# *Visual electrodiagnosis*

**April 2001**

**MSAC application 1005**

**Assessment report**

**ISBN 0642 82002 3**
**ISSN (Print) 1443-7120**
**ISSN (Online) 1443-7139**

**First printed**



Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at:

http://www.msac.gov.au

Hard copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 107
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 is an independent committee which has been established to provide advice to the Commonwealth 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.

This report was prepared by the Medical Services Advisory Committee (MSAC) with the assistance of Ms Elizabeth Burrows, Dr Renea Johnston, Ms Alexandra Raulli and Dr Elmer Villanueva of the Centre for Clinical Effectiveness, Monash Institute of Public Health, Monash University.

The report was endorsed by the Commonwealth Minister for Health and Aged Care on 19 June 2001.

Publication approval number: 3005

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

# Contents

**Executive summary** ..... **vi**

**Introduction** ..... **1**

**Background** ..... **2**

Visual electrodiagnosis ..... 2

The procedures ..... 2

Intended purpose ..... 3

Clinical need ..... 4

Existing procedures and comparators ..... 5

Marketing status ..... 5

Current reimbursement arrangements ..... 5

**Approach to assessment** ..... **6**

Review of literature ..... 6

Expert advice ..... 11

**Results of assessment** ..... **12**

Is it safe? ..... 12

Is it effective? ..... 12

What are the economic considerations? ..... 28

**Conclusions** ..... **29**

**Recommendation** ..... **31**

**Appendix A MSAC terms of reference and membership** ..... **33**

**Appendix B Supporting committee** ..... **34**

**Appendix C Visual electrodiagnosis: synonyms** ..... **35**

**Appendix D Included and excluded studies** ..... **36**

**Appendix E Focal ERG tables** ..... **47**

**Appendix F Multifocal ERG tables** ..... **74**

**Appendix G Multifocal VEP tables** ..... **83**

**Appendix H STR tables** ..... **86**

**Appendix I IRF tables** ..... **92**

**Abbreviations** ..... **95**

**References** ..... **97**

## List of Tables


Table 1 Electronic databases (including edition) accessed for the literature review ..... 7

Table 2 Search terms used to identify citations focusing on focal ERG, multifocal ERG, multifocal VEP, STR and IRF ..... 7

Table 3 Selection process by type of test: number of citations in each rejection category and final number of articles for in-depth review ..... 9

Table 4 Criteria and definitions for assessing validity of included articles ..... 10

Table 5 Levels of evidence for diagnostic tests ..... 11

Table 6 Eye diseases investigated in included studies by type of vision test ..... 14

Table 7 Study design of articles examining focal ERG compared with another test ..... 15

Table 8 Diagnostic characteristics of focal ERG ..... 19

Table 9 Study design of articles examining multifocal ERG compared with another test ..... 20

Table 10 Study design of included articles examining multifocal VEP ..... 22

Table 11 Study design of included articles examining STR ..... 24

Table 12 Study design of included articles examining intensity response function ..... 26

Table E1 Descriptive characteristics of studies examining focal ERG compared with another test ..... 47

Table E2 Validity of focal ERG studies with a comparator test ..... 52

Table E3 Results of studies comparing focal ERG with another test ..... 53

Table E4 Descriptive characteristics of case control studies of focal ERG ..... 57

Table E5 Results of case control studies of focal ERG ..... 64

Table E6 Descriptive characteristics of case series studies of focal ERG ..... 70

Table E7 Results of case series studies of focal ERG ..... 72

Table F1 Descriptive characteristics of studies examining multifocal ERG compared with another test ..... 74

Table F2 Validity of studies comparing multifocal ERG with another test ..... 74

Table F3 Results of studies comparing multifocal ERG with another test ..... 75

Table F4 Descriptive characteristics of case control studies of multifocal ERG ..... 76

Table F5 Results of case control studies of multifocal ERG ..... 79

Table G1 Descriptive characteristics of studies examining multifocal VEP compared with another test ..... 83

Table G2 Validity of studies comparing multifocal VEP with another test ..... 83

Table G3 Results of studies comparing multifocal ERG with another test ..... 84

Table G4 Descriptive characteristics of case control study of multifocal VEP ..... 84

Table G5 Results of case control studies of multifocal VEP ..... 85

Table H1 Descriptive characteristics of studies examining STR compared with another test ..... 86

Table H2 Validity of studies comparing STR with another test ..... 88

Table H3 Results of studies comparing STR with another test ..... 89

Table H4 Descriptive characteristics of case control study of STR ..... 90

Table H5 Results of case control studies of STR ..... 91

Table I1 Descriptive characteristics of case control study of IRF ..... 92

Table I2 Results of case control studies of IRF ..... 93

Table I3 Descriptive characteristics of case series of IRF ..... 94

Table I4 Results of case control studies of IRF ..... 94

# Executive summary

## The procedure

Visual electrodiagnosis (VED) is used to study a variety of eye diseases. Five VED tests to be used for the diagnosis of retinal disease, optic nerve damage and visual field defects were the focus of this evaluation: focal electroretinography (focal ERG), multifocal electroretinography (multifocal ERG), multifocal visual evoked potential (multifocal VEP), scotopic threshold response (STR) and intensity response function (IRF). Four of the five tests, focal ERG, multifocal ERG, STR and IRF, are conducted by measuring the response of the eye to a flash of light with the electroretinogram. By varying the light intensity and colour, the frequency of light presentation and the state of retinal (light) adaptation, the clinician studies different retinal structures. The multifocal VEP examines the response of the occipital cortex to light, allowing the clinician to examine components of the visual field.

Electroretinography, dark adaptometry, pattern electroretinography, electrooculography and visual evoked responses are well established tests recognised by the International Society of Clinical Electrophysiology of Vision (ISCEV). They were not part of the present review. The current reimbursement arrangements for these tests under Medicare are detailed in the section headed 'Current reimbursement arrangements'.

## Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health-financing decisions in Australia. MSAC advises the Commonwealth 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 the Centre for Clinical Effectiveness was engaged to conduct a systematic review of literature on VED. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

## MSAC's assessment of visual electrodiagnosis

### Clinical need

Several eye disorders were included in this evaluation, but prevalence rates of the majority of diseases could not be found. Data related to the older Australian population (born prior to 1943) was available only for glaucoma, age-related macular degeneration, diabetic retinopathy and amblyopia. Open-angle glaucoma has a prevalence of 3.0% in this population and ranges from 0.4% in those younger than 60 years up to 11.4% in those aged 80 years and older. Prevalence is slightly higher in females. Age-related macular degeneration has a prevalence of 1.9% in this population and also increases with age, ranging from a prevalence of 0% in those under 55 years to 18.5% in those aged 85 years and older. Diabetic retinopathy has a prevalence of 2.3% that does not vary significantly with age. Amblyopia has a prevalence of 3.2% that does not vary with age.

### Safety

As VED is non-invasive, risks to patients are expected to be minimal. There were three reports of corneal irritation associated with ERG recording. No frequencies of adverse events were reported.

No significant consumer issues were identified in relation to the evaluated electrodiagnostic tests.

### Effectiveness

Two factors were considered in determining the effectiveness of the visual electrodiagnostic tests: accuracy and usefulness in improving outcomes for patients. Accuracy is measured by diagnostic characteristics such as sensitivity and specificity.

#### Focal electroretinogram

Studies of focal ERG were generally of poor quality and thus subject to bias in terms of the ideal diagnostic study. All studies were ranked only as level IV evidence in the hierarchy of evidence of diagnostic studies. Few studies provided diagnostic characteristics, and all offered little discussion of patient management options as a result of undertaking such a test. Studies that did provide diagnostic characteristics were fundamentally flawed due to their selection of patients who were already diagnosed with the disease or to the lack of a reference test, and thus overestimated the accuracy of focal ERG as a diagnostic test.

#### Multifocal electroretinogram

All the studies of multifocal ERG were classified as level IV evidence. They did not present diagnostic characteristics or sufficient data to compute them. Although the studies showed that the multifocal ERG was able to discriminate between some visual parameters of patients with disease and controls with normal vision, they had little consistency and comparability. It is apparent from the available studies that much of the attention is focused on the mechanics of the technique and issues concerned with averaging signals and presentation of results. Thus, the clinical benefits of this technique are not yet apparent.

#### Multifocal visual evoked potential

Little evidence of the effectiveness of multifocal VEP in diagnosing visual field defects was found. Studies were of poor quality compared with the ideal study design for a diagnostic test, and thus were ranked as level IV evidence in the hierarchy of evidence of diagnostic tests. The studies did not provide diagnostic characteristics or discussion of patient management options as a result of undertaking such a test.

#### Scotopic threshold response

There is little evidence for the diagnostic value of STR. Studies failed to report diagnostic characteristics or the data to compute them, and none of the studies addressed how the STR would influence patient management.

#### Intensity response function

Three studies that met inclusion criteria show little evidence of the effectiveness of IRF in diagnosing retinal disease or optic nerve damage. Studies were methodologically poor and were ranked as level IV evidence in the hierarchy of evidence of diagnostic tests. The studies failed to provide adequate diagnostic characteristics and offered little discussion of patient management options as a result of undertaking such a test.

## Cost effectiveness

Since there is insufficient evidence of the accuracy of the tests and their usefulness in improving patient outcomes, an economic evaluation could not be undertaken.

## Recommendation

On the strength of evidence pertaining to visual electrodiagnostic tests, MSAC recommends that:

1. public funding be supported for the following well-established tests recognised by the International Society of Clinical Electrophysiology of Vision –
    - electroretinography
    - pattern electroretinography
    - dark adaptometry
    - electrooculography
    - visual evoked responses; and
2. due to insufficient evidence, public funding should not be supported at this time for the following tests –
    - focal electroretinography
    - multifocal electroretinography
    - multifocal visual evoked potential
    - scotopic threshold response
    - intensity response function.

The Minister for Health and Aged Care accepted this recommendation on 19 June 2001.

# Introduction

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

MSAC's terms of reference and membership are at Appendix A. 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 affairs and health administration.

This report summarises the assessment of current evidence for VED.

# Background

## Visual electrodiagnosis

### The procedures

Electrophysiology of the eye is used to distinguish the function of the two types of photoreceptors present in the retina - the rods and the cones (Carr & Siegel 1990). Rods and cones are distributed uniquely throughout the retina, with cones concentrated mostly in the centre (foveola) of the retina, while rods are concentrated more at the periphery. There is a disproportionate number of rods to cones (130 million to 7 million). Rods are primarily responsible for coarse acuity, slowly adapting vision in dim light, while cones provide fine visual acuity in light conditions of moderate and high intensity (Carr & Siegel 1990).

The electroretinogram (ERG) is the electrical recording of the response of the eye to a flash of light. Rod and cone responses to light differ markedly. Manipulating stimulus variables such as the light flash intensity and colour, the frequency of flash presentation and the state of retinal (light) adaptation can produce different waveform responses. By doing this, the clinician may examine the response of different structures of the retina, and can deduce the location of disease in the retina and possibly the aetiology of the disease.

Visual evoked potential (VEP) is generated in the occipital cortex of the brain in response to retinal stimulation. VEP provides information about the end-stages of visual processing and is essentially an indirect measure of retinal activity dependent on the integrity of the visual pathways.

Four of the five VED tests evaluated in this report are conducted by measuring the response of the eye to a flash of light with the ERG. These are focal electroretinography (focal ERG), multifocal electroretinography, scotopic threshold response (STR) and intensity response function (IRF). The fifth test is the measurement of the VEP. Both ERG and VEP therefore measure electrically the response of the retina to light stimulation. With the ERG, responses are recorded using electrodes placed directly on the eye or attached to the lower eyelid and, in the case of the VEP, the electrodes are placed on the scalp.

ERG involves measuring responses generated by large areas of the retina. Focal ERG involves measuring responses derived from small areas of the macular region of the retina and is termed 'focal ERG' because it is essentially a response evoked by a small (10° or less) focal stimulus (Carr & Siegel 1990). Two devices used for conducting focal ERG are:

- a small flickering stimulus which is surrounded by a larger steady background light contained within a modified ophthalmoscope (Sandberg et al 1977) and which is usually placed near the macular region under observation; and

- several light-emitting diodes grouped together as a small, diffuse red stimulus that produces waxing and waning light in a sinusoidal pattern (Seiple et al 1986).

The multifocal ERG is conducted similarly to the focal ERG. The basic difference is in the presentation of stimuli, such that several focal responses are recorded simultaneously to primarily examine the function of the cones (Kreschtmann et al 1998). The procedure involves stimulating each area of the retina with a sequence of bright and dark stimuli (m-sequences) such that from a single recording a summed response is generated from several areas of the retina. It is possible to extract responses from individual retinal areas from the summed signal since the response from an individual area is not affected by responses from other areas (Finger and Stasche 2000).

Similarly, STR is measured after dark adaptation using dim light flashes. STR originates not from the photoreceptors but from the more proximal retinal layers (Korth and Koca 1993).

The IRF is obtained by stimulating the retina with light of different intensities. IRF is the relationship between ERG amplitude and the stimulus luminance. The log of this relationship is a non-linear, roughly sigmoidal curve (Roecker et al 1992).

ERG, pattern ERG, electrooculography and visual evoked responses are well established tests recognised by the International Society of Clinical Electrophysiology of Vision (ISCEV). They were not part of the present review. The current reimbursement arrangements under Medicare for these tests are detailed in the section headed 'Current reimbursement arrangements'.

## Intended purpose

The VED tests assessed in this report are used to investigate patients who present with a variety of visual disorders. Diseases may be quite rare and ophthalmologists may refer patients to highly qualified retinal specialists to perform the tests. The literature search revealed several indications for which the tests have been used, such as various types of macular dystrophy, glaucoma, retinitis pigmentosa, optic neuritis and unexplained visual loss (see Table 6).

Thus, the scope of the evaluation was not limited to particular disorders, but was broad to ensure that as far as possible all relevant diseases were included in the evaluation. Thus, for the ERG derivatives (focal ERG, multifocal ERG, STR and IRF), studies discussing VED for retinal disease and optic nerve defects were sought and, for the VEP test, studies that examined diagnosis of visual field defects were sought.

## Clinical need

Although a number of diseases are studied with the five VED tests, there was a paucity of data pertaining to prevalence rates of eye diseases. Data retrieved was restricted to an older Australian population and came from the Blue Mountain Eye Study (BMES) (Attebo et al 1996; Mitchell et al 1997). This study 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, age-related maculopathy, diabetic retinopathy and amblyopia.

Open-angle glaucoma was found in 108 people, a prevalence of 3.0% (95% CI=2.5, 3.6). An exponential rise in prevalence was observed with increasing age. The prevalence of glaucoma was 0.4% for people younger than 60 years of age, 1.3% for people 60 to 69 years of age, 4.7% for people 70 to 79 years of age, and 11.4% 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). Ocular hypertension was present in 3.7% of this population (95% CI=3.1, 4.3), but there was no significant age-related increase in prevalence and there was no sex difference in the age-adjusted prevalence of ocular hypertension (Mitchell et al 1996).

Age-related macular degeneration was present in 1.9% of the population (Mitchell et al 1995) and was the leading cause of blindness (Attebo et al 1996). Bilateral age-related macular degeneration occurred in over half (56%) of the population, with prevalence ranging from nil among people younger than 55 years of age to about 18.5% among those aged 85 years and over (Mitchell et al 1995).

The prevalence of diabetic retinopathy in the BMES was 2.3% (95% CI=1.9, 2.8). Age-specific prevalences were 1.7% in persons younger than 60 years of age, 2.4% in persons 60 to 69 years of age, 2.7% in persons 70 to 79 years of age, and 2.3% in persons aged 80 and over (Mitchell et al 1998).

The prevalence of amblyopia was 3.2% (95% CI=2.7, 3.8) using a visual acuity criterion of 20/30 or less. No statistically significant associations were found between amblyopia and gender or eye affected (Attebo et al 1998).

The Australian Institute of Health and Welfare calculated measures of 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 (DALYs) were calculated at 21,056 for age-related vision disorders overall (4,356 DALYs for males, 16,700 DALYs for females) and 1,850 for glaucoma (408 DALYs for males and 1,442 DALYs for females).

## Existing procedures and comparators

VED is used to investigate patients with a variety of diseases. Expert clinical opinion provided by the supporting committee revealed that diagnosis of eye diseases is usually complex, and established comparator reference (gold) standards for each of the five vision tests under review do not exist. In practice many eye diseases are diagnosed after employing more than one test and clinical examination; thus the comparison of each of the diagnostic tests with a single reference standard is not realistic. Therefore, no restriction was placed on comparators while conducting the literature search, and studies comparing any of the five tests against any other test or procedure were included in the evaluation.

## Marketing status

The specified diagnostic tests are not based on pharmacological diagnostic kits, reagents or standard commercial devices needing registration under the Therapeutic Goods Administration's Australian Register of Therapeutic Goods.

## Current reimbursement arrangements

Currently reimbursements for visual electrodiagnostic tests are classified under four item numbers in the Medicare Benefits Schedule (MBS):

- Item number 11206 – Electroretinography of one or both eyes OR electrooculography of one or both eyes (Reimbursement $85.60)

- Item number 11209 – Electroretinography of one or both eyes AND electrooculography of one or both eyes (Reimbursement $126.90)

- Item number 11024 – Central nervous system evoked responses, investigation of, by computerised averaging techniques, not being a service involving quantitative topographic mapping of event-related potentials – one or two studies (Reimbursement $88.70)

- Item number 11027 – Central nervous system evoked responses, investigation of, by computerised averaging techniques, not being a service involving quantitative topographic mapping of event-related potentials – three or more studies (Reimbursement $131.50)

# Approach to assessment

## Review of literature

An investigation of the quality of evidence to support the use of five vision tests was undertaken. These tests included focal ERG, multifocal ERG, multifocal VEP, STR and IRF – for diagnosing retinal disease, optic nerve damage and visual field defects.

Specifically, the evaluation sought to answer the following questions:

- What are the diagnostic characteristics of focal ERG in diagnosing optic nerve damage or retinal disease?
- What are the diagnostic characteristics of multifocal ERG in diagnosing optic nerve damage or retinal disease?
- What are the diagnostic characteristics of multifocal VEP in diagnosing visual field defects?
- What are the diagnostic characteristics of STR in diagnosing optic nerve damage or retinal disease?
- What are the diagnostic characteristics of IRF in diagnosing optic nerve damage or retinal disease?

For each of the above, the term 'diagnostic characteristics' refers to the accuracy and precision with which these tests are applied. The most clinically relevant information is in the form of proportions of diseased and non-diseased populations accurately characterised by application of the test (sensitivity, specificity, predictive values and likelihood ratios).

### Literature search

Literature searches conducted for each of the five tests covered the period from 1966 to September 2000. Table 1 lists the electronic databases accessed.

**Table 1 Electronic databases (including edition) accessed for the literature review**

| Database | Period covered |
|---|---|
| Cochrane Library including the:<br>• Cochrane Databases of Systematic Reviews<br>• Database of Abstracts of Reviews of Effectiveness<br>• Cochrane Controlled Trials Register<br>• National Health Service Economic Evaluation Database<br>• Health Technology Database | Issue 3, 2000 |
| Best Evidence (OVID) | 1998 to 2000 |
| Medline (OVID & PubMed)<br>PreMedline (OVID) | 1966 to October 2000 week 3<br>August 31 2000 |
| HealthSTAR (Internet GratefulMed) | 1998 to April 2000 |
| Current Contents (OVID) | 1993 week 26 to 2000 week 36 |
| Biological Abstracts (OVID) | 1980 to June 2000 |

## Search strategy

The following search strategies were used to find relevant articles focusing on focal ERG, multifocal ERG, multifocal VEP, STR and IRF. Sensitive (broadly defined) search strategies were used due to the non-standardised nature of database indexing of eye diseases. Similarly, due to the lack of standardised index terms for the five vision tests in the databases accessed, subject headings were not employed, and searching was conducted using text words. The expert supporting committee identified synonyms for each test. The synonyms for each vision test are listed in Appendix C. Table 2 presents the search terms employed to identify articles.

**Table 2 Search terms used to identify citations focusing on focal ERG, multifocal ERG, multifocal VEP, STR and IRF**

| Vision test | Search terms |
|---|---|
| Focal electroretinogram | focal$ electro?retino$, focal$ ERG, focal cone electro?retino$, focal cone ERG, focal macular electro?retino$, focal macular ERG, focal flash electr?retino$, focal flash ERG, foveal$ electro?retino$, foveal$ ERG, foveal cone electro?retino$, foveal cone ERG, smallfield electr?retino$, smallfield ERG, macular electro?retino$, macular ERG, paramacular electro?retino$, paramacular ERG, steady?state focal electro?retino$, steady?state ERG |
| Multifocal electroretinogram | multi$ electro?retino$, multi$ ERG |
| Multichannel visual evoked potential | multi$ visual$ evoke$ potent$, multi$ VEP<br>multi$ visual$ evoke$ respon$, multi$ VER |
| Scotopic threshold response | scotop$ thresh$ respons$ |
| Intensity response function | intens$ respons$ funct$ |

Note: Electronic databases apply different characters as "wildcard" symbols. These symbols refer to characters or groups of characters that appear in the terminus of a word fragment. For the Ovid databases, the wildcard character is the dollar sign ("$"); the Cochrane Library uses the asterisk ("*"). In this case, "respons$" expands to "response", "responses", etc.

## Inclusion and exclusion criteria

The following *a priori* criteria were developed to identify relevant literature:

### Patient population

*Inclusion*: Studies in humans with retinal disease or optic nerve damage (focal ERG, multifocal ERG, STR, IRF) or visual field defects (multifocal VEP).

### Diagnostic test

*Inclusion*: Use of focal ERG, multifocal ERG, multifocal VEP, STR, IRF.

*Exclusion:* Other electroretinography tests.

