per cent for those between the ages of 70 and 79 and 11.4 per cent for those aged 80 years and over. The estimated cumulative incidence of glaucoma for both patients and suspects was 2.7 per cent based on a five-year follow-up survey by Mukesh et al (2002).

Safety

There is a paucity of data relating to the safety of MMOP. However, as the test is non-invasive the risks to subjects should be minimal. The frequency of skin irritation or minor trauma caused by the scalp electrodes used for MMOP is unknown.

Effectiveness

Due to the limitations of the available evidence it is unclear whether MMOP is equivalent to static automated perimetry (SAP) in terms of diagnostic accuracy in patients with undiagnosed visual field defects.

Overall, the diagnostic accuracy of MMOP could not be established as there were wide variations in the sensitivity (75 to 100 per cent) and specificity (45 to 97 per cent). Sensitivity results were highly dependent on the MMOP thresholds of positivity used. Such variations may affect the use of mVEP in practice as it is unclear which threshold is most likely to be used and which is most likely to give an accurate result. Specificities were usually dependent on the population. For example, they were highest in studies that included normal controls and lower in those studies which used glaucoma suspects as controls.

The ability of MMOP to diagnose pre-perimetric patients was not adequately addressed in any of the studies due to the unknown disease status for the majority of patients. In order to determine the true predictive value of mVEP, longitudinal data would be necessary to determine if patients actually developed disease.

In general, 80 per cent of the validity criteria outlined in Table 5 were unmet. Furthermore, it is unclear where the true diagnostic accuracy of MMOP lies, given that these results are subject to study bias. The majority of patients were pre-diagnosed based on their visual field results and other diagnostic criteria, the reference test was not applied independently of test results and assessment of results was not blinded. Due to the high potential for additional clinical information to influence the overall diagnostic results in these studies, it is unclear whether mVEP can be used as a stand-alone test given.

In patients for whom the test is indicated, it is uncertain what the diagnostic value of MMOP would be since none of the studies recruited an appropriate spectrum of subjects. Furthermore, since the majority of studies recruited glaucoma patients, it is uncertain how these results can be applied to those with visual field defects resulting from other pathologies. Indeed, MMOP may be of limited use in the diagnosis of other diseases where damage is not localised to the visual cortex. For example, Klistorner

(unpublished) showed that MMOP may be a poor test for the diagnosis of quadrantinopic patients when damage was in the extrastriate area.

Cost analysis

A cost-effectiveness analysis could not be undertaken as there was insufficient evidence to demonstrate the relative effectiveness of MMOP. Instead, a cost analysis based on the applicant's model is presented. The analysis did not demonstrate cost savings for AccuMap® compared to the Humphrey® visual field (HVF) analyser.

A modelled cost comparison of MMOP and the HVF test for the diagnosis of glaucoma has been calculated under reasonable assumptions about the capital and variable cost of each test. The results are that MMOP has an additional cost of $36.80 per test compared to the HVF analyser, assuming the capital cost of the HVF analyser is $25,000. If the capital cost of the HVF analyser is $45,000 (ie newer machines with upgraded software), the cost difference per test is $27.30. If we assume that the use of AccuMap® will diagnose patients earlier than the HVF test, then commencement of treatment may be brought forward by up to six months.

Taking this into account along with the single predictive value of the two tests, the cost of treatment following a positive diagnosis of glaucoma has been estimated. The results of this analysis show that only if there is a very low rate of glaucoma among patients being assessed will there be cost savings from the substitution of MMOP for the HVF test. While the exact distribution of glaucoma status of patients referred for diagnosis is unknown, it seems highly unlikely that there would be cost savings associated with the replacement of the HVF test with MMOP.

Recommendation

Multifocal multichannel objective perimetry for the diagnosis of visual field defects appears to be safe but there is insufficient evidence to demonstrate that it is as effective as alternative technologies. Therefore, its cost-effectiveness could not be determined. MSAC does not recommend public funding.

The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of multifocal multichannel objective perimetry (MMOP), a diagnostic technique for detecting visual field defects. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for MMOP for the diagnosis of visual field defects.

Background

Multifocal Multichannel Objective Perimetry for the Diagnosis of Visual Field Defects

In November 2002 the MSAC reviewed MMOP (MSAC Reference 13) and recommended that since there was insufficient evidence pertaining to MMOP, public funding of the procedure should not be supported. The Minister for Health and Ageing accepted this recommendation on 6 December 2002.

At the time Reference 13 was reviewed, only two studies (Klistorner & Graham 2000, Goldberg et al 2002) were identified as meeting the *a priori* criteria developed to identify relevant MMOP articles. Although the results of these studies showing 95 to 100 per cent sensitivity and 93 to 97 per cent specificity appeared promising, their validity was uncertain, given the constraints on the study design.

Both studies failed to meet important validity criteria, such as consecutive selection of an appropriate spectrum of patients with unknown disease status. In addition, given that patient management and clinical outcomes were not addressed in any of the available studies, it was unclear whether MMOP would improve patient management or related outcomes such as disease progression and quality of life. Furthermore, the financial implications to the Commonwealth were difficult to estimate.

This review is in response to an application by Objectivision Pty Ltd for the funding of the AccuMap® device through the Medicare Benefits Scheme. This report aims to provide an updated review of the evidence, incorporating unpublished data. An evaluation of the applicant's economic model is also provided.

Disease indicated by the loss of the visual field

The visual field is defined as the area perceived simultaneously by a fixating eye. It maps the peripheral extent of the visual world (James et al 1997). The limits of the normal field of vision are 60 degrees into the superior field, 75 degrees into the inferior field, 110 degrees temporally and 60 degrees nasally. The field is often described as a hill or island of vision as depicted in Figure 1 (James et al 1997), with the centre of the field able to detect smaller objects than the periphery. The contour of the hill of vision relates to the anatomy of the visual system in which objects are resolved in the finest detail at the peak of the hill (James et al 1997).

Any deviation from the normal shape of the hill of vision can be considered a visual field defect. Field defects usually refer to the deterioration of the peripheral field made up of the retinal areas outside the macula area. Central vision may be unaffected in conditions where there is an abnormality in the visual field, for example, glaucoma and retinitis pigmentosa.

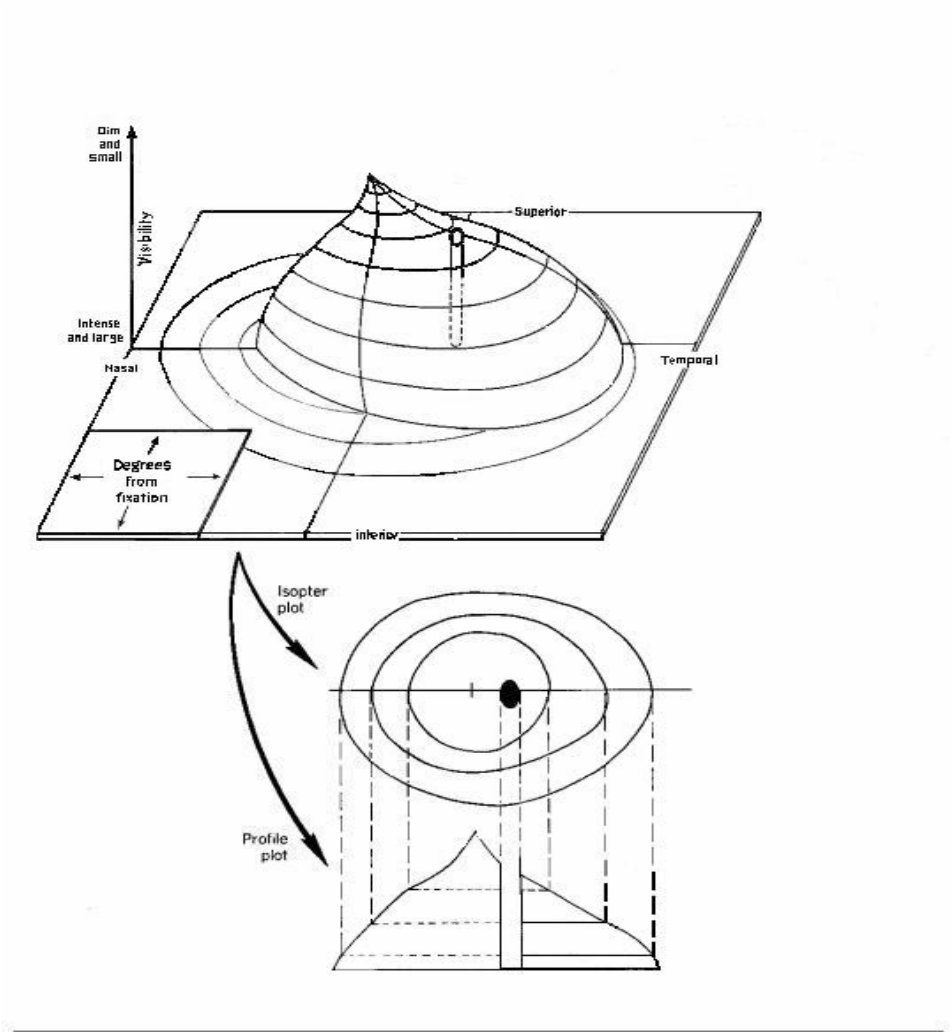


Figure 1 The normal hill of vision
(Reprinted from Anderson 1984)

Visual field defects can result from a number of conditions. These include diseases such as glaucoma, compression of the visual pathways by pituitary tumours, diseases of the optic nerves such as ischaemic optic neuropathy, and retinal disease such as ischaemic retinal branch vein occlusions and various forms of chorioretinitis. For patients whose cataracts cause a diminution of central vision, detection on examination of abnormalities of the visual fields necessitates the exclusion of other suspected pathologies (Associate Professor Justin O'Day, personal communication, MSAC Advisory Panel, 2002).

The most common visual field defect appears to be glaucoma which is indicated by a number of pathologies (Flammer et al 1985).

- Localised defects that conform to nerve fibre bundle patterns. These may be indicated by a single, deep scotoma or several small depressions of the sensitivity scattered over the visual field or nasal step.

- Diffuse depression of the differential light sensitivity resulting from an overall or widespread sinking of the island of vision that may reflect diffuse loss of nerve fibres of the retina.

- Increased short- and long-term threshold fluctuation in combination or singly.

Diagnosis usually involves taking a detailed patient history and also a physical examination (American Academy of Ophthalmology guidelines 2002, 2003). A physical examination for glaucoma is generally composed of the following nine elements:

- Assessment of pupillary function
- Slit-lamp biomicroscopy of the anterior segment
- Measurement of intraocular pressure (IOP)
- Determination of central corneal thickness
- Gonioscopy
- Evaluation of the optic nerve head and retinal nerve fibre layer
- Documentation of the optic nerve head appearance
- Evaluation of the fundus
- Evaluation of the visual field using automatic static threshold perimetry

Follow-up visits for primary open angle glaucoma suspects also involve the monitoring of these nine components. The frequency of each follow-up visit can range from every two days to every 18 months. The time between visits generally depends on a number of factors such as treatment regimen, IOP and the presence of additional risk factors. Although visual field evaluation is not necessary at each follow-up visit it is recommended at intervals of three to 18 months based on IOP levels and the number of risk factors associated with optic nerve damage (American Academy of Ophthalmology 2003).

Visual field defects in patients with glaucoma are permanent, irreversible and often progressive. Therefore, the principal aim in treatment is to stabilise the visual field defect or at least to slow its progression (Larena & Gronella 1992).

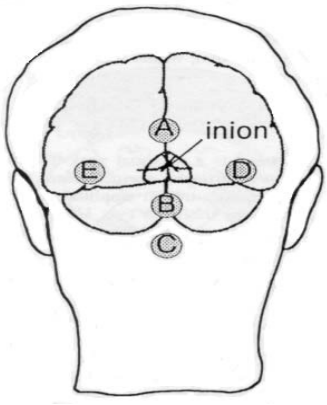
The procedure

The measurement of visually evoked potentials (VEPs) is an objective, electrophysiological technique used to detect visual field defects. The technique examines the response of the occipital cortex to light, allowing the clinician to examine components of the visual field. Multifocal VEPs are 60 VEP responses obtained by a multi-input procedure (Hood et al 2000). Multifocal VEPs are recorded from scalp electrodes on the occipital region while the patient views a screen displaying a rapidly alternating checkerboard pattern with multiple zones, each changing according to a different sequence in time (Graham & Balachandran unpublished). The stimulus is correlated with the electrical response and attributed to the location of the visual stimulus to generate a map of visually evoked responses, where a prolongation in latency and a lowering of amplitude is associated with a defect in the visual field (Balachandran et al unpublished).

Multifocal VEPs were first recorded by Baseler et al (1994) who used the method of presenting multifocal stimulation pseudorandomly with cortical scaling of the size of stimulated patches while recording via a single channel sequential technique. Multifocal single channel objective perimetry was evaluated in a previous MSAC review 'Visual Electrodiagnosis' (MSAC 2001).

The mVEP technique was updated and multichannel techniques with the signal being sequentially recorded were implemented by Wang et al (2001). Klistorner et al (1998) further modified the technique by using a bipolar electrode straddling the inion. Development of a four-channel system employing an occipital cross electrode holder (Figure 2) and simultaneous recording with multiple channels increased the amplitude of the signal in some field locations (Klistorner & Graham 2000) and is termed 'multifocal multichannel objective perimetry (MMOP)' in this report.

There are two perimeters available that measure mVEPs using this multichannel simultaneous stimulus method – the AccuMap® (a registered trademark of ObjectiVision Inc., Sydney, Australia) and the VERIS® (a registered trademark of Electrodiagnostics Imaging Inc., California, USA). In addition to the four-channel system, the AccuMap® system uses a scaling algorithm based on underlying electroencephalogram (EEG) amplitudes, which is applied during the recording to attempt to compensate for inter-individual variability (Klistorner & Graham 2001). The underlying EEG levels are used to normalise VEP signals for each patient in an attempt to minimise the influence of factors such as differences in gender and age, general level of brain activity and conductivity of underlying tissues. The AccuMap® system also uses a spread spectrum technique to drive the stimulus with different pseudorandom sequences for each stimulated area of the field and different sequences for each zone and consecutive run. The m-sequences used by the VERIS® perimeter are the same but shifted in time (Klistorner & Graham 2001).



A ↔ B	BOS
A ↔ C	extended BOS
D ↔ E	horizontal
C ↔ D	right oblique
C ↔ E	left oblique

Figure 2 Bipolar electrode positions for multichannel recording of the multifocal VEP
(Reprinted from Klistorner & Graham 2000)

Intended purpose

Consistent with Medicare Benefits Schedule (MBS) item number 11221, the intended use of MMOP is to detect visual field defects in patients being investigated or monitored for a visual field defect indicated by either the presence of relevant ocular disease or suspected pathology of the visual pathways or brain.

Clinical need/burden of disease

Although many ocular diseases cause defects in the visual field, there are limited data available on the burden of disease for most ocular conditions. In Australia, the self-reported prevalence rate of visual impairment, including blindness, is about 1 per cent (range 0.7–1.0%; AIHW 2003). The projected visual impairment is shown in Figure 3 (Taylor 2001).

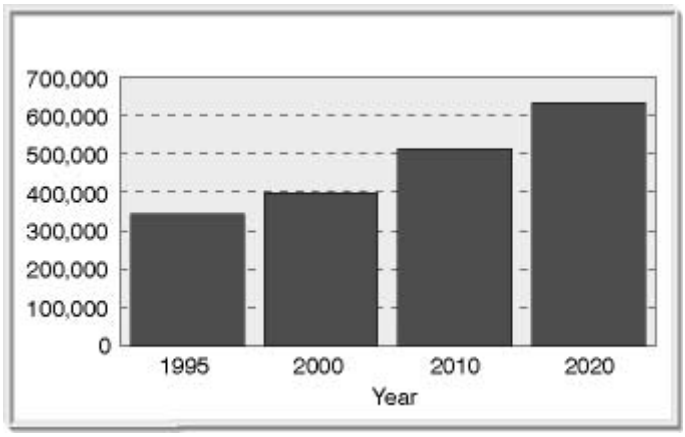


Figure 3 Projected visual impairment in Australia
(Taylor 2001)

Although data on the incidence and prevalence of glaucoma are available, no data have been published for visual field defects in glaucoma or other ocular diseases. Current Australian data for glaucoma are available for an urban New South Wales population aged over 49 years and for a randomised sample of the Victorian population aged over 40 years.

The New South Wales study known as the Blue Mountains Eye Study (BMES) (Attebo et al 1996, Mitchell et al 1997) assessed the prevalence and causes of visual impairment in a representative older urban Australian population sampled from community residents and a nursing home between January 1992 and January 1994. All permanent non-institutionalised residents with birth dates before 1 January 1943 were invited to attend a detailed eye examination at a local clinic. Of the 4,433 eligible people, 3,654 (82.4%) participated in the study. The BMES assessed the prevalence of open-angle glaucoma, ocular hypertension (OHT), age-related maculopathy, diabetic retinopathy and amblyopia.

The BMES found 88.9 per cent of the study subjects had no visual impairment, 7.5 per cent had correctable impairment and 3.6 per cent had non-correctable impairment (Foran et al 2002). Likewise, the prevalence of definite or probable homonymous visual field defects within the sample was 0.8 per cent (95% CI: 0.5%, 1.1%; Gilhotra et al 2002).

Open-angle glaucoma (OAG) was found in 108 people, a prevalence of 3.0 per cent (95% CI: 2.5, 3.6). An exponential rise in prevalence was observed with increasing age. The prevalence of glaucoma was 0.4 per cent for people younger than 60 years of age,

1.3 per cent for people 60 to 69 years of age, 4.7 per cent for people 70 to 79 years of age, and 11.4 per cent for people aged 80 years and older. Women had a slightly higher prevalence of glaucoma for each age group [OR=1.55, 95% CI: 1.03, 2.32 (Mitchell et al 1996)]. Although OHT was present in 3.7 per cent of this population (95% CI: 3.1, 4.3), there was no significant age-related increase in prevalence and there was no sex difference in the age-adjusted prevalence of OHT (Mitchell et al 1996).