### Outcomes

*Inclusion:* All outcomes that address the diagnostic characteristics of the particular test in the diagnosis of any retinal disease or optic nerve damage.

### Methodology

*Inclusion:* Individual studies (including case series) and systematic reviews of studies that evaluate the diagnostic characteristics of a specific vision test in diagnosing a specific retinal disease or type of optic nerve damage.

*Exclusion:* Narrative reviews, editorials, letters.

### Also excluded

- publications in a language other than English,
- articles identified as preliminary reports when results are published in later versions,
- articles published in abstract form only,
- articles that examined a test in normal patients only, and
- case reports and collections of case reports in which results are only presented by individual study patient and not summarised.

The following five-step process was employed to select and exclude articles:

1. Initial search
2. Initial rejection
3. Full text assessment
4. Final rejection
5. Articles accepted

Three independent reviewers examined each citation for inclusion. Discrepancies in selection were discussed and resolved through consensus. An initial assessment of abstracts for the citations retrieved after the initial search (step 1) allowed for the exclusion of articles that did not meet the selection criteria (step 2). Ambiguous or uncertain citations proceeded to the next stage (step 3).

**Table 3 Selection process by type of test: number of citations in each rejection category and final number of articles for in-depth review**

| Vision test | Number of studies by category code* | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| Focal ERG | 131 | 16 | 16 | 14 | 14 | 71 |
| Multifocal ERG | 84 | 21 | 10 | 2 | 12 | 39 |
| Multifocal VEP | 34 | 4 | 1 | 1 | 11 | 17 |
| Scotopic threshold response | 47 | 1 | 28 | 3 | 6 | 9 |
| Intensity response function | 41 | 1 | 26 | 0 | 8 | 6 |
| Total | 337 | 43 | 81 | 20 | 51 | 142 |

***** Category codes: 1=initial search; 2=foreign language; 3=animal study, model; 4=test used in study designed to measure response to a treatment; 5=study in humans without retinal disease or optic nerve damage; 6=article accepted for in-depth review.

From an initial search of 337 articles, 195 were rejected. This left 142 articles to be assessed in full text form. The final decision to accept or reject articles was based on applying the inclusion/exclusion criteria after a thorough reading of the full text article.

## Assessment of validity

Diagnostic evidence for each of the five tests was evaluated separately. To determine the effectiveness of the five vision tests, included articles were critically appraised and assigned a level of evidence. The quality of research evidence available about VED is relevant because to a large extent this determines the expected health gains from these techniques. In general terms, the assessment of diagnostic tests requires valid – preferably blind – comparisons of their performance against suitable reference tests in appropriate groups of patients. The process by which research evidence is formally assessed is termed critical appraisal.

Critical appraisal refers to the process of evaluating the study design of included articles. The most rigorous study design for assessing the validity of diagnostic tests is considered to be a prospective blind comparison of the test and a reference (or 'gold') standard in a consecutive series of patients from a relevant clinical population (Jaschke et al 1994; Sackett et al 2000).

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 a reference (gold) standard.
- Study test and reference test are measured independently (blind) of each other.

- Choice of patients who were assessed by the reference standard is made independently of the study test's results.
- Study test is measured independently of all other clinical information.
- Reference standard is measured before any interventions are started with knowledge of test results.
- Tests are compared in a valid study design: tests are done independently on each person (most valid); different tests are done on randomly allocated individuals; all tests are done on each person but not assessed independently; different tests are done 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 4.

**Table 4 Criteria and definitions for assessing validity of included articles**

| Validity criteria | Definition |
|---|---|
| Test is compared with a reference (gold) 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 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 control) 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 were initiated prior to the application of the reference (or study) test. |

Based on critical appraisal of the methodology, included studies were also classified according to a hierarchy of evidence (Table 5). At present there is not a National Health and Medical Research Council (NHMRC) of Australia system for assigning a hierarchy of evidence to studies of diagnostic tests. Thus, the system developed by the Centre for Evidence Based Medicine, National Health Service Research and Development, United Kingdom (1999) was adapted for use (Table 5).

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 differ from those used by the Centre for Evidence Based Medicine (1999) in that they include systematic reviews of studies of diagnostic tests as level I evidence, which we excluded from the hierarchy (Table 5).

**Table 5 Levels of evidence for diagnostic tests**

| Level of evidence | Criteria |
|---|---|
| I | Independent blind comparison of an appropriate spectrum* of consecutive patients, all of whom 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:<br>Reference standard was not applied blinded or not applied independently.<br>Positive and negative tests were verified using separate reference standards.<br>Study was performed in an inappropriate spectrum* of patients.<br>Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'. |

* An appropriate spectrum is a cohort of patients who would normally be tested for the target disorder. An inappropriate spectrum compares patients already known to have the disease with patients diagnosed with another condition, or with a separate group of normal patients (case control).

Critical appraisal was conducted by three reviewers with expertise in basic science, clinical research, epidemiology and biostatistics. Prior to commencing the full-scale critical appraisal, a test set of five articles for each vision test was selected and appraised by the three reviewers to verify reliability and consistency of approach in extracting study data. Subsequently, reviewers examined papers independently. Articles that presented difficulties in interpretation were discussed among reviewers and consensus reached.

## Expert advice

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

# Results of assessment

## Is it safe?

The extensive literature search revealed a paucity of safety data. However, as VED tests are non-invasive, the risks to patients should be minimal. All five tests examined use surface electrodes. To record the response, electrodes are placed on the cornea of the eye over the lower eyelid or float on the marginal meniscus of tears on the edge of the lid. To record VEPs electrodes are placed on the back of the scalp over the area of the occipital cortex. For electrodes placed on the cornea, local anaesthetic may be used; thus irritation and infection of the cornea are theoretical risks. Skin abrasions 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 papers reviewed.

Bankes (1967) reported that patients usually tolerate the ERG well and report no particular adverse events. Vaegan et al (1984) state that the contact lens ERG electrodes they used make direct contact with the cornea without discomfort or interference with the normal optics of the eye. Chan & Brown (1998) also report that the particular contact lens electrode they chose does not usually cause irritation, while Graham & Vaegan (1991) employed an electrode that did not make direct contact with the eye, allowing them to record for over two hours without evidence of ocular irritation or corneal oedema.

Only three studies explicitly reported complications in recording the ERG. Arden et al (1982) reported that they discontinued the routine use of benoxinate (anaesthetic) drops since they tended to produce more irritation than the electrodes. Birch & Fish (1988) reported that some of their subjects experienced mild corneal irritation during and after the testing. Vaegan et al (1984) discovered that the gold used in a foil electrode was not well bonded and tended to leave flecks in the eye.

## Is it effective?

Two factors are considered necessary to determine the effectiveness of a diagnostic test:

- accuracy of the test; and
- usefulness of the test in improving outcomes for patients.

## Accuracy of the tests

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder. Accuracy is measured by diagnostic characteristics – sensitivity and specificity. The diagnostic characteristics of each of the five vision tests were reviewed, subject to the availability of studies in which patients are tested with both the study test and the reference standard and subject to the reporting of sufficient data. Minimum requirements for computing sensitivity are data to compute the proportion of patients with the disorder whose tests were correctly identified as positive, and for specificity data to be able to compute the proportion of patients without the disorder whose tests were correctly identified as negative. Likelihood ratios, which indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the target disorder, were also computed if appropriate data could be extracted from individual articles. Results from those studies that do not compare the study test with an appropriate reference standard, or do not provide diagnostic characteristics (level IV studies) were summarised narratively.

In studies where the particular vision test is being used to diagnose the fellow (unaffected) eyes of patients with unilateral eye disease, ie screening studies, test accuracy must also be evaluated by longer-term follow-up of study patients. Patients should be observed over time to determine whether the test accurately predicted the presence or absence of disease in the fellow eye. It is therefore insufficient to find a positive test result when patients are first tested since this may or may not be indicative of later development of disease.

## Patient outcomes

Even if the diagnostic test under consideration is able to detect pathology, this is not a good indicator of the usefulness of the test. Application of the test should improve patient management options, otherwise the usefulness of the test is limited. The ideal method for assessing patient outcomes after using the diagnostic test is a randomised controlled trial that compares outcomes of patients who have had the test with those who have not had the test. No trials of this type were identified. Critical appraisal of the diagnostic test articles included an assessment of whether patient management options were discussed as a result of subjecting patients to the diagnostic test.

## Findings

This review assessed the effectiveness of each visual test separately. These diagnostic tests have been used in the investigation of patients with various types of visual diseases (Table 6).

**Table 6 Eye diseases investigated in included studies by type of vision test**

| Diseases investigated | Vision test | | | | |
|---|---|---|---|---|---|
| | Focal ERG | Multifocal ERG | Multifocal VEP | STR | IRF |
| Age-related macular dystrophy | ✓ | ✓ | | | |
| Amblyopia | ✓ | | | | |
| Aphakic macular oedema | ✓ | | | | |
| Autosomal dominant optic atrophy | | ✓ | | | |
| Autosomal dominant progressive cone degeneration | ✓ | | | | |
| Best's disease | ✓ | | | | |
| Branch retinal artery occlusion | ✓ | | | | |
| Central serous chorioretinopathy | | ✓ | | | |
| Cone dystrophy | ✓ | ✓ | | ✓ | ✓ |
| Congenital retinoschisis | ✓ | | | | |
| Central retinal vein occlusion | | | | | ✓ |
| Congenital rod monochromacy | ✓ | | | | |
| Congenital stationary night blindness | | | | ✓ | |
| Decreased visual acuity and hemeralopia | ✓ | | | | |
| Diabetes with no retinopathy | | ✓ | | | |
| Diabetes mellitus with retinopathy | ✓ | | | ✓ | |
| Familial cone dystrophies | ✓ | | | | |
| Fundus flavimaculatus | | | | | ✓ |
| Foveal pigment epithelipathy | ✓ | | | | |
| Glaucoma, ocular hypertension | ✓ | ✓ | ✓ | ✓ | |
| Gronblad-Strandberg syndrome | ✓ | | | | |
| Hydroxycholoroquine retinopathy | ✓ | | | | |
| Idiopathic central serous chorioretinopathy | ✓ | | | | |
| Idiopathic epimacular membrane | ✓ | | | | |
| Ischemic optic neuropathy | | ✓ | | | |
| Juvenile hereditary macular disease | ✓ | | | | |
| Macular chorioretinal scars | ✓ | | | | |
| Macular degeneration | | | | | ✓ |
| Macular hole | ✓ | | | | |
| Non-proliferative diabetic retinopathy | | ✓ | | | |
| Occult macular dystrophy | ✓ | ✓ | | | |
| Optic atrophy | ✓ | | | ✓ | |
| Pattern dystrophy | ✓ | | | | |
| Pericentral pigmentary retinal dystrophy | ✓ | | | | |
| Retinitis pigmentosa | ✓ | ✓ | | ✓ | ✓ |
| Solar burn | ✓ | | | | |
| Stargardt's macular dystrophy | ✓ | ✓ | | ✓ | |
| Temporal retinal ischaemia | ✓ | | | | |
| Tumour in sella turcica | | | ✓ | | |
| Unexplained visual symptoms or acuity loss | ✓ | | | | |
| Vitelliform degeneration | ✓ | | | | |

### Focal electroretinogram

Forty-one studies have been included in this evaluation after examination of the full text articles. Reasons for exclusion of 30 studies are provided in Appendix D. The included articles were categorised by three study designs:

- cross-sectional studies that compared focal ERG with another test;
- cross-sectional studies that examined focal ERG in a group of diseased patients and a group of normal controls (termed 'case control' studies for the purpose of this assessment); and
- case series that examined focal ERG in a single cohort of diseased patients.

Table 7 identifies the studies according to design.

**Table 7 Study design of articles examining focal ERG compared with another test**

| Study design | Number of included studies | First author and year of publication |
|---|---|---|
| Cross-sectional studies with another test | 15 | Arden 1982, Birch 1982, Falsini 1992, Falsini 1999, Gaudio 1998, Holopigian 1990, Matthews 1992, Miyake 1996, Porciatti 1997, Remulla 1995, Salzman 1986, Seiple 1993, Small 1996, Vaegan 1986, Vaegan 1987 |
| Case control studies | 19 | Bagolini 1988, Bagolini 1989, Birch 1988, Brodie 1992, Deschenes 1998, Di Leo 1994, Falsini 1994, Falsini 1996, Falsini 2000, Fish 1989, Ghirlanda 1991, Jacobsen 1979, Miyake 1988, Miyake 1993, Sandberg 1993, Sandberg 1979, Seiple 1986, Weiner 1998*a,b* |
| Case series | 7 | Biersdorf 1982, Birch 1988, Fish 1986, Holopigian 1996, Sandberg 1998, Tanikawa 1999, Weiner 1997 |

Tables listing study characteristics, validity and results are in Appendix E.

Fifteen articles compared patients' visual parameters assessed with focal ERG with another visual diagnostic test in a single group of patients. A description of each study appears in Table E1. The included studies were published from 1982 to 1999. The smallest study (Matthews et al 1992) included five patients, and the largest study (Gaudio & Sandberg 1998) included 67 patients. The patients varied in age from children to elderly adults. However, two studies failed to give any description of age or sex of their study population (Arden et al 1992, Vaegan & Bilson 1987); only one (Holopigian et al 1990) provided a complete description of the mean age and variation in age, and sex ratio of their study population. The remaining 12 studies provided incomplete descriptions (Table E1).

#### *Patient selection criteria of focal ERG studies with a comparator test*

A range of optic nerve and retinal diseases were present in the included studies. Table E1 presents a breakdown of the number of patients studied by individual disease within each included study, as well as the selection criteria used for enrolment in the study.

### *Tests examined in focal ERG studies with a comparator test*

Table E1 presents the vision tests performed in the included studies. The majority of studies included patients already diagnosed with a particular disease although the method of diagnosis of that disease was not consistently provided. A difficulty is that many of the diseases examined are not diagnosed with a single gold standard test, but rather are diagnosed by a variety of tests. Thus, there is not a single true gold standard or reference test for many of the diseases. Rather the method of diagnosis was implied, and focal ERG was compared with a third, explicitly stated test which, in Table E1, is referred to as the 'test compared with focal ERG'.

### *Validity of focal ERG studies with a comparator test*

Critical appraisal revealed that overall study quality was poor in terms of providing valid evidence for the clinical diagnostic usefulness of focal ERG (Table E2). All studies comparing focal ERG with another visual test failed to meet the five criteria of validity stated in Table 4. If the first three criteria of validity (appropriate spectrum of patients, masked assessment of both tests, all patients examined with both tests) had been met, a study would have been labelled as level I evidence. However, no study met these criteria and therefore all were assigned level IV evidence in the hierarchy of evidence for diagnostic tests (see Table 5).

A major shortcoming was that all studies, except Matthews et al (1992), examined patients previously diagnosed with a visual disorder, but the majority of studies failed to state the method used to reach this diagnosis. Furthermore, all included papers failed to compare the focal ERG results with the method of diagnosis of the disease, which presumably would be considered the gold standard. Rather, focal ERG was compared with a third test, which presumably is not considered the gold standard for the diagnosis of each disease. As discussed, and as is evident from Table E1, many of these diseases are diagnosed by several criteria (eg Falsini et al 1999; Gaudio & Sandberg 1998), which renders a direct comparison of focal ERG with a gold standard test difficult. Nevertheless, the failure of some studies to identify the gold standard of diagnosis for each disease and the failure of all studies to compare focal ERG with the implied or stated gold standards resulted in the labelling of each study as level IV evidence.

The first stated validity criterion in Table E2, an 'appropriate spectrum of patients', was met in only one study (Matthews et al 1992). The remaining studies included patients already diagnosed with a disease before they were examined with focal ERG, casting doubt upon whether the patient spectrum included in each study was the most appropriate. The second stated criterion in Table E2, 'masked assessment of study and reference test results' was explicitly met in only one study (Remulla et al 1995). Ten of fifteen studies (Table E2) met the third criterion, 'all study subjects tested with both study and reference tests. No study explicitly stated that the focal ERG was measured independently of clinical information, or that the reference test was measured prior to the start of the intervention. Matthews et al (1992) and Remulla et al (1995) met two validity criteria; the remaining studies met only one or none. Thus, as stated, no studies met enough criteria to be rated higher than level IV evidence.

### *Summary of findings of focal ERG studies with a comparator test*

As the implied or stated gold standard reference test was not compared with focal ERG, there was no information in any of the papers to allow comparison of focal ERG with the gold standard in the diagnosis of the source of visual acuity loss. However, all included articles compared focal ERG with the second comparator test, but only two papers (Remulla et al 1995; Salzman et al 1986) presented diagnostic characteristics (Table E3). The majority of studies presented comparisons of patients' mean results, which does not provide clinically useful information for diagnosis since the proportion of patients with normal and abnormal test results is unknown. Furthermore, other papers presented only graphical and individual patient responses (Table E3). The majority of articles described in some detail the characteristics of the focal ERG response more from a physiological or academic perspective than as a diagnostic tool to be used in a clinical environment.

The diagnostic characteristics of focal ERG compared with the explicit comparator test in the studies of Remulla et al (1995) and Salzman et al (1986) are presented in Table E3. Remulla et al (1995) presented the sensitivity and specificity of focal ERG implicit times compared with fluorescein angiography. A sensitivity of 61% and a specificity of 72% were calculated. Salzman et al (1986) compared the focal ERG with the multifocal ERG and with VEP. For focal ERG compared with multifocal ERG, data provided allowed us to calculate a sensitivity of 44% and a specificity of 82%. Data comparing focal ERG with VEP allowed us to calculate a sensitivity of 36% and a specificity of 73%. Studies that did present diagnostic characteristics may be of limited use because, as already discussed, it is questionable whether the included patients were the most appropriate in the studies and the true gold standard reference test was implied. There is evidence that if the reference standard is not properly described, accuracy tends to be overestimated (Lijmer et al 1999).

It should be noted that none of the papers comparing focal ERG with another test explicitly addressed the effects of their results on the clinical management of the patients (Table E3).

## Studies of focal ERG in diseased and normal subjects (case control studies)

Nineteen full text articles that compare focal ERG in a group of patients already known to have a disease and a separate group of normal patients (case control studies) were assessed. Table E4 lists some of the pertinent descriptive characteristics of these studies. In one study the control group did not have normal vision; the patients had maculopathy and the controls were those with reduced visual acuity due to causes other than maculopathy (Fish and Birch 1987). Patients from all age groups were included in all the studies, with age ranging from five to 80 years. The publication date ranged from 1979 to 2000, and several diseases were included in the patient groups.

### *Patient selection criteria in case control studies of focal ERG*

A range of optic nerve and retinal diseases were present in the included studies. Table E4 presents a breakdown of the number of patients studied by individual disease and the number of normal controls within each study, as well as the selection criteria used for enrolment in the study.

### *Validity of case control studies of focal ERG*

The 'case' patients in these case control studies consist of those already diagnosed with a particular disease but the method of diagnosis of that disease was stated in only five studies (Table E4). None of the studies compared focal ERG with the unstated gold standard. Rather, focal ERG was compared in the diseased patients and a group of normal patients. Thus, according to the criteria used to assess studies of diagnostic tests, the studies were all assigned as level IV evidence. Case control studies are considered poor designs for evaluating diagnostic tests as they overestimate the accuracy of the test (Lijmer et al 1999).

### *Summary of findings of case control studies of focal ERG*

The results of studies are summarised in Table E5. All studies described reduced components of the focal ERG response in diseased patients compared with normal patients. The majority of studies presented comparisons of mean focal ERG responses, which does not provide clinically useful information for diagnosis since the proportion of patients with normal results is unknown and diagnostic characteristics such as sensitivity and specificity cannot be calculated. Fish et al (1999) and Weiner et al (1998b) provided enough data to calculate sensitivity and specificity but, as noted above, diagnostic characteristics are overestimated in case control study designs and thus are of limited use in determining the effectiveness of the diagnostic test. Furthermore, as the accuracy of the test is not certain, the effects of the results on patient management cannot be determined and were not addressed in the studies.

## Studies of focal ERG in case series

Seven articles describing focal ERG in a series of patients were included. Table E6 lists some of the pertinent descriptive characteristics of these studies. Six studies were conducted in the USA, and the seventh was conducted in Japan. The dates of publication of the studies ranged from 1982 to 1999. The smallest study (Weiner et al 1997) contained 18 patients, and the largest study (Sandberg et al 1998) consisted of 127 patients. Biersdorf (1981) examined a series of 79 patients, and compared the 10 non-diseased fellow eyes from the group of 79 diseased eyes. Biersdorf (1981), Fish et al (1986) and Tanikawa et al (1999) failed to describe the sex ratio of their patient groups. Age was not adequately described in five studies.

### *Patient selection criteria in case series studies of focal ERG*

The diseases studied included various macular disorders and retinitis pigmentosa. Table E6 presents a breakdown of the number of patients studied by individual disease and the selection criteria used for enrolment in the study. Sandberg et al (1998) included patients with unilateral macular degeneration, but measured focal ERG in the non-diseased fellow eye.

### *Validity of case series studies of focal ERG*

Case series studies are considered level IV evidence. Level IV studies are susceptible to bias, and the accuracy of their results cannot be verified outside their immediate setting. Thus, case series provide little useful information about the effectiveness of diagnostic tests.

### *Summary of findings of case series studies of focal ERG*

The results of the case series studies examining focal ERG are summarised in Table E7. Case series do not provide adequate data to calculate diagnostic characteristics such as sensitivity and specificity; thus the results from the included studies are described narratively. Birch et al (1988), Biersdorf (1981) and Tanikawa et al (1999) described the results of focal ERG (amplitude and implicit times) in their patients with eye disease against values found in non-diseased eyes. Biersdorf (1981) and Tanikawa et al (1999) obtained normal values from unaffected fellow eyes of included patients, while Birch et al (1988) obtained normal values from previously published literature. Patient management options as a result of undergoing focal ERG were not addressed in the studies.

However, Sandberg et al (1998) speculated that a delayed focal ERG implicit time may be an early sign of macular degeneration, but it is unclear whether this information was used to treat patients.

### Summary of findings of focal ERG studies

A sensitive search strategy identified 71 articles for evaluation. In-depth review of the full text led to the rejection of 30 articles that did not meet the inclusion criteria. The 41 articles critically appraised for this review provide very little evidence of the effectiveness of focal ERG in the diagnosis of visual disorders. Studies were generally of poor quality and thus subject to bias in terms of the ideal diagnostic study.

Fifteen studies compared focal ERG with another visual test, but it is questionable whether this comparator test was the gold standard used in diagnosis, casting doubts upon the validity of results. Nineteen articles examined focal ERG in a group of patients already diagnosed with a disease and a group of normal controls, which overestimates the accuracy of a diagnostic test. The remaining seven studies reported case series of focal ERG measurements. All studies were methodologically flawed in terms of diagnostic studies and were considered level IV evidence.

Table 8 presents sensitivity, specificity and positive and negative likelihood ratios (LRs) of focal ERG from four studies.

**Table 8 Diagnostic characteristics of focal ERG**

| First author, year of publication | Disease | Study design | Sensitivity | Specificity | LR+ | LR- |
|---|---|---|---|---|---|---|
| Fish 1986 | MD | Case control | 85%* | 92%* | 10.63 | 0.16 |
| Remulla 1995 | ARMD (fellow eyes) | Comparator test | 61% | 72% | 2.18 | 0.54 |
| Salzman 1986 | ACMO | Comparator test | 44% (PERG)<br>36% (VEP) | 82%(PERG)<br>73% (VEP) | 2.44 (PERG)<br>1.33 (VEP) | 0.68 (PERG)<br>0.74 (VEP) |
| Weiner 1998b | Glaucoma | Case control | 96% | 83% | 5.56 | 0.05 |

LR+ = positive likelihood ratio; LR- = negative likelihood ratio. MD = macular disease; ARMD = age-related macular disease, ACMO = aphakic cystoid macular oedema; PERG = pattern ERG; VEP = visual evoked potential. * Based on abnormal amplitude and/or implicit time.

Since LR positive values below 2 and LR negative values above 0.5 generally do not provide important changes in pre- to post-test probability, the analysis in Table 8 demonstrates that case control studies are likely to have overestimated focal ERG accuracy.

Regardless of the methodological flaws in included studies, the majority of studies lacked data of effectiveness. Few studies provided diagnostic characteristics and all offered little discussion of patient management options as a result of undertaking such a test. Studies that did provide diagnostic characteristics were fundamentally flawed in their use of a comparison test or patient populations, and thus overestimated the accuracy of focal ERG as a diagnostic test.

### Multifocal electroretinogram

The full text of 39 studies identified from the literature search was evaluated. Eleven studies met the selection criteria and were critically appraised. References for the excluded studies of multifocal ERG with the reason for their exclusion is provided in Appendix D.

**Table 9 Study design of articles examining multifocal ERG compared with another test**

| Study design | Number of included studies | First author and year of publication |
|---|---|---|
| Cross-sectional studies with another test | 1 | Kretschmann 1998a |
| Case control studies | 10 | Chan 1998, Chan 1999, Fortune 1999, Hasegawa 2000, Hood 2000, Kretschmann 1998b, Marmor 1999, Palmowski 1997, Piao 2000, Seeliger 1998 |

Tables listing study characteristics, validity and results are in Appendix F.

#### Studies of multifocal ERG compared with another test

One study (Kretschmann et al 1998b) compared visual parameters using multifocal ERG with Ganzfeld ERG in 51 patients with Stargardt's macular dystrophy (SMD). Descriptive details of this study are presented in Table F1.

##### *Patient selection criteria of multifocal ERG studies with a comparator test*

The criteria used to select patients with SMD were not described.

##### *Tests examined in multifocal ERG studies with a comparator test*

Study patients' test results using multifocal ERG are compared with their results using Ganzfeld ERG. The patients in this study were already diagnosed as having SMD (and the controls already known to have normal vision). Diagnosis was based on a combination of history and diagnostic tests. The true gold standard or reference test used to diagnose the disease was not stated but rather was implied, and multifocal ERG was compared with a third explicitly stated test – that is the Ganzfeld ERG, which was compared with the findings from multifocal ERG.

##### *Validity of multifocal ERG studies with a comparator test*

None of the six criteria for validity of diagnostic test (see Table 4) was met.

### *Summary of findings of multifocal ERG studies with a comparator test*

Fourteen (17%) SMD patients' eyes that had abnormal Ganzfeld ERG also had subnormal multifocal ERG; ten eyes (12%) with normal Ganzfeld ERG had subnormal multifocal ERG. This is insufficient to calculate the diagnostic characteristics of multifocal ERG compared with Ganzfeld ERG. Although the authors state that multifocal ERG can be useful in the diagnosis and differential diagnosis of SMD, this is not supported by the study findings.

## Studies of multifocal ERG in diseased and normal subjects (case control studies)

Ten full text articles that compare focal ERG in a group of patients already known to have a disease and a separate group of patients with normal vision have undergone critical assessment (case control studies). These studies have all been published within the last several years: publication dates ranged from 1997 to 2000. Patients with diseases including retinitis pigmentosa, glaucoma, diabetic retinopathy, Stargardt's macular dystrophy and age-related macular dystrophy were tested with multifocal ERG. Their ages ranged from 11 years to 73 years and in general included equal numbers of males and females. Table F4 lists some of the pertinent descriptive characteristics of these studies.

### *Patient selection criteria of case control studies of multifocal ERG*

A range of optic nerve and retinal diseases was present in the included studies. Table F5 presents a breakdown of the number of patients studied by individual disease and the number of normal controls within each study, as well as the selection criteria used for enrolment in the study.

### *Validity of case control studies of multifocal ERG*

The 'case' patients in these case control studies consist of those already diagnosed with a particular disease. Only half of the studies provided details of the criteria used for making the diagnosis. Since multifocal ERG is being used to compare the visual parameters of patients with known visual disorder with patients with known normal vision, test accuracy will be exaggerated. These studies are classified as Level IV evidence based on the levels of evidence for studies evaluating diagnostic tests.

### *Summary of findings of case control studies of multifocal ERG*

Some parameters of the multifocal ERG could discriminate between those with eye diseases and those with normal vision, but others could not. However, diagnostic characteristics were not provided or not computable from data in any of the 10 case control studies. According to the hierarchy for classifying strength of evidence from diagnostic studies, these case control studies provide only level IV evidence. Although some authors (Chan 1998; Fortune 1999; Kretschmann 1998; Palmoski 1997) suggest that there is diagnostic potential with the use of multifocal ERG, an obvious clinical role has not been demonstrated.

### Summary of findings of multifocal ERG studies

Studies of multifocal ERG have been published only recently. Although the studies showed that the multifocal ERG was able to discriminate between some visual parameters of patients with disease and controls with normal vision, there was little in the way of consistency and comparability among the studies. All the studies were classified as level IV evidence and none presented diagnostic characteristics or sufficient data to compute them. It is apparent from the available studies that much of the attention is focused on the mechanics of the technique and issues concerned with averaging signals and presentation of results. Thus the clinical benefits of this technique are not yet apparent.

## Multifocal visual evoked potential

The full text of 17 studies was examined to determine whether they fit the inclusion and exclusion criteria for this evaluation. Of these, 15 studies were excluded (Appendix D), leaving two articles suitable for critical appraisal. Wang et al (1988) describe a cross-sectional study that compares multifocal VEP with another reference test. Graham et al (2000) describe a cross-sectional study examining multifocal VEP in a group of diseased patients and a group of normal controls (termed a 'case control' study for the purpose of this assessment). Table 10 identifies the studies according to design.

**Table 10 Study design of included articles examining multifocal VEP**

| Study design | Number of included studies | First author and year of publication |
|---|---|---|
| Cross-sectional studies with another test | 1 | Wang 1988 |
| Case control studies | 1 | Graham 2000 |

Tables listing study characteristics, validity and results are in Appendix G.

### Studies of multifocal VEP compared with another test

One study (Wang et al 1988) comparing multifocal VEP with another test in a group of patients was suitable for full text evaluation. Wang et al (1988) measured multifocal VEP in 30 patients with a sella turcica tumour (Table G1). The study was set in China, but other descriptive details of study setting and patient characteristics were not available (Table G1).

#### *Patient selection criteria of multifocal VEP studies with a comparator test*

Patients included in Wang et al (1988) had a tumour of the sella turcica in the visual pathway, confirmed by computed tomography (Table G1). Patients were being assessed for visual field defects, which may result from compression of the visual neural pathway by the tumour.

#### *Tests examined in multifocal VEP studies with a comparator test*

Table G1 presents the vision tests performed in the included study. Multifocal VEP was used to assess visual field defects compared with the Goldman perimeter test in patients with a confirmed sella turcica tumour.

### *Validity of multifocal VEP studies with a comparator test*

Critical appraisal of Wang et al (1988) revealed that the study rated poorly using the six criteria of validity stated in Table 4, only meeting one of the criteria, namely that study patients were tested with both the study (VEP) and reference (Goldman perimeter) tests (Table G2). Wang et al (1988) failed to describe whether:

- the results of the VEP and the Goldman perimeter test were assessed by a person unaware of the results of the other test;
- VEP was measured independently of clinical information; or
- the reference test was measured prior to initiating any treatment interventions (Table G2).

The study is also not explicit about the spectrum of patients included, or how they were selected. Because of these characteristics, the study was assigned as Level IV evidence in the hierarchy of evidence for diagnostic tests (see Table 5).

### *Summary of findings of multifocal VEP studies with a comparator test*

Diagnostic characteristics could not be calculated (Table G3) from the data in Wang et al (1988). Four patients with a sella turcica tumour had no gross visual field defects as assessed by the Goldman perimeter examination, but two of these four patients did show abnormal VEP topography. The authors suggest therefore that the VEP is more sensitive in detecting functional changes in the visual pathway due to compression of the neural pathways by the tumour, prior to visual field defects becoming apparent via the Goldman perimeter test. They also suggest that computed tomography may not have detected these changes, but this was not tested. There was insufficient data to calculate diagnostic characteristics (sensitivity and specificity) to confirm whether VEP truly is more effective than the Goldman perimeter test. The authors did not state what effect this finding had on management of patients.

## Studies of multifocal VEP in diseased and normal subjects (case control studies)

One full text article that compared multifocal VEP in a group of patients already known to have a disease and a separate group of normal patients was assessed (case control study). Table G4 lists some of the pertinent descriptive characteristics of the study.

### *Patient selection criteria of case control studies of multifocal VEP*

Table G4 presents a breakdown of the number of patients studied by individual disease and the number of normal controls within the study, as well as the selection criteria used for enrolment in the study.

### *Validity of case control studies of multifocal VEP*

The 'case' patients in this case control study consist of those already diagnosed with glaucoma by several diagnostic criteria as stated in Table G4. Multifocal VEP was not assessed in relation to these diagnostic criteria but rather by comparing a group of normal control patients and a group of patients considered at risk for glaucoma, as well as those already diagnosed with glaucoma. Thus, according to the criteria used to assess studies of diagnostic tests, the study was assigned as level IV evidence. Case control studies are considered poor designs for evaluating diagnostic tests as they overestimate the accuracy of the test (Lijmer et al 1999).

### *Summary of findings of case control studies of multifocal VEP*

The results of the study are summarised in Table G5. VEP was used to assess the presence of scotomas in diseased eyes by comparing the inter-eye asymmetry in diseased eyes at various locations in the visual field with the asymmetry at corresponding locations in control eyes. Sensitivity and specificity were calculated from available data (Table G5). However, these values overestimate the diagnostic capabilities of the test since the patients are already known to have the disease (Lijmer et al 1999). The effects of the results on patient management was not addressed in the study except to state that patients at risk for glaucoma would be followed up. Control patients should also be followed. It is only when this follow-up data is available that it will be possible to evaluate the diagnostic role of the VEP test in this group of study subjects.

### Summary of findings of studies of multifocal VEP

Little evidence of the effectiveness of multifocal VEP in diagnosing visual field defects was found. A sensitive search strategy identified 17 articles of multifocal VEP for evaluation. Review of the full text articles left only two that met the inclusion criteria and thus underwent critical appraisal. These studies were of poor quality compared with the ideal study design for a diagnostic test, and ranked as level IV evidence in the hierarchy of evidence of diagnostic tests employed for this evaluation.

One study compared multifocal VEP with a reference test to determine visual field defects in a group of patients with a sella turcica tumour. However, this study rated poorly against criteria used to assess validity and lacked data of effectiveness. The study did not provide diagnostic characteristics and offered little discussion of patient management options as a result of undergoing the test. The second study examined multifocal VEP in patients already known to have a disease, a group of patients at risk for the disease and a group of normal controls. This type of study design overestimates the accuracy of a diagnostic test.

A third article (Greenstein et al 2000), listed among excluded VEP articles, could not be critically appraised as it was only available as an abstract. This study compared multifocal VEP with Humphrey perimetry in detecting visual field defects. The authors stated that multifocal VEP was a more sensitive test and that they were undertaking a prospective trial, suggesting that results assessing the diagnostic accuracy of multifocal VEP may be available in the future.

## Scotopic threshold response

Nine studies of STR identified from the literature were evaluated in full text. Four studies met the selection criteria and were critically appraised. References from the five excluded studies with the reason for their exclusion are provided in Appendix D. Table 11 identifies the included articles according to study designs.

**Table 11 Study design of included articles examining STR**

| Study design | Number of included studies | First author and year of publication |
|---|---|---|
| Cross-sectional studies with another test | 2 | Aylward 1989, Graham 1991 |
| Case control studies | 2 | Korth 1994, Miyake 1994 |

Tables listing study characteristics, validity and results are in Appendix H.

### Studies of STR compared with another test

Two included studies compared STR with another test. In one study Aylward (1989) compared STR recordings with the pattern ERG, scotopic b-wave and oscillatory potentials in 50 insulin-dependent diabetes mellitus (IDDM) patients with varying degrees of diabetic retinopathy (Aylward 1989). In the second study STR recordings were compared with the absolute psychophysical threshold in 127 patients with eight classifications of visual diseases – retinitis pigmentosa, cone dystrophy, diabetes, central retinal vein occlusion, glaucoma, optic nerve disease, macular disorders, Stargardt's disease and mixed eye diseases (Graham 1991). In neither study was the time period during which the study actually took place reported, and one study (Graham 1991) did not indicate the age or sex of the patients involved. Descriptive details of these studies are presented in Table H1.

#### *Patient selection criteria of STR studies with a comparator test*

Only one of the studies reported selection criteria for inclusion/exclusion of patients (Table H1). Briefly, patients were included if they had IDDM for more than ten years and had any grade of retinopathy and were excluded if they had previously received photocoagulation therapy (Aylward 1989). No details of the method used for patient selection were reported in the second study (Graham 1991).

#### *Validity of STR studies with a comparator test*

Neither study met all the criteria for validity of a diagnostic test (Table H2). In the study by Graham & Vaegan (1991), none of the validity criteria was met. Patients in Aylward (1989) appeared to have all been tested with both study and reference test. In addition, since patients were ineligible if they had previously been treated with photocoagulation, it was concluded that the test was applied prior to treatment.

#### *Summary of findings of STR studies with a comparator test*

Diagnostic characteristics were not reported in either study, nor was there sufficient data to compute them. Both studies based their finding on correlations between recordings using STR and the comparator test(s) (Table H3). Although these correlations ranged as high as 0.71, this statistic can be used only to generate hypotheses and is not particularly informative in a clinical situation. Level IV evidence is provided by these two studies.

### Studies of STR in diseased and normal subjects (case control studies)

Two studies compared STR in a group of patients known to have a visual disease with a group of subjects known to have normal vision. Korth et al (1993) studied 65 patients, 30 patients with glaucoma and 35 normal controls. Miyake et al (1994) included 10 subjects: six patients had congenital stationary night blindness (CSNB) – two complete and four incomplete – and four were normal controls. Further details of the descriptive details of these two studies are presented in Table H4.

#### *Patient selection criteria of case control studies of STR*

Neither study reported the basis on which patients were selected or excluded from the study (Table H4).

### *Validity of case control studies of STR*

The two studies compared STR results in patients already diagnosed with the disease with normal patients. According to the validity criteria for evaluating diagnostic tests, a case control study design overestimates the diagnostic accuracy of STR (Lijmer et al 1999).

### *Summary of findings of case control studies of STR*

Diagnostic characteristics of STR in the patients studied were not provided, nor could they be calculated from study data. Although STR amplitudes were significantly reduced in glaucoma patients compared with controls, the difference was small and peak times did not differ. Thus STR was not found to be useful in patients with glaucoma (Korth et al 1994). In Miyake et al (1994) STR was recordable in patients with incomplete CSNB but not in patients with the complete form of this disorder of vision. Table H5 presents the results of these studies.

### Summary of findings of studies of STR

Based on the critical appraisal of four studies, there is little evidence for the diagnostic value of STR. In two of the studies STR was compared with another test, and in two other studies STR was used to compare patients with visual diseases with patients with normal vision. STR test accuracy was based on the level of correlation with pattern ERG, scotopic b-wave, oscillatory potentials in one study of IDDM patients and with absolute psychophysical threshold in another study among patients with a variety of visual problems. The correlation statistic is not a reliable measure of test performance. STR was found to be of little use in the diagnosis of glaucoma in one study, and in the other study STR was recordable in patients with incomplete CSNB but was absent in patients with the complete form of this vision disorder. No study reported diagnostic characteristics or the data to compute them, and none of the studies addressed how the STR would influence patient management.

## Intensity response function

The ERG IRF describes the relationship between ERG amplitude (R) and stimulus intensity (log I). This relationship produces a sigmoidal curve described non-linearly by the Nakta-Rushton equation:

$$R = R_{\max} I^n + I^n + K^n$$

$R_{max}$ is the maximum ERG amplitude, K is the half-saturation constant or sensitivity, and n is a dimensionless constant describing the slope of the relationship (Massof et al 1984).

The full text of six studies was examined to determine whether they fit the inclusion and exclusion criteria for this evaluation. Of these, three studies were excluded (Appendix D), leaving three articles suitable for critical appraisal. Table 12 identifies the studies according to design.

**Table 12 Study design of included articles examining intensity response function**

| Study design | Number of included studies | First author and year of publication |
|---|---|---|
| Case control studies | 2 | Massof 1984, Wu 1985 |
| Case series | 1 | Breton 1989 |

Tables listing study characteristics, validity and results are in Appendix I.

### Studies of IRF in diseased and normal subjects (case control studies)

Two studies examining IRF in diseased and normal patients met inclusion criteria and thus were critically appraised. Massof et al (1984) examined the IRF in patients with retinitis pigmentosa and in normal controls, while Wu et al (1985) included patients with a variety of retinal diseases as well as normal controls. Further descriptions of the study characteristics appear in Table I1.

#### *Patient selection criteria of case control studies of IRF*

Table I1 presents a breakdown of the number of patients studied by individual disease and the number of normal controls within the study, as well as the selection criteria used for enrolment in the study. Both studies provided scant details of selection criteria and failed to adequately describe how disease states were diagnosed.

#### *Validity of case control studies of IRF*

The 'case' patients in these studies consist of those already diagnosed with retinal disease, although details of method of diagnoses were scarce (Table I1). IRF was compared in a group of normal control patients and groups of patients already diagnosed with retinal disease. Thus, according to the criteria used to assess studies of diagnostic tests, the study was assigned as level IV evidence.

#### *Summary of findings of case control studies of IRF*

The included studies reported abnormal components of the IRF in patients with retinal disease (Table I2). Massof et al (1984) reported a reduced maximum response (Rmax) in retinitis pigmentosa compared with controls, implying compression of the ERG response to light, and an elevated half-saturation constant (K), implying a loss in retinal sensitivity in these patients. Similarly, Wu et al (1985) reported abnormal Rmax and K values in some patients with retinal disease. The studies did not provide diagnostic characteristics, which are limited in usefulness in case control studies anyway as they tend to overestimate accuracy. Patient management options as a result of undergoing the IRF test were not discussed.

### Studies of IRF in case series

One study (Breton et al 1989) met inclusion criteria. IRF was examined in 24 patients with central retinal vein occlusion (CRVO) to try and predict the development of neovascular complication (rubeosis). Table I3 describes further characteristics of this study.

#### *Patient selection criteria of case series of IRF*

Patient selection criteria were described only briefly (Table I3). Patients with disease in both eyes were excluded. The study does not provide a detailed description of diagnosis of CRVO in the patients except to say it was diagnosed by clinical examination.

### *Validity of case series of IRF*

Case series are considered level IV evidence in the hierarchy of evidence for diagnostic studies. A major flaw is the failure to compare the test with another reference test. Breton et al (1989) used IRF and other components of the ERG to predict the development of rubeosis in CRVO, but it appeared as though the status of the patient was known prior to testing with IRF, which may bias the results toward a positive finding. Only patients with rubeosis were followed; thus the outcomes of the other patients is unknown.

### *Summary of findings of case series studies of IRF*

The included study used IRF as a prognostic tool to describe the risk of development of rubeosis in CRVO. The authors state that components of the ERG, including components of the IRF, were useful in predicting the development of rubeosis. However, the results are limited by the fact that IRF was applied retrospectively after patients were assessed for rubeosis clinically and with fluorescein angiography. Furthermore, components of IRF itself were not judged to be better predictors of rubeosis than other components of the ERG. Patients with rubeosis or judged clinically to be at risk were treated.

### Summary of findings of studies of IRF

There is little evidence of the effectiveness of IRF in diagnosing retinal disease or optic nerve damage based on three studies that met inclusion criteria. Studies were methodologically poor and were ranked as level IV evidence in the hierarchy of evidence of diagnostic tests. Accurate diagnostic characteristics could not be calculated, and the studies offered little discussion of patient management options as a result of undertaking such a test.