The Melbourne Visual Impairment Project (MVIP) was undertaken in Victoria from 1992 to 1996 to determine the prevalence of eye disease (Weih et al 2001). A sample was drawn from nine pairs of Census Collector Districts (CCDs) selected randomly from the Melbourne statistical division, four pairs of non-metropolitan CCDs and a nursing home population. Participants were aged over 40 years and had resided for six months or longer in the same district at the time of recruitment to the study. Of the 4,744 eligible persons, 4,498 had complete data and were included in the analysis. A consensus panel of six ophthalmologists common to both the MVIP and BMES diagnosed glaucoma.

The prevalence of possible glaucoma cases was 1.2 per cent (95% CI: 0.6, 1.7), of probable cases was 0.7 per cent (95% CI: 0.39, 1.0) and of definite cases was 1.8 per cent (95% CI: 1.4, 2.2). When prevalence was adjusted for age, the strongest risk factor found for glaucoma was a positive family history of glaucoma [OR=3.1, 95% CI: 1.6, 5.3 (Weih et al 2001)].

A five-year follow up survey by Mukesh et al (2002) produced data for the five-year incidence of OAG among the 3,271 participants included in the original Melbourne-only cohort (Wensor et al 1998). In this study, the five-year cumulative incidence was 0.5 per cent (95% CI: 0.3, 0.7) for definite OAG, 1.1 per cent (95% CI: 0.8, 1.4) for probable and definite cases of glaucoma and, when combined, a further 2.7 per cent (95% CI: 1.7, 2.8) for possible, probable and definite OAG. Rochtchina & Mitchell (2000) estimated that the number of Australians aged 50 and over with glaucoma in the year 2030 would be between 307,000 (BMES) and 337,000 (MVIP), assuming similar age-specific rates.

The total annual direct costs associated with vision loss and five major eye diseases (refractive error, cataract, diabetes, glaucoma and macular degeneration) to the Australian government is more than $2 billion (Taylor 2001). Explicitly, visual impairment (vision loss) caused by diabetes and glaucoma costs the government about $326 million and $320 million, respectively (Taylor 2001).

Burden of disease is the total significance of disease for society beyond the immediate cost of treatment (WHO 2000). The Australian Institute of Health and Welfare calculated the burden of disease for age-related vision impairment and glaucoma for the Australian population in 1996 (Mathers et al 1999). Disability-adjusted life-years were calculated to be 1,850 for glaucoma – 408 for males and 1,442 for females).

Existing procedures and comparator

One of the established methods for measuring visual field defects is static automated perimetry (SAP). Static perimetry is a subjective test in which participants must be able to cooperate and respond to a stationary random visual stimulus by pressing a button. It is a three-dimensional assessment of the height of a pre-determined area of the hill of vision

and involves the presentation of stimuli of varying luminance in the same position to obtain a vertical boundary of the visual field (Kanksi 1999). Using SAP, the retinal sensitivity at a specific location is determined by varying the brightness while the shape of the hill is defined by repeating the threshold measurement at various locations. Automated static perimeters incorporate numerous computer programs and test strategies covering the central and peripheral fields. Several procedures for statistical analysis have been developed for the visual field evaluations (Hills & Johnson 1988).

The Humphrey® visual field (HVF) analyser has been in use for many years and is viewed by some to be the current standard in the field of perimetry (Wong et al 1995). Other commercially available perimeters include the Medmont®, Squid®, Octopus®, Dicon®, Digilab®, Fieldmaster®, Henson® and Perikon® devices.

The numbers of services for SAP are outlined in Table 1. These figures include services for both diagnosis and monitoring of various ocular diseases. Therefore, it is not possible to distinguish specific usage for the different types of perimeters and whether the services provided were for diagnostic or monitoring purposes.

Table 1 Number of Medicare Benefits Schedule rebates for SAP

Item no.	Item Description	Cost ($)	Number of Services					
			1999	2000	2001	2002	2003	YTD (May 2004)
11221	Full quantitative computerised perimetry (automated absolute static threshold), performed by or on behalf of a specialist in the practice of his or her specialty, where indicated by the presence of relevant ocular disease or suspected pathology of the visual pathways or brain with assessment and report, bilateral - to a maximum of 2 examinations (including examinations to which item 11224 applies) in any 12 month period.	56.30	170,793	180,637	191,402	197,791	204,815	84,678
11224	Full quantitative computerised perimetry (automated absolute static threshold), performed by or on behalf of a specialist in the practice of his or her specialty, where indicated by the presence of relevant ocular disease or suspected pathology of the visual pathways or brain with assessment and report, unilateral - to a maximum of 2 examinations (including examinations to which item 11221 applies) in any 12 month period.	33.95	7,135	7,438	7,482	7,414	7,376	3,067

Source: http://www.hic.gov.au

Differences between the new test and reference standard

Although MMOP and SAP are indicated for the same group of patients (ie those with suspected visual field loss secondary to ocular disease or pathology of the visual pathways or brain), it has been proposed that MMOP is also able to detect ganglion cell damage prior to the development of visual field loss (ie pre-perimetric disease) (Klistorner et al 1998, Graham et al 2000, Hood et al 2000; Hood & Zhang 2000, Betsuin et al 2001, Hasegawa & Abe 2001, Hood & Greenstein 2003). However, the validity of this claim is uncertain as a result of which this review has evaluated the value of MMOP in diagnosing patients with pre-perimetric disease.

One of the main limitations of SAP is the learning curve associated with the test which may complicate the interpretation of results for new patients (Klistorner & Graham 2000). Patients can generally be taught how to use the test in order to produce meaningful results, although for some patients, it is not possible to obtain reliable, reproducible visual fields. (Hood & Greenstein 2003). For example, reliable results are difficult to obtain from patients who are uncooperative, who find the test difficult to understand, and who lose their concentration or become fatigued during testing (Marra & Flammer 1991).

It has been suggested that the use of MMOP can produce reliable records in patients with unreliable SAP, although these patients may also be difficult to test with the mVEP, particularly if sleepy, tense or uncooperative (Hood & Greenstein 2003). Patients may also produce mVEPs poorly, particularly those who generate extensive alpha EEG waves which cannot be suppressed. This is particularly common in younger subjects (Hood & Greenstein 2003).

The perimetrist may also have a major influence on the outcome of the examination, however the introduction of computer-assisted, automated techniques appears to have minimised the subjective influences of the perimetrist in the collection of visual field data (Hirsbrunner et al 1990). The experience of the mVEP operator may also affect the overall reliability of the results due to the importance in obtaining accurate results of additional factors such as correct placement of electrodes during the initial test, and their same placement at subsequent visits in order to obtain comparable data to follow patients over time (Hood & Greenstein 2003). Interpretation of mVEP results also requires competent and experienced electrophysiologists (Hood & Greenstein 2003).

Marketing status of the device

The only device currently listed on the Australian Register of Therapeutic Goods is the AccuMap® (ObjectiVision), as AUST L 74921.

Current reimbursement arrangement

There is currently no reimbursement arrangement with the Medicare Benefits Schedule regarding MMOP.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews published since the Reference 13 report (MSAC 2002). All identifiable terms that can be used to describe MMOP, SAP and the appropriate patients formed the core of the search. The search strategy was developed to cover all core terms and was used to search the databases detailed in Table 2 on the dates indicated.

Table 2 Electronic databases used in this review

Database	Search date
Cochrane Library	4 May 2004
Medline	11 May 2004
Medline in-process & other non-indexed citations	10 May 2004 No relevant records were retrieved
EMBASE	11 May 2004
CINAHL	10 May 2004 No relevant records were retrieved
Current contents	4 May 2004
Biological Abstracts	10 May 2004

The resulting references from all databases were scanned to identify those that fitted the inclusion criteria.

A safety filter was also applied to the core terms to filter out references applying to the safety aspects of MMOP. A further search was applied to the core terms to identify test retest references relating to MMOP and SAP. This search was not limited by year and included the complete Medline database.

Other search strategies

Relevant Health Technology Assessment websites (listed in Appendix D) were searched to identify completed reviews or economic evaluations of MMOP. Relevant clinical trial register websites (listed in Appendix D) were searched to identify clinical trials currently under way.

Unpublished studies provided by the applicant were also considered for inclusion in the review.

Selection criteria

Various criteria were developed *a priori* to determine eligibility of relevant studies. Table 3 outlines inclusion and exclusion criteria for assessing the diagnostic accuracy of MMOP and Table 4 outlines the selection criteria for studies assessing patient management and

outcomes following testing. These criteria were based on those agreed upon by the members of the MSAC Advisory Panel.

Table 3 Inclusion and exclusion criteria for diagnostic accuracy of MMOP

What are the diagnostic characteristics of MMOP compared to the reference standard (SAP), in detecting visual field defects?		
Characteristics	**Inclusion**	**Exclusion**
Patients	Patients being investigated or monitored for a visual field defect indicated by either the presence of relevant ocular disease or suspected pathology of the visual pathways or brain	None defined
Test	Multifocal VEPs recorded using MMOP such as AccuMap® or VERIS® and other commercially available mVEPs	Multifocal VEPs recorded using a multichannel sequential perimeter, mVEPs recorded using a single channel perimeter, single focal VEPs using a single channel perimeter
Reference standard	SAP (eg, HVF analyser and its derivatives)	Kinetic perimeters and manual static perimeters
Outcomes	Diagnostic characteristics of MMOP in detecting visual field defects, ie, sufficient data should be available to allow construction of the diagnostic two by two table with its four cells: true positive, true negative, false positive and false negative	Studies from which diagnostic characteristics could not be calculated
Study design	Cross-sectional studies that report the diagnostic characteristics in an independent blind comparison of MMOP and an appropriate reference standard (SAP, eg, Humphrey® visual field analyser) in a consecutively selected group of patients. In the absence of such studies, studies that report diagnostic characteristics in an independent blind or objective comparison in non-consecutively selected patients or studies that report diagnostic characteristics in which the reference standard was not applied to all patients. If none of the above exists, studies that report diagnostic accuracy without a reference standard in a consecutively selected case series may be considered	Narrative reviews, editorials, letters, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports and collections of case reports in which results are only presented by individual study patient and are not summarised
Publication	None defined	None defined

Table 4 Inclusion and exclusion criteria for patient management and health outcomes following MMOP

What is the effectiveness of MMOP for patient management and patient health outcomes?		
Characteristics	**Inclusion**	**Exclusion**
Patients	Patients being investigated or monitored for a visual field defect indicated by either the presence of relevant ocular disease or suspected pathology of the visual pathways or brain	None defined
Test	Multifocal VEPs recorded using MMOP such as AccuMap® or VERIS® and other commercially available mVEPs	Multifocal VEPs recorded using a multichannel sequential perimeter or a single channel perimeter, single focal VEPs using a single channel perimeter
Comparator (reference standard)	SAP (eg, Humphrey® visual field analyser and its derivatives)	Kinetic and manual static perimeters
Outcomes	Patient management options and health outcomes following application of the test (eg, measures of disease progression or quality of life)	None defined
Study design	Health technology assessments, systematic reviews, meta-analyses and randomised controlled trials will be sought initially. If these are unavailable, other controlled trials, comparative studies and cohort studies may be assessed. In the event that these are also unavailable, case series of consecutively selected patients may be considered	Narrative reviews, editorials, letters, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports and collections of case reports in which results are only presented by individual study patient and not summarised
Publication	None defined	None defined

Assessment of validity

Safety

Studies identified after the application of the safety filter to the search strategy were retrieved and examined. Adverse event data relating to MMOP were extracted and tabulated. Studies of any design were included in the review of safety because information indicating whether or not a procedure is safe is as important as its safety compared to other alternatives.

Effectiveness

Articles meeting inclusion criteria for assessment of effectiveness underwent critical appraisal to evaluate the potential for bias of their study designs. Critical appraisal was performed to determine:

- the accuracy of the test, ie the diagnostic characteristics; and
- the effectiveness of the test for subsequent patient management options and patient health outcomes.

Part 1: Diagnostic accuracy of MMOP

The most rigorous study design for assessing the validity of diagnostic tests is considered to be a prospectively-designed, cross-sectional study that independently compares the diagnostic characteristics of the test with an appropriate reference standard in consecutively-selected patients from a relevant clinical population (Jaeschke et al 1994a, Sackett et al 2000, Knotterus & van Weel 2002). The Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests (1996) expands on this definition and recommends the following criteria for assessment of validity of evidence pertaining to diagnostic tests:

- Test being evaluated (study test) is compared with an appropriate reference standard.
- Study test and reference test are measured independently (blind) of each other.
- Choice of patients assessed by the reference standard was independent of the results of the study test.
- Study test was measured independently of all other clinical information.
- Reference standard was measured before any interventions were started with knowledge of test results.
- Tests were compared in a valid study design: tests done independently on each person (most valid), different tests done on randomly allocated individuals, all tests done on each person but not assessed independently, different tests on different individuals, not randomly allocated (least valid).

Based on these criteria, the validity of the methodology of included articles was assessed against the checklist in Table 5.

Table 5 Criteria and definitions for assessing validity of diagnostic studies

Validity criteria	Definition
Test is compared with an appropriate reference standard	Patients in the study should have undergone both the diagnostic test in question and a reference test that would provide confirmatory proof that they do or do not have the target disorder
Appropriate spectrum of consecutive patients	Study included patients that the test would normally be used on in clinical practice, ie patients covering the spectrum of mild to severe cases of the target disorder, early and late cases, and patients with other, commonly confused diagnoses. An inappropriate spectrum compares patients already known to have the disorder with a group of normal non-diseased patients (case-referent) or with patients diagnosed with another condition
Masked assessment of study and reference tests results	The study test and the reference test should be interpreted separately by persons unaware of the results of the other (avoidance of review bias)
All study subjects tested with both study and reference tests	The reference test should be applied regardless of a positive or negative result from the study test (avoidance of work-up/verification bias)
Study test measured independently of clinical information	The person interpreting the test should be masked to clinical history and results of any other tests performed previously
Reference test measured prior to any interventions	No treatment interventions should be initiated prior to the application of the reference test

Source: The Cochrane Methods Working Group 1996

Reporting accuracy outcomes

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared to the most appropriate reference standard. Accuracy is measured by diagnostic characteristics such as sensitivity and specificity. The diagnostic characteristics of MMOP were reviewed, subject to the availability of sufficient data to compute diagnostic two-by-two tables. For computing sensitivity, sufficient data must be available to compute the proportion of subjects with the disorder whose tests were correctly identified as positive. For specificity, data are required to compute the proportion of patients without the disorder whose tests were correctly identified as negative.

Diagnostic test results are summarised in two-by-two tables (Table 6). Individuals who test positive for the disease in both the study test under investigation and the reference test are represented in cell "a" and are called true positives (TP). Individuals without the disease who test negative in both tests (the "d" cell) are called true negatives (TN).

A diagnostic test may produce discordance between the test result and the true disease status of the subject. In this case, a false result is reported. Cells "b" and "c" in Table 6 illustrate these situations. In the former, the test is positive in individuals without the disease. In the latter case, the test is negative in individuals with the disease. These two sets of false results are called false positives (FP) and false negatives (FN), respectively.

Table 6 The generic relationship between results of the diagnostic test and disease status

Study Test Results	True Disease Status (Reference standard)		
	Diseased	Not Diseased	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Abbreviations: a=number of diseased individuals detected by the test; b=number of individuals without disease detected by the test; c=number of diseased individuals not detected by the test; d=number of individuals without disease not detected by the test; a+b=total number of individuals testing positive; c+d=total number of individuals testing negative; a+c=total number of diseased individuals; b+d=total number of individuals without disease; a+b+c+d=total number of individuals studied

Included studies were also classified according to a hierarchy of evidence (Table 7) using an adaptation of the system developed by the UK Centre for Evidence Based Medicine, National Health Service Research and Development (1999) because the National Health and Medical Research Council (NHMRC) of Australia does not have a system for assigning a hierarchy of evidence to studies of diagnostic tests. The levels of evidence reflect the methodological rigour of the studies. A study assigned as Level I evidence is considered the most rigorous and least susceptible to bias, while a study deemed to contain Level IV evidence is considered the least rigorous and most susceptible to bias. It should be noted that these levels exclude categorisation of systematic reviews of Level I studies of diagnostic tests which would be considered Level I evidence.

Table 7 Levels of evidence for diagnostic tests

Level of Evidence	Criteria
I	Independent blind comparison of an appropriate spectrum of consecutive patients, all of who have undergone both the diagnostic test and the reference standard
II	Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard
III	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients
IV	Any of: Reference standard was not applied blinded or not applied independently. No reference test applied (case series)

Sensitivity and Specificity

Sensitivity is a measure of the probability of correctly diagnosing someone with the disease, or the probability that any given case will be identified by the test.

$$Sensitivity = \frac{a}{a+c} = \frac{TP}{TP+FN}$$

Conversely, specificity is the probability of correctly identifying a person without disease or the proportion of individuals without disease who test negative.

$$Specificity = \frac{d}{b+d} = \frac{TN}{TN+FP}$$

Part 2: Patient management and patient health outcomes following MMOP

Detection of the pathology of the diagnostic procedure under consideration is not the only indicator of the usefulness of the test. Unless application of the procedure improves patient management options, and ultimately patient health outcomes, its usefulness is considered limited (Sackett et al 2000). In order to establish whether a diagnostic test is superior in effectiveness compared to the reference standard, the most rigorous study design is considered to be a randomised controlled trial (Guyatt et al 1993, Sackett et al 2000) comparing outcomes in a group of patients who have undergone the diagnostic test with outcomes in a group of patients who have undergone the reference standard.

The evidence identified for this section of the review was assessed and classified using the dimensions of evidence defined in NHMRC (2000), as presented in Table 8.

These dimensions consider important aspects of the evidence supporting a particular intervention and include the three domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. Determination of the last two requires expert clinical input.

Table 8 Evidence dimensions (NHMRC 2000)

Dimensions	Definition
Strength of the evidence:	
- Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
- Quality	The methods used by investigators to minimise bias within a study design
- Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a]See Table 9

The three sub-domains level, quality and statistical precision are together a measure of the strength of the evidence. The level of evidence is a measure of the susceptibility to bias of various study designs. Level I evidence implies a study design that is least susceptible to bias, while Level IV evidence implies a study design that is most susceptible to bias. The designations of the levels of evidence are shown in Table 9.