## What are the economic considerations?

Since there is insufficient evidence of the accuracy of the tests and their usefulness in improving patient outcomes, an economic evaluation could not be undertaken.

# Conclusions

## Safety

There is limited evidence available on the safety of the five visual tests. A few minor complications have been reported but no incidence rates are available. Since the tests are non-invasive, adverse events should be minor.

## Effectiveness

Two factors were considered in determining the effectiveness of the visual electrodiagnostic tests: accuracy and usefulness in improving outcomes for patients.

### Focal electroretinogram

Studies of focal ERG were generally of poor quality and thus subject to bias in terms of the ideal diagnostic study. All studies were ranked only as Level IV evidence in the hierarchy of evidence of diagnostic studies. Few studies provided diagnostic characteristics and all offered little discussion of patient management options as a result of undertaking such a test. Studies that did provide diagnostic characteristics were fundamentally flawed in their use of a comparison test or patient populations, and thus overestimated the accuracy of focal ERG as a diagnostic test.

### Multifocal electroretinogram

All the studies of multifocal ERG were classified as level IV evidence and none presented diagnostic characteristics or sufficient data to compute them. Although the studies showed that the multifocal ERG was able to discriminate between some visual parameters of patients with disease and controls with normal vision, there was little consistency and comparability among the studies. It is apparent from the available studies that much of the attention is focused on the mechanics of the technique and issues concerned with averaging signals and presentation of results. Thus the clinical benefits of this technique are not yet apparent.

### Multifocal visual evoked potential

Little evidence of the effectiveness of multifocal VEP in diagnosing visual field defects was found. The two included studies were of poor quality compared with the ideal study design for a diagnostic test, and thus were ranked as level IV evidence in the hierarchy of evidence of diagnostic tests. The studies did not provide diagnostic characteristics or discussion of patient management options as a result of undertaking such a test.

### Scotopic threshold response

There is little evidence for the diagnostic value of STR based on the critical appraisal of four studies. No study reported diagnostic characteristics, or the data to compute them, and none of the studies addressed how the STR would influence patient management.

### Intensity response function

There is little evidence of the effectiveness of IRF in diagnosing retinal disease or optic nerve damage based on three studies that met inclusion criteria. Studies were methodologically poor and were ranked as level IV evidence in the hierarchy of evidence of diagnostic tests. The studies failed to provide adequate diagnostic characteristics and offered little discussion of patient management options as a result of undertaking such a test.

## Cost-effectiveness

Since there is insufficient evidence of the accuracy of the tests and their usefulness in improving patient outcomes, an economic evaluation could not be undertaken.

# Recommendation

On the strength of evidence pertaining to visual electrodiagnostic tests, MSAC recommends that:

1. public funding be supported for the following well-established tests recognised by the International Society of Clinical Electrophysiology of Vision –

    - electroretinography
    - pattern electroretinography
    - dark adaptometry
    - electrooculography
    - visual evoked responses; and

2. due to insufficient evidence, public funding should not be supported at this time for the following tests –

    - focal electroretinography
    - multifocal electroretinography
    - multifocal visual evoked potential
    - scotopic threshold response
    - intensity response function.

The Minister for Health and Aged Care accepted this recommendation on 19 June 2001.

# Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Commonwealth 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 Commonwealth 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 Commonwealth Minister for Health and Ageing on references relating either to new 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 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** |
|---|---|
| Professor David Weedon (Chair) | pathology |
| Ms Hilda Bastian | consumer health issues |
| Dr Ross Blair | vascular surgery (New Zealand) |
| Mr Stephen Blamey | general surgery |
| Dr Paul Hemming | general practice |
| Dr Terri Jackson | health economics |
| Professor Brendon Kearney | health administration and planning |
| Mr Alan Keith | Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing |
| Associate Professor Richard King | internal medicine |
| Dr Michael Kitchener | nuclear medicine |
| Professor Peter Phelan | paediatrics |
| Dr David Robinson | plastic surgery |
| Professor John Simes | clinical epidemiology and clinical trials |
| Professor Bryant Stokes | neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1 January 1999) |

# Appendix B Supporting committee

### Supporting committee for MSAC Application 1005 – Visual Electrodiagnosis

| | |
|---|---|
| **Professor Peter Phelan (Chair)**<br>BSc, MBBS, MD, FRACP<br>Emeritus Professor of Paediatrics<br>University of Melbourne | member of MSAC |
| **Associate Professor Frank Fisher**<br>MEnvSt(Hons), BA(Geog)(Hons), BE(Elec)(Hons), FEIA<br>Associate Professor and Director<br>Graduate School of Environmental Science<br>School of Geography and Environmental Science,<br>Monash University, Melbourne | consumer representative nominated by the Consumers' Health Forum of Australia |
| **Dr Con Yiannikas**<br>MB, BS(Hons), FRACP, MAAEE<br>Neurologist<br>Neurophysiology Specialist Centre, Burwood | nominated by the Australian Association of Neurologists |
| **Associate Professor Hector Maclean**<br>MB, ChB, FRCS(Ed), FRANZCO, FRCOphth, DO<br>Centre for Eye Research Australia<br>Department of Ophthalmology<br>University of Melbourne | co-opted ophthalmologist |
| **Associate Professor Denis Stark**<br>MB, BS, FRCS (Edinburgh), FRANZCO<br>Clinical Associate Professor<br>Department of Child Health<br>University of Queensland | nominated by the Royal Australian and New Zealand College of Ophthalmologists |
| **Associate Professor Justin O'Day**<br>MBBS, FRACS, FRACP, FRCS, FRANZCO, FRC Ophth<br>Eye Specialist<br>Victoria Parade Eye Consultants<br>St Vincent's Medical Centre, Fitzroy | nominated by the Royal Australian and New Zealand College of Ophthalmologists |
| **Associate Professor Ian Favilla**<br>DO, FRACS, FRANZCO<br>Ophthalmic Surgeon and<br>Clinical Associate Professor of Surgery<br>Monash University, Melbourne | co-opted ophthalmic surgeon |

# Appendix C Visual electrodiagnosis: synonyms

| |
|---|
| **Focal ERG** |
| Foveal ERG |
| Focal cone ERG |
| Focal macular ERG |
| Focal flash ERG |
| Smallfield ERG |
| Macular ERG |
| Paramacular ERG |
| Steady-state focal ERG |
| Foveal cone ERG |
| **Multifocal ERG** |
| Multichannel ERG |
| **Multifocal VEP** |
| Multichannel VEP |

# Appendix D Included and excluded studies

**Focal ERG articles critically appraised in this review**


Arden G.B., Vaegan and Hogg C.R. 1982, 'Clinical and experimental evidence that the pattern electroretinogram is generated in more proximal retinal layers than the focal electroretinogram', *Annals of the New York Academy of Sciences*, 388: 580–607.

Bagolini B., Porciatti V., Falsini B. et al 1988, 'Simultaneously recorded macular and paramacular ERGs in diseases affecting the central retina', *Documenta Ophthalmologica*, 68: 273–82.

Bagolini B., Porciatti V., Falsini B. et al 1989, 'Simultaneous foveal and parafoveal electroretinograms in hereditary degeneration of the central retina', *Documenta Ophthalmologica*, 71: 435–43.

Biersdorf W.R. 1981, 'Temporal factors in the foveal electroretinogram', *Current Eye Research*,1: 1981–2.

Birch D.G., Sandberg M.A. and Berson E.L. 1982, 'The Stiles-Crawford effect in retinitis pigmentosa', *Investigative Ophthalmology & Visual Science*, 22: 157–64.

Birch D.G. and Fish G.E. 1988a, 'Focal cone electroretinograms: ageing and macular disease', *Documenta Ophthalmologica*, 69: 211–20.

Birch D.G., Jost B.F. and Fish G.E. 1988b, 'The focal electroretinogram in fellow eyes of patients with idiopathic macular holes', *Archives of Ophthalmology*,106: 1558–63.

Brodie S.E., Naidu E.M. and Goncalves J. 1992, 'Combined amplitude and phase criteria for evaluation of macular electroretinograms', *Ophthalmology*, 99: 522–30.

Deschenes M.C., Coupland S.G., Ross S.A. et al 1997, 'Early macular dysfunction detected by focal electroretinographic recording in non-insulin-dependent diabetics without retinopathy', *Documenta Ophthalmologica*, 94: 223–37.

Di Leo M.A., Caputo S., Falsini B. et al 1994, 'Presence and further development of retinal dysfunction after 3-year follow-up in IDDM patients without angiographically documented vasculopathy', *Diabetologia*, 37: 911–16.

Falsini B., Minnella A., Buzzonetti L. et al 1992, 'Macular electroretinograms to flicker and pattern stimulation in lamellar macular holes', *Documenta Ophthalmologica*, 79: 99–108.

Falsini B., Iarossi G., Porciatti V. et al 1994, 'Postreceptoral contribution to macular dysfunction in retinitis pigmentosa', *Investigative Ophthalmology & Visual Science*, 35: 4282–90.

Falsini B., Porciatti V., Porrello G. et al 1996, 'Macular flicker electroretinograms in Best's vitelliform dystrophy', *Current Eye Research*, 15: 638–46.

Falsini B., Serrao S., Fadda A. et al 1999, 'Focal electroretinograms and fundus appearance in non-exudative age-related macular degeneration – Quantitative

relationship between retinal morphology and function', *Graefes Archive for Clinical & Experimental Ophthalmology*, 237: 193–200.

Falsini B., Fadda A., Iarossi G. et al 2000, 'Retinal sensitivity to flicker modulation: Reduced by early age-related maculopathy', *Investigative Ophthalmology & Visual Science*, 41: 1498–506.

Fish G.E., Birch D.G., Fuller D.G. et al 1986, 'A comparison of visual function tests in eyes with maculopathy', *Ophthalmology*, 93: 1177–82.

Fish G.E. and Birch D.G. 1989, 'The focal electroretinogram in the clinical assessment of macular disease', *Ophthalmology*, 96: 109–14.

Gaudio A.R. and Sandberg M.A. 1998, 'The effect of a lower blood pressure on choroidal filling in age-related macular degeneration', *Retina*, 18: 439–42.

Ghirlanda G., Di Leo M.A., Caputo S. et al 1991, 'Detection of inner retina dysfunction by steady-state focal electroretinogram pattern and flicker in early IDDM', *Diabetes*, 40: 1122–7.

Holopigian K., Seiple W., Mayron C. et al 1990, 'Electrophysiological and psychophysical flicker sensitivity in patients with primary open-angle glaucoma and ocular hypertension', *Investigative Ophthalmology & Visual Science*, 31: 1863–8.

Holopigian K., Greenstein V., Seiple W. et al 1996, 'Rates of change differ among measures of visual function in patients with retinitis pigmentosa', *Ophthalmology* 103: 398–405.

Jacobson S.G., Sandberg M.A., Effron M.H. et al 1979, 'Foveal cone electroretinograms in strabismic amblyopia: comparison with juvenile macular degeneration, macular scars, and optic atrophy', *Transactions of the Ophthalmological Societies of the United Kingdom*, 99: 353–6.

Matthews G.P., Sandberg M.A. and Berson E.L. 1992, 'Foveal cone electroretinograms in patients with central visual loss of unexplained etiology', *Archives of Ophthalmology*, 110: 1568–70.

Miyake Y., Shiroyama N., Ota I. et al 1988, 'Local macular electroretinographic responses in idiopathic central serous chorioretinopathy', *American Journal of Ophthalmology*, 106: 546–50.

Miyake Y., Shiroyama N., Ota I. et al 1993, 'Focal macular electroretinogram in X-linked congenital retinoschisis', *Investigative Ophthalmology & Visual Science*, 34: 512–15.

Miyake Y., Horiguchi M., Tomita N. et al 1996, 'Occult macular dystrophy', *American Journal of Ophthalmology*, 122: 644–53.

Porciatti V., Moretti G., Ciavarella P. et al 1993, 'The second harmonic of the electroretinogram to sinusoidal flicker: spatiotemporal properties and clinical application', *Documenta Ophthalmologica*, 84: 39–46.

Remulla J.F., Gaudio A.R., Miller S. et al 1995, 'Foveal electroretinograms and choroidal perfusion characteristics in fellow eyes of patients with unilateral neovascular age-related macular degeneration', *British Journal of Ophthalmology*, 79: 558–61.

Salzman J., Seiple W., Carr R. et al 1986, 'Electrophysiological assessment of aphakic cystoid macular oedema', *British Journal of Ophthalmology* 70: 819–24.

Sandberg M.A., Jacobson S.G. and Berson E.L. 1979, 'Foveal cone electroretinograms in retinitis pigmentosa and juvenile macular degeneration', *American Journal of Ophthalmology*, 88: 702–7.

Sandberg M.A., Miller S. and Gaudio A.R. 1993, 'Foveal cone ERGs in fellow eyes of patients with unilateral neovascular age-related macular degeneration', *Investigative Ophthalmology & Visual Science*, 34: 3477–80.

Sandberg M.A., Weiner A., Miller S. et al 1998, 'High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration', *Ophthalmology*, 105: 441–7.

Seiple W.H., Siegel I.M., Carr R.E. et al 1986, 'Evaluating macular function using the focal ERG', *Investigative Ophthalmology & Visual Science*, 27: 1123–30.

Seiple W.H., Holopigian K., Greenstein V.C. et al 1993, 'Sites of cone system sensitivity loss in retinitis pigmentosa', *Investigative Ophthalmology & Visual Science*, 34: 2638–45.

Small K.W. and Gehrs K. 1996, 'Clinical study of a large family with autosomal dominant progressive cone degeneration', *American Journal of Ophthalmology*, 121: 1–12.

Tanikawa A., Horiguchi M., Kondo M. et al 1999, 'Abnormal focal macular electroretinograms in eyes with idiopathic epimacular membrane', *American Journal of Ophthalmology*, 127: 559–64.

Vaegan and Billson F.A. 1986, 'Macular electroretinograms and contrast sensitivity as sensitive detectors of early maculopathy', *Documenta Ophthalmologica,* 63: 399–406.

Vaegan and Billson F.A. 1987, 'The Differential Effect of Optic Nerve Disease on Pattern and Focal Electroretinograms', *Documenta Ophthalmologica*, 65: 45–56.

Weiner A., Christopoulos V.A., Gussler C.H. et al 1997, 'Foveal Cone Function in Non-proliferative Diabetic Retinopathy and Macular Edema', *Investigative Ophthalmology & Visual Science*, 38: 1443–9.

Weiner A., Ripkin D.J., Patel S. et al 1998a, 'Foveal dysfunction and central visual field loss in glaucoma', *Archives of Ophthalmology*, 116: 1169–74.

Weiner A., Schmidt M.E., Patel S. et al 1998b, 'Foveal outer retinal function in eyes with unexplained visual symptoms or acuity loss', *Archives of Ophthalmology*, 116: 1161–8.

#### Focal ERG articles excluded from the review [reason for exclusion]

Abe H., Usui T., Takagi M. et al 1993, 'A new focal pattern stimulator under direct observation of ocular fundus', *Ophthalmologica*, 207: 42–5. **[no diseased subjects]**

Arden G.B. and Bankes J.L. 1966, 'Foveal electroretinogram as a clinical test', *British Journal of Ophthalmology*, 50: 740. **[narrative review]**

Bagolini B., Porciatti V., Falsini B. et al 1988, 'Macular electroretinogram as a function of age of subjects', *Documenta Ophthalmologica*, 70: 37–43. **[narrative review]**

Bankes J.L. 1967, 'The foveal electroretinogram', *Transactions of the Ophthalmological Societies of the United Kingdom*, 87: 249–62. **[narrative review]**

Biersdorf W.R. 1989, 'The clinical utility of the foveal electroretinogram: a review', *Documenta Ophthalmologica*, 73: 313–25. **[narrative review]**

Horiguchi M., Miyake Y. and Yagasaki K. 1986, 'Local macular ERG in patients with Best's disease', *Documenta Ophthalmologica*, 63: 325–31. **[case reports]**

Horiguchi M., Miyake Y., Nakamura M. et al 1993, 'Focal electroretinogram and visual field defect in multiple evanescent white dot syndrome', *British Journal of Ophthalmology*, 77: 452–5. **[case reports]**

Kondo M., Miyake Y., Horiguchi M. et al 1995, 'Clinical evaluation of multifocal electroretinogram', *Investigative Ophthalmology & Visual Science*, 36: 2146–50. **[case reports]**

Litao R.E., Miyake Y. and Yagasaki K. 1986, 'Oscillatory potentials and pattern electroretinogram: are they related?' *Japanese Journal of Ophthalmology*, 30: 402–8. **[not testing focal ERG]**

Marmor M.F., Tan F., Sutter E.E. et al 1999, 'Topography of cone electrophysiology in the enhanced S cone syndrome', *Investigative Ophthalmology & Visual Science*, 40: 1866–73. **[case report]**

Miyake Y., Ichikawa K, Shiose Y. et al 1989a, 'Hereditary macular dystrophy without visible fundus abnormality', *American Journal of Ophthalmology*, 108: 292–9. **[case reports]**

Miyake Y., Shiroyama N., Horiguchi M. et al 1989b, 'Asymmetry of focal ERG in human macular region', *Investigative Ophthalmology & Visual Science*, 30: 1743–9. **[case report]**

Miyake Y. 1990, 'Macular oscillatory potentials in humans. Macular OPs', *Documenta Ophthalmologica*, 75: 111–24. **[case reports]**

Miyake Y. 1998, 'Focal macular electroretinography', *Nagoya Journal of Medical Science*, 61: 79–84. **[no diseased subjects]**

Muller W. and Wunscher J. 1993, 'Intraoperative diagnosis of retinal function', *Documenta Ophthalmologica*, 84: 83–8. **[study designed to test effects of a treatment]**

Parisi V. and Falsini B. 1998a, 'Electrophysiological evaluation of the macular cone system: focal electroretinography and visual evoked potentials after photostress', *Seminars in Ophthalmology*, 13: 178–88. **[narrative review]**

Parisi V., Pierelli F., Restuccia R. et al 1998b, 'Impaired VEP after photostress response in multiple sclerosis patients previously affected by optic neuritis', *Electroencephalography & Clinical Neurophysiology*, 108: 73–9. **[no diseased subjects]**

Porciatti V. 1987, 'Non-linearities in the focal ERG evoked by pattern and uniform-field stimulation. Their variation in retinal and optic nerve dysfunction', *Investigative Ophthalmology & Visual Science*, 28:1306–13. **[case reports]**

Sandlberg M.A., Effron M.H. and Berson E.L. 1978, 'Focal cone electroretinograms in dominant retinitis pigmentosa with reduced penetrance', *Investigative Ophthalmology & Visual Science*, 17: 1096–1101. **[case report]**

Scholl H.P. and Zrenner E. 2000, 'Electrophysiology in the investigation of acquired retinal disorders', *Survey of Ophthalmology*, 45: 29–47. **[narrative review]**

Seiple W., Greenstein V., Holopigian K. et al 1988, 'Changes in the focal electroretinogram with retinal eccentricity', *Documenta Ophthalmologica*, 70: 29–36. **[no diseased subjects]**

Siegel I.M., Greenstein V.C., Seiple W.H. et al 1987, 'Cone function in congenital nyctalopia', *Documenta Ophthalmologica*, 65: 307–18. **[case report]**

Sunness J.S. and Massof R.W. 1986, 'Focal electro-oculogram in age-related macular degeneration', *American Journal of Optometry & Physiological Optics* 63: 7–11. **[not testing focal ERG]**

Suzuki S., Miyake Y., Kondo M. et al 2000, 'Focal macular electroretinogram in retinitis pigmentosa with normal visual acuity', *Investigative Ophthalmology & Visual Science*, 41: S894. **[narrative review]**

Suzuki T., Terasaki H., Kojima T. et al 2000, 'Optical coherence tomography and focal macular electroretinogram of epiretinal membranes with macular pseudoholes', *Investigative Ophthalmology & Visual Science*, 41: S174. **[narrative review]**

ten Hove M.W., Siatkowski R.M. and Smith J.L. 1998, 'Foveal cone dysfunction syndrome' [see comments], *Journal of Neuro-ophthalmology*,18: 9–14. **[case reports]**

Vaegan, Billson F., Kemp S. et al 1984, 'Macular electroretinograms: their accuracy, specificity and implementation for clinical use', *Australian Journal of Ophthalmology*,12: 359–72. **[case reports]**

Van Lith G.H. 1971, 'The combined use of the macular electroretinogram (M-ERG) and the visually evoked responses (VER)', *Ophthalmologica*, 162: 208–12. **[case reports**]

Weiner A., Sandberg M.A., Gaudio A.R. et al 1991, 'Hydroxychloroquine retinopathy', *American Journal of Ophthalmology*, 112: 528–34. **[case reports]**

Yoon I.H., Shiroyama N., Miyake Y. et al 1990, 'Oscillatory potentials of local macular ERG in diabetic retinopathy', *Korean Journal of Ophthalmology*, 4: 40–5. **[case reports]**

#### Multifocal ERG articles critically appraised in this review

Chan H.L. and Brown B. 1998, 'Investigation of retinitis pigmentosa using the multifocal electroretinogram', *Ophthalmic & Physiological Optics*, 18: 335–50.

Chan H.L. and Brown B. 1999, 'Multifocal ERG changes in glaucoma', *Ophthalmic & Physiological Optics*, 19: 306–16.

Fortune B., Schneck M.E. and Adams A.J. 1999, 'Multifocal electroretinogram delays reveal local retinal dysfunction in early diabetic retinopathy', *Investigative Ophthalmology & Visual Science*, 40: 2638–51.

Hasegawa S., Takagi M., Usui T. et al 2000, 'Waveform changes of the first-order multifocal electroretinogram in patients with glaucoma', *Investigative Ophthalmology & Visual Science* 41: 1597–1603.