Table 9 Designations of levels of evidence (modified from NHMRC 2000)

Levels of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

All accepted articles were assessed for study validity (Table 10) based on criteria related to important aspects of study design (Schulz et al 1995, Jadad et al 1996, NHS Centre for Reviews and Dissemination 2001).

Table 10 Validity criteria according to study design

Study design	Validity criteria
Systematic review	Focused research question; explicit inclusion/exclusion criteria; explicit and comprehensive search strategy; validity of included studies appraised; homogeneity between studies assessed; summary of main results; strengths and limitations
Randomised controlled trial	Randomised method; allocation concealment; blinding of patients, investigators and outcome assessors; proportion lost to follow-up; intention to treat analysis
Cohort	Prospective/ retrospective; comparable groups at inception; identification and adjustment for confounding factors; blind outcome assessment; sufficient duration of follow-up; proportion lost to follow-up
Case-control	Explicit definition of cases; adequate details of selection of controls; comparable groups with respect to confounding factors; interventions and other exposures assessed in same way for cases and controls; appropriate statistical analysis
Case series	Indication was comparable across patients; disease severity was comparable across patients; explicit entry criteria; outcome assessed in all patients; follow-up time uniform; outcomes assessed objectively; outcomes assessed in a blinded manner; outcome measures quantified

Adapted from NHS Centre for Reviews and Dissemination (2001)

Data extraction

Data were extracted using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus. Contact with corresponding authors was attempted to clarify specific issues relating to validity or results.

Expert advice

An Advisory Panel with expertise in ophthalmology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for the Advisory Panel, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Search results

The search strategy identified 461 articles (Figure 4). From the review of the abstracts, 24 articles were ordered for full text assessment. Of these, nine articles met the inclusion criteria and 15 were excluded for the following reasons: inappropriate patient group (n= 3), not multichannel mVEP (n=6), narrative review (n=1), case report (n=1), no reference test (n=2), could not extract data (n=1) and not investigating diagnosis (n=1). Additional references provided by the applicant were also reviewed. Of the 20 articles provided, 11 were excluded before full-text review for the following reasons: abstract only (n=10) and sequential multichannel VEP (n=1).

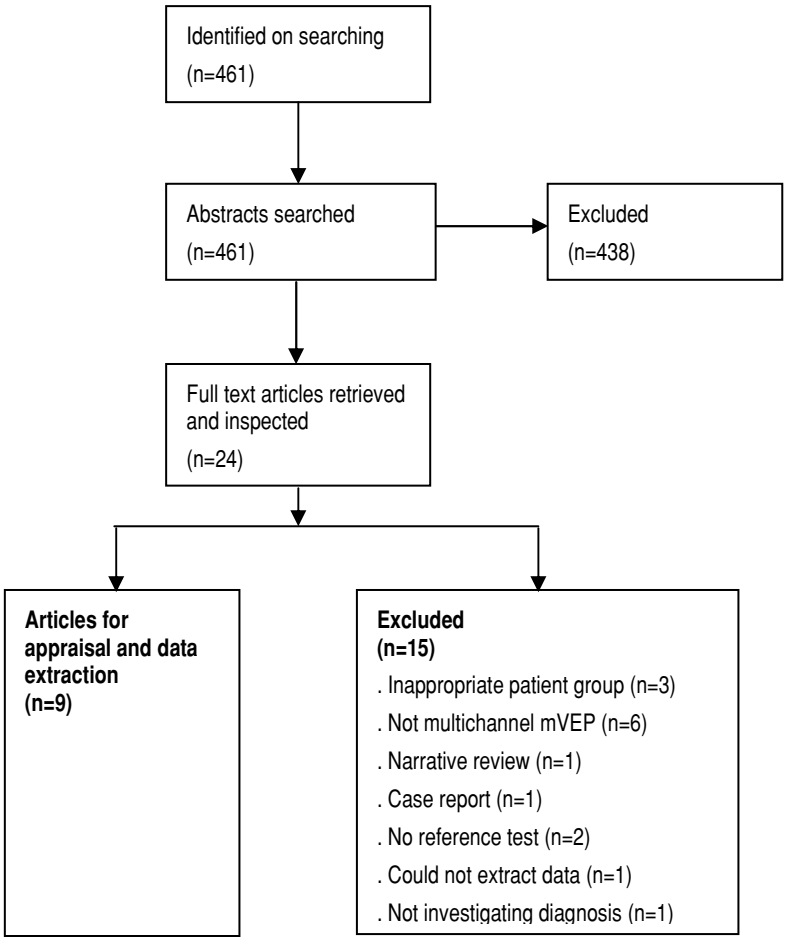


Figure 4 **Selection of articles assessing the effectiveness of MMOP for the diagnosis of visual field defects**

Is it safe?

Although an extensive literature search revealed a lack of safety data, the risks to subjects should be minimal as the test is non-invasive. To record mVEPs, four electrodes are placed on the back of the scalp over the area of the occipital cortex. Skin irritation may be associated with the use of scalp electrodes. Although these possibilities are acknowledged in the literature (Graham & Vaegan 1991, Chan & Brown 1998), no frequencies of adverse events were reported in any of the papers reviewed.

Is it effective?

Item I: Diagnostic characteristics

Nine studies were identified that met the inclusion criteria for diagnostic characteristics: five case referent (Klistorner & Graham 2000, Bengtsson 2002, Goldberg et al 2002, Thienprasiddhi et al 2003, Fortune et al unpublished) and four case series (Woodward & Wall 2002, Balachandran et al unpublished, Graham et al unpublished[1], Klistorner et al unpublished). The majority of studies assessed the diagnostic characteristics of mVEP in adults with glaucoma or suspected glaucoma. One study assessed patients with neurological lesions (Klistorner et al unpublished) and one study investigated patients with functional visual loss (Woodward & Wall 2002). The majority of studies compared the test results of the AccuMap® with those of the HVF analyser 24-2 (SITA or full threshold) (Table 11). Only the study by Klistorner & Graham (2000) investigated the diagnostic accuracy of MMOP using the VERIS® device.

[1] At the time of searching this citation was unpublished and was subsequently published: Graham, S.L., Klistorner, A. & Goldberg, I. 2005. 'Clinical application of multifocal VEP objective perimetry in glaucoma practice.' Arch Ophthalmol, 123 (6), 729-39.

Table 11 Study characteristics of included studies

Study	Setting[a]	Spectrum of subjects					Reference Standard
		Study design	Disease	Sample size	Age (years) Mean (SD), range	Sex ratio (M:F)	
Balachandran et al (unpublished)	Sydney, Australia	CS	Glaucoma	128 (glaucoma) 128 (high risk suspects)	60 (12) 57 (12)	1.2:1 1:1.5	HVF 24-2[c]
Bengtsson (2002)	Malmö, Sweden	CR	Glaucoma	33 (normal) 33 (glaucoma)	41 24-66 71 58-82	1:2 6:5	HVF 30-2 (SITA fast)
Fortune et al (unpublished)	Portland, USA	CR	Glaucoma	35 (normal)	53.2 (13.7)	NR	HVF 24-2[c]
Goldberg et al (2002)	Sydney, Australia	CR	Glaucoma	100 (normal) 100 (glaucoma)	58.9 (10.7) 62.2 (9.8), 42-72	NR 11:9	HVF 24-2[c]
Graham et al (unpublished)	Sydney, Australia	RCR	Glaucoma	83 (Low risk 107 (high risk suspects) 245 (glaucoma)	NR NR NR	NR NR NR	HVF 24-2[c]
Klistorner[b] & Graham (2000)	Sydney, Australia	CR	Glaucoma	30 (normal) 30 (suspected) 30 (glaucoma)	54.1 (9.7), 39-75 53.1 (9.6), 25-71 58.9 (9.5), 42-72	8:7 8:7 8:7	HVF 24-2[c]
Klistorner et al (unpublished)	Sydney, Australia	CS	Neurologic lesions	18 (Hemianopia or quadrant-anopia)	62 (11.5), 43-80	1:1	HVF 24-2[c]
Thienprasiddhi et al (2003)	New York, USA	CR	Glaucoma	30 normal 16 (glaucoma)	36 (13) 56 (6)	NR NR	HVF 24-2[c]
Woodward & Wall (2002)	Iowa USA	CS	Functional visual loss	8	25.5 (8.83), 16-40	NR	HVF 24-2 (SITA)

[a]Dates of enrolment were not reported for any of the included studies
[b]Klistorner 2000 used VERIS for the MMOP and all other studies used AccuMap
[c]SITA or full threshold
Abbreviations: NR, not reported; CR, case referent; CS, case series; RCR, retrospective case referent

Study design

The majority of studies were of case referent design in which patients with a known diagnosis of glaucoma were compared with either normal controls or glaucoma suspects who had normal visual fields. With the exception of Graham et al (unpublished), all studies were prospective – patients were diagnosed with glaucoma prior to the application of MMOP. The study by Graham et al (unpublished) was retrospective – patients tested with MMOP over a 12-month period were selected. Clinical diagnosis of these patients was retrospectively reviewed based on optic disc appearance and visual fields. Patients were then classified as either high- or low-risk suspects or glaucoma subjects. For all three patient groups, MMOP results were compared against visual field results and/or optic disc data.

For all studies, analysis of sensitivity and specificity was based on two study populations, since patients were generally preselected or predefined according to their visual field results. Therefore, sensitivity calculations were derived only for patients with glaucoma

while specificity results were solely based on control and/or suspect patients. Generally diagnostic characteristics were only calculated for patients with reliable visual fields (Klistorner & Graham 2000; Bengtsson 2002, Goldberg et al 2002, Balachandran et al unpublished, Fortune et al unpublished) although the study by Graham et al (unpublished) investigated those with variable or unconfirmed visual field results.

Patients

The patients recruited for the included studies generally consisted of glaucoma subjects, glaucoma suspects and normal controls. Selection criteria for all study groups are described in Appendix G.

Glaucoma was generally defined by a number of criteria such as confirmed visual defect with the HVF analyser 24-2, a glaucomatous optic disc judged by stereo disc photography and an abnormal glaucoma hemifield test. Additional criteria such as raised IOP (Bengtsson 2002) and a minimum specification of scotoma (Klistorner & Graham 2000, Goldberg et al 2002, Balachandran et al unpublished) were not consistently used across studies to confirm disease.

Subjects with normal visual fields were either normal controls or glaucoma suspects who had normal visual fields. Generally, normal controls were patients with normal intraocular pressure and ophthalmoscopy and no family history of glaucoma or retinal dystrophy. In these patients, visual fields were generally confirmed by the HVF analyser (Klistorner & Graham 2000, Bengtsson 2002, Goldberg et al 2002, Fortune et al unpublished), although the study by Thienprasiddhi et al (2003) used a combination of tests (Goldmann applanation tonometry, stereoscopic optic nerve photography and HVF test).

Glaucoma suspects were investigated in three studies (Klistorner & Graham 2000; Balachandran et al unpublished, Graham et al unpublished). Graham et al (unpublished) divided suspects into high and low risk, where low-risk subjects were defined as having OHT greater than 21 mm Hg and/or a family history of glaucoma, but normal optic discs and visual fields. High-risk suspects were classified as having suspicious or abnormal optic appearance and/or asymmetrical discs (>0.2 difference in cup/disc ratio) with or without raised IOP, but still normal visual field. Balachandran et al (unpublished) identified two groups of pre-perimetric patients with normal visual fields. Those in the high-risk glaucoma group included patients with a "suspicious" optic disc (cup/disc ratio $\geq$ 0.8 and inter-eye cup/disc ratio difference $\geq$ 0.2) regardless of IOP, while those in the OHT group included patients with IOP $\geq$ 23 mm Hg, and no optic disc abnormality.

Two studies were identified which evaluated MMOP for indications other than glaucoma (Klistorner et al unpublished, Woodward & Wall 2002). Klistorner et al (unpublished) evaluated visual field in patients with neurological disease (hemianopia or quadrantanopia) and Woodward & Wall (2002) evaluated patients with functional visual loss.

Diagnostic tests and thresholds of positivity

Although the majority of studies assessed the test results of the AccuMap® with those of the HVF analyser 24-2 (SITA or full threshold) the criteria (thresholds) used to classify patients as normal or abnormal were not consistently applied across studies (Table 12). For the majority of studies, the threshold of positivity used to define disease was a

combination of any of the following criteria: presence of scotoma in the Humphrey 24-2 pattern deviation plot, abnormal on the glaucoma hemifield test and glaucomatous optic disc (Klistorner & Graham 2000, Goldberg et al 2002, Thienprasiddhi et al 2003, Balachandran et al unpublished, Fortune et al unpublished, Graham et al unpublished). The combination of tests was not consistent between studies and often different scotoma criteria were used to define visual field defects. With regards to MMOP, different scotoma criteria were generally used to define visual field abnormalities although some studies also used severity indices (Klistorner 2000, Bengtsson 2002, Fortune et al unpublished, Graham et al unpublished).

Table 12 Thresholds of positivity for MMOP and reference test

Study	Reference test	MMOP thresholds
Balachandran et al (unpublished)	Humphrey 24-2 pattern deviation plot: A minimum scotoma required at least 3 abnormal points and at least 2 points depressed by p<0.005[b] and presence of glaucomatous optic disc	A scotoma was diagnosed if on the amplitude deviation plot there were ≥3 non-rim points less than p<0.05 of the normal database, with ≥1 point <0.02, or there were ≥3 contiguous points with p<0.05
Bengtsson (2002)	Humphrey® 30-2 field test (thresholds not provided)	Used RAC to designate results as 'outside normal limits', 'within normal limits' or 'borderline'
Fortune et al (unpublished)	Humphrey 24-2 thresholds, p<0.05 for mean defect, pattern standard deviation (thresholds not specified) or glaucoma hemifield test abnormal glaucomatous optic disc	Number of abnormal VEP points below p=0.02 As above but below p=0.01 Severity index: Normal <30; borderline 30-39 and Abnormal >39 A cluster of ≥3 abnormal sectors on the interocular asymmetry plot (p<0.1%) plus monocular amplitude criteria
Goldberg et al (2002)	Humphrey® 24-2 pattern deviation plot. A minimum scotoma required at least 3 adjacent points depressed by p<0.005[b] and glaucoma hemifield as abnormal	Localised field defects defined as: A cluster of three zones with a p value <0.05 with at least one zone with a p value <0.02
Graham et al (unpublished)	Humphrey® glaucoma hemifield test abnormal and abnormal optic disc	The AccuMap® Severity index (ASI): Normal: 0-11, borderline: 11-19 and abnormal ≥20 mVEP amplitude deviation plot: A cluster of 3 points in one hemifield, with p < 0.02 and at least one point p < 0.01 mVEP asymmetry plot: A cluster of 3 points with p < 0.01 or 2 points with p < 0.005
Klistorner & Graham[a] (2000)	Humphrey® 24-2 pattern deviation plot. A minimum scotoma required at least 3 adjacent points depressed by p<0.005[b] and glaucoma hemifield as abnormal and glaucomatous optic disc by stereo disc photography and IOP>21	A signal amplitude of less than 120 nV in at least three adjacent points in the matching area A signal amplitude p<0.05 in at least three adjacent points in the matching area Response Asymmetry Coefficient (RAC) p<0.05 Response Asymmetry Coefficient p<0.01
Klistorner et al (unpublished)	Humphrey® visual field analyser (thresholds not specified) and neuroimaging findings	mVEP amplitudes in the combined trace array were compared with the normals database percentiles and a probability plot was constructed. Clusters of points (>10) for which p<0.1 was used to indicate scotoma
Thienprasiddhi et al (2003)	Humphrey® 24-2 pattern deviation plot. >2 adjacent points with p<0.01 or >3 adjacent points with p<0.05. Other hemifields in affected eye and both hemifields in the unaffected eye did not have points satisfying the above criteria and glaucomatous optic nerve damage	2 or more adjacent points with p<0.01 or 3 or more adjacent points p<0.02 and at least one point p<0.01
Woodward & Wall (2002)	Humphrey® visual field analyser (thresholds not specified), Goldmann neuro-ophthalmological examinations	Criterion for visual field defect was three contiguous points at p < 0.01 found in the amplitude deviation probability plot

[a]Klistorner & Graham (2000) used VERIS for the MMOP and all other studies used AccuMap®
[b]The cluster of abnormal points could not cross the horizontal meridian and points immediately above or below the blind spot could not quantify as part of the scotoma

Study validity

All studies were classified as level IV evidence based on the validity criteria outlined in Table 5. Critical appraisal was measured against five validity criteria: i) recruitment of an appropriate spectrum of patients, ii) masked assessment of study and reference test results, iii) whether all subjects were tested with study and reference tests, iv) whether the tests were performed independently (blinded) to clinical information and v) measurement of reference test prior to any intervention. Validity criteria of included studies are outlined in Table 13.

Table 13 Validity of the included studies

Study	Validity of study methods				
	Appropriate spectrum of consecutive subjects	Masked assessment of study and reference test results	All subjects tested with both study and reference tests	Tests measured independently of clinical information	Tests measured prior to start of intervention
Balachandran et al (unpublished)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Not stated
Bengtsson (2002)	No (pre-diagnosed subject groups)	Not stated	No[a]	No	Not stated
Fortune et al (unpublished)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Not stated
Goldberg et al (2002)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Not stated
Graham et al (unpublished)	No (pre-diagnosed subject groups)	Unclear	Yes	Unclear	Not stated
Klistorner & Graham (2000)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Not stated
Klistorner et al (unpublished)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Yes
Thienprasiddhi et al (2003)	No (pre-diagnosed subject groups)	Not stated	Yes	No	Not stated
Woodward & Wall (2002)	No (pre-diagnosed subject groups)	No	Yes	No	Not stated

[a]Controls not tested with reference test

None of the studies recruited an appropriate spectrum of subjects (ie undiagnosed patients with suspected visual field defects) since patients were prediagnosed with disease or suspected disease before the application of MMOP. This was also true for the study by Graham (unpublished) in which patients were characterised as low- or high-risk subjects. Generally, disease was confirmed using a number of methods such as HVF analysis, stereo disc photography and a glaucoma hemifield test. Furthermore, since the majority of patients being investigated had glaucoma or suspected glaucoma, it is unclear whether these results can be applied to other diseases where visual field loss is indicated.