Hood D.C., Greenstein V.C., Holopigian K. et al 2000, 'An attempt to detect glaucomatous damage to the inner retina with the multifocal ERG, *Investigative Ophthalmology & Visual Science*, 41: 1570–9.

Kretschmann U., Seeliger M., Ruether K. et al 1998a, 'Spatial cone activity distribution in diseases of the posterior pole determined by multifocal electroretinography', *Vision Research*, 38: 3817–28.

Kretschmann U., Seeliger M.W., Ruether K. et al 1998b, 'Multifocal electroretinography in patients with Stargardt's macular dystrophy', *British Journal of Ophthalmology*, 82: 267–75.

Marmor M.F. and Tan F. 1999, 'Central serous chorioretinopathy: bilateral multifocal electroretinographic abnormalities', *Archives of Ophthalmology*, 117: 184–8.

Palmowski A.M., Sutter E.E., Bearse M.A. Jr et al 1997, 'Mapping of retinal function in diabetic retinopathy using the multifocal electroretinogram', *Investigative Ophthalmology & Visual Science*, 38: 2586–96.

Piao C.H., Kondo M., Tanikawa A. et al 2000, 'Multifocal electroretinogram in occult macular dystrophy', *Investigative Ophthalmology & Visual Science*, 41: 513–17.

Seeliger M.W., Kretschmann U.H., Apfelstedt-Sylla E. et al 1998, 'Implicit time topography of multifocal electroretinograms', *Investigative Ophthalmology & Visual Science*, 39: 718–23

#### Multifocal ERG articles excluded from the review [reason for exclusion]

Arai M., Nao-i N., Sawada A. et al 1998, 'Multifocal electroretinogram indicates visual field loss in acute zonal occult outer retinopathy', *American Journal of Ophthalmology*, 126: 466–9. **[case report]**

Bearse M.A. Jr and Sutter E.E. 1996, 'Imaging localized retinal dysfunction with the multifocal electroretinogram', *Journal of the Optical Society of America A-Optics & Image Science* 13: 634–40. **[case report]**

Felius J. and Swanson W.H. 1999, 'Photopic temporal processing in retinitis pigmentosa', *Investigative Ophthalmology & Visual Science*, 40: 2932–44. **[case report]**

Fletcher W.A., Imes R.K., Goodman D. et al 1988, 'Acute idiopathic blind spot enlargement. A big blind spot syndrome without optic disc edema', *Archives of Ophthalmology*, 106: 44–9. **[case report]**

Hood D.C., Seiple W., Holopigian K. et al 1997, 'A comparison of the components of the multifocal and full-field ERGs', *Visual Neuroscience*, 14: 533–44. **[no diseased subjects]**

Hood D.C., Wladis E.J., Shady S. et al 1998, 'Multifocal rod electroretinograms', *Investigative Ophthalmology & Visual Science*, 39: 1152–62. **[case report]**

Hood D.C. 2000, 'Assessing retinal function with the multifocal technique', *Progress in Retinal & Eye Research*, 19: 607–46. **[narrative review]**

Huang H.J., Yamazaki H., Kawabata H. et al 1996, 'Multifocal electroretinogram in multiple evanescent white dot syndrome', *Documenta Ophthalmologica*, 92: 301–9. **[case report]**

Kellner U. 1998, 'Cone-rod dystrophy with serpentine-like retinal deposits', *Archives of Ophthalmology*, 116: 1307–13. **[case report]**

Kellner U., Kraus H. and Foerster M.H. 2000, 'Multifocal ERG in chloroquine retinopathy: regional variance of retinal dysfunction', *Graefes Archive for Clinical & Experimental Ophthalmology*, 238: 94–7. **[case report]**

Kondo M., Miyake Y., Horiguchi M. et al 1995, 'Clinical evaluation of multifocal electroretinogram' *Investigative Ophthalmology & Visual Science*, 36: 2146–50. **[case report]**

Kondo M., Miyake Y., Horiguchi M. et al 1997, 'Recording multifocal electroretinograms with fundus monitoring', *Investigative Ophthalmology & Visual Science*, 38: 1049–52. **[case report]**

Kondo M., Miyake Y., Horiguchi M. et al 1998, 'Recording multifocal electroretinogram on and off responses in humans', *Investigative Ophthalmology & Visual Science*, 39: 574–80. **[no diseased subjects]**

Kondo M., Miyake Y., Piao C.H et al. 1999, 'Amplitude increase of the multifocal electroretinogram during light adaptation', *Investigative Ophthalmology & Visual Science*, 40: 2633–7. **[no diseased subjects]**

Kretschmann U., Ruether K., Usui T. et al 1996a, 'ERG campimetry using a multi-input stimulation technique for mapping of retinal function in the central visual field', *Ophthalmic Research*, 28: 303–11. **[case report]**

Kretschmann U., Usui T., Ruether K. et al 1996b, 'Electroretinographic campimetry in a patient with crystalline retinopathy', *German Journal of Ophthalmology*, 5: 399–403. **[case report]**

Kretschmann U., Gendo K., Seeliger M. et al 1997, 'Multifocal ERG recording by the VERIS technique and its clinical applications', *Developments in Ophthalmology*, 29: 8–14. **[case report]**

Kretschmann U., Stilling R., Ruether K. et al 1999, 'Familial macular cone dystrophy: diagnostic value of multifocal ERG and two-color threshold perimetry', *Graefes Archive for Clinical & Experimental Ophthalmology*, 237: 429–32. **[case report]**

Marmor M.F., Tan F., Sutter E.E. et al 1999, 'Topography of cone electrophysiology in the enhanced S cone syndrome.' *Investigative Ophthalmology & Visual Science*, 40: 1866–73. **[case report]**

Oh K.T., Boldt H.C., Maturi R.K. et al 2000, 'Evaluation of patients with visual field defects following macular hole surgery using multifocal electroretinography', *Retina,* 20: 238–43. **[case report]**

Parks S., Keating D., Evans A.L. et al 1996, 'Comparison of repeatability of the multifocal electroretinogram and Humphrey perimeter', *Documenta Ophthalmologica,* 92: 281–9. **[no diseased subjects]**

Sasoh M., Yoshida S., Kuze M. et al 1997, 'The multifocal electroretinogram in retinal detachment', *Documenta Ophthalmologica*, 94: 239–52. **[response to a treatment]**

Schmidt D., Bach M. and Gerling J. 1997, 'A case of localized retinal damage in thallium poisoning', *International Ophthalmology*, 21: 143–7. **[case report]**

Seeliger M., Kretschmann U., Apfelstedt-Sylla E. et al 1998, 'Multifocal electroretinography in retinitis pigmentosa', *American Journal of Ophthalmology*, 125: 214–26. **[preliminary results - updated results published in later paper]**

Seeliger M.W., Biesalski H.K., Wissinger B. et al 1999, 'Phenotype in retinol deficiency due to a hereditary defect in retinol binding protein synthesis', *Investigative Ophthalmology & Visual Science*, 40: 3–11. **[case report]**

Yoshii M., Murakami A., Akeo K. et al 1998a, 'Visual function in retinitis pigmentosa related to a codon 15 rhodopsin gene mutation', *Ophthalmic Research*, 30: 1–10. **[case report]**

Yoshii M., Murakami A., Akeo K. et al 1998b, 'Visual function and gene analysis in a family with Oguchi's disease', *Ophthalmic Research*, 30: 394–401. **[case report]**

Yoshii M, Yanashima K, Matsuno K. et al 1998c, 'Relationship between visual field defect and multifocal electroretinogram', *Japanese Journal of Ophthalmology,* 42: 136–41. **[case report]**

#### Multifocal VEP articles critically appraised in this review

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

Wang J., Chen B.H. and Tan Y.L. 1988, 'Application of Visual Evoked Potential in the Evaluation of Visual Field Defects Due to Chiasmal Lesions', *Chinese Medical Journal,* 101: 257–62.

#### Multifocal VEP articles excluded from the review [reason for exclusion]

Barber C. and Wen Y. 2000, 'The multifocal visually evoked potential (VEP) can be used to dissect the standard VEP', *Investigative Ophthalmology & Visual Science*, 41(4): S334. **[abstract only]**

Flanagan J.G. and Harding G.F. 1988, 'Multi-channel visual evoked potentials in early compressive lesions of the chiasm', *Documenta Ophthalmologica*, 69: 271–81. **[not testing multifocal VEP]**

Fletcher W.A., Imes R.K., Goodman D. et al 1988, 'Acute idiopathic blind spot enlargement. A big blind spot syndrome without optic disc edema', *Archives of Ophthalmology*, 106: 44–9. **[not testing multifocal VEP]**

Graham S.L. and Klistorner A. 1998, 'Electrophysiology – A review of signal origins and application to investigating glaucoma', *Australian & New Zealand Journal of Ophthalmology*, 26: 71–85. **[narrative review]**

Graham S.L., Klistorner A., Grigg J.R. et al 1999, 'Objective perimetry in glaucoma: Recent advances with multifocal stimuli', *Survey of Ophthalmology*, 43: S199–S209. **[pre-clinical model]**

Greenstein V.C., Zhang X., Hood D.C. et al 2000, 'The multifocal visual evoked potential technique and detection of early local damage to the ganglion cell/optic nerve', *Investigative Ophthalmology & Visual Science*, 41(4): S520. **[abstract only]**

Heatley G.A., Ver Hoeve J.N., Murdock T.J. et al 2000, 'Multifocal visual evoked potentials and field loss in glaucoma', *Investigative Ophthalmology & Visual Science*, 41(4): S285. **[abstract only]**

Hood D.C., Zhang X., Greenstein V.C. et al 2000, 'An interocular comparison of the multifocal VEP: a possible technique for detecting local damage to the optic nerve', *Investigative Ophthalmology & Visual Science*, 41: 1580–7. **[experimental]**

Kaplan Peter W., Kruse B., Tusa Ronald J. et al 1995, 'Visual system abnormalities in adrenomyeloneuropathy', *Annals of Neurology*, 37: 550–2. **[not testing multifocal VEP]**

Klistorner A.I., Graham S.L., Grigg Jr et al 1998a, 'Multifocal topographic visual evoked potential – improving objective detection of local visual field defects', *Investigative Ophthalmology & Visual Science*, 39: 937–50. **[case reports]**

Klistorner A.I., Graham S.L., Grigg Jr et al 1998b, 'Electrode position and the multi-focal visual-evoked potential: role in objective visual field assessment', *Australian & New Zealand Journal of Ophthalmology*, 26: S91–4. **[no diseased subjects]**

Kondo Y., Mochizuki K. and Kitazawa Y. 2000, 'Multifocal visual evoked potential and electroretinogram in glaucoma eyes with hemifield visual field defect', *Investigative Ophthalmology & Visual Science*, 41(4): S291. **[abstract only]**

Manolas M.G., Stamoulos T.D. and Anninos P.A. 1999, 'Differences in human visual evoked potentials during the perception of colour as revealed by a bootstrap method to compare cortical activity: A prospective study', *Neuroscience Letters*, 270: 21–4. **[case reports]**

Odel J.G., Hood D.C., Zhang X. et al 2000, 'The multifocal VEP is abnormal in regions of the field affected in optic neuritis', *Investigative Ophthalmology & Visual Science*, 41(4): S310. **[abstract only]**

Zhang X. and Hood D.C. 2000, 'Quantitative methods for comparing changes in multifocal visual evoked potentials to visual field defects', *Investigative Ophthalmology & Visual Science*, 41(4): S292. **[abstract only]**

#### STR articles critically appraised in this review

Aylward G.W. 1989, 'The scotopic threshold response in diabetic retinopathy', *Eye*, 3: 626–37.

Graham S.L. and Vaegan 1991, 'High correlation between absolute psychophysical threshold and the scotopic threshold response to the same stimulus', *British Journal of Ophthalmology*, 75: 603–7.

Korth M., Nguyen Nhung X., Horn F. et al 1994, 'Scotopic threshold response and scotopic PII in glaucoma', *Investigative Ophthalmology & Visual Science*, 35: 619–25.

Miyake Y., Horiguchi M., Terasaki H. et al 1994, 'Scotopic threshold response in complete and incomplete types of congenital stationary night blindness', *Investigative Ophthalmology & Visual Science*, 35: 3770–5.

#### STR articles excluded from the review [reason for exclusion]

Graham S.L. and Klistorner A. 1998, 'Electrophysiology – a review of signal origins and applications to investigating glaucoma', *Australian & New Zealand Journal of Ophthalmology*, 26: 71–85. **[narrative review]**

Korth M. and Koca M. 1993, 'Clinical electrophysiology relevant for early glaucoma diagnosis', *Current Opinion in Ophthalmology*, 4: 22–8. **[narrative review]**

Korth M. 1997, 'The value of electrophysiological testing in glaucomatous diseases' *Journal of Glaucoma*, 6: 331–43. **[narrative review]**

Seeliger M.W., Biesalski H.K., Wissinger B. et al 1999, 'Phenotype in retinol deficiency due to a hereditary defect in retinol binding protein synthesis', *Investigative Ophthalmology & Visual Science*, 40: 3–11. **[not a study of STR]**

Vaegan, Graham S.L., Goldberg I. et al 1991, 'Selective reduction of oscillatory potentials and pattern electroretinograms after retinal ganglion cell damage by disease in humans or by kainic acid toxicity in cats', *Documenta Ophthalmologica*, 77: 237–53. **[not a study of STR]**

#### IRF articles critically appraised in this review

Breton M.E., Quinn G.E., Keene S.S. et al 1989, 'Electroretinogram parameters at presentation as predictors of rubeosis in central retinal vein occlusion patients', *Ophthalmology*, 96: 1343–52.

Massof R.W., Wu L., Finkelstein D. et al 1984, 'Properties of Electroretinographic Intensity-Response Functions in Retinitis', *Pigmentosa. Documenta Ophthalmologica*, 57: 279–96.

Wu L.Z., Massof R.W. and Starr S.J. 1985, 'Electroretinographic intensity-response function in retinal disease', *Chinese Medical Journal*, 98: 250–6.

**IRF articles excluded from the review [reason for exclusion]**

Roecker E.B., Pulos E., Bresnick G.H. et al 1992, 'Characterization of the electroretinographic scotopic B-wave amplitude in diabetic and normal subjects', *Investigative Ophthalmology & Visual Science*, 33: 1575–83. **[pre-clinical model]**

Sandberg M.A., Miller S. and Berson E.L. 1990, 'Rod electroretinograms in an elevated cyclic GMP type human retinal degeneration comparison with retinitis pigmentosa', *Investigative Ophthalmology & Visual Science*, 31: 2283–7. **[pre-clinical, includes animal]**

Sverak J., Peregrin J., Hejcmanova D. et al 1984, 'Long-term observation of retinal electrical activity in dialyzed and renal transplantation patients', *Artificial Organs*, 8: 355–8. **[response to a treatment]**

**Table E1 Descriptive characteristics of studies examining focal ERG compared with another test**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with focal ERG |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | | | |
| Arden 1982 | UK, dates not stated | 28 patients<br>+ 3 controls | Glaucoma n=9<br>Traumatic optic atrophy n=12<br>Amblyopia n=4<br>Controls n=3 | ? | ? | ? | ? | Pattern ERG |
| Birch 1982 | USA, dates not stated | 22 patients<br>+ 7 controls | Retinitis pigmentosa n=22 | ? (?), 14–34 | ? | Best-corrected visual acuity of at least 20/40, stable central fixation | ? | Psychophysical (flicker-threshold technique) |
| Falsini 1992 | Italy, dates not stated | 18 patients<br>+ 14 controls | Inner lamella macular holes (LMH) n=14<br>Full-thickness macular holes (FMH) n=4<br>Controls (C) n=14 | LMH 57 (9), 41–72<br>FMH ? (?), 53–68<br>C 52 (12), 40–78 | LMH 4:10<br>FMH 1:3<br>C ? | Diagnosis of macular holes was based on biomicroscopic examination of the macular, stereofundus photography and fluorescein angiography. | The diagnosis of ILH or full-thickness hole was based on biomicroscopic examination of the macula using a Goldmann lens, stereofundus photography and fluorescein angiography. An estimate of the macular hole diameter was made with a graticule by examination of fundus photographs. | Pattern ERG |

**Table E1** **Descriptive characteristics of studies examining focal ERG compared with another test (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with focal ERG |
| Falsini 1999 | Italy, dates not stated | 25 patients + 10 controls | Non-exudative age-related macular disease (NE-AMD) n=25 | 66 (7), ? | 11:14 | Diagnosis of NE-AMD according to stated criteria, best corrected visual acuity =0.4 in study eye, central fixation assessed by direct ophthalmoscopy, no signs of other retinal or optic nerve disease, clear optical media. | Diagnosis was established by direct and indirect ophthalmoscopy as well as retinal biomicroscopy when any of the following primary lesions in the macular area was identified: (1) soft distinct or indistinct drusen (2) areas of hyperpigmentation associated with drusen or (3) areas of hyperpigmentation of the retinal pigment epithelium (RPE) associated with drusen without any visibility of choroidal vessels. In addition, the presence of any area of demarcated geographic RPE atrophy with the macular area was considered as a sufficient diagnosis criterion. | Fluorescein angiography |
| Gaudio 1998 | USA, dates not stated | 67 | Unilateral neovasuclar age-related macular degeneration n=67 | ? (?), 61–89 | 30:37 | Inclusion for fellow eye (unaffected): macular drusen (hard or soft), corrected Snellen visual acuity =30/60, sufficiently clear media to allow adequate visualisation of the fundus, a readable fluorescein angiogram, no sign of retinal disease. | Existence of a choroidal neovascular membrane in the affected (non-study) eye was based on prior fluorescein angiography or current ophthalmoscopic signs of a choroidal neovascular membrane (haemorrhage, exudates, discoloration, elevation of macula, scarring). | Fluorescein angiography |

**Table E1** **Descriptive characteristics of studies examining focal ERG compared with another test (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with focal ERG |
| Holopigian 1990 | USA, dates not stated | 24 patients + 10 controls | Primary open-angle glaucoma (POAG) n=13<br>Ocular hypertension (OHT) n=11 | POAG 67 (10), 44–88<br>OHT 64 (10), 49–79 | POAG 13:0<br>OHT 7:4 | ? | ? | Psychophysical flicker sensitivity<br>Visual evoked potentials |
| Matthews 1992 | USA, dates not stated | 5 | Unexplained central visual loss n=5 | 45f (?), 24–66 | ? | ? | Non-diagnostic history and ocular examinations | Fluorescein angiography<br>Full-field ERG |
| Miyake 1996 | Japan, 1995 | 13 | Occult macular dystrophy n=13 | ? (?), 16–65 | 8:5 | ? | ? (Authors state that the patients were diagnosed with the disease.) | Full-field ERG |
| Porciatti 1987 | Italy, dates not stated | 13 patients + 86 controls | Otpic atrophy n=5<br>Temporal retinal ischaemia n=8<br>Controls (C) n=86 | P 38 (?), 12–60<br>C 34 (?), 12–60 | P 6:7<br>C ? | ? | ? | Pattern ERG |
| Remulla 1995 | USA, dates not stated | 67 | Unilateral neovasuclar age-related macular degeneration n=67 | ? (?), 61–89 | ? | Inclusion for fellow eye: corrected Snellen visual acuity =20/60; sufficiently clear media to allow detailed evaluation of the fundus, macular drusen, no sign of other retinal disease in the study eye. | ? | Fluorescein angiography |

**Table E1** **Descriptive characteristics of studies examining focal ERG compared with another test (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with focal ERG |
| Salzman 1986 | USA, dates not stated | 30 patients + 17 controls | Aphakic with cystoid macular oedema | 72.4 (?), 40–85 | ? | Exclusion: evidence of preoperative optic nerve disease, previous retinal detachment, macular degeneration, glaucoma, other retinal disease, corneal pathology, history of preoperative inflammatory eye disorder | ? | Pattern ERG<br>Visual evoked potentials (VEP) |
| Seiple 1993 | USA, dates not stated | 11 patients + 10 controls | Retinitis pigmentosa n=11 | 37 (?), 20–47 | ? | ? | ? | Psychophysical modulation thresholds |
| Small 1996 | USA, dates not stated | 73 | Autosomal dominant progressive cone degeneration (affected and unaffected) n=73 | 29 (?), 5–76 | ? | Members of single, large family with autosomal dominant cone degeneration | ? | Full-field ERG |

**Table E1 Descriptive characteristics of studies examining focal ERG compared with another test (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with focal ERG |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | | | |
| Vaegan 1986 | Australia, dates not stated | 18 patients + 13 controls | Stargardt's disease n=7<br>Familial cone dystrophies n=5<br>Best's disease n=1<br>Vitelline degeneration n=1<br>Gronblad-Strandberg syndrome n=1<br>Solar burns n=2<br>Foveal pigment epithelipathy n=1<br>Controls n=13 | 30 (17), 6–62 | ? | Patients with visual diseases: selection was biased toward the most mildly affected cases. | ? (However, authors stated that for some patients diagnosis was provisional or atypical.) | Pattern ERG and four alternative forced choice (4AFC) contrast sensitivity |
| Vaegan 1987 | Australia, dates not stated | 15 patients* + 13 controls (*later excluded 8 patients who didn't meet selection criteria) | Retobulbar neuritis with confirmed multiple sclerosis (RN) n=9, 5 unilateral, 4 bilateral<br>Optic atrophy n=6, 4 juvenile, 2 long-standing)<br>Normal controls n=13<br>*Note*: It is not clear which patients were later excluded. | ? | ? | All patients had comparable test conditions and certainty of diagnosis.<br>Unilateral RN: experienced primary acute phase within previous year. | ? (However, certainty of diagnosis was stated as a selection criteria.) | Pattern ERG |

?=Data not provided.