For all studies, it is uncertain whether assessment of MMOP and SAP results were masked, since the majority of studies had used the reference to identify patients for inclusion. Although one study (Graham et al unpublished) reported that investigators were masked to both MMOP and visual field results, it is unclear whether blinded assessment occurred when these tests were performed, given that the study was retrospective. In addition, none of the studies adequately addressed whether the tests were measured independently of clinical information.

It is unclear whether any of the studies measured patients before the start of medication. However, given that glaucoma is irreversible, the use or otherwise of medication is unlikely to affect the diagnosis of the disease.

Most of the studies were case referent or phase one, which are generally designed to determine whether the results differ for patients with the target disorder compared to those without disease (Sackett & Haynes 2002). In general, these studies are unable to answer adequately whether the new test can distinguish patients of different disease severities or stages. In fact, a study by Lijmer et al (1999) demonstrated that case referent

tests often omit mild or difficult to diagnose cases, thereby causing an overestimation of sensitivity. The studies by Klistorner & Graham (2000), Bengtsson (2002) and Graham et al (unpublished) attempted to address this possibility by analysing patients at different stages of glaucoma. Furthermore, for the majority of studies (Bengtsson 2002, Goldberg et al 2002, Woodward & Wall 2002, Thienprasiddhi et al 2003, Balachandran et al unpublished, Fortune et al unpublished, Klistorner et al unpublished) patient selection was non-consecutive, which can result in selection bias if patients who are likely to perform poorly on MMOP or have poor mVEP results are omitted. For example, the majority of studies excluded patients with unreliable or unreproducible visual fields, which may bias the results in favour of MMOP if the same patients were also poor performers on MMOP.

Another factor which may influence the results is the time interval between the reference test and MMOP, as disease may have developed during this period. For Goldberg et al (2002) and Bengtsson (2002), visual field results were obtained at least six months prior to inclusion, and it is unclear whether this applies to when MMOP was conducted. Only the study by Klistorner & Graham (2000) reported that SAP and MMOP were performed on the same day. Similarly, in the study by Graham et al (unpublished), the majority of tests were conducted on the same day, although in some instances, the difference was as much as four months between tests (personal correspondence with author).

Results

Glaucoma

Diagnostic characteristics for patients with glaucoma are outlined in Table 14. Overall, the sensitivity of MMOP ranged from 75 to 100 per cent, with the majority of studies reporting sensitivities over 90 per cent. Variations in sensitivity may be explained by the different MMOP thresholds used to classify disease. This was demonstrated by Fortune et al (unpublished) and Graham et al (unpublished) for which specificities ranged from 75 to 97 per cent depending on the threshold used. It is unclear whether differences in patient populations have contributed to the variation in specificity, as no clear pattern of difference was observed between those studies which used patients at different stages of disease and those that did not.

The specificity of MMOP varied almost two-fold, from 45 to 93 per cent, depending on the population under study and/or MMOP thresholds. Generally, specificity was highest for analyses using normal controls or low risk suspects (Klistorner & Graham 2000, Goldberg et al 2002, Fortune et al unpublished, Graham et al unpublished).

Table 14 Diagnostic characteristics for glaucoma patients

Study	Humphrey® test	AccuMap®	Sample size Sensitivity	Sensitivity %[a]	Sample size Specificity	Specificity %[b]
Balachandran et al (unpublished)	GHT and disk photography	Scotoma criteria (see Table 12, this report)	128 glaucoma	93	OHT (number not stated) High risk suspects (number not stated)	45 64
Bengtsson (2002)	30-2	RAC severity index	47 glaucoma eyes	81		Not calculable
Fortune et al (unpublished)	24-2 program, stereo disc photographs and GHT	Number of abnormal VEP points below p=0.02	36 glaucoma	75	35 Normal	90
		Number of abnormal VEP points below p=0.01	36 glaucoma	82	NR	NR
		Severity index	36 glaucoma	78	NR	NR
		A cluster of ≥3 abnormal sectors on the interocular asymmetry plot (p<0.1%) plus monocular amplitude criteria	36 glaucoma	97	NR	NR
Goldberg et al (2002)	24-2 program, stereo disk photography and GHT	Scotoma criteria (see table EF2)	100 glaucoma	95	100 controls	97
Graham et al (unpublished)	GHT and disk photography and	AccuMap®severity index	286 glaucoma eyes	98	398 suspect eyes	86
		mVEP amplitude deviation plot: a cluster of 3 points in one hemifield, with p < 0.02 and at least one point p < 0.01	286 glaucoma eyes	96	180 low risk eyes	92
		mVEP asymmetry plot: a cluster of 3 points with p < 0.01 or 2 points with p < 0.005	286 glaucoma eyes	89	180 low risk eyes	92
Klistorner & Graham (2000)	24-2 program, stereo disk photography and GHT	Trace amplitude 3 pts <120nV	30 glaucoma	100	60 (30 normal + 30 suspects)	93
		Trace amplitude 3 pts <0.05	30 glaucoma	100	60 (30 normal + 30 suspects)	95
		RAC values p<0.05	30 glaucoma	100	60 (30 normal + 30 suspects)	82
		RAC values p<0.01	30 glaucoma	100	60 (30 normal + 30 suspects)	93
Thienprasiddhi et al (2003)	24-2 program, stereo disk photography	Scotoma criteria (see Table 12, this report)	16 glaucoma	94	60 control hemifields	97

[a]Sensitivity is based only on patients with a known diagnosis of glaucoma
[b]Specificity is based on patients with normal visual fields (controls and suspect)
Abbreviations: NR, not recorded; OHT, ocular hypertension, GHT, glaucoma hemifield test

Pre-perimetric disease

The results from Klistorner & Graham (2000), Balachandran et al (unpublished) and Graham et al (unpublished) were evaluated to determine if MMOP was able to diagnose patients with pre-perimetric disease. All of the studies in Table 14 investigated glaucoma suspects who had risk factors for glaucoma but normal visual fields.

Klistorner & Graham (2000) evaluated 30 glaucoma suspects with normal visual fields using four different criteria for abnormality on MMOP. Depending on the criteria used, the number of false positives in the suspect group changed. For example, when the criterion 'Response Asymmetry Coefficient values of 3 points $p<0.05$' was used, 33 per cent of patients were classified as false positives, compared to 6 per cent when 'trace amplitude 3 points $p<0.05$' was used. As the disease status of patients was not confirmed, it is unclear if MMOP was actually selecting out pre-perimetric disease or whether diagnosis of patients in this group was an anomaly of the test.

In the study by Graham et al (unpublished), which used a combination of low- and high-risk eyes, specificity was 86 per cent. Of the 56 false positives, 12 were low risk eyes, 30 were high-risk eyes and 14 were from the fellow eyes (with a normal visual field) of patients with glaucoma. The authors made further investigations in order to confirm the diagnosis of glaucoma for patients with false positive results.

Of the 12 low-risk eyes, 66 per cent appeared to have medium to high refractive error, a known cause of reduced mVEP central amplitude. Of the 30 high-risk eyes classified as false positives, 16 were borderline and 14 eyes were abnormal. The authors report that 74 per cent of these eyes (22/30) were classified as either pre-perimetric or as having asymmetric discs. The significance of this result is unclear, given that high-risk subjects were already defined as having suspicious or abnormal optic disc appearance and/or asymmetrical discs (see Appendix G). Seven of the 14 (50%) high-risk eyes were classified as pre-perimetric based on optic disc analysis. For all risk categories it is unclear whether MMOP was detecting pre-perimetric disease, as confirmation of disease was not reported for those patients classified as true negatives. There may also be additional factors, such as refractive error, that explain these false positive results.

Furthermore, given that the study was retrospective, it is unclear what the time interval was between tests. For example, if there was a significant time lag, patients with a normal HVF may have developed a visual field defect by the time they were tested with MMOP. Therefore, it may be that MMOP is actually diagnosing visual field loss and not pre-perimetric disease.

The highest false positive rates of 46 per cent for high-risk suspects and 55 per cent for OHT patients were reported by Balachandran et al (unpublished). The result for high risk patients was almost double that observed for high risk subjects in Graham et al (unpublished). This result may be explained by the fact that definition of high risk was different between studies and that different MMOP thresholds were used. It could not be confirmed that MMOP was able to diagnose pre-perimetric disease because disease status, confirmed as retinal nerve fibre loss or disease progression, was not reported. In order to demonstrate whether MMOP can accurately diagnose pre-perimetric disease, longitudinal studies are required to determine if those patients with pre-perimetric disease diagnosed by MMOP actually develop glaucoma.

Patients with unconfirmed, variable or irregular SAP

Graham et al (unpublished) evaluated the results of mVEP in patients with variable/unconfirmed SAP and also patients with excessive loss who had a mild to normal disc. It is unclear what the overall value of mVEP is in this group of subjects as mVEP results were not verified.

Neurological lesions

Klistorner et al (unpublished) evaluated MMOP in 11 patients with hemianopia and eight patients with quadrantanopia. All patients had positive HFV results. Overall MMOP was able to detect visual field loss in all the hemianopia patients and four of seven quadrantanopia patients. The authors reported that further investigation of quadrantinopic patients revealed that of the three misdiagnosed patients, all had features consistent with an extra-striate lesion while the other four cases had field defects characteristic of lesions at or prior to the striate cortex. Therefore, low sensitivity in the quadrantinopic patients could be explained by the fact that their lesions may have been in the extra-striate area which would be missed by MMOP for which the signal is derived from the V1 visual cortex.

There is some suggestion that MMOP has the potential to detect functional visual loss. For example, in a small study on a selected group of patients by Woodward & Wall (2002), patients with confirmed diagnosis of functional visual loss (by neuro-ophthalmological examination) who were misdiagnosed using HVF were assessed using MMOP. Eight of 13 patients were correctly diagnosed by MMOP but it should be noted that the investigators were not blinded to the patient's diagnosis.

Discussion

Due to the limitations of the available evidence, it is unclear whether MMOP is equivalent to SAP in terms of diagnostic accuracy in patients with undiagnosed visual field defects.

Overall the diagnostic accuracy of MMOP could not be established as there were wide variations in the sensitivity (75–100 per cent) and specificity (45–97 per cent). Such differences may have been due to study design and methods. For example, sensitivity results were highly dependent on the MMOP thresholds used to characterise disease. The applicant states that the accepted threshold for the AccuMap® is the AccuMap Severity Index or a cluster of three or more abnormal points in one hemifield. Such variations however may affect the use of MMOP in practice as it is unclear which threshold is most likely to give an accurate result. Furthermore, specificities were usually dependent on the population used. For example, specificities were highest in studies that used normal controls and lower where glaucoma suspects were used.

The ability of MMOP to diagnose pre-perimetric patients was not adequately addressed in any of the studies as the disease status for the majority of patients was unknown. In order to determine the true predictive value of MMOP, longitudinal data are required to determine if patients actually developed disease.

In general, 80 per cent of the validity criteria outlined in Table 5 were unmet. Furthermore, it is unclear where the true diagnostic accuracy of MMOP lies, given that these results are subject to study bias. For example, the majority of patients were already

prediagnosed based on their visual field results and other diagnostic criteria, the reference test was not applied independently of test results and assessment of results was not blinded. With the high potential for additional clinical information to influence the overall diagnostic results in these studies, it is unclear whether MMOP can be used as a stand alone test.

As none of the studies recruited an appropriate spectrum of subjects, the diagnostic value of MMOP is uncertain. In addition, the majority of studies recruited glaucoma patients so it is unclear how the results can be applied to patients with visual field defects resulting from other pathologies. Indeed, MMOP may be of limited use in the diagnosis of other diseases where damage is not localized to the visual cortex. For example, Klistorner et al (unpublished) showed that MMOP may be a poor test for the diagnosis of quadrantinopic patients with damage in the extrastriate area.

Item II: Patient management and patient health outcomes data

No studies that examined patient outcomes and patient management options as a result of MMOP were identified that met the inclusion criteria.

Item III: Test retest reliability

It has been suggested by the applicant that an advantage of MMOP over SAP is higher diagnostic accuracy and good repeat reliability, allowing accurate diagnosis with only one test (MSAC Application 1078). The recognised learning curve associated with SAP (Klistorner & Graham 2000) may require that patients undergo a number of tests before an accurate diagnosis can be made. A systematic review was therefore conducted to assess whether the repeat reliability of MMOP was superior to that of SAP.

Included MMOP or SAP studies were those that used appropriate methods for assessing agreement between test sessions for outcomes relating to diagnosis. For binary outcomes such as diagnosis as diseased or non-diseased, the statistic most often used to evaluate repeat reliability is 'kappa', defined as the agreement beyond chance divided by the maximum possible agreement beyond chance. For outcomes measured on a numerical scale, agreement can be measured using the coefficient of variation which is defined as the standard deviation divided by the mean multiplied by 100 per cent. The test results are presumed to be consistent if the coefficient of variation is similar between tests or test sessions.

Another method for measuring agreement between tests is that of Bland & Altman (1986). As a first step, the point-wise numeric difference between tests is plotted against the means of the point-wise values for both tests, in order to investigate how much the observed values deviate from that of perfect agreement. The limits of agreement can then be calculated as the difference $\pm$ 2 standard deviations to determine the clinical significance of the results as well as the 95% confidence interval to establish the precision of the estimate.

The approach used to identify relevant articles was similar to that used for effectiveness however the term 'test adj retest' was added as an 'and' term to the overall search. Of the 184 studies identified, 24 evaluated the repeat reliability of either MMOP (n=3) or SAP (n=21). Only five of the 24 studies, all of which were case series, met the above inclusion

criteria. No head-to-head trials examining the repeat reliability of MMOP and SAP were identified.

Repeat reliability of MMOP

Study characteristics

Three studies were identified that evaluated the repeat reliability of the amplitude variation of the MMOP signal (Klistorner & Graham 2000, Goldberg et al 2002, Chen 2003) (Table 15). None of the studies reported the repeat reliability of MMOP in terms of visual field diagnosis.

The studies of Klistorner & Graham (2000) and Goldberg et al (2002) assessed the reproducibility of results for normal subjects. Goldberg et al (2002) evaluated 15 normal subjects tested on five separate days while Klistorner & Graham (2000) evaluated five healthy volunteers tested on four separate occasions. The time interval between tests was not reported for either study. The reproducibility of MMOP was expressed as the mean coefficient of variation for amplitude across all test zones for both studies. This estimate was derived from the mean and standard deviation of the amplitude across all testing sessions for each of the 58 test zones.

The study by Chen (2003) investigated 17 normal and 10 glaucoma subjects. Overall, subjects were tested on two separate sessions, separated by two weeks to three months, whereby two 7 minute runs were recorded within each session for each eye. This study reported the reproducibility of a response for an individual as the ratio of the amplitude of each mVEP response [root mean square (RMS) between day one and day two ie log ratio of RMS day 1/RMS day 2]. These log ratios were also multiplied by 10 to convert them to dB for comparisons with SAP. To obtain a measure of repeat reliability for each subject, the standard deviation of the mVEP ratio expressed as dB units was obtained for the 60 traces of each eye. Agreement between tests was also measured by correlation coefficient *r*. Analyses of the variations between days, and within a day, were also reported for control eyes. To determine the within session variability with regards to mVEP ratio, the first run of each eye on day one was compared with the first run of the corresponding eye on day two. Second runs were similarly compared for each respective eye.

Table 15 Patient and study characteristics for repeat reliability of MMOP

Study	Setting[a]	Spectrum of subjects			MMOP test	Time between tests	Outcome
		Sample number and status	Age in years Mean ±SD (range)	Sex ratio (M:F)			
Chen et al (2003)	New York, USA and Caracas, Venezuela	15 normal subjects 10 subjects: 8 with known and 2 with suspected glaucoma	32 (17-57) 60 (45-78)	Not stated	VERIS®	Between 2 weeks and 2 months	Ratio of day1 and day2 for the amplitude of each mVEP response RMS (ie 10* log ratio of RMS day1/RMS day2)
Goldberg et al (2002)	Sydney, Australia	15 normal subjects	Not stated	Not stated	AccuMap®	Not stated	Coefficient of variation for amplitude across all test zones for left and right eyes
Klistorner & Graham (2000)	Sydney, Australia	5 normal subjects	Not stated	Not stated	VERIS®	Not stated	Coefficient of variation for amplitude across all test zones

[a] Dates of enrolment were not stated
Abbreviations: RMS, root mean square

Results

In the study by Goldberg et al (2002), the average coefficient of variation was approximately 16±2 per cent for both eyes with a range of 10-20 per cent and for Klistorner & Graham (2000) it was 15±4.5 per cent with a range of 6.8 to 25.9 per cent.

The study by Chen (2003) reported a correlation coefficient between the two sessions of 0.85. In terms of repeat reliability, the mean standard deviation of the 60 mVEP ratios for controls was 1.63 dB for both eyes. For glaucomatous eyes, the repeat reliability of the less affected eye was superior to that of the more affected eye (1.57 dB vs 1.88 dB) with similar correlations observed (0.80 and 0.83, respectively). With regards to the repeat reliability within and across days, the mean standard deviation within a day was 1.52 and across days was 1.77.

The authors also compared their results with those of SAP using the data reported by Johnson & Spry (1999) which could not be verified as the abstract by Johnson and Spry (1999) did not contain the information cited by Chen (2003). According to Chen (2003), the study by Johnson & Spry (1999) tested 100 normal controls on two different days using SAP [24-2 Humphrey visual field (HVF) test]. Excluding the two points near the blind spot, the difference in sensitivity (dB) at each test site was calculated for each subject. The mean standard deviation of the difference over each test point was calculated. The result cited by Chen (2003) was for 100 individuals. The repeat reliability of SAP had a mean standard deviation of 2.54 dB compared with 1.63 dB for MMOP.

Discussion

Based on the results presented, the repeat reliability of MMOP in diagnosing visual field defects is unclear. None of the studies adequately validated the repeat reliability with regards to agreement between tests and none evaluated the primary outcome of

diagnosis. Furthermore, comparisons between MMOP and SAP are uncertain, given that the results for Johnson & Spry (1999) could not be validated.

The studies by Klistorner & Graham (2000) and Goldberg et al (2002) reported less than 20 per cent variation (expressed as the coefficient of variation) across all test points over a number of testing sessions. These studies also reported that their results were consistent with those of other electrophysiological measures, although it is unclear how these results compare with SAP. Neither of the studies compared the coefficient of variation between each test session in order to determine whether there was consistency in the results from one test to the next.

The study by Chen (2003) reported the correlation coefficient of the 60 mVEP responses in order to determine the agreement in test results across days and within days. However, correlation is not a true measure of agreement as the correlation coefficient only measures the strength of a relationship between two variables. For example, perfect agreement is only observed if the points lie along the line of equality, with a slope of one and an intercept of zero, whereas perfect correlation can be observed if the points lie along any straight line. This study also measured the reproducibility of an individual response using the mean standard deviation for the mVEP ratio (expressed in dB units) (ie10* log ratio of RMS day 1/RMS day 2). This measure is only useful in determining the reproducibility of the ratios, not as a measure of the reproducibility of the results from day one to day two. The level of agreement between tests is unclear as the mean ratios were not reported in this study. The method of Bland & Altman (1986) would have been more informative.

Repeat reliability of SAP

Study characteristics

Two studies were identified which adequately evaluated the repeat reliability of SAP for outcomes related to diagnosis. Repeat reliability was investigated for a number of outcomes such as threshold estimates (Spry 2003), visual field diagnosis and global indices (Katz 1995) (see Table 16). The study by Spry (2003) was excluded from the review as it compared agreement between different threshold estimates.

The study by Katz (1995) analysed the agreement of test results with SAP performed four and 12 months apart. For the purposes of this assessment, only the results at four months are presented as agreement between tests at 12 months is likely to be affected by disease progression. The patients in this study were recruited from the Glaucoma Screening Study which included normal, OHT and glaucoma patients. All subjects were routinely tested by SAP and the final two results were used in the analysis. Overall, the mean number of automated tests performed prior to those used in the analysis was 3 or 4 (depending on disease group). The results were then classified as normal or abnormal using the glaucoma hemifield test.

Table 16 Patient and study characteristics for repeat reliability of SAP

Study	Setting, dates of enrolment	Spectrum of subjects			Test (algorithms)	Time interval between tests	Outcome
		Sample number and status	Age in years[a] Mean ±SD (range)	Sex ratio (M:F)			
Katz et al (1995)	Baltimore, USA 1981–1992	14 normal 54 OHT 22 glaucoma	57.0 ± 13.6 (24-86) 59.2 ± 13.3 (21-92) 65.1 ± 11.9 (34-86)	Not stated	Humphrey 30-2 (Not stated)	4 months and 12 months	Visual field classified as normal or abnormal using glaucoma hemifield test

[a] Based on total sample glaucoma (95), OHT (407), normal subjects (41)
Abbreviations: OHT, ocular hypertension

Results

Katz (1995) calculated the percent agreement between two consecutive tests using the kappa statistic. For the total sample the overall agreement between tests was 89 per cent with a kappa statistic of 0.77 (95% CI: 0.64, 0.90). When agreement was calculated for each patient group, SAP showed near perfect agreement for patient with OHT. Agreement between tests for glaucoma patients was fair, although the confidence intervals were wide, with a negative value at the lower bound indicating extremely poor agreement. For normal patients, agreement was extremely poor, with a negative kappa indicating that agreement was occurring less than we would expect to see by chance (Table 17).

Table 17 Agreement between glaucoma hemifield results for two consecutive visual field tests

Test results		Patient group			
First test	Second test[a]	Normal (n=14)	Ocular hypertension (n=54)	Glaucoma (n=22)	Total[b] (n=90)
Normal	Normal	11 (78.6)	37 (68.5)	1 (4.5)	49
Normal	Abnormal	2 (14.3)	0 (0.0)	1 (4.5)	3
Abnormal	Normal	1 (7.1)	4 (7.4)	2 (9.1)	7
Abnormal	Abnormal	0 (0.0)	13 (24.1)	18 (81.8)	31
Agreement (%)		78.6	92.6	86.4	88.9
Kappa (95% CI)		-0.11 (-0.25, 0.04)[c]	0.82 (0.65, 0.99)	0.33 (-0.25, 0.91)	0.77 (0.64, 0.90)

[a] Second test four months after first test
[b] Extracted from Katz (1995)
[c] The 95% CI intervals reported for kappa are incorrect
Source: Katz 1995

Given that patients were experienced in the procedure for SAP, it is understandable that the agreement between tests for the total populations and patients with OHT were good. Poor kappa estimates for normal and glaucoma groups, particularly where there is discordance between the diagnosis and the test results, may be due the fact that calculations were based on small patient numbers. In order to establish reliable estimates of agreement, adequate study power is required. The generalisability of the results is also uncertain as study patients were experienced in SAP. It is therefore unclear whether such a high level of agreement would be observed in patients who are naïve to testing, given the learning curve associated with SAP.

What are the economic considerations?

Summary of key issues in clinical effectiveness for an economic analysis

The cost model in MSAC Application 1078 explicitly refers to the population of patients presenting for glaucoma assessment. Accordingly, the review of the model is based on the literature that assesses effectiveness of MMOP in relation to glaucoma patients. On the basis of available evidence, it is uncertain whether MMOP is as effective as SAP in diagnosing glaucoma patients with suspected visual field defects. Furthermore, no studies were identified that adequately addressed whether MMOP would improve the management of glaucoma patient by slowing the progression of glaucoma or any other disease that results in visual field defects.

Neither SAP nor MMOP is 100 per cent accurate in diagnosing early glaucoma. In clinical practice, decisions are based on a combination of results of diagnostic investigations and the characteristics of patients. In the case of a discrepancy between the visual field assessment and optic disc appearance, other factors such as intra-optic pressure and/or family history of glaucoma play a part in the decision to assign the treatment immediately or postpone it until the follow-up visit. Due to the lack of long term follow-up, it is unclear whether the estimates of MMOP specificity in detecting glaucoma in the group of high risk patients with abnormal optic disc appearance but normal visual fields [ie 14 per cent, Graham et al (unpublished) and 63.8 per cent, Balachandran et al (unpublished)] reflect the underlying prevalence of early glaucoma in this group or a high false positive rate in MMOP testing. Graham et al (unpublished) does not report the statistical significance of the difference in the estimate of test accuracy, therefore it remains uncertain whether the specificities of MMOP and SAP are significantly different for the low-risk glaucoma group.

If MMOP were used as a supplementary test for identifying visual field loss, clinicians may have additional confidence in the diagnosis. (Graham et al unpublished). However, there is no reliable evidence in support of this strategy and therefore its cost-effectiveness has not been assessed in this report. Instead, this report has assessed the cost-effectiveness of MMOP as a replacement test for SAP, which is consistent with the approach used by the applicant.

While there may be subgroups for whom MMOP may be useful, such as children, patients who have difficulty in performing the subjective perimetry test in a reliable and reproducible fashion and patients with 'non-organic' visual loss (Woodward & Wall 2002), there is insufficient evidence on the effectiveness of MMOP in these subgroups to allow a reliable estimate of cost-effectiveness.

Cost-comparison

There are no published studies comparing the cost of SAP with the cost of MMOP. Therefore, the assumptions of the model described in the application are discussed in this section which presents alternative estimates of comparative costs of the HVF analyser for SAP and the AccuMap® for MMOP.

Review of assumptions of the cost model included in MSAC application 1078

Table 18 lists assumptions of the cost model described in the application with the assessors' view of their acceptability in a model of the cost of the AccuMap®.

Table 18 Review of the assumptions of the model included in MSAC application 1078

Assumptions of the cost model	Outcome of assessors' review of the assumptions	Comments
The applicant proposed that the AccuMap® will replace the HVF analyser. "After the initial changeover period, the AccuMap® est will replace the HVF analyser rather than being used in addition to the reference standard"	Accepted	It is unlikely that ophthalmologist practices would start replacing the existing HVF analyser with the AccuMap® until the capital life of the existing HVF analyser was over. In the short term, replacement of the HVF analyser is more likely for those analysers that have not been recently upgraded with the latest software, which is continually developed and marketed by Carl Zeiss Pty Ltd
Cost of AccuMap®, $54,500 Lower estimate of the cost of the HVF analyser, $25,000; higher estimate of the cost of the HVF analyser, $45,000	Accepted Accepted	The lower estimate of $25,000 for the HVF analyser was provided by the applicant. This is likely to refer to a model with restricted capability. The higher estimate of $45,000 was provided by the members of the MSAC Advisory Panel
Discount rate of 4% Capital life of five years for AccuMap® and seven years for the HVF analyser	Accepted	
Duration of a single AccuMap® test is 30 min	Not accepted. The test time is assumed to be 40 min	The testing of both eyes of a patient using AccuMap® perimetry took an average 35 min, which included 15 min of preparation during which electrodes were applied to the scalp (Bengtsson, 2002). Also, in the previous application to the MSAC (MSAC ref.13) the time taken to perform a single AccuMap® test was 45 min. Expert opinion also supports the 45 min estimate. The average between these two independent estimates was chosen
Duration of a single HVF test is 20 min	Accepted	The assumption was accepted, although according to Bengtsson, 2002, (p.622) the test time is 15 min, or 12 min if the SITA (fast algorithm) program is used. The applicant's suggested time of 20 min favours the AccuMap®.
Fee for diagnostic test MBS Item Numbers 11221, 11222, 11224, and 11225	Accepted, but not used in the model	The fee for 11221 ($56.30), full quantitative computerised perimetry - (automated absolute static threshold), bilateral, is the same as the fee for 11222 (the third and subsequent perimetry in the same 12 month period). The fees for 11224, and 11225 full quantitative computerised perimetry, unilateral. The perspective of cost modelling is that of the health care system, not that of Medicare. The MBS fees are provided here for reference only
MBS Item Numbers 104 'initial consultation of a specialist' ($71.10) and 105 ($35.65) a subsequent consultation of a specialist	Accepted	Used in the model as a proxy for the actual cost of the consultations and do not differentiate between HVF and the AccuMap® analyser. The current charge for the initial assessment using the HVF is $70

Table 18 (cont'd) Review of the assumptions of the model included in MSAC application 1078

Assumptions of the cost model	Outcome of the assessors' review of the assumptions	Comments
Other unit costs: Technicians salary ($40,000 pa) on-costs, consumables, software, operational costs etc	Accepted	
Cost of 28 days treatment $34.12 with Bimatoprost, Latanoprost or Travoprost	Accepted	
Number of tests performed on a single HVF or AccuMap® is 500 tests per year	Number of tests on a single HVF or AccuMap® is assumed to be 300 per year	The revised estimate is based on expert advice from the MSAC Advisory Panel using HIC data on a random sample of ophthalmologist practices
In the model it is assumed that in some patients, disease progression may be monitored biannually before the treatment is assigned. Once the treatment is assigned, a single follow-up visit is made in six months, with all consecutive visits made once annually	Accepted for both the AccuMap® and the HVF analyser	This scenario is equally possible in patients at the pre-perimetric and early to moderate stages of glaucoma who were assessed with the HVF analyser. The wait-and-see approach is not exclusively reserved for the patients assessed with the AccuMap® (See discussion below)

Abbreviations: HIC, Health Insurance Commission

Critical review of the cost model in the MSAC application 1078

The model included in the application is based on the alternative treatment pathways that the patients follow depending on the stage of their glaucoma progression, which is determined by an ophthalmologist from the visual field assessment at the first visit. The model does not include any probability estimates or estimates of the proportion of the patients who are likely to follow each of the treatment pathways. The applicant has not quantified the benefits of diagnosing glaucoma patients with the AccuMap®, but has commented on the possible effects on the patient's quality of life.

The model assumes that use of an HVF analyser can result in:

- an accurate diagnosis of glaucoma
- a misdiagnosis that the patient does not have glaucoma (false negative in pre-perimetric patients) and withholding of treatment[2],
- a misdiagnosis of a healthy patient as having early and moderate stage glaucoma (false positive) and prescription of unnecessary treatment.

The patients' quality of life is negatively affected in the case of a false negative diagnosis, although manifestation of the effect of irreversible optic disc damage may be delayed far into the future. There may be adverse effects on quality of life in the case of false positive diagnosis. The patient may have unnecessary treatment with possible side effects and additional out-of-pocket expenses.

[2] This contradicts another assumption of the model that the existing standard is administration of two HVF tests, one month apart, as a way of dealing with high number of false negatives at the first visit.

The cost model in the application does not include the possibility of a true negative outcome for the HVF analyser. The probabilities of false negative and false positive outcomes of visual field assessment, although not quantified, are reserved exclusively for the HVF analyser. The AccuMap® is assumed to be 100 per cent accurate. The review of the effectiveness does not support this assumption.

The applicant's model also assumes that clinicians will withhold treatment in favour of monitoring disease progression in some patients diagnosed with the AccuMap.

> The objective nature of the mfVEP will result in clinicians being more comfortable in using the test to monitor the progress of the disease rather than deciding to treat the disease when first diagnosed. (p 21)

Although the suggestion that:

> Treatment may be delayed if we make a careful distinction between those patients where follow-up is acceptable and those where it is not. (p 21)

is reasonable, the applicant allows such a possibility only after the AccuMap® replaces the HVF analyser. This assumption does not seem to be substantiated.

In current clinical practice, the decision of whether to start treatment or to monitor progression of the suspected disease is based on clinical indicators of which visual field assessment is only one factor. The wait-and-see approach is not uncommon for patients in which slow progression of the disease is likely, including a subgroup with inconclusive or unreliable initial HVF analyser results[3] and/or results that are inconsistent with other risk factors.

The model allows for the probability that the HVF analyser will produce true positive results in patients in the advanced stage of glaucoma.

> At this advanced stage both tests have an equally high probability of a true positive. The main difference is that the diagnosis is achieved with AccuMap® in one test at a cost saving compared to two tests using Humphrey. The positive impact on quality of life is the same resulting from the slowing of the progression of the disease due to correct treatment. (p 23)

It seems reasonable to assume that, with the exception of advanced glaucoma cases detected unequivocally at the first presentation, it will take two HVF tests before the treatment decision is made. It is a current practice that in most cases a second test is performed between one and six months after the initial visit. However, from the cost perspective, it makes no difference whether the second test is done in the same year with the purpose of differentiating between the false positive and true positive results of the

[3] It is acknowledged, that "some groups of patients perform poorly on subjective tests… there is also a learning curve associated with perimetry that complicates interpretation in new patients" (Klistorner 2000). On the other hand, there is evidence that, at least in 'accurate patients' and regardless of the examiner, there is no significant learning effect after two consecutive HVF tests. (Muirhead & Johnson 2003).

initial HVF test or for monitoring glaucoma progression at six-monthly intervals until the treatment is determined, as assumed in the model[4].

The 2003-2004 Health Insurance Commission (HIC) statistics show that only 344 patients, including those with established glaucoma who require more frequent monitoring due to the surgery or adverse effects of medications, needed more than two subjective perimetries in one year. This number contradicts the S1 'Humphrey' scenarios in the application which stated that three tests were needed in the first 12 months to diagnose (whether correctly or not) the patients with early/moderate or advanced glaucoma.

The conclusion is that the model included in the application is based on a number of assumptions that, on face value, would appear to favour the AccuMap® over the HVF analyser.

In the following section we present cost estimates based on the alternative assumptions.

Calculating the cost of a single visual field assessment by the HVF test or the AccuMap® test

In the revised cost model, we assume that the AccuMap® test is no worse than the HVF test in diagnosing glaucoma in the general population presented at a typical ophthalmology practice. Neither the HVF analyser nor the AccuMap® has 100 per cent specificity or sensitivity in the population of patients at early stages of the disease. We cannot assume the superior effectiveness of one diagnostic technique over the other on the basis of available evidence. Table 19 summarises the cost of a single visual field test.

[4] The Preferred Practice Pattern™ of the American Academy of Ophthalmology generally allows for six months between the follow-up visits involving optic nerve head assessment and visual field evaluation for the patients newly diagnosed with glaucoma and 3-12 months for glaucoma suspects in the high risk category. (http://www.aao.org/aao/education/library/ppp/index.cfm). The Preferred Practice Pattern™ identified automatic static threshold perimetry as the preferred technique for evaluating visual field, but does not specify how many visual field tests are needed to establish a diagnosis. See page 35 in the Preferred Practice Pattern™ Primary Open-Angle Glaucoma and page 23 in the Preferred Practice Pattern™ Primary Open-Angle Glaucoma Suspect (American Academy of Ophthalmology 2002, 2003)

Table 19 Estimated costs of a single visual field test

Assumptions	Cost of AccuMap® test[a] ($)	Cost of HVF test ($)	Incremental cost ($)
Assumptions in the application[b]: Number of tests per analyser, 500; time of the AccuMap® test, 30 min; capital cost of the AccuMap, $54,500; capital cost of the HVF analyser,$25,000	40.47	18.54	21.93
Revised assumptions (lower cost of HVF analyser): Number of tests per analyser, 300; time of the AccuMap® test, 40 min; capital cost of the AccuMap, $54,500; capital cost of the HVF analyser, $25,000	61.97	25.18	36.79
Revised assumptions (upper cost of HVF analyser: Number of tests per analyser, 300; time of the AccuMap® test, 40 min; capital cost of the AccuMap, $54,500; capital cost of the HVF analyser, $45,000	61.97	34.71	27.27

[a]The estimates costs do not include production of a report which is considered to be the same for each test
[b]These figures are reported on page 25 of the Application

The applicant's calculations suggest that the cost of an AccuMap® test is $22 higher than that of an HVF test. Under the revised assumptions, the cost difference is $36.80 assuming the capital cost of the HVF analyser to be $25,000 and $27.30 assuming it to be $45,000. If there was complete, albeit gradual, replacement of the HVF analyser with the AccuMap, the increase in the societal cost in any particular year will be (cost per test) x 300 (number of tests per analyser per year) x (number of analysers replaced in this year) *ceteris paribus*. Assuming that 50 to 70 machines were replaced every year, the additional cost will be between $400,000 and $570,000 if the incremental cost is assumed to be about $27.30, or between $550,000 and $770,000 if the incremental cost is assumed to be $36.80.

Calculating the total cost of three-year treatment and monitoring under the revised assumptions of the patient management

Figure 5 shows the alternative treatment pathways for patients assessed with the HVF analyser and the AccuMap.

It is assumed in the revised model that disease progression in some patients may be monitored every six months before treatment is assigned. Since there is no reliable evidence of the superior diagnostic accuracy of the AccuMap® over the HVF analyser, patients follow the same treatment pathways regardless of the type of visual field analyser used at the first visit.