**Table E2 Validity of focal ERG studies with a comparator test**

| First author and year of publication | Validity of study methods | | | | |
|---|---|---|---|---|---|
| | Appropriate spectrum of study subjects | Masked assessment of study and reference test results | All study subjects tested with both study and reference test | Study test measured independently of clinical information | Reference test measured prior to start of intervention |
| Holopigian 1990 | No | *? | ? | No | ? |
| Matthews 1992 | Yes (Patients have not been diagnosed with a disease.) | No | Yes | ? | ? |
| Miyake 1996 | No | ? | Yes | No | ? |
| Porciatti 1987 | No | ? | ? | No | ? |
| Remulla 1995 | No | Yes | Yes | No | ? |
| Salzman 1986 | No | ? | Yes | No | ? |
| Seiple 1993 | No | ? | Yes | No | ? |
| Small 1996 | No | ? | No | No | ? |
| Vaegan 1986 | No | ? | Yes | No | ? |
| Vaegan 1987 | No | ? | Yes | No | ? |

*? = Data not provided.

**Table E3 Results of studies comparing focal ERG with another test**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Arden 1982 | In 27 amblyopes of various types, the pattern ERG was reduced in 23 where orthoptic treatment had failed. In 4 patients responding to treatment, pattern ERGs of the amblyopic eyes were as large as, or larger than, those of the fellow eye. | Not addressed |
| Birch 1984 | Only graphical and individual patient results were presented.<br>In 7/22 (32%) of patients tested with both psychophysical and foveal cone ERG procedures, there was a close correspondence between focal ERG and psychophysical measurements of the Stiles-Crawford effect (alignment of photoreceptors and optical properties of individual receptors). Only graphical and individual results were presented.<br>Mean difference in Rho values determined from psychophysical (2° or 4° stimulus and focal ERG (4° stimulus): < 0.01. | Not addressed |
| Falsini 1992 | The 2F amplitude was reduced in patients by 38.4% and the 2F phase was delayed by 30.25° compared with controls, which was statistically significant.<br>The IF amplitude was reduced in patients by 15% compared with controls, which was not statistically significant. The 1F phase in patients was similar to that of controls.<br>The 2P amplitude was reduced in patients by 47.2% and 2P phase was delayed by 22.82° compared with controls, which was statistically significant.<br>Among 19 affected eyes, 16 (84%) had a significant alteration for at least one component. In the remaining 14 eyes, 2F and/or 2P, but not 1F, were abnormal. All components were altered in two eyes.<br>The mean IF amplitude was 0.33µV, the mean 2F amplitude was 0.23µV, and the mean 2P amplitude was 0.21µV in patients with FMH. | Not addressed (The authors mentioned that the focal ERG may be useful in identifying eyes at risk for hole formation; however, this was not addressed in the study.) |
| Falsini 1999 | Only graphical presentation of results. Not all patients had both tests (proportion not stated).<br>The focal ERG amplitude but not focal ERG phase was negatively correlated with the extent of macular area in which pathological hyperfluorescein was detectable. | Not addressed |

**Table E3 Results of studies comparing focal ERG with another test (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Gaudio 1998 | Study was done in fellow eyes (unaffected).<br>Foveal ERG implicit time was inversely related to the mean arterial pressure controlling for age, gender and intake of hypertension medication. Implicit time fell about 0.5 ms for each 10 mmHg increase in mean arterial pressure.<br>Foveal ERG implicit time was not significantly related to intake of hypertensive medication. | Not addressed |
| Holopigian 1990 | Only graphical presentation of results.<br>Focal ERG, VEP and PFS were measured at various temporal frequencies (10–50 Hz).<br>POAG patients (compared with C): reduced focal ERG, reduced PFS, reduced VEP (especially at intermediate and high frequency).<br>OHT patients (compared with C): normal focal ERG amplitudes at all frequencies, elevated PFS thresholds only at high frequencies, VEP losses only at high frequencies. | Not addressed |
| Matthews 1992 | No data presented comparing patients' test results on focal ERG with full-field ERG or fluorescein angiography. All 5 patients had normal results on full-field ERG and fluorescein angiography and abnormal results on focal ERG (<0.18 µV amplitude, =39 ms implicit time). | Abnormal focal ERGs help to exclude optic atrophy, central visual pathways dysfunction or hysteria as explanations for the visual loss. |
| Miyake 1996 | Full-field ERGs were within normal range for all patients compared with age-matched control.<br>The focal macular ERG showed non-detectable responses in 11 out of 13 patients. | Not addressed. (The authors state that only the results of focal macular ERG or multifocal ERG can identify OMD.) |
| Porciatti 1987 | In normal eyes the second harmonic of the uniform-field response is smaller (mean value 62%) than that of the optimal pattern (around .5 cycles/degree). The second harmonic of the pattern response in patients is reduced in cases of optic atrophy. Only graphical results presented. | Not addressed |

**Table E3 Results of studies comparing focal ERG with another test (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Remulla 1995 | Study done in unaffected fellow eyes.<br>Focal ERG implicit time results compared with fluorescein angiography:<br>Sensitivity 61%<br>Specificity 72%.<br>Prolonged choroidal filling phase: non-uniform fluorescence extending over =5 disc diameters of the posterior pole persisting through the onset of the venous phase of the retinal circulation. | Although angiographic evidence of prolonged choroidal filling was found to be significantly associated with delayed foveal ERG, only 6 in 10 patients with prolonged filling time will also have delayed foveal ERG implicit time, which reduces clinical usefulness of the test. |
| Salzman 1986 | Results were based on number of eyes (not patients).<br>*Focal ERG vs pattern ERG*<br>Of 10 eyes with abnormal focal ERG, 7 also had abnormal pattern ERG. Of 23 eyes with normal focal ERG, 14 eyes also had normal pattern ERG:<br>Sensitivity: 44%<br>Specificity: 82%<br>*Focal ERG vs VEP*<br>Of 10 eyes with abnormal focal ERG, 4 also had abnormal VEP. Of 23 eyes with normal focal ERG, 16 also had normal VEP:<br>Sensitivity: 36%<br>Specificity: 73%<br>Focal ERG amplitudes were abnormal in 35% of patients with ACMO. Pattern ERG amplitudes were abnormal in 53% of ACMO, with over half of these patients having normal focal ERG. | Not addressed |
| Seiple 1993 | Only graphical presentation of results. No direct comparisons of patients' focal ERG results with psychophysical findings.<br>RP patients showed similar patterns of cone sensitivity losses using both techniques. | Not addressed |

**Table E3 Results of studies comparing focal ERG with another test (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Small 1996 | Of the 73 family members, 34 were affected. The photopic full-field electroretinogram was important in establishing the diagnosis, although the results of the electroretinographic measurements varied across individuals. Either the focal ERG amplitudes were abnormally low or the foveal/parafoveal ratio was abnormal in all affected subjects.<br>No single test or finding was completely sensitive or specific for accurate diagnosis of autosomal dominant cone degeneration. | The authors stated that if any of the affected individuals had been initially examined out of context of their family history it would have been extremely difficult to group some of the subjects together as having autosomal dominant cone degeneration. |
| Vaegan 1986 | At high intensity the mean amplitudes in the pattern ERG for controls and patients were 5.94µV and 2.36µV respectively.<br>At high intensity the mean amplitudes in the focal ERG for controls and patients were 6.70µV and 2.99µV respectively.<br>At low intensity the mean amplitudes in the pattern ERG for controls and patients were 4.75µV and 1.41µV respectively.<br>At low intensity the mean amplitudes in the focal ERG for controls and patients were 5.01µV and 1.84µV respectively.<br>Contrast sensitivity was markedly reduced in patients. | Not addressed. The authors state that contrast sensitivity tests and macular ERGs together provide the most sensitive, objective, non-invasive, early evidence for the functional and structural losses that indicated maculopathy for their series of patients, although this was not tested directly in the study. |
| Vaegan 1987 | Only graphical results and pattern ERG/focal ERG ratios were provided.<br>Pattern ERGs were less than focal ERGs in patients with OA. Pattern ERG was reduced while focal ERG was not affected.<br>In RN, both pattern ERGs and focal ERGs were reduced. | Not addressed |

**Table E4 Descriptive characteristics of case control studies of focal ERG**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Bagolini 1988 | Italy, dates not stated | 54 patients + 34 controls | Unilateral macular disease (MD) n=15<br>Bilateral macular disease n=39<br>Controls (C) n=34 | MD 41 (19), *?<br>C 42 (18), ? | ? | MD: clear media | Diagnoses were based on biomicroscopic examination of the macula using a three-mirror Goldmann lens, fundus photography and fluorescein angiography. |
| Bagolini 1989 | Italy, dates not stated | 26 patients + 14 controls | Stargardt's disease n=14 eyes<br>Cone dystrophy n=12 eyes<br>Vitelliform degeneration n=4 eyes<br>Pattern dystrophy n=18 eyes<br>Controls (C) n=14 | P 24 (?), 7–43<br>C 30 (?), 11–48 | ? | Diagnoses were based on family history, biomicroscopic examination of the macula with a Goldmann lens, fluroescein angiography, and standard electrophysiological tests (Ganzfeld scotopic and photopic ERGs and electrooculogram). All affected eyes had clear media and had no ocular or systemic diseases present. | Diagnoses were based on family history, biomicroscopic examination of the macular with a Goldmann lens, fluorescein angiography and standard electrophysiological tests (Ganzfeld scotopic and photopic ERGs and electrooculogram). |
| Birch 1988a | USA, dates not stated | 134 patients (100 reported on)<br>+ 100 controls | Macular disease n=100<br>Controls (C) n=100 | MD ?<br>C ? (?), 5–79 | ? | MD – *Inclusion*: diagnosis of macular disease made by ophthalmologist specialist in retinal disorders. *Exclusion*: eyes with idiopathic macular holes.<br>C – Normal subjects recruited to obtain equal numbers from each decade of life. | Not specified, except authors state that diagnosis was determined by an ophthalmologist specialised in retinal disorders. |

**Table E4** **Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Brodie 1992 | USA, dates not stated | 48 patient eyes<br>+ 35 control eyes | Various diseases (numbers not specified) including: Stargardt's disease, macular hole, retinitis pigmentosa, multiple evanescent white dot syndrome, diabetic macular oedema, aphakic or pseudophakic macular oedema, atrophic and exudative macular degeneration, retinal artery occulsion, retinal vein occulsion and retinoschisis of the macular.<br>Control eyes included the contralateral eyes of patients with uniocular pathology and eyes of asymptomatic patients referred for evaluation of innocuous variations of ophthalmoscopic appearance. | ? | ? | ? | Diagnosis made by visual acuity, ophthalmoscopic examination, or fluorescein angiography. |
| Deschenes 1998 | Canada, dates not stated | 14 patients<br>+ 28 controls | Non-insulin-dependent diabetes mellitus (NIDDM) n=14<br>Controls (C) n=28 | NIDDM 58 (11), 46–70<br>C 55 (8) ? | NIDDM 6:1<br>C 5:9 | Patients were recruited from the Southern Alberta Study of Diabetic Retinopathy. | ? |

**Table E4 Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Di Leo 1994 | Italy, dates not stated | 21 patients + 25 controls | Diabetes (D) n=21<br>Control (C) n=25 | D 20 (8), ?<br>C 21 (6), ? | D 8:13<br>C 12:13 | D – *Exclusion*: patients previously treated with two or less daily injections of insulin or who showed severe and recurrent hypoglycaemia and had any eye or systemic diseases.<br>C – sex and age matched. | ? |
| Falsini 1994 | Italy, dates not stated | 34 patients + 17 controls | Retinitis pigmentosa (RP) n=22<br>Cone dystrophy (CD) n=7<br>X-linked congenital retinoschisis (XLR) n=5<br>Control subjects (C) n=17 | RP 28 (?) 9–51<br>C 25 (?), 9–52<br>CD 31 (?) 20–48<br>XLR 19 (?), 13–28 | RP 8:3<br>CD 3:4<br>XLR 1:0<br>C 12:5 | *Inclusion*: clear optical media and stable foveal fixation. | ? |
| Falsini 1996 | Italy, dates not stated | 24 patients + 29 controls | Best vitelliform macular dystrophy (BMD) n=11<br>Stargardt macular dystrophy (STD) n=13<br>Normal controls (C) n=29 | BMD 23 (?), 10–53<br>STD 19 (?), 9–28<br>C: 23 (?), 8–51 | BMD 5:6<br>STD 6:7<br>C 14:15 | MD – clear media.<br>C – absence of macular disease confirmed after cataract surgery when all eyes achieved >20/45 visual acuity. | ? |
| Falsini 2000 | Italy, dates not stated | 19 patients + 11 controls | Age-related maculopathy (ARM) n=19<br>Control (C) n=11 | ARM: 67 (7), 54–84<br>C: 65 (7), 54–84 | ARM 7:12<br>C 4:7 | ARM – *Inclusion*: best-corrected visual acuity of 20/30 or better in the study eye, central fixation, normal colour vision, no signs of other retinal or optic nerve disease and clear optical media.<br>C – *Inclusion*: as above for patients except best corrected visual acuity was 20/20. | Diagnosis was established by direct and indirect ophthalmoscopy and retinal biomicroscopy. |

**Table E4 Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Fish 1989 | USA, dates not stated | 108 patients<br>+ 50 controls | Macular disease (MD) n=108, n of eyes = 142<br>Controls: patients with reduced acuity due to causes other than maculopathy (C) n=50 | MD 41 (?) ?<br>C 49 (?) ? | ? | ? | ? |
| Ghirlanda 1991 | Italy, dates not stated | 60 patients<br>+ 39 controls | Insulin-dependent diabetes mellitus with early retinopathy (IDDM-er) n=10<br>Insulin-dependent diabetes mellitus with no retinopathy (IDDM) n=50<br>Control patients (C) n=39 | IDDM-er 21.9 (4.1) ?<br>IDDM 18.9 (7.1), ?<br>C 20.3 (6.4) ? | IDDM 4:6<br>IDDM-er 23:27<br>C 17:22 | ? | Clinical diagnosis for each IDDM patient was established by general and ophthalmological routine examination (including anterior segment biomicroscopy, corrected visual acuity, applanation tonometry, and direct and indirect ophthalmoscopy).<br>C – ? |
| Jacobson 1979 | USA, dates not stated | 30 patients<br>+ 25 controls | Strabismic amblyopia (SA) n=15<br>Well-healed macular chorioretinal scars no longer than one disc diameter in size (MCS) n=5<br>Juvenile hereditary macular degeneration (MD) n=6<br>Optic atrophy (OA) n=4<br>Normal controls (C) n=20 | SA ? (?), 9–68<br>MS ? (?), 5–73<br>MD ? (?), 11–37<br>OA ? (?), 10–43 | ? | All subjects had clear media and no greater than 1.5 dioptres difference in refraction between their two eyes. | ? |

**Table E4 Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Miyake 1988 | Japan, dates not stated | 24 patients + 54 controls | Idiopathic central serous chorioretinopathy (CSC) n=24<br>Fellow eyes: non-affected fellow eyes of patients (FE)<br>Controls (C) n=54 | CSC 40 (?), 24–51 | ? | Patients – *Inclusion*: relatively recent onset of central serous chorioretinopathy and best corrected visual acuity ranging from 20/50 to 30/20.<br>*Exclusion*: patients with a history or ophthalmoscopic evidence of previous detachment.<br>C – ? | ? |
| Miyake 1993 | Japan, dates not stated | 20 patients + 72 controls | Congenital retinoschisis without degeneration (CR) n=17<br>Congenital retinoschisis with degeneration (CRD) n=3<br>Controls (C) n=3 | CR 41 (?), 8–32<br>CRD 66 (?), 60–72<br>C ? (?), ? | ? | ? | ? |
| Sandberg 1979 | USA, dates not stated | 40 patients + 23 controls | Well-healed macular chorioretinal scars (1 disc diameter in size) and visual acuities of 6/60 or less (MCS) n=5<br>Stargardt's disease (SD) n=17 eyes<br>Retinitis pigmentosa (RP) n=16<br>Congenital rod monochromacy (CRM) n=1<br>Strabismic amblyopia (SA) n=1<br>Controls (C) n=23 | MCS ? (?), 5–73<br>SD ? (?), 9–36<br>RP ? (?), 5–32<br>CRM 59 (?), ?<br>SA 35 (?) ?<br>C ? (?), ? | ? | Clear media. Patients with retinitis pigmentosa were subnormal in amplitude and delayed in b-wave implicit time for full-field ERGs. | Well-healed MCS: 1 disc diameter in size |
| Sandberg 1993 | USA, dates not stated | 73 patients + 28 controls | Unilateral neovascular age-related macular degeneration (AMD) n=73 | AMD 72.1 (?), ?<br>C 69.7 (?), ? | AMD 37:36<br>C 13:15 | ? | AMD – no evidence of choroidal neovascular membrane<br>C – normal ocular examination |

**Table E4 Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Seiple 1986 | USA, dates not stated | 27 patients<br>+ 9 controls | Retinitis pigmentosa (RP) n=19<br>Stargardt's disease (SD) n=8<br>Best's disease (BD) n=1<br>Controls (C) n=9 | RP ? (?), 24–51<br>SD & BD ? (?), 14–52<br>C ?, (?), 9–35 | RP 11:8<br>SD & BD 1:0<br>C 8:1 | ? | ? |
| Weiner 1998a | USA, 1996–97 | 44 patients<br>+ 39 controls | Unexplained visual symptoms or acuity loss (UEVS) n=44<br>Maculopathy (M) n=7<br>Control (C) n=39 | UEVS 51 (18), ?<br>M ? (?), ?<br>C age-matched | UEVS 21:23<br>C ?<br>M ? | UEVS, M – *Inclusion*: visual symptoms or acuity loss determined to be of unexplained nature by =2 opthalmologists.<br>*Exclusion*: patients that had best corrected Snellen visual acuity <20/300, inability to maintain fixation for foveal cone ERG testing, significant media opacities, or small pupils preventing continuous observation of the foveal ERG test target, any intraocular surgery, intraocular pressure =22 mmHg, overt retinopathy, maculopathy or general medical conditions that may affect foveal responses, such as diabetes.<br>C – matched for age, sex, refractive error, ethnicity.<br>*Inclusion*: No visual complaints, no ocular history except for refractive error, not related to study patients.<br>*Exclusion*: as for patients as well as best corrected visual acuity <20/25, family history of visual loss other than related to trauma. | Presumably undiagnosed patients |

**Table E4 Descriptive characteristics of case control studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Weiner 1998b | USA, dates not stated | 37 patients + 47 controls | Normal pressure glaucome (NPG) n=27<br>Primary open-angle glaucoma (POAG) n=10<br>Controls (C) n=47) | P 67 (8.5), 39–80<br>C: 63 (12), ? | ? | NPG, POAG – *Inclusion*: diagnosis of NPG or POAG based on the characteristic combination of optic disc cupping, progressive visual field loss and intraocular pressure. *Exclusion*: patients with media opacities or insufficient pupillary dilation, best corrected visual acuity (BCVA) of <20/50 impeding fixation; any maculopathy or other retinopathy on opthalmoscopic examination; previous ocular surgery; any general medical condition that may affect retinal function; and family history +ve for retinal or macular dystrophies.<br>C – *Inclusion*: no ocular history except for refractive error. *Exclusion*: criteria includes those described for patients as well as visual complaints – a BCVA of <20/25; intra-ocular pressure greater than 21 mmHg; any abnormal finding on dilated ocular examination; vertical or horizontal cup-disc ration of =0.4 on slit-lamp biomicroscopy. | Diagnosis was based on the characteristic combination of optic disc cupping, progressive visual field loss, and intraocular pressure. |

?=Data not provided.

**Table E5 Results of case control studies of focal ERG**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Bagolini 1988 | Mean amplitude of focal ERG and the mean M/P ratio were significantly lower than normal values.<br>Mean focal ERG amplitude was 0.97μV in control patients and 0.51μV in patients. focal ERG amplitude was abnormal in 57 (61.3%) of eyes.<br>The mean M/P ratio in controls was 1.76 and 1.21 in patients. M/P ratio was abnormal in 56 (60.2%) of eyes. At least one of these two parameters was reduced in 78.5% (73) of affected eyes. | Effect on clinical management of patients was not addressed in this study other than to state that macular ERG declines progressively in amplitude with age and therefore should be considered when results from elderly patients are examined. |
| Bagolini 1989 | The mean amplitude of the focal ERG in all the patient groups (0.43μV±0.06(SD)) was significantly lower than the control mean (1.13μV±0.09(SD)). Focal ERG amplitude range for the controls was 0.55–1.78μV; 69.2% of affected eyes were below the normal range.<br>The implicit time showed a trend to an increase in all patients; however, it was not statistically significant.<br>The mean amplitude ratio between foveal and parafoveal ERG in controls was 2.07±0.19 (SD) in controls and 1.06±0.20 (SD) in patients; 55.8% of affected eyes were below the normal range. At least one of these three parameters was abnormal in 46 of 52 affected eyes (88.5%). | Not addressed |
| Birch 1988a | Foveal ERGs were significantly reduced in many eyes with macular disease retaining near-normal Snellen acuity. | No details of the proportion of patients identified with abnormal test results.<br>Authors state that a normal focal ERG in patients with an acuity loss of =20/40 may assist in ruling out diagnoses of the types of macular diseases experienced by study patients. |
| Brodie 1992 | The difference between the normal and abnormal response distribution was statistically significant. Only graphical and individual results presented. | Not addressed |
| Deschenes 1998 | In control eyes the implicit time of FERG increased with age with a rate of change of 0.444 ms per year, for diabetic eyes the rate was 0.134 ms per year, which was significantly different. Patients had focal ERG implicit times that were significantly longer than those of the control eyes of similar age range.<br>The amplitude of the focal ERG was significantly more reduced in the diabetic group with increasing age than in the control group. | Not addressed |

**Table E5 Results of case control studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Di Leo 1994 | *At baseline*<br>Compared with C: after 3 years of follow-up IDDM patients had no significant differences in photoreceptor activity (measured by focal ERG 1F). Postreceptor neuronal function (measured by focal ERG 2F) was significantly impaired (Control vs IDDM: mean difference from baseline 2F: 0μV vs –0.15μV). | Not addressed |
| Falsini 1994 | *Focal ERG amplitude*<br>Compared with C: RP patients had significantly reduced fundamental amplitude (mean difference –0.17μV) and 2nd harmonic amplitude (mean difference –0.27μV) at 8 Hz. At 32 Hz amplitude was also significantly reduced (mean difference –0.41μV).<br>Compared with C: CD patients had no significant difference in fundamental amplitude but significantly reduced 2nd harmonic amplitude (mean difference –0.29μV) at 8 Hz and at 32 Hz (mean difference 0.64μV).<br>Compared with C: XLR had mean fundamental amplitudes that were similar but 2nd harmonic was significantly reduced (mean difference 0.64μV) at 8Hz. At 32 Hz mean amplitudes were identical.<br>*Focal ERG phase*<br>Compared with C: RP patients had similar fundamental phase and significantly reduced 2nd harmonic phase (mean difference –53°) at 8 Hz but not at 32 Hz.<br>Compared with C: RP patients had similar fundamental phase and significantly reduced 2nd harmonic phase (mean difference 54.4°) at 8 Hz but not at 32 Hz (mean difference 53.4°).<br>Compared with C: XLR patients were not different on any phase component of focal ERG. | Not addressed |
| Falsini 1996 | Compared with C: BMD had significantly reduced fundamental and 2nd harmonic amplitude reduced (mean difference 0.3μV and 0.28μV respectively). For the phase component of focal ERG only the 2nd harmonic phase was significantly reduced (mean difference 26.4°).<br>Compared with STD: BMD had significantly higher fundamental and 2nd harmonic amplitude (mean difference –0.43μV and 0.07μV respectively). 2nd harmonic phase was significantly reduced (mean difference 29.1°). | Not addressed |

**Table E5 Results of case control studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Falsini 2000 | For control patients the focal ERG slope function was 1.72±0.08 whereas for ARM patients the function was 1.15±0.05 and 1.3±0.12 for early lesion and advanced lesion patients respectively.<br>The focal ERG threshold for controls was 1.18±0.03 whereas for ARM patients the threshold was 1.11±0.04 and 1.53±0.06 for early lesion and advanced lesion patients respectively. | Not addressed |
| Fish 1989 | *Focal ERG* (based on abnormal amplitude: <0.18 μV; abnormal implicit time= >36.6 ms)<br>All eyes (n=138): 85% sensitivity; 92% specificity<br>Eyes with macular holes only and controls (n=93): 86% sensitivity; 92% specificity<br>*Focal ERG amplitude*<br>All eyes (n=138): 77% sensitivity; 96% specificity<br>Eyes with macular holes only and controls (n=93): 79% sensitivity; 96% specificity<br>*Focal ERG implicit time*<br>All eyes (n=138): 46% sensitivity; 96 specificity<br>Eyes with macular holes only and controls (n=93): 46% sensitivity, 96% specificity | Effect on clinical management of patients was not addressed in this study other than to state that focal ERG was used to discriminate between macular disease and other causes of acuity loss. |

**Table E5 Results of case control studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Ghirlanda 1992 | *Uniform field focal ERG*<br><u>Amplitude – 1F</u><br>IDDM patients with early retinopathy vs C: no significant difference in amplitude (mean(SD): 0.74(0.19) vs 1.0(0.34)).<br>IDDM patients with normal fundus vs C: no significant difference in amplitude (mean(SD): 0.98(0.45) vs 1.0(0.34)).<br><u>Amplitude – 2F</u><br>IDDM patients with early retinopathy vs C: significantly lower amplitude (mean(SD): 0.32(0.16) vs 0.51(0.13), p<0.001).<br>IDDM patients with normal fundus vs C: significantly lower amplitude (mean(SD): 0.37(0.13) vs 0.51(0.13), p<0.001).<br><u>Phase – 1F</u><br>IDDM patients with early retinopathy vs C: no significant difference in phase (mean(SD): -79.9(59.2) vs -112(35.6)).<br>IDDM patients with normal fundus vs C: no significant difference in phase (mean(SD): -105.7(38.4) vs -112(35.6)).<br><u>Phase – 2F</u><br>IDDM with early retinopathy vs C: no significant difference in phase (mean(SD): -42.6(45.4) vs -30.8(18.4)).<br>IDDM with normal fundus vs C: no significant difference in phase (mean(SD): -50.5(52.2) vs -30.8(18.4)). | Not addressed |
| Jacobson 1979 | Focal ERGs from the controls showed amplitudes that ranged from 0.18–0.55μV and implicit times from 31–38 ms. Focal ERGs from SA patients were normal in amplitude and implicit time (0.19–0.53μV and 33–37 ms respectively) and no differences were found to be statistically significant.<br>MD patients had abnormal focal ERGs with amplitudes of 0.08–0.17μV. Implicit times were either normal or delayed. | Not addressed |

**Table E5 Results of case control studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Miyake 1988 | RP vs unaffected fellow eye: % of amplitude in unaffected fellow eye, a-wave (photoreceptors): 64.6±22.7%; b-wave: 49.6±21.0%; oscillatory potentials: 15.0±21.6%.<br>*RP vs C: amplitude*<br>a-wave: RP 0.82±0.26μV vs C: 1.25±0.24μV<br>b-wave: RP 1.45±0.64μV vs C: 2.91±0.79μV<br>oscillatory pot: RP 0.16±0.21μV vs C: 1.10±0.70μV | Not addressed |
| Miyake 1993 | For patients the mean amplitude of b-waves and of OPs were significantly reduced, whereas mean amplitude of a-waves was not significantly different from normal control subjects.<br>For the 17 eyes of the CR group the b-wave amplitudes of 15 eyes (88%) and a-wave amplitude of 2 eyes were lower than normal when evaluated with a 10˚ spot. The implicit times of the b-wave of 15 eyes (88%) were longer than normal as were the implicit times of the a-wave of 14 eyes (82%).<br>Two of the three patients in the CRD group showed non-recordable macular response. One of them showed recordable response only with the 10˚ and 15˚ spots. The amplitude of a-wave and b-wave and the b/a ratio of this patient were significantly smaller than those of a normal controlled subject. The implicit times of the a- and b-waves with the 10˚ and 15˚ spots were significantly delayed. | Not addressed |
| Sandberg 1979 | Three RP patients had reduced amplitude (0.11–0.17μV) and normal implicit time (31–38 ms).<br>Eight RP patients had normal amplitude (0.18–0.55μV) and normal implicit time (31–38 ms).<br>No results were tested for statistical significance. | Not addressed |

**Table E5 Results of case control studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Sandberg 1993 | Study done in unaffected fellow eyes of patients.<br>Adjusted mean amplitudes – normal for patients and controls (0.26μV).<br>Adjusted implicit time: patients had longer implicit times than controls (mean 37.2 ms vs 35.1 ms). | Not addressed |
| Seiple 1986 | Only graphical results presented. There was a general relationship between decreased visual acuity and reduced focal ERG amplitude as a function of temporal frequency for all RP patients. Patients with lower visual acuity showed greater amplitude losses at progressively lower temporal frequencies. | Not addressed |
| Weiner 1998a | Abnormal foveal cone ERG data were recorded in 23 (52%) of the 44 patients (35 or 48% of 73 eyes) – normal defined as 0.18μV from normal controls). In 7 of those eyes (10%), implicit times were above the normal value of 38 ms. Among the 35 eyes with abnormal retinal responses, amplitude was significantly correlated with best corrected Snellen visual acuity. | Foveal cone dysfunction was diagnosed in approximately half of study patients with unexplained visual symptoms or acuity loss. Management of patients was not discussed. |
| Weiner 1998b | The mean (±SD) amplitude in patients with glaucoma was 0.236–0.103μV, which was significantly lower than in controls (mean 0.310±0.098μV). Of the 37 eyes with glaucoma, 14 (37.8%) had subnormal amplitudes.<br>Mean (±SD) implicit time did not differ significantly between patients and controls (34.81±1.78 ms and 34.28±1.69 ms respectively).<br>False positive rate was determined based on data collection from the 47 normal eyes; 2 eyes had an amplitude less than the normal range, giving a specificity rate of 95.7%.<br>The false negative rate was determined based on test vs retest data collected from 12 eyes with known maculopathy; 2 eyes had abnormal test results in the first test and normal in the second, suggesting a sensitivity rate of 83.3%. | The authors state that their results may have some future therapeutic implications as a focal ERG could be considered a monitoring tool to determine the therapeutic effect of various agents on foveal function in glaucoma. |

**Table E6 Descriptive characteristics of case series studies of focal ERG**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Biersdorf 1982 | USA, dates not stated | 79 diseased eyes<br>+ 10 control eyes | Senile macular degeneration (SMD) n=16<br>Retinitis pigmentosa (RP) n=29<br>Stargardt's dystrophy (SD) n=34 | SMD 57 (11), *?<br>RP 32 (19), ?<br>SD 32 (12), ? | ? | ? | ? |
| Birch 1988b | USA, dates not stated | 35 | Unilateral, idiopathic full-thickness macular hole | 63 (6), 51–77 | MH 6:29 | *Exclusion*: a best corrected visual acuity worse than 20/40 in the fellow eye and residence too distant for follow-up visits. | ? |
| Fish 1986 | USA, dates not stated | 48 | Known maculopathy | ? | ? | *Inclusion*: Clear media | ? |
| Holopigian 1996 | USA, dates not stated | 26 | Retinitis pigmentosa | 36.9 (?), 20–68 | RP 18:8 | *Inclusion*: best-corrected Snellen visual acuity of =20/40, central visual fields of =10°, no significant opacities of the lens, no evidence of cystoid macular oedema on fluorescein angiography.<br>*Exclusion*: patients with other types of hereditary retinal degenerative diseases or other retinal or systemic disease (not diagnosed as retinitis pigmentosa). | Diagnosis based on characteristic funduscopic findings, elevated dark-adapted thresholds, constricted visual fields and non-recordable or severely reduced ERGs. |
| Sandberg 1998 | USA, 1990–92 | 127 | Unilateral neovascular age-related macular degeneration | ? (?), 58–89 | 57:70 | *Inclusion*: corrected Snellen visual acuity of 20/60 or better in the fellow eye with sufficiently clear media, the presence of a choriodal neovascular membrane in the macular of the affected eye, macular drusen in both eyes.<br>*Exclusion*: no sign of other retinal diseases. | ? |

**Table E6 Descriptive characteristics of case series studies of focal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Tanikawa 1999 | Japan, dates not stated | 30 | Idiopathic epimacular membrane | 58.3 (10.5), 25–75 | ? | ? | Diagnosis was made by biomicroscopy with a slit lamp or a scanning laser ophthalmoscope. |
| Weiner 1997 | USA, dates not stated | 18 | Non-proliferative diabetic retinopathy with unilateral clinically significant macular oedema | ? (?), 35–73 | 8:10 | *Inclusion*: presence of diabetes type 2, bilateral NPDR, unilateral CSMO, none or minimal media opacities, sufficient pupillary dilation enabling continuous observation of the foveal ERG test target on the fovea throughout testing.<br>*Exclusion*: significant media opacities, inability to dilate the pupils, evidence of ocular neovascularisation, macular capillary non-perfusion on fluorescein angiography, previous laser treatment within the tested area, signs or family history of retinopathy from causes other than diabetes. | Diagnosis of NPDR with no evidence of proliferation was made by ophthalmoscopy and fluorescein angiography.<br>Diagnosis of CSMO was based on criteria published in another study. |

?=Data not provided.

**Table E7 Results of case series studies of focal ERG**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Biersdorf 1982 | Only 7% of SMD eyes had an abnormally delayed focal ERG; whereas in eyes with SD and RP 47% and 31% of eyes respectively were abnormally delayed. | Not addressed |
| Birch 1988b | Implicit time was longer in eyes with macular holes than in the normal eye (mean 36.8 ms $p<0.001$) but shorter than normal parafoveal implicit times (mean 34.5 ms $p<0.05$). Focal ERG amplitude was inversely proportional to the diameter of the macular hole ($p<0.001$). Twenty-six (79%) of 33 patients with full-thickness macular holes in one eye had normal focal ERGs in the fellow eye at their initial visit. | Not addressed |
| Fish 1986 | The potential acuity meter, laser interferometer and white light interferometer overread relative to Snellen acuity. Blue field and focal ERG were categorised as normal or abnormal. Abnormal results from blue field and focal ERG corresponded with poor Snellen acuity in 65% and 91% of patients respectively. Chi-square analysis suggests a significant ($p<0.01$) association between focal ERG results and Snellen acuity. | Not addressed |
| Holopigian 1996 | Patients were followed annually for 9 years.<br>*Focal ERG (10 Hz) at 9 years*<br>Mean amplitude was 1.36 μV (62% of average control amplitude).<br>5 patients had increase in amplitude, 7 had no change, 14 had decrease.<br>*Focal ERG (40 Hz) at 9 years*<br>Mean amplitude was 1.04 μV (34% of average control amplitude).<br>6 patients had increase in amplitude, 6 had no change, 14 had decreased amplitude.<br>There was no correlation between patients' test results of visual acuity, visual field and Farnsworth-Munsell, and focal ERG (only 1 patient had declines in all 5 measures). | Not addressed |
| Horiguchi 1993 | Patients were measured at onset of disease and 1-month and 12-month intervals. For patient 1, focal ERG amplitudes remained abnormal at each interval. For patient 2, focal ERG amplitudes remained abnormal beside the disc but returned to normal in the macular. | Not addressed |

**Table E7 Results of case series studies of focal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Sandberg 1998 | On average 8.8% of patients had a choroidal neovascular membrane develop each year. Of the fellow eyes that converted, the interval to have a choroidal neovascular membrane develop was inversely related to focal ERG implicit time. | A slower focal ERG implicit time may be a sign of early stage choroidal neovascular membrane development. The clinical management implications are that patients at high risk of having a potentially treatable form of AMD can be monitored and treated before AMD develops. |
| Tanikawa 1999 | In the affected eyes of patients with idiopathic epimacular membrane, focal ERG amplitudes of the a and b waves were significantly reduced and the implicit times were significantly prolonged compared with the patients' unaffected eyes.<br>*Amplitude:* affected eyes vs fellow eyes (μV)<br>a waves, mean (SD): 0.87(0.06) vs 1.29 (0.07), p<0.001<br>b waves, mean (SD): 1.71(0.15) vs 2.86 (0.16), p<0.001<br>*Implicit time:* affected eyes vs fellow eyes, ms<br>a waves, mean (SD): 21.7(0.5) vs 19.4 (0.2), p<0.001<br>b waves, mean (SD): 45.4 (0.8) vs 42.5 (0.6), p=0.004 | Not addressed |
| Weiner 1997 | *Focal ERG amplitude (μV)*<br>NPDR without CSMO had significantly lower mean amplitude compared with normal eyes: NPDR vs normal – mean (SD): 0.19(0.10) vs 0.37(0.14), p=0.0001.<br>NPDR with CSMO had significantly lower mean amplitude compared with normal eyes: NPDR–CSMO vs normal – mean(SD): 0.15 (0.11) vs 37(0.14), p=0.0001.<br>NPDR with CSMO eyes had significantly lower mean amplitude compared with eyes without CSMO: NPDR–CSMO vs NPRD mean(SD): 0.19(0.1) vs 0.15(0.11), p=0.01.<br>*Focal ERG implicit times (ms)*<br>NPDR without CSMO had similar mean implicit time compared with normal eyes: NPDR vs normal – mean(SD): 34.27 (2.13) vs 34.27 (1.69).<br>NPDR with CSMO did not have significantly longer mean implicit time compared with normal eyes: NPDR–CSMO vs normal – mean (SD): 36.76 (3.59) vs 34.27 (1.69).<br>NPDR with CSMO eyes had significantly longer implicit times compared with eyes without CSMO: NPDR–CSMO vs NPRD – mean(SD): 36.76 (2.13) vs 34.27 (3.59), p=0.0001. | Not addressed |

**Table F1 Descriptive characteristics of studies examining multifocal ERG compared with another test**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | 'Gold standard' used to diagnose the disease | Test compared with multifocal ERG |
| Kretschmann 1998b | Germany, dates not stated | 51 patients + 30 controls | Stargardt's macular dystrophy | Median 29 *(?), 7–68 | 27:24 | Diagnosis was based on history, symmetric bilateral involvement, the typical alterations of the pigment epithelium layer, assessed by fluorescein angiography if necessary, by visual field and Ganzfeld ERG according to the ISCEV standard. | Ganzfeld ERG |

**?=Data not provided.**

**Table F2 Validity of studies comparing multifocal ERG with another test**

| First author and year of publication | Validity of study methods | | | | |
|---|---|---|---|---|---|
| | Appropriate spectrum of study subjects | Masked assessment of study and reference test results | All study subjects tested with both study and reference test | Study test measured independently of clinical information | Reference test measured prior to start of intervention |
| Kretschmann 1998b | Patients already known to have disease | No | No | *? | ? |

*? = Data not provided.

**Table F3 Results of studies comparing multifocal ERG with another test**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Kretschmann 1998b | *Multifocal ERG vs Ganzfeld ERG*<br>17%, 14 eyes, had subnormal in multifocal ERG (0–30°) as well as pathological Ganzfeld ERG.<br>12%, 10 eyes, had subnormal multifocal ERG (0–30°) but had normal Ganzfeld ERG.<br>*Multifocal ERG in SMD patients vs normal controls*<br>Peak amplitude (nV/deg$^2$):<br>Compared with normal controls – ring 1 and ring 2 up to 7° eccentricity, median response density of SMD patients was significantly lower. For ring 3, ring 4 and ring 5, SMD patients had lower results but 5–95% confidence intervals overlapped with normal results.<br>*Peak implicit time (ms)*<br>Compared with normal controls – median SMD patients' times were not significantly longer implicit times.<br>45 of 51 (88%) of SMD patients had photopic Ganzfeld ERG. Pathological responses to white flash stimulation were found in 8 cases (17.8%). 8/8 showed a delay in b-wave implicit time, 3/8 showed reduced amplitudes. Patients who had abnormal Ganzfeld ERG had abnormal multifocal ERG up to 30° eccentricity. | Management of patients not discussed but authors state that multifocal ERG can be useful for the diagnosis and differential diagnosis of SMD. |

**Table F4 Descriptive characteristics of case control studies of multifocal ERG**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic Test |
| Chan 1998 | Hong Kong, dates not stated | 22 patients + 44 controls | Retinitis pigmentosa (RP) n=22<br>Normal controls (C) n=44 | RP 43.2 *(?), 20–67<br>C: 38.9 (?), 21–67 | RP 15:7<br>C 15:29 | ? | RP: ?<br>C: passed preliminary tests (visual acuity, colour vision, tonometry, ophthalmoscopy) |
| Chan 1999 | Hong Kong | 12 patients + 15 controls | Glaucoma (G) n=12<br>Normal controls (C) n=15 | G 48.3 (?), 28–64<br>C 49.3 (?), 26–67 | G 8:4<br>C 6:9 | ? | G: glaucomatous visual field losses on Humphrey visual analyser – central 30–2 threshold 2 program<br>C: passed an eye examination to exclude the presence of glaucoma (details provided) and other ocular pathologies |
| Fortune 1999 | USA, dates not stated | 8 patients + 8 controls | Non-proliferative diabetic retinopathy (NPDR) n=8, 16 eyes<br>Diabetic with no retinopathy (C) n=8, 16 eyes | NPDR 46 (11), 30–58<br>C 50 (8), 32–57 | NPDR: 3:5<br>C: 4:4 | *Exclusion*: visible media opacity or other history of ocular disease or surgery | Overall retinopathy grade was determined according to Early Treatment Diabetic Retinopathy Study |
| Hasegawa 2000 | Japan, dates not stated | 14 patients + 26 controls | Primary open-angle glaucoma (POAG) n=14, 26 eyes<br>Normal controls (C) n=14 | POAG 47.2 (10.2), ?<br>C 46.1 (13.5), ? | ? | ? | ? |
| Hood 2000 | USA, dates not stated | 23 patients + 13 controls | Open angle glaucoma (OAG) n=18<br>Suspected glaucoma (SG) n=4<br>Ischaemic optic neuropathy (ION) n=1<br>Normal controls (C) n=13 | OAG 55.8 (13.0), 29–72<br>SG ? (?), 46–67<br>ION 61<br>C 52.7 (10.9), 35–72 | ? | ? | ? |

*? = Data not provided.

**Table F4 Descriptive characteristics of case control studies of multifocal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Kretschmann 1998a | Germany, dates not stated | 30 patients<br>+ 30 controls | Early Stargardt's macular dystrophy (SMD) n=5<br>Advanced SMD n=5<br>Age-related macular degeneration (AMD) n=5<br>Cone dystrophy (CD) n=5<br>Central retinal vein occlusion (CRVO) n=5<br>Autosomal dominant optic atrophy (ADOA) n=5 | Early SMD *? (?), 12–34<br>Advanced SMD ? (?), 27–54<br>AMD ? (?), 54–66<br>CD ? (?), 11–40<br>CRVO ? (?), 34–72<br>ADOA ? (?), 13–33 | Early SMD 4:1<br>Advanced SMD 2:3<br>AMD 3:2<br>CD 5:0<br>CRVO 3:2<br>ADOA 3:2 | ? | Diagnosis of SMD was based on history, symmetrical bilateral involvement, the typical alterations of the pigment epithelium layer (assessed by fluorescein angiography if necessary), by visual field, and by Ganzfeld ERG according to the ISCEV standard. |
| Marmor 1999 | USA, dates not stated | 6 patients<br>+ 5 controls | Central serous chorioretinopathy (CSC)<br>Normal controls (C) | CSC ? (?), 34–52<br>C ? (?), 24–73 | CSC 4:2<br>C 3:2 | CSC: Central macular serous detachment<br>C: no known retinal disease | |
| Palmowski 1997 | USA, dates not stated | 16 patients<br>+ 19 controls | Non-proliferative diabetic retinopathy (NPDR) n=8, 14 eyes<br>Diabetic with no retinopathy (D) n=8, 14 eyes<br>Normal controls (C) n=19, 33 eyes | All patients 53 (?), 32–74<br>C 40 (?), 29–60 | All patients 11:5<br>C 6:13 | ? | ? |

*? = Data not provided.