However, it seems reasonable to assume that a certain proportion of patients will require at least two HVF tests, six months apart, to allow confident assessment before the decision about treatment is made. If the AccuMap® is used at the first visit, the decision to treat may be made after a single visit, which means that some patients may start treatment six months earlier. Once the treatment is assigned, a single follow-up visit occurs at six months to evaluate efficacy of treatment, followed by annual visits. We have assumed that the third visit takes place on the thirteenth month, which is consistent with the HIC data on the number of three consecutive tests in the same year. We have assumed that true positive and true negative, as well as false positive and false negative, results occur at the same rate regardless of the type of the analyser, however, it takes two

HVF tests to diagnose a new patient[5]. Once the treatment is determined and its efficacy is confirmed, patients have an annual review visit and remain on treatment indefinitely.

The model assumes three possible outcomes after the initial assessment:

- glaucoma positive outcome results in treatment with Bimatoprost, Latanoprost or Travoprost eye drops,
- glaucoma negative result involves no treatment; and
- glaucoma suspect involves regular visits and visual field testing at six-month intervals until the patient is either cleared from glaucoma diagnosis or the treatment begins.

There are no reliable data on the proportion of patients in each outcome category, nor is it known how long it would take on average for a glaucoma 'suspect' to be either cleared from glaucoma diagnosis or to begin treatment. Following the assumption made by the applicant's model, the suspects start their treatment in the middle of the first year following the year of assessment.

Figure 5 is consistent with the algorithms for treatment and monitoring of patients with definite glaucoma and glaucoma suspects as outlined in the Preferred Practice Pattern™ of the American Academy of Ophthalmology, and recommended by the International Council of Ophthalmology (2005).

The revised model for the cost of three years of treatment and monitoring (Figure 5) is consistent with many of the assumptions in the model provided by the applicant. The revised model differs from the applicant's with respect to the following:

- different unit costs are used (See the revised unit costs in Table 12)
- interval of six months (rather than one month) between the first and the second HVF test for all newly presented patients (consistent with the HIC statistics)
- treatment postponement in glaucoma risk patients occurs at the same rate in those assessed with the HVF and those assessed with the AccuMap.

We also assume that other diagnostic investigations are performed to complement the results of visual field testing. However, the cost of these investigations is assumed to be the same regardless of the type of the visual field analyser.

[5] In practice, some patients may be diagnosed with definite glaucoma after a single HFV assessment, however the proportion of such patients is unknown. The assumption that it takes two HVF tests for diagnosing all the patients newly presented at a typical ophthalmologist practice, as opposed to a single AccuMap® diagnostic test, is consistent with the applicant's claim that objective perimetry does not involve any learning effect.

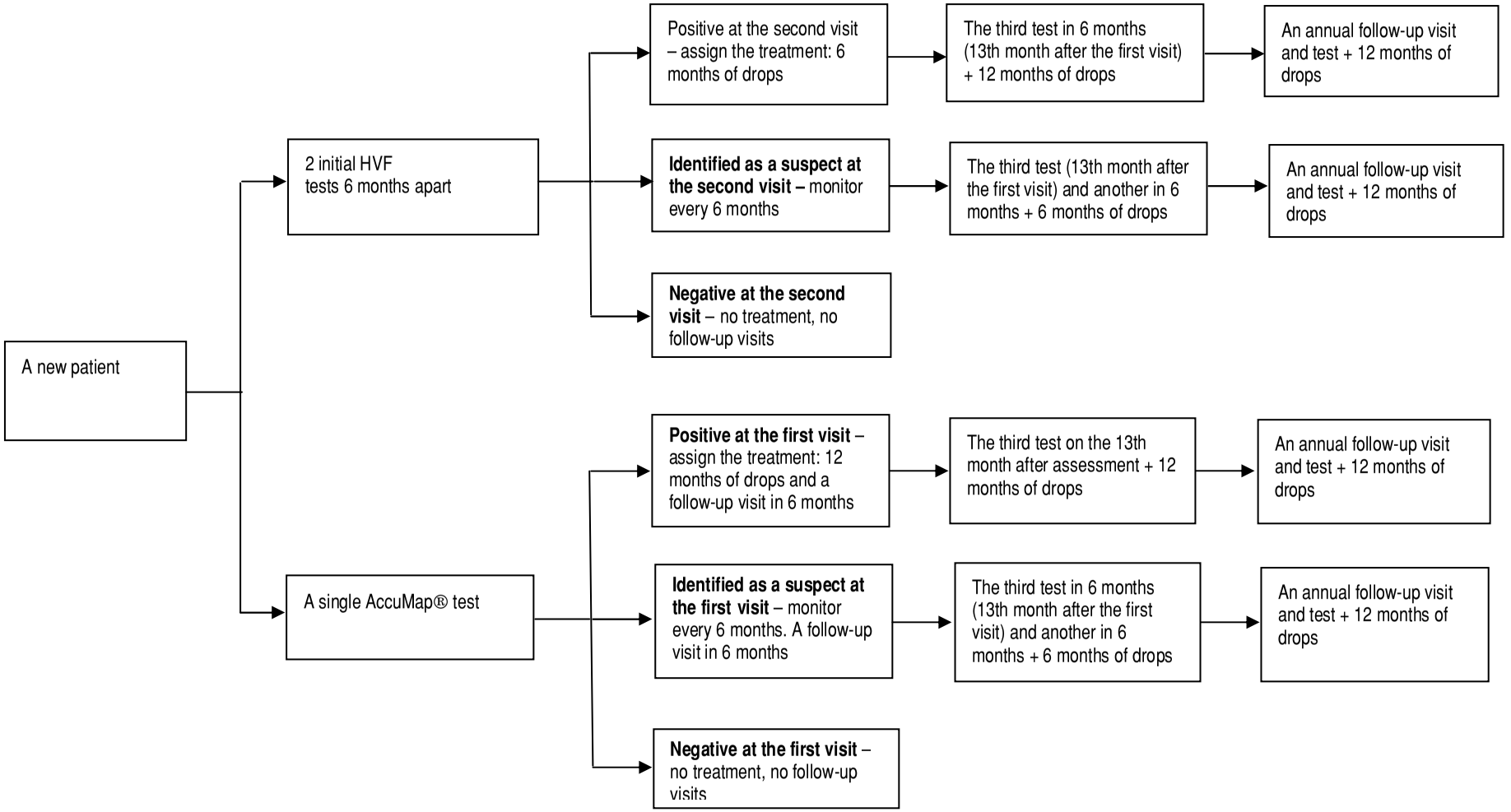


Figure 5 Alternative treatment pathways for patients assessed with the HVF analyser and the AccuMap®

Table 20 shows the three-year cost of assessment, treatment and monitoring of patients assessed with the AccuMap® and the HVF analyser where the capital cost of the latter is assumed to be $25,000.

Table 20 Three-year costs for the AccuMap® and the HVF analyser, capital cost $25,000

Diagnostic outcome	Three-year cost ($)		
	Regular AccuMap® testing	Regular HVF testing	Increment
Glaucoma positive	1,654	1,302	+352
Glaucoma suspect	1,137	954	+184
Glaucoma negative	133	157	–24

With the assumption of a similar diagnostic accuracy for both visual field analysers, the cost of treatment using the AccuMap® is higher in two out of three diagnostic outcome categories of patients. Only the category of patients confirmed as not having glaucoma would benefit financially by a reduction from two initial tests to one. This results in a saving to society of $24 per patient. The total savings would depend on the proportion of patients that are referred to ophthalmologists with suspicion of glaucoma.

The figures in Table 20 show that there would need to be at least 14 patients initially assessed as glaucoma negative to offset the extra cost of about $350 of diagnosing and monitoring a glaucoma patient over three years using the AccuMap® at the first assessment. In other words, of 15 patients referred to a typical ophthalmologist practice with potential glaucoma, one would need to be diagnosed with definite glaucoma after an initial assessment, while the other 14 would need to have a negative diagnosis of glaucoma after the initial assessment.

Alternatively, if we assume that definite glaucoma patients and glaucoma suspects present in equal proportion, it would take at least 22 patients with negative diagnosis at the first presentation [($352+$184)/$24=22] to offset the extra cost of treating and monitoring the patients from the first two groups. Based on the opinion of practising ophthalmologists, it is unlikely that the patient population with possible glaucoma referred to ophthalmologists would have such a high rate of negative cases.

This is a very simplistic model that does not account for all aspects of patient management in practice. For example, some of the glaucoma suspects may eventually be diagnosed as non-glaucoma without starting treatment. In the absence of longitudinal studies of the population referred to ophthalmologists, we cannot reliably estimate either the proportion of glaucoma suspects in this category, nor the proportion of patients who are cleared after the initial assessment. Sensitivity analysis was performed for the alternative scenario where the 50 per cent of glaucoma suspects are identified as glaucoma negative in the seventh month following the year of assessment instead of starting the treatment. The results of the sensitivity analysis are reported in Table 21. There is little difference between the results in Table 21 and Table 20 and the model seems to be robust to variation in the treatment of suspected glaucoma.

Table 21 below shows the three-year cost for the AccuMap® and the HVF analyser where the capital cost of the HVF is taken as $45,000

Table 21 Three-year cost for the AccuMap® and the HVF analyser, capital cost $45,000

Diagnostic outcome	Three-year cost ($)		
	Regular AccuMap® testing	Regular HVF testing	Increment
Glaucoma positive	1,654	1,340	314
Glaucoma suspect	1,137	1,001	136
Glaucoma negative	133	176	–-43

The figures in Table 21 show that to offset the extra cost of about $314 of diagnosing and monitoring a glaucoma patient over three years using the AccuMap® at the first assessment, there would need to be at least seven patients initially assessed as glaucoma negative. If we assume that definite glaucoma patients and glaucoma suspects present in equal proportion it would take at least 10 patients with negative diagnosis at the first presentation [($314+$136)/$43=10] to offset the extra cost of treating and monitoring the patients from the first two groups. Although these break-even numbers are lower than the numbers derived on the basis of the cost data in Table 14, they do not suggest any possible cost-savings to the society resulting from replacement of the HVF analyser[6] with the AccuMap®.

From the perspective of cost, the wait-and-see approach involving regular follow up visits is a cost-saving strategy, since the 12-month cost of eye-drops is higher then the cost of periodic assessments. However, since the cost of a single HVF test is less than the cost of a single AccuMap® test, the saving is greater if the HVF analyser is used to monitor disease progression.

Major areas of uncertainty in the economic evaluation

The revised costing model presented here is based on the best estimates available. Nevertheless, in the absence of high quality evidence on the use of both tests in clinical practice, a number of uncertainties remain that may impact on the cost comparisons presented.

In particular:

- The capital cost of the HVF analyser to be replaced with the AccuMap®. Although it is unlikely that the newer HVF models will be replaced with the AccuMap® before the end of their capital life, the difference in the cost of equipment affected the estimated cost of a single test and ultimately the cost of the three years of treatment and monitoring.

- The proportion of patients who were diagnosed as glaucoma negative after a single AccuMap® test or two consecutive HVF tests.

---

[6] Unconfirmed calculations based on the estimates of prevalence and incidence of glaucoma in general population (as opposed to the population presented at a typical ophthalmology practice) indicate that no more than one in five patients (20%) may eventually be cleared from glaucoma. This estimate includes some of the glaucoma 'suspects' who will never develop glaucoma, though may be monitored for years.

- The revised model is based on the assumption that two consecutive tests are required to diagnose a patient with the HVF analyser while only one test is needed if AccuMap® is used. This may not be supported by the current practice, where a certain proportion of patients is diagnosed with definite glaucoma at the first presentation. The proportion of such patients is unknown.

- Other areas of uncertainty include the proportion of suspects who are monitored after the first assessment and the average time it takes to either clear a glaucoma suspect from glaucoma diagnosis or begin the treatment.

Conclusions

Safety

An extensive literature search revealed a lack of safety data. However, as the test is non-invasive, the risks to subjects should be minimal.

Effectiveness

Due to the limitations of the available evidence, it is unclear whether MMOP is equivalent to SAP in terms of diagnostic accuracy in patients with undiagnosed visual field defects. Furthermore, patient management and clinical outcomes were not addressed in any of the available studies. Therefore, it is unclear whether MMOP would improve the management of patients or help to slow progression of disease. Additional studies of good methodological quality that meet essential validity criteria are required to establish the effectiveness of MMOP in diagnosing patients with suspected visual field loss for glaucoma and other indications. Longitudinal studies are required for evaluation of the predictive value of MMOP in diagnosing pre-perimetric disease.

It is unclear whether the repeat reliability of MMOP is superior to that of SAP. Overall, the strength of the evidence was poor in that all of the identified studies were Level IV evidence, where study validity in terms of design and analysis were inadequate. Finally, the value of whether MMOP has high reproducibility is irrelevant, given that the diagnostic accuracy of the test is uncertain.

Cost analysis

As there was insufficient evidence to demonstrate the relative effectiveness of MMOP, a cost-effectiveness analysis could not be undertaken. Instead, a cost analysis based on the applicant's model was examined and discussed. The analysis did not demonstrate cost savings for the AccuMap® compared to the HFA test.

Recommendation

Multifocal multichannel objective perimetry for the diagnosis of visual field defects appears to be safe but there is insufficient evidence to demonstrate that it is as effective as alternative technologies. Therefore, its cost-effectiveness could not be determined. MSAC does not recommend public funding.

The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	Medicare Benefits Branch, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Associate Professor Donald Perry-Keene	endocrinology
Dr Ewa Piejko	general practice
Mrs Sheila Rimmer	consumer representative
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor John Simes	clinical epidemiology and clinical trials
Professor Michael Solomon	colorectal surgery and clinical epidemiology
Professor Bryant Stokes	neurology
Professor Ken Thomson	radiology
Dr Doug Travis	urology

Appendix B Advisory panel

Advisory Panel for MSAC application 1078 - Multifocal multichannel objective perimetry for the diagnosis of visual field defects

Professor Bryant Stokes (Chair) AMRFD, MBBS, FRACS, FRCS Consultant Neurosurgeon St John of God Hospital Subiaco, WA	member of MSAC
Associate Professor Ian Favilla DO, FRACS, FRANZCO Ophthalmic Surgeon and Clinical Associate Professor of Surgery Clayton, VIC	co-opted ophthalmologist
Associate Professor Justin O'Day MBBS, FRACS, FRACP, FRCS, FRANZCO, FRCOphth Eye Specialist St Vincent's Medical Centre Fitzroy, VIC	co-opted ophthalmologist
Dr Denis Stark MBBS, FRCS (Edinburgh), FRANZCO Warana, QLD	co-opted ophthalmologist
Ms Sheila Rimmer BSc Hons (Econ), MA (Political Science), AM Ranelagh Darling Point, NSW	MSAC member
Dr Timothy Roberts MBBS, FRANZCO, FRACS Consultant Ophthalmic Surgeon in Royal North Shore Hospital The Eye Institute Chatswood, New South Wales.	Royal Australian and New Zealand College of Ophthalmologists nominee
Ms June Ashmore Dip Phys, AM President, Canberra Blind Society Canberra, ACT	Consumers' Health Forum of Australia nominee

Appendix C Search strategies

Table C1 Cochrane search

Set #	Terms
1.	multifocal multichannel objective perimetry in All Fields in Cochrane Reviews, DARE, CENTRAL, Methodology Reviews, HTA, NHS EED and About
2.	MeSH descriptor Visual Fields explode all trees in MeSH products
3.	MeSH descriptor Vision Disorders explode all trees in MeSH products
4.	MeSH descriptor Costs and Cost Analysis explode all trees in MeSH products
5.	[(#2 OR #3) AND #4] in All Fields in Cochrane Reviews, DARE, CENTRAL, Methodology Reviews, HTA, NHS EED and About
6.	(#1 OR #5) in All Fields in Cochrane Reviews, DARE, CENTRAL, Methodology Reviews, HTA, NHS EED and About

Table C2 Medline core terms

Set #	Terms
1.	multifocal multichannel objective perimetry.mp.
2.	(multifoc$ adj2 multichannel$ adj2 objective adj2 perimet$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3.	mmop.mp.
4.	(automated adj2 perimetry).mp.
5.	(multichannel$ adj2 record$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6.	mop.mp.
7.	multichannel$.mp.
8.	multifocal$.mp.
9.	accumap.mp.
10.	objectivision.mp.
11.	veris.mp.
12.	(electrodiagnostic$ adj2 imag$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
13.	(multifocal$ adj2 visual$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
14.	Evoked Potentials, Visual/
15.	vep$.mp.
16.	"Perimetry"/
17.	"Photic Stimulation"/
18.	"Visual Fields"/
19.	(visual field$ adj defect$).mp.
20.	optic neuritis.mp. or exp Optic Neuritis/
21.	exp Optic Nerve Diseases/
22.	"Visual Pathways"/
23.	visual cortex.mp. or Visual Cortex/
24.	"Cataract"/
25.	(unexplained adj visual adj2 loss).mp.
26.	"Visual Acuity"/
27.	exp Vision Disorders/

Table C2 (cont'd) Medline core terms

Set #	Terms
28.	save sight.in.
29.	28 and (14 or 15)
30.	exp Glaucoma/
31.	Perimetry/
32.	Intraocular Pressure/
33.	static$.mp.
34.	(humphrey and vep).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
35.	mfVEP.mp.
36.	"Electroretinography"/
37.	Humphrey.mp.
38.	HVF.mp.
39.	subjective perimetry.mp.
40.	or/1-12
41.	mt.fs. or di.xs.
42.	or/13-19,22-23,26,31-32
43.	or/7-8,41
44.	42 and 43
45.	or/20-21,24-25,27,30
46.	or/33-39
47.	(40 or 44) and 45 and 46
48.	limit 47 to yr=2002-2004

Table C3 EMBASE core terms

Set #	Terms
1.	multifocal multichannel objective perimetry.mp.
2.	(multifoc$ adj2 multichannel$ adj2 objective adj2 perimet$).mp
3.	mmop.mp
4.	(multichannel$ adj2 record$).mp
5.	accumap.mp
6.	objectivision.mp
7.	veris.mp.
8.	or/1-7
9.	limit 8 to yr=2002-2004

Table C4 CINAHL core terms

Set #	Terms
1.	multifocal multichannel objective perimetry.mp.
2.	(multifoc$ adj2 multichannel$ adj2 objective adj2 perimet$).mp.
3.	mmop.mp.
4.	(multichannel$ adj2 record$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
5.	mop.mp.
6.	multichannel$.mp.
7.	multifocal$.mp.
8.	accumap.mp.
9.	objectivision.mp.
10.	veris.mp.
11.	(visual field$ adj defect$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
12.	optic neuritis.mp.
13.	exp Optic Nerve Diseases/
14.	"Cataract"/
15.	(unexplained adj visual adj2 loss).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
16.	exp Vision Disorders/
17.	save sight.in.
18.	exp Glaucoma/
19.	static$.mp.
20.	(humphrey and vep).mp.
21.	mfVEP.mp.
22.	Humphrey.mp.
23.	HVF.mp.
24.	subjective perimetry.mp.
25.	or/1-10
26.	or/11-18
27.	or/19-24
28.	25 and 26
29.	25 and 27
30.	limit 29 to yr=2002 – 2004

Table C5 Current Contents core terms

Set #	Terms
1.	(#1 OR #2 OR #3) AND #4
2.	VISION OR VISUAL*
3.	MULTIFOCAL
4.	MULTICHANNEL
5.	MMOP

Table C6 Biological Abstracts core terms

Set #	Terms
1.	multifocal multichannel objective perimetry.mp.
2.	(multifoc$ adj2 multichannel$ adj2 objective adj2 perimet$).mp.
3.	mmop.mp.
4.	(multichannel$ adj2 record$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
5.	mop.mp.
6.	multichannel$.mp.
7.	multifocal$.mp.
8.	accumap.mp.
9.	objectivision.mp.
10.	veris.mp.
11.	(visual field$ adj defect$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
12.	optic neuritis.mp.
13.	exp Optic Nerve Diseases/
14.	"Cataract"/
15.	(unexplained adj visual adj2 loss).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
16.	exp Vision Disorders/
17.	save sight.in.
18.	exp Glaucoma/
19.	static$.mp.
20.	(humphrey and vep).mp.
21.	mfVEP.mp.
22.	Humphrey.mp.
23.	HVF.mp.
24.	subjective perimetry.mp.
25.	or/1-10
26.	or/11-18
27.	or/19-24
28.	25 and 26
29.	25 and 27
30.	limit 29 to yr=2002 – 2004

Table C7 Safety filter for Medline core terms

Set #	Terms
1.	exp cohort studies/
2.	exp risk/
3.	(odds and ratio$).tw.
4.	(relative and risk).tw.
5.	(case and control$).tw.
6.	case-control studies/
7.	or/49-54
8.	Set 7 was combined with Medline core terms set 48

Table C8 Test-retest terms applied to Medline

Set #	Terms
1.	"reproducibility of results"/
2.	(test$ adj2 retest$).mp
3.	1 or 2
4.	Set 3 was combined with Medline core terms set 48

Appendix D Internet sites searched

HTA sites

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (Aetmis) http://www.aetmis.gouv.qc.ca/en/ [Accessed 11 June 2004]

Agency for Healthcare Research and Quality – technology assessments (AHRQ) http://www.ahcpr.gov/clinic/techix.htm [Accessed 11 June 2004]

Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/hta/ [Accessed 11 June 2004]

BCBS Technology Evaluation Center http://www.bcbs.com/tec/index.html [Accessed 11 June 2004]

Bundesaertekammer HTA [in German] http://www.bundesaerztekammer.de/30/HTA/ [Accessed 11 June 2004]

Canadian Coordinating Office for Health Technology Assessment (CCOHTA) http://www.ccohta.ca/ [Accessed 11 June 2004]

Catalan Agency for Health Technology Assessment and Research (CAHTA) http://www.aatrm.net/ang/ang.html [Accessed 11 June 2004]

CEDIT: Comité d'Evaluation et des Diffusion des Innovations Technologiques http://cedit.aphp.fr/ [Accessed 11 June 2004]

Center for Health Services and Policy Research (CHSPR) http://www.chspr.ubc.ca/ [Accessed 11 June 2004]

Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en [Accessed 11 June 2004]

EUROSCAN: The European Information Network on New and Changing Health Technologies http://www.publichealth.bham.ac.uk/euroscan/ [Accessed 11 June 2004]

Finnish Office for Health Care Technology Assessment http://www.stakes.fi/finohta/ [Accessed 11 June 2004]

Health Council of the Netherlands http://www.gr.nl/ [Accessed 11 June 2004]

HSTAT : Health Services/Technology Assessment Text http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat [Accessed 11 June, 2004]

Health Technology Assessment (HTA) Database http://nhscrd.york.ac.uk/htahp.htm [Accessed 11 June 2004]

Health Technology Assessment Unit at McGill University Health Center
http://www.mcgill.ca/tau/ [Accessed 11 June 2004]

Institute for Clinical Systems Improvement (ICSI) http://www.icsi.org/index.asp
[Accessed 11 June 2004]

Institute of Technology Assessment of the Austrian Academy of Science
http://www.oeaw.ac.at/ita/welcome.htm [Accessed 11 June 2004]

International Network of Agencies for Health Technology Assessment
http://www.inahta.org/ [Accessed 11 June 2004]

Medical Technology Assessment Group (M-TAG)
http://www.m-tag.net/flash_index.htm [Accessed 11 June 2004]

The National Coordinating Centre for Health Technology Assessment (NCCHTA)
http://www.hta.nhsweb.nhs.uk/ [Accessed 11 June 2004]

National Horizon Scanning Centre http://www.publichealth.bham.ac.uk/horizon/
[Accessed 11 June 2004]

National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk/Cat.asp?pn=professional&cn=toplevel&ln=en
[Accessed 11 June 2004]

The Norwegian Center for Health Technology Assessment [some reports in En]
http://www.oslo.sintef.no/smm/News/FramesetNews.htm
[Accessed 11 June 2004]

NZHTA Clearing House [critical appraisals, evidence reports etc]
http://nzhta.chmeds.ac.nz/ [Accessed 11 June 2004]

SBU Evaluates Health Care Technology http://www.sbu.se/www/index.asp
[Accessed 11 June 2004]

Swiss Network for Health Technology Assessment (SNHTA)
http://www.snhta.ch/home/portal.php [Accessed 11 June, 2004]

West Midlands Health Technology Assessment Collaboration (WMHTAC)
http://www.publichealth.bham.ac.uk/wmhtac/ [Accessed 11 June 2004]

Clinical trial register websites

CenterWatch clinical trials listing service http://www.centerwatch.com/
[Accessed 11 June 2004]

ClinicalTrials.com http://www.clinicaltrials.com/ [Accessed 17 June 2004]

ClinicalTrials.gov http://www.clinicaltrials.gov/ [Accessed 17 June 2004]

Current Controlled Trials http://www.controlled-trials.com/ [Accessed 17 June 2004]

Society for Clinical Trials http://www.sctweb.org/ [Accessed 17 June 2004]

TrialsCentral http://www.trialscentral.org/ [Accessed 17 June 2004]

The UK National Research Register http://www.update-software.com/national/ [Accessed 17 June 2004]

Appendix E Studies included in this review

Balachandran, C., Graham, S.L., Klistorner, A., Goldberg, I. & Landers, J. Unpublished. 'Comparison of objective tests in glaucoma: structure vs function'.

Bengtsson B, 2002. 'Evaluation of VEP perimetry in normal subjects and glaucoma patients', *Acta Ophthalmologica Scandinavica*, 80 (6), 620–626.

Fortune, B., Goh, K., Demirel, S., Novitsky, K., Mansberger, S., Johnson, C. & Cioffi G. Unpublished. 'Detection of Glaucomatous Visual Field loss using Multifocal VEP'.

Goldberg, I., Graham, S.L. & Klistorner, A.I. 2002. 'Multifocal objective perimetry in the detection of glaucomatous field loss', *American Journal of Ophthalmology*, 133 (1), 29–39.

Graham, S.L., Klistorner, A. & Goldberg, I. Unpublished[7]. 'Clinical application of multifocal VEP objective perimetry in glaucoma practice.' P*ublished in 2005* in: *Arch Ophthalmol,* 123 (6), 729-39.

Klistorner, A. & Graham, S.L. 2000. 'Objective perimetry in glaucoma', *Ophthalmology*, 107 (12), 2283–2299.

Klistorner, A., Graham, S.L., Grigg, J. & Balachandran, C. Unpublished. 'Objective perimetry using the multifocal VEP in central visual pathway lesions'.

Thienprasiddhi, P., Greenstein, V.C., Chen, C.S., Liebmann, J.M., Ritch, R. & Hood, D.C. 2003. 'Multifocal visual evoked potential responses in glaucoma patients with unilateral hemifield defects', *American Journal of Ophthalmology*, 136 (1), 34–40.

Woodward, K. & Wall, M. 2002. 'The Multifocal visual evoked potiental in functional visual loss'. In: update P (Ed.) Proceedings of the XVth International Perimetric Society Meeting, Kugler Publications, England, 261–264.

[7] At the time of searching this citation was unpublished and was subsequently published: Graham, S.L., Klistorner, A. & Goldberg, I. 2005. 'Clinical application of multifocal VEP objective perimetry in glaucoma practice.' Arch Ophthalmol, 123 (6), 729-39.

Appendix F Studies excluded from this review

Inappropriate patient group

Hood, D.C., Zhang, X. & Winn, B.J. 2003. 'Detecting glaucomatous damage with multifocal visual evoked potentials: How can a monocular test work?', *Journal of Glaucoma*, 12 (1), 3–15.

Kikuchi, Y., Yoshii, M., Yanashima, K., Enoki, T., Ide, T., Sakemi, F. & Okisaka, S. 2002. 'Multifocal visual evoked potential is dependent on electrode position', *Japanese Journal of Ophthalmology*, 46 (5), 533–539.

Schimiti, R.B., Avelino, R.R., Kara-Jose, N. & Costa, V.P. 2002. 'Full-threshold versus Swedish Interactive Threshold Algorithm (SITA) in normal individuals undergoing automated perimetry for the first time', *Ophthalmology*, 109 (11), 2084–2092; discussion 92.

Not multifocal multichannel VEP

Heijl, A., Leske, M.C., Bengtsson, B., Hyman, L. & Hussein, M. 2002. 'Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial', *Archives of Ophthalmology*, 120 (10), 1268–1279.

Heijl, A., Leske, M.C., Bengtsson, B. & Hussein, M. 2003. 'Measuring visual field progression in the Early Manifest Glaucoma Trial', *Acta Ophthalmologica Scandinavica*, 81 (3), 286–293.

Johnson, C.A., Keltner, J.L., Cello, K.E., Edwards, M., Kass, M.A., Gordon, M.O., Budenz, D.L., Gaasterland, D.E. & Werner, E. 2002. 'Baseline visual field characteristics in the ocular hypertension treatment study', *Ophthalmology*, 109 (3), 432–437.

Leske, M.C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L. & Komaroff, E. 2003. 'Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial', *Archives of Ophthalmology*, 121 (1), 48–56.

Leskea, M.C., Heijl, A., Hyman, L., Bengtsson, B. & Komaroff, E. 2004. 'Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial', *Current Opinion in Ophthalmology*, 15 (2), 102–106.

National Eye Institute (NEI) 2002, Early Manifest Glaucoma Trial [Internet]. Bethesda, USA. Available from: www.nei.nih.gov/neitrials/static/study31.htm [Accessed 2 August 2003].

Narrative review

Johnson, C.A. 2002. 'Recent developments in automated perimetry in glaucoma diagnosis and management', *Current Opinion in Ophthalmology*, 13 (2), 77–84.

Case report

Maturi, R.K., Yu, M. & Sprunger, D.T. 2003. 'Multifocal electroretinographic evaluation of acute macular neuroretinopathy', *Archives of Ophthalmology*, 121 (7), 1068–1069.

No reference test

Balachandran, C., Klistorner, A.I. & Billson, F. 2004. 'Multifocal VEP in children: its maturation and clinical application', *British Journal of Ophthalmology*, 88 (2), 226–232.

Chen, C.S., Hood, D.C., Zhang, X., Karan, E.Z., Liebmann, J.M., Ritch, R., Thienprasiddhi, P. & Greenstein, V.C. 2003. 'Repeat reliability of the multifocal visual evoked potential in normal and glaucomatous eyes', *Journal of Glaucoma*, 12 (5), 399–408.

Could not extract data

Hood, D.C., Greenstein, V.C., Odel, J.G., Zhang, X., Ritch, R., Liebmann, J.M., Hong, J.E., Chen, C.S. & Thienprasiddhi, P. 2002. 'Visual field defects and multifocal visual evoked potentials - Evidence of a linear relationship', *Archives of Ophthalmology*, 120 (12), 1672–1681.

Not investigating diagnosis

Hood, D.C., Thienprasiddhi, P., Greenstein, V.C., Winn, B.J., Ohri, N., Liebmann, J.M. & Ritch, R. 2004. 'Detecting early to mild glaucomatous damage: A comparison of the multifocal VEP and automated perimetry', *Investigative Ophthalmology & Visual Science*, 45 (2), 492–498.

Abstract only

Balachandran, C., Klistorner, A. & Billson, F. 2002. 'Development of multifocal VEP in children', Association for Research in Vision and Ophthalmology, conference abstract.

Fortune, B. 2002. International Perimetric Society, conference abstract. Full abstract or further details not provided.

Gih, D.E., Ringger, C., Woodward, K., Doyle, C., Allen, J. & Wall, M. 2004. 'Separating demyelinating and ischemic optic neuropathies using multifocal visual evoked potential recordings', Association for Research in Vision and Ophthalmology, conference abstract.

Graham, S.L., Klistorner, A., Balachandran, C. & Goldberg, I. 2002. 'Comparisons of objective tests in glaucoma – multifocal objective perimetry and Heidelberg retinal tomography', Association for Research in Vision and Ophthalmology, conference abstract.

Grigg, J.R., Mahmood, A., Bjerre, A., Spencer, F., Parry, N. & Henson, D. 2002. 'Multifocal objective perimetry in the early detection of glaucoma', Royal College of ophthalmologists, conference abstract.

Greenstein, V.C., Thienprasiddhi, P., Chu, D.H., Ritch, R., Liebmann, J.M. & Hood, D.C. 2004. 'Are multifocal VEP findings in glaucoma suspects consistent with structural findings?', Association for Research in Vision and Ophthalmology, conference abstract.

Hedges, T.R. & Massicotte, E. 2004. 'Multifocal visual evoked potential in functional visual field loss', Association for Research in Vision and Ophthalmology, conference abstract.

Liebmann, 2003. American Academy of Ophthalmology, conference abstract. Full abstract or further details not provided.

Liebmann, 2003. Association for Research in Vision and Ophthalmology, conference abstract. Full abstract or further details not provided.

Wall, 2002. International Perimetric Society, conference abstract. Full abstract or further details not provided.

Sequential multichannel VEP

Hood, D.C., Zhang, X. Greenstein, V.C., Kangovi, S., Odel, J.G., Liebmann, J.M. & Ritch, R. 2000. 'An interocular comparison of the multifocal VEP: A possible technique for detecting local damage to the optic nerve', *Investigative Ophthalmology & Visual Science*, 41 (6), 1580–1587.

Appendix G Patient selection criteria

First author (year)	Selection criteria
Balachandran unpublished	Inclusion criteria: corrected visual acuity of 6/9 or better, pupil diameters at least 2.5 mm without dilatation, refractive error <+/-6D and no history of diabetes, previous cataract surgery, or ocular disorders other than glaucoma Glaucoma subjects: Scotoma was diagnosed by a cluster of ≥3 abnormal points including ≥2 points depressed by p<0.5%. and glaucomatous optic disc with typical loss or neuroretinal rim as judged by stereoscopic ophthalmoscopy High-risk criteria: No scotoma on Humphrey 24-2, but ≥1 of the following; cup/disc ratio ≥0.8 on direct ophthalmoscopy, inter-eye cup/disc ratio difference ≥0.2, IOP ≥23 mm Hg. The eye selected for study was the worse eye; if there was no difference then selection was random
Bengtsson (2002)	Inclusion criteria for normal subjects: Corrected visual acuity of 1.0 determined using the Humphrey Automatic Refractor 595 (one subject had a VA of 0.8), discs without any signs of glaucomatous damage, and intraocular pressure less than 21 mm Hg Exclusion criteria for normal subjects: None listed Inclusion criteria for glaucoma subjects: Selected to represent all stages of glaucoma as defined by the appearance of threshold greyscale representations and probability plots of visual fields obtained less than 6 months prior to inclusion. Required to have glaucomatous visual field defects in at least one eye, with the glaucoma hemifield test results outside the normal range Exclusion criteria for glaucoma subjects: Subjects who had previously shown obvious difficulties in performing conventional visual field tests
Fortune unpublished	Diagnosis of glaucoma was based upon optic disc appearance (glaucomatous optic neuropathy in at least one eye) as determined by clinical examination and stereo disc photographs, as well as visual field loss measured by Humphrey® 24-2 with at least one of the following criteria: p<0.05 for mean defect , pattern standard deviation; or glaucoma hemifield test outside normal limits, confirmed in at least one eye Control subjects had normal visual fields (by the above criteria) and normal optic disc appearance in both eyes according to clinical examination. No history of ocular disease, surgery, or trauma or systemic disease known to affect the visual system
Goldberg (2002)	Inclusion criteria for both normal and glaucoma subjects: corrected visual acuity of 6/9 or better and pupils at least 2.5 mm without dilation Exclusion criteria for both normal and glaucoma subjects: subjects with diabetes, previous cataract surgery, or any other ocular disorders Inclusion criteria for normal subjects: normal intraocular pressure and ophthalmoscopy and no family history of glaucoma or retinal dystrophy. All required normal Humphrey® threshold field tests, confirmed by a normal result on the glaucoma hemifield test analysis, and showed no clusters of points that could constitute a scotoma (as defined for the glaucoma subjects) Inclusion criteria for glaucoma subjects: diagnosis of glaucoma by confirmed visual field defect on Humphrey® 24-2 and a glaucomatous optic disk as judged by stereo disk photography. Intraocular pressure not used. The definition of a field defect used pattern deviation plot on the Humphrey® 24-2 program. A minimum scotoma required a cluster of three or more abnormal points including at least two points depressed by a p value less than 0.5% on the pattern deviation probability plot. The cluster of abnormal points could not cross the horizontal meridian and points immediately above and below the blind spot could not qualify as part of the overall scotoma. Peripheral rim points could qualify as part of the scotoma but as least two of the points qualifying as the nucleus had to be non-rim. The glaucoma hemifield test needed to be abnormal