**Table F4 Descriptive characteristics of case control studies of multifocal ERG (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic test |
| Piao 2000 | Japan, dates not stated | 8 patients + 20 controls | Occult Macular Dystrophy (OMD) n=8*<br>*Note:* 5 patients were reported in Miyake 1996 )<br>Normal controls (C) n=20 | OMD 52.9 *(?), 43–66<br>C 53.3 (?), 38–69 | OMD 5:3<br>C ? | ? | OMD: bilateral involvement, normal ophthalmoscopic findings, normal fluorescein angiography, decreased visual acuity, normal full-field ERG for both rod and cone components, decreased focal macular cone ERGs.<br>C: had normal visual acuity, normal colour vision, normal full-field ERGs. |
| Seeliger 1998 | Germany, dates not stated | 38 patients + 30 controls | Retinitis pigmentosa of various forms (RP) n=38<br>Normal controls (C) n=30 | RP 36, 9–61<br>C median 33, 21–55 | ? | ? | ? |

*? = Data not provided.

**Table F5 Results of case control studies of multifocal ERG**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Chan 1998 | Compared with normal controls, photopic condition RP patients had significantly lower mean macular and pericentral response densities (nV/sq unit) at all eccentricities (0–30°). Some patients had relatively better ERG responses in the macula than in the pericentral region.<br>When subjects were grouped by age (below/above 50), only macular response function was significantly reduced in older age group.<br>Compared with normal controls, scotopic condition RP patients had significantly lowered mean macular and pericentral response densities (nV/sq unit).<br>When subjects were grouped by age (below/above 50), macular response function was not affected by age. Age did have a significant effect on pericentral retina responses. | Authors state that MERG can be used to assess the different retinal regions in more detail than the conventional flash ERG, allowing more careful monitoring of patients. Effect on patients' outcomes was not discussed. |
| Chan 1999 | Compared with normal controls, first-order kernel patients with G had significantly lower mean response densities on both a-wave and b-wave across 5 rings.<br>Compared with normal controls, second-order kernel patients with G had significantly lower mean response densities on both a-wave and b-wave across 5 rings. | Not discussed |
| Fortune 1999 | *Implicit times*<br>In diabetic patients with retinopathy (NPDR), implicit time responses from retinal sites with lesions were markedly delayed (up to 7 ms from normal). Implicit time responses from adjacent retinal sites showed smaller delays (2–5 ms).<br>In diabetic patients without retinopathy (C), implicit times were significantly delayed.<br>*Amplitude*<br>NPDR eyes: amplitude responses showed no consistent relationship to fundus abnormalities.<br>C eyes: amplitude responses were typically normal. | Not addressed other than to state that the multifocal ERG changes may provide a very early indicator of local retinal dysfunction in diabetes. |

**Table F5 Results of case control studies of multifocal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Hasegawa 2000 | Waveforms were compared: normal eyes versus POAG eyes which were grouped as POAG(A) eyes with relatively slight damage, POAG(B) eyes with severe damage.<br>*Implicit time: 1st negative trough, mean(SD) ms*<br>POAG (severe damage) was not different from POAG (slight damage): 15.5(1.0) vs 15.5(1.3).<br>POAG (severe damage) was significantly slower than C (normal):<br>15.5(1.0) vs 14.9(1.1), p<0.005.<br>POAG (slight damage) was significantly longer than normal (C): 15.5(1.3) vs 14.9(1.1), p<0.01).<br>*Implicit time: 1st positive peak, mean(SD) ms*<br>POAG (severe damage) was significantly smaller than for POAG (slight damage): 29.1(1.4) vs 28.8(1.5), p<0.05.<br>POAG (severe damage) was significantly slower than C (normal): 29.1(1.4) vs 27.6(1.2), p<0.001.<br>POAG (slight damage) was significantly longer than normal (C): 28.8(1.5) vs 41.4(1.1), p<0.001.<br>*Implicit time: 2nd negative trough, mean(SD) ms*<br>POAG (severe damage) was significantly smaller than for POAG (slight damage): 43.5(1.7) vs 42.6(1.7), p<0.05.<br>POAG (severe damage) was significantly slower than C (normal): 43.5(1.7) vs 41.4(1.1), p<0.001.<br>POAG (slight damage) was significantly longer than normal (C): 42.6(1.7) vs 41.4(1.1), p<0.001.<br>*Amplitude*: no significant differences in mean amplitudes between POAG (severe damage) and POAG (slight damage) and either group and normal controls. | Not addressed |
| Hood 2000 | *POAG patients*: mean ratio (amplitude at 8 ms after peak response to amplitude at peak) was significantly lower than control ratio.<br>Only 6 of 18 patients had ratios which fell outside normal range.<br>*All patients*: correlations between local field loss and multifocal ratio measure was poor. | Not discussed |

**Table F5 Results of case control studies of multifocal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Kretschmann 1998a | Foveal ERG compared with multifocal ERG.<br>Study presents results of multifocal ERGs at 5 eccentricities (ring1 to ring 5) for each of 6 disease groups compared with normal controls.<br>Ring 1 (0–2$^{o}$): Diminished mean amplitude in all diseases except ADOA; diminished mean implicit time in AMD, CRVO, ADOA.<br>Ring 2 (1.8–7$^{o}$): Diminished mean amplitude in all diseases except ADOA; diminished mean implicit time in all diseases except early SMD.<br>Ring 3 (5–13$^{o}$): Diminished mean amplitude in all diseases except ADOA; diminished mean implicit time in all diseases except early SMD, ADOA.<br>Ring 4 (11–22$^{o}$): Diminished mean amplitude in all diseases except ADOA; diminished mean implicit time in all diseases except early SMD, ADOA.<br>Ring 5 (17–20.5$^{o}$): Diminished mean amplitude in advanced AMD, CD, CRVO; diminished mean implicit time in all diseases except early SMD, ADOA. | Multifocal ERG not diagnostic in patients with autosomal dominant optic atrophy.<br>Effect on clinical management of patients not addressed in the study. |
| Marmor 1999 | Results presented graphically only.<br>All central serous chorioretinopathy (CSC) patients' eyes had depressed multifocal ERG responses compared with normal eyes (C). Responses of fellow eyes of CSC patients were depressed relative to periphery.<br>*Times-to-peak*: delayed response everywhere in CSC eye and slightly delayed in fellow-eyes.<br>*Amplitudes*: severely depressed in the central retina of affected eyes, reduced beyond area of detachment in affected eye and across entire posterior pole in fellow eye. | Not discussed |
| Palmowski 1997 | *Amplitudes:* In diabetic patients with retinopathy (NPDR) overall amplitudes were significantly reduced compared with controls (C): mean(SD)<br>In diabetic patients without retinopathy (D), only amplitudes of the second-order component were reduced.<br>*Implicit times:* NPDR had increased overall implicit times compared with C.<br>D patients' implicit times did not differ significantly from C. | Not addressed other than to state that the multifocal ERG can detect early impairment of retinal function in patients before retinopathy becomes clinically apparent. |

**Table F5 Results of case control studies of multifocal ERG (continued)**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Piao 2000 | Multifocal ERG showed severely depressed responses from the central retina but relatively well-preserved responses in the peripheral retina.<br>*Implicit times*<br>5 of 8 patients had abnormally delayed implicit times at the most peripheral ring (20–30° ).<br>4 patients had implicit times within normal range for the central ring.<br>OMD group implicit times were significantly delayed at all (5) concentric rings compared with controls.<br>*Response density (response amplitude divided by retinal area)*<br>All 8 patients had severely reduced response densities, especially in rings 1 and 2.<br>2 of 8 patients had 'gray zone' responses for ring 3.<br>4 patients had 'gray zone' responses for ring 4.<br>6 of 8 patients had abnormal responses for ring 5.<br>*Amplitude*<br>2 patients had normal amplitude at rings 4 and 5 but had delayed implicit times. | Not discussed |
| Seeliger 1998 | For normal controls, high implicit times were found at the blind spot, upper and lower borders of stimulated field and macula. Low implicit time responses were present in area encircling macula and most prominent in temporal region.<br>For retinitis pigmentosa, implicit times were unchanged in central region but prolonged in peripheral regions. | Not discussed |

# Appendix G Multifocal VEP tables

**Table G1 Descriptive characteristics of studies examining multifocal VEP compared with another test**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with multifocal VEP |
| Wang 1988 | China, dates not stated | 30 patients | Tumour in the sella turcica, possibly causing visual field defects | *? | ? | Tumour documented by computed tomography (CT) | Tumour: CT | Goldman perimeter examination to assess visual field defects |

*? = Data not provided.

**Table G2 Validity of studies comparing multifocal VEP with another test**

| First author and year of publication | Validity of study methods | | | | |
|---|---|---|---|---|---|
| | Appropriate spectrum of study subjects | Masked assessment of study and reference test results | All study subjects tested with both study and reference test | Study test measured independently of clinical information | Reference test measured prior to start of intervention |
| Wang 1988 | Recruitment not described | *? | Yes | No | ? |

*? = Data not provided.

**Table G3 Results of studies comparing multifocal ERG with another test**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Wang 1988 | 26/30 patients had field defects recorded on the Goldman perimeter examination (their VEP results are not explicitly stated).<br>23/30 patients had abnormal (crossed asymmetry) or absent VEP mapping; 2 had signifcantly increased P100 latency.<br>4/30 had normal Goldman perimeter examination; 2 of the 4 had abnormal VEP topography. | Not explicitly stated; suggested that VEP has advantages over Goldman perimeter to examine early compression of visual pathway before visual field defects are apparent by Goldman perimeter test. |

**Table G4 Descriptive characteristics of case control study of multifocal VEP**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | Selection criteria | Diagnostic test |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | | |
| Graham 2000 | Australia, dates not stated | 101 patients<br>+ 34 controls | Glaucoma (G) n=70<br>At risk for glaucoma (RG) n=31<br>Normal controls (C) n=24 | G 60.0 (14.6), 15–89<br>RG 57.8 (10.8), 34–81<br>C 55.6 (14.2), 16–79 | G 34:36<br>RG 18:13<br>C 12:12 | G, RG – *Inclusion*: corrected visual acuity of 6/12 or better, pupils at least 2.5 mm without dilation.<br>*Exclusion*: diabetes, previous cataract surgery, any other ocular disorders.<br>Controls – *? | G: confirmed visual-field defect on Humphrey 24–2 field tests and a glaucomatous optic disc present on stereo-disc photography, with or without an intraocular pressure >21 mmHg measured on the applanation tonometer.<br>RG: normal Humphrey glaucoma hemifield test, definite structural change or an asymmetry in the neuroretinal rim without visual-field defects that represent preperimetric glaucoma, or presence of 'long-standing' ocular hypertension plus family history of glaucoma.<br>C: normal intraocular pressure and ophthalmoscopy and no family history of glaucoma, normal Humphrey 24–2 field-test. |

*? = Data not provided.

**Table G5 Results of case control studies of multifocal VEP**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Graham 2000 | Intereye asymmetry was calculated by dividing the difference in amplitude between the left and right eyes by their sum.<br>Response asymmetry coefficient (RAC) values of glaucoma and high risk for glaucoma subjects were compared with the mean RAC values of control subjects from all 60 locations of the visual field. Three adjacent points significantly different ($p < 0.05$) from control RAC values were considered as possibly representative of a scotoma.<br>Glaucoma: 69/70 had scotomas (sensitivity 98.6%).<br>Risk for glaucoma: 10/31 had scotomas.<br>Controls: 1/24 false-positive (specificity: 95.8%). | All patients at risk for glaucoma will be followed to determine if the VEP changes precede subsequent field loss. |

**Table H1 Descriptive characteristics of studies examining STR compared with another test**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with multifocal VEP |
| | | | | | | | | |
| Aylward 1989 | Australia, dates not stated | 50 patients + 10 controls | Diabetes (D) – insulin-dependent with various degrees of diabetic retinopathy n=50 | 37 *(?), 15–55 | 22:28 | *Inclusion*: age 15–55 with insulin-dependent diabetes mellitus for >10 years; any grade of retinopathy; no ocular or systemic disease; clear media. *Exclusion*: had received photocoagula-tion therapy to both eyes. | Diabetic retinopathy was assessed using colour fundus photographs for grade of retinopathy and with fluorescein angiograms for leakage, and capillary non-perfusion. | 1) pattern electroretinogram, 2) scotopic b-wave 3)oscillatory potential. |

**Table H1 Descriptive characteristics of studies examining STR compared with another test (continued)**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | 'Gold standard' used to diagnose the disease | Test compared with multifocal VEP |
| Graham 1991 | Australia, date not stated | 127 patients | Various disease groups: Retinitis pigmentosa (n=52 eyes); Cone dystrophy (n=24 eyes); Diabetes (n=36 eyes); CRVOs (n=4 eyes); Glaucoma etc (n=24 eyes); optic nerve disease (n=34 eyes); macular disorders (n=14 eyes); Stargardt's etc (n=16 eyes); Mixed (n=20 eyes) | ? | ? | ? | ? | Absolute psychophysical threshold |

*? = Data not provided.

**Table H2 Validity of studies comparing STR with another test**

| First author and year of publication | Validity of study methods | | | | |
|---|---|---|---|---|---|
| | Appropriate spectrum of study subjects | Masked assessment of study and reference test results | All study subjects tested with both study and reference test | Study test measured independently of clinical information | Reference test measured prior to start of intervention |
| Aylward 1989 | Patients already known to have disease | No | Yes | No | Yes |
| Graham 1991 | Patients already known to have disease | No | *? | No | No |

*? = Data not provided.

**Table H3 Results of studies comparing STR with another test**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Aylward 1989 | Test performance on measures of retinopathy was only assessed using simple correlations, multivariate regression and ANOVA. Parameter with strongest correlation is presented.<br>*Amplitude*: Correlations between grade (severity), fluorescein leakage and capillary non-perfusion and test parameters:<br>• PERG (P1) – significant for grade (-0.51), leakage (-0.36), non-perfusion (-0.38)<br>• STR (Smax) – significant for grade (0.63), leakage (0.61) non-perfusion (0.55)<br>• scotopic b-wave: – not significant for any measure<br>• OP (OP3 amplitude) – significant for grade (-0.71), leakage (-0.61), non-perfusion (-0.64).<br>Implicit time/latency: Correlation between grade (severity), fluorescein leakage and capillary non-perfusion of retinopathy and test parameters:<br>• PERG – not significant for any measure of retinopathy<br>• STR (Smin) – significant for -grade (0.64), leakage (0.62) non-perfusion (0.59)<br>• scotopic b-wave – only significant for non-perfusion: CR100 (0.36)<br>OP (OP1 implicit time) – grade (0.66), leakage (0.51) non-perfusion (0.60). | Not discussed |
| Graham 1991 | In patients with recordable STR, projected thresholds (amplitude versus intensity function) were directly correlated with subjective thresholds (r=0.59).<br>*Note*: Authors state that the purpose was not to report various changes of STR seen in individual diseases. | Not addressed except to state that the absolute psychophysical threshold is always recordable while the STR is not recordable in some diseases. |

**Table H4** **Descriptive characteristics of case control study of STR**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | Selection criteria | Diagnostic tests used to diagnose presence or absence of disease |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | | |
| Korth 1994 | Germany, dates not stated | 30 patients + 35 controls | Glaucoma (G) n=30<br>Normal controls (C) n=35 | G 58.1 (16.4), *?<br>C 50.3 (14.3), ? | ? | ? | G: 10P>21 mmHg (Goldmann applanation tonometry), visual field defects (computerised static projection perimeter) and optic disc damage (colour optic-disc photographs).<br>C: thorough ophthalmological examination. |
| Miyake 1994 | Japan, dates not stated | 6 patients + 4 controls | Congenital stationary night blindness, (CSNB) n=6; complete (C-CSNB) n=2; incomplete I-CSNB n=4<br>C normal (n=4) | C-CSNB 38 (?),18–58<br>I-CSNB 29 (?), 27–32<br>C ?, 28–50 | C-CSNB 1:1<br>I-CSNB 4:0 | ? | CSNB: Psychophysical dark adaptometry with Goldmann-Weekers adaptometer taken in the superior retina and white test target presented 11° below fixation. |

*? = Data not provided.

**Table H5 Results of case control studies of STR**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Korth 1994 | Only results of STR in glaucoma patients (G) versus control (C) patients are presented:<br>*Amplitudes (µV)*<br>STR amplitudes of G were significantly reduced compared with C: G vs C, mean(SD): 5.3(1.3) vs 6.0(1.5), p=0.046.<br>*Peak times (ms)*<br>STR peak times of G were not significantly different from those of C: G vs C, mean(SD): 196.8(23.5) vs 186.4(20.9), p=0.08. | Authors state that the STR is of little use in the diagnosis of glaucoma. |
| Miyake 1994 | C-CSNB – STR not recordable.<br>I-CSNB – STR clearly recorded. Compared with normal controls, the stimulus threshold was slightly elevated and the peak response was extremely delayed. | Not addressed as study designed to illustrate differences in complete and incomplete CSNB. |

**Table I1 Descriptive characteristics of case control study of IRF**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | Selection criteria | Diagnostic tests used to diagnose presence or absence of disease |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | | |
| Massof 1984 | USA, dates not stated | 18 patients<br>+ 15 controls | Retinitis pigmentosa (RP) n=18<br>Normal controls (C) n=15 | RP 35 (14), 13–61<br>C median age 30, 19–50 | RP 7:11<br>C *? | RP – patients were selected from a larger group participating in a long-term study based on the recordability of the ERG.<br>C – ? | RP – ?<br>C – 'ophthalmologically normal' (not defined) |
| Wu 1985 | USA, dates not stated | 106 patients<br>+ 15 controls | Retinitis pigmentosa (RP) n=15<br>Cone dystrophy (CD) n=6<br>Macular degeneration (MD) n=6<br>Fundus flavimaculatus (FF) n=10<br>Other retinal diseases n=69<br>Normal controls (C) n=15 | ? | ? | ? | ? |

*? = Data not provided.

**Table I2 Results of case control studies of IRF**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Massof (1984) | B-wave amplitude of the response as function of log stimulus luminance was fitted by non-linear regression with the Naka-Rushton equation:<br>Maximum response ($R_{max}$): reduced in RP vs C, implying response compression.<br>Half-saturation constant (K): elevated by 0.76 log unit in RP vs C, implying small losses in retinal sensitivity. | Not discussed |
| Wu 1985 | *RP* – $R_{max}$: abnormal in 15/15 patients<br>K: abnormal in 14/15 patients<br>Slope (n): abnormal in 6/15 patients.<br>*CD* – $R_{max}$ abnormal in 1/6<br>K abnormal in 1/6<br>n abnormal in 2/6.<br>*MD* – $R_{max}$ abnormal in 0/6<br>K abnormal in some (number not given)<br>n abnormal in 0/6.<br>*FF* – $R_{max}$ abnormal in 1/10<br>K abnormal in 1/10<br>n abnormal in 0/10.<br>*Other retinal diseases*: results not stated. | Not discussed |

**Table I3 Descriptive characteristics of case series of IRF**

| First author and year of publication | Setting, dates of enrolment | Spectrum of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample size | Disease | Mean age (years) (SD), range | Sex ratio (M:F) | Selection criteria | Diagnostic tests used to diagnose presence or absence of disease |
| Breton 1989 | USA, dates not stated | 24 patients | Central retinal vein occlusion (CRVO) | *? | ? | Patients with CRVO. Excluded were patients with ocular disease in both eyes. | Clinical examination |

*? = Data not provided.

**Table I4 Results of case control studies of IRF**

| First author and year of publication | Results | Effect of results on patient management |
|---|---|---|
| Breton 1989 | 10/21 patients had neovascular complications (rubeosis) or were at clinical risk of developing them.<br>Discriminant analysis of ERG parameters found the b-wave to a-wave ratio had the highest predictive value for the development of rubeosis, followed by K, b-wave implicit time and $R_{max}$ with a false-positive rate of 14%. | IRF components combined with other ERG components could be used as a prognostic tool for the development of rubeosis in CRVO, but the authors also used fluorescein angiography and clinical examination. |

# Abbreviations

| | |
|---|---|
| 1F | first harmonic at the stimulus |
| 2F | second harmonic at the stimulus |
| A | ambylopia |
| ACMO | aphakic cystoid macular oedema |
| ADOA | autosomal dominant optic atrophy |
| ARM | age-related maculopathy |
| ARMD | age-related macular disease/dystrophy/degeneration |
| BCVA | best corrected visual acuity |
| BD | Best's disease |
| BMD | Best's vitelliform macular dystrophy |
| BMES | Blue Mountain Eye Study |
| C | controls |
| CD | cone dystrophy |
| CI | confidence interval |
| CR | congenital retinoschisis |
| CRD | congenital retinoschisis with degeneration |
| CRM | congenital rod monochromacy |
| CRVO | central retinal vein occlusion |
| CSC | central serous chorioretinopathy |
| CSMO | clinically significant macular oedema |
| CSNB | congenital stationary night blindness |
| C-CSNB | complete CSNB |
| CT | computed tomography |
| D | diabetic |
| DALY | disability-adjusted life year |
| ERG | electroretinography |
| F | female |
| FCD | familial cone dystrophy |
| FE | fellow eye |
| FF | fundus flavimaculatus |
| FMH | full