First author (year)	Selection criteria
Graham unpublished	Selection criteria were based on patients attending an Australian glaucoma referral practice who had been tested with the AccuMap® Low risk subjects: Ocular hypertension > 21 mm Hg and/or family history of glaucoma, but normal optic discs and visual fields High risk subjects: Suspicious or abnormal optic disc appearance in at least one eye (eg large cup > 0.6, nerve fibre layer thinning, notch or haemorrhage) and/or asymmetrical discs with cup/disc ratio difference of more than 0.2, with or without raised IOP, but still normal visual field Glaucoma subjects: At least one eye with abnormal optic disc with characteristic glaucomatous cupping with corresponding visual field defect, with or without raised IOP and with or without family history of glaucoma Patients with excessive field loss or uninterpretable field in at least one eye
Klistorner (2000)	Inclusion criteria for both normal and glaucoma subjects: corrected visual acuity of 6/9 or better and pupils at least 2.5 mm without dilation Exclusion criteria for both normal and glaucoma subjects: subjects with diabetes, previous cataract surgery, or any other ocular disorders Inclusion criteria for normal subjects: normal intraocular pressure and ophthalmoscopy and no family history of glaucoma or retinal dystrophy. Normal Humphrey® 24-2 test confirmed by a normal result on the glaucoma hemifield test analysis Inclusion criteria for suspected glaucoma subjects: either a definite structural change or an asymmetry in the neuroretinal rim but in whom visual field defects had not developed representing 'preperimetric glaucoma'. Most had ocular hypertension, a family history of glaucoma or both Inclusion criteria for glaucoma subjects: primary open angle glaucoma – confirmed visual field defect on Humphrey® 24-2, a glaucomatous optic disc as judged by stereo disc photography and intraocular pressure more than 21 mm Hg. Normal tension glaucoma – as above except intraocular pressure less than 20 mm Hg A minimum scotoma required at least three adjacent points depressed by p value less than 0.5% on the pattern deviation probability plot. The cluster of abnormal points could not cross the horizontal meridian and points immediately above and below the blind spot could not qualify as part of the scotoma. The results of the hemifield test needed to be abnormal
Klistorner unpublished	Inclusion criteria: Homonymous or bitemporal field loss due to lesions of the posterior visual pathway (pituitary to visual cortex) Exclusion criteria: None stated
Thienprasiddhi (2003)	All patients had visual acuity 20/40 or better and refractive errors not exceeding 5.00 diopter sphere or 2 diopter cylinder Glaucomatous optic neuropathy were defined as having either cup/disk asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation or retinal nerve fibre layer defects. Glaucoma patients had optic nerve damage and associated achromatic visual field loss in the corresponding hemifield location Control subjects had no history of ocular disease, IOP 21 mm Hg or less by Goldmann applanation tonometry on at least two occasions, normal optic disk appearance based upon clinical examination and review of stereoscopic optic nerve head photography and normal AAP
Woodward (2002)	Patients with clinical presentations of functional visual loss

Abbreviations

AIHW	Australian Institute of Health and Welfare
CCD	census collector districts
CI	confidence intervals
HIC	Health Insurance Commission
HVF	Humphrey visual field
TP	true positive
TN	true negative
FP	false positive
FN	false negative
MBS	medical benefits scheme
MMOP	multifocal multichannel objective perimetry
MSAC	Medical Services Advisory Committee
mVEP	multifocal visually evoked potentials
NHMRC	National Health and Medical Research Council
OAG	open-angle glaucoma
OHT	ocular hypertension
RCT	randomised controlled trial
SAP	static automated perimetry
VEP	visually evoked potentials

References

American Academy of Ophthalmology 2002, *Primary open-angle glaucoma suspect* [Internet] American Academy of Opthalamogy, USA. Available from: http://www.aao.org/education/library/ppp/poags_new.cfm [Accessed 15 June 2004].

American Academy of Ophthalmology 2003, *Primary open-angle glaucoma* [Internet] American Academy of Opthalamogy, USA. Available from: http://www.aao.org/education/library/ppp/poag_new.cfm [Accessed 15 June 2004].

Anderson, D.R. 1984. *Testing the field of vision*, Mosby, St Louis.

Attebo, K., Mitchell, P. & Smith, W. 1996. 'Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study', *Ophthalmology,* 103 (3), 357–364.

Australian Institute of Health and Welfare (2003). *Disability prevalence and trends*. AIHW, Canberra.

Balachandran, C., Graham, S.L., Klistorner, A., Goldberg, I. & Landers, J. Unpublished. 'Comparison of objective tests in glaucoma: structure vs function'.

Baseler, H.A., Sutter, E.E., Klein, S.A. & Carney, T. 1994. 'The topography of visual evoked response properties across the visual field', *Electroencephalography Clinical Neurophysiology*,90 (1), 65–81.

Bengtsson, B. 2002. 'Evaluation of VEP perimetry in normal subjects and glaucoma patients', *Acta Ophthalmologica Scandinavica*, 80 (6), 620–626.

Betsun, Y., Mashima, Y., Ohde, H., Inoue, R. & Oguchi, Y. 2001. 'Clinical application of the multifocal VEPs', *Current Eye Research*, 22, 54–63.

Bland, J.M. & Altman, D.G. 1986. 'Statistical methods for assessing agreement between two methods of clinical measurement', *The Lancet*, 1 (8476), 307–310.

Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L.M., Lijmer, J.G., Moher, D. & Rennie, D., de Vet, H.C.W. 2003. 'Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative', *British Medical Journal*, 326, 41–44.

Chalmers, I. & Altman, D.G. 1995, Systematic Reviews, BMJ Publishing Group, London.

Chan, K.M. & Brown, W.F. 1998. 'Quantitation in EMG'. *Canadian Journal of Neurological Sciences*, 25 (1), S27–31.

Chen, C.S., Hood, D.C., Zhang, X., Karan, E.Z., Liebmann, J.M., Ritch, R., Thienprasiddhi, P. & Greenstein, V.C. 2003. 'Repeat reliability of the multifocal visual evoked potential in normal and glaucomatous eyes', *Journal of Glaucoma*, 12 (5), 399–408.

Cochrane Methods Working Group 1996, *Systematic review of screening and diagnostic tests: Recommended methods*. [Internet]. Available from: http://www.cochrane.org/docs/sadtdoc1.htm [Accessed 4 January 2002]

Flammer, J., Drance, S.M., Augustiny, L. & Funkhouser, A. 1985. 'Quantification of glaucomatous visual field defects with automated perimetry', *Investigative Ophthalmology & Visual Science*, 26 (2), 176–181.

Foran S, Wang JJ & Mitchell P, 2002. 'Causes of incident visual impairment: the Blue Mountains Eye Study'. *Arch Ophthalmol,* 120 (5), 613-9.

Fortune, B., Goh, K., Demirel, S., Novitsky, K., Mansberger, S., Johnson, C. & Cioffi, G. Unpublished. 'Detection of Glaucomatous Visual Field loss using Multifocal VEP'.

Gilhotra, J.S., Mitchell, P., Healey, P.R., Cumming, R.G. & Currie, J. 2002. 'Homonymous visual field defects and stroke in an older population', *Stroke*, 33 (10), 2417–2420.

Goldberg, I., Graham, S.L. & Klistorner, A.I. 2002. 'Multifocal objective perimetry in the detection of glaucomatous field loss', *American Journal of Ophthalmology*, 133 (1), 29–39.

Graham, S.L. & Balachandran, C. Unpublished. 'Electrophysiology in the detection of glaucomatous field loss - a review of techniques'. [8]

Graham, S.L., Klistorner, A.I., Grigg, J.R. & Billson, F.A. 2000. 'Objective VEP perimetry in glaucoma: asymmetry analysis to identify early deficits', *Journal of Glaucoma*, 9, 10–19.

Graham, S.L., Klistorner, A. & Goldberg, I. Unpublished. 'Clinical application of multifocal VEP objective perimetry in glaucoma practice.'

Graham, S.L. & Vaegan, 1991. 'High correlation between absolute psychophysical threshold and the scotopic threshold response to the same stimulus', *British Journal of Ophthalmology*, 75 (10), 603-607.

Guyatt, G.H., Sackett, D.L. & Cook, D.J. 1993. 'Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group', *Journal of the American Medical Association*, 270 (21), 2598–2601.

Hasegawa, S. & Abe, H. 2001. 'Mapping of glaucomatous visual field defects by multifocal veps', *Investigative Ophthalmology & Visual Science*, 42, 3341–3348.

Hills, J.F. & Johnson, C.A. 1988. 'Evaluation of the t test as a method of detecting visual field changes', *Ophthalmology*, 95 (2), 261–266.

[8] At the time of searching this citation was unpublished and was subsequently published: Graham, S.L., Klistorner, A. & Goldberg, I. 2005. 'Clinical application of multifocal VEP objective perimetry in glaucoma practice.' Arch Ophthalmol, 123 (6), 729-39.

Hirsbrunner, H.P., Fankhauser, F., Jenni, A. & Funkhouser, A. 1990. 'Evaluating a perimetric expert system: experience with Octosmart', *Graefes Archives of Clinical Experimental Ophthalmology*, 228 (3), 237–241.

Hood, D.C. & Zhang, X. 2000. 'Multifocal ERG and VEP responses and visual fields: comparing disease-related changes', *Ophthalmology*, 100, 115–137.

Hood, D.C., Zhang, X., Greenstein, V.C., Kangovi, S., Odel, J.G., Liebmann, J.M. & Ritch, R. 2000. 'An interocular comparison of the multifocal VEP: a possible technique for detecting local damage to the optic nerve', *Investigative Ophthalmology & Visual Science*, 41 (6), 1580–1587.

Hood, D.C. & Greenstein, V.C. 2003. 'Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma', *Progress in Retinal and Eye Research*, 22, 201–251.

Hood, D.C., Thienprasiddhi, P., Greenstein, V.C., Winn, B.J., Ohri, N., Liebmann, J.M. & Ritch, R. 2004. 'Detecting early to mild glaucomatous damage: A comparison of the multifocal VEP and automated perimetry', *Investigative Ophthalmology & Visual Science*, 45 (2), 492–498.

International Council of Ophthalmology 2005, *ICO International guidelines: Primary open-angle glaucoma (Initial evaluation).* [Internet]. Available from: www.icoph.org/guide/guidepri.html [Accessed 25 May 2004]

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J. & McQuay, H.J. 1996. 'Assessing the quality of reports of randomized clinical trials: is blinding necessary?', *Controlled Clinical Trials*, 17 (1), 1–12.

Jaeschke, R., Guyatt, G. & Sackett, D. 1994a. 'Users' guide to the medical literature III: how to use an article about a diagnostic test. A. Are the results of the study valid?', *Journal of the American Medical Association*, 271 389–391.

Jaeschke, R., Guyatt, G.H. & Sackett, D.L. 1994b. 'Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group', *Journal of the American Medical Association*, 271 (9), 703–707.

James, B., Chew, C. & Bron, A. 1997, *Ophthalmology*, Blackwell Science Ltd, Oxford.

Johnson, C.A. & Spry, P. 1999. 'Normal age related sensitivity loss for perimetry test that evaluate a variety of different visual functions (abstract)', *Investigative Ophthalmology & Visual Science*, 40, S67.

Kanksi, J.J. 1999, *Clinical ophthalmology, a systematic approach*, 4th edn, Butterworth-Heinemann, Oxford.

Katz, J., Quigley, H.A. & Sommer, A. 1995. 'Repeatability of the Glaucoma Hemifield Test in automated perimetry', *Investigative Ophthalmology & Visual Science*, 36 (8), 1658–1664.

Klistorner, A.I. & Graham, S.L., Grigg, J.R. & Billson, F.A. 1998. 'Multifocal VEP topographic visual evoked potential: improving objective detection of local visual defects', *Investigative Ophthalmology & Visual Science*, 39, 937–950.

Klistorner, A. & Graham, S.L. 2000. 'Objective perimetry in glaucoma', *Ophthalmology,* 107 (12), 2283–2299.

Klistorner, A.I. & Graham, S.L. 2001. 'Electroencephalogram-based scaling of multifocal visual evoked potentials: effect on intersubject amplitude variability', *Investigative Ophthalmology & Visual Science*, 42 (9), 2145–2152.

Klistorner, A., Graham, S.L., Grigg, J. & Balachandran, C. Unpublished. 'Objective perimetry using the multifocal VEP in central visual pathway lesions'.

Knottnerus, J.A. & van Weel, C. 2002, 'General introduction: evaluation of diagnostic procedures', In: Knottnerus, J.A. *The evidence base of clinical diagnosis*, BMJ Books, London, 1–18.

Larena, C. & Gironella, R. 1992. 'Rate of campimetric improvement during medical treatment of simple chronic glaucoma', *Chibret International Journal of Ophthalmology*, 9 (1), 6–13.

Lijmer, J.G., Mol, B.W., Heisterkamp, S., Bonsel, G.J., Prins, M.H., van der Meulen, J.H. & Bossuyt, P.M. 1999. 'Empirical evidence of design-related bias in studies of diagnostic tests', *Journal of the American Medical Association*, 282 (11), 1061–1066.

Marra, G. & Flammer, J. 1991. 'The learning and fatigue effect in automated perimetry', *Graefes Archives of Clinical Experimental Ophthalmology*, 229 (6), 501–504.

Mathers, C., Vos, T. & Stevenson, C. 1999. The burden of disease and injury in Australia. Australian Institute of Health and Welfare, Canberra.

Mitchell, P., Smith, W., Attebo, K. & Healey, P.R. 1996. 'Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study', *Ophthalmology*, 103 (10), 1661–1669.

Mitchell, P., Hayes, P. & Wang, J.J. 1997. 'Visual impairment in nursing home residents: the Blue Mountains Eye Study', *Medical Journal of Australia*, 166 (2), 73–76.

MSAC. 2001. *Visual electrodiagnosis* Application 1005. Commonwealth of Australia, Canberra.

MSAC. 2002. *Multifocal multichannel objective perimetry* - Reference 13. Department of Health and Aged Care, Canberra.

Muirhead, P.G. & Johnston, A.W. 2003. 'Reproducibility of central field results using the Humphrey Field A in normal subjects', *Clinical and Experimental Optometry*, 73 (5), 1475

Mukesh, B.N., McCarty, C.A., Rait, J.L. & Taylor, H.R. 2002. 'Five-year incidence of open-angle glaucoma: the visual impairment project', *Ophthalmology*, 109 (6), 1047–1051.

NHMRC. 2000. *How to use the evidence: assessment and application of scientific evidence*, National Health and Medical Research Council, Canberra.

NHS Centre for Reviews and Dissemination 2001, *Undertaking systematic review of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews* [Internet]. NHS Centre for Reviews and Dissemination, Available from: http://www.york.ac.uk/inst/crd/report4.htm [Accessed 23 June 2003].

Rochtchina, E. & Mitchell, P. 2000. 'Projected number of Australians with glaucoma in 2000 and 2030', *Clinical & Experimental Ophthalmology*, 28 (3), 146–148.

Sackett, D. & Haynes, R.. 2002, 'The architecture of diagnostic research', *British Medical Journal*, 324, 539–541.

Sackett, D., Strauss, S., Richardson, W., Rosenberg, W. & Haynes, R. 2000, 'Diagnosis and screening.' In: Evidence-Based Medicine: How to Practice and Teach EBM, Churchill Livingstone, Edinburgh, 67–93.

Schulz, K.F., Chalmers, I., Hayes, R.J. & Altman, D.G. 1995. 'Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials', *Journal of the American Medical Association*, 273 (5), 408–412.

Spry, P.G., Johnson, C.A., McKendrick, A.M. & Turpin, A. 2003. 'Measurement error of visual field tests in glaucoma', *British Journal of Ophthalmology*, 87 (1), 107–112.

Taylor, H.R. 2001, Ageing and Visual loss in Australia [Internet]. Melbourne. Available from: http://cera.unimelb.edu.au/eyecarecommunity/austloss.html [Accessed 18 June 2004].

Thienprasiddhi, P., Greenstein, V.C., Chen, C.S., Liebmann, J.M., Ritch, R. & Hood, D.C. 2003. 'Multifocal visual evoked potential responses in glaucoma patients with unilateral hemifield defects', *American Journal of Ophthalmology*, 136 (1), 34–40.

Vaegan, G. S. L. 1991. 'High correlation between absolute psychophysical threshold and the scotopic threshold response to the same stimulus'. *British Journal of Ophthalmology*, 75 (10), 603–607.

Wang, L., Barber, C., Kakigi, R., Kaneoke, Y., Okusa, T. & Wen, Y. 2001. 'A first comparison of the human multifocal visual evoked magnetic field and visual evoked potential', *Neuroscience Letters*, 315 (1-2), 13–16.

Weih, L.M., Nanjan, M., McCarty, C.A. & Taylor, H.R. 2001. 'Prevalence and predictors of open-angle glaucoma: results from the visual impairment project', *Ophthalmology*, 108 (11), 1966–1972.

Wensor, M.D., McCarty, C.A., Stanislavsky, Y.L., Livingston, P.M. & Taylor, H.R. 1998. 'The prevalence of glaucoma in the Melbourne Visual Impairment Project', *Ophthalmology*, 105 (4), 733–739.

Wong, A.Y., Dodge, R.M. & Remington, L.A. 1995. 'Comparing threshold visual fields between the Dicon TKS 4000 automated perimeter and the Humphrey Field Analyzer', *Journal of the American Optometry Association*, 66 (11), 706–711.

Woodward, K. & Wall, M. 2002/2003, 'The Multifocal visual evoked potiental in functional visual loss'. In: update P (Ed.) Proceedings of the XVth International Perimetric Society Meeting, Kugler Publications, England, 261–264.

World Health Organisation (WHO) 2000, Health systems: improving performance. [Internet]. Geneva. Available from: http://dixit.terminotics.com/dixitdemo/Co.../ViewWHRTerm.asp?ILG=GB&ID=23924 [Accessed 25 June 2004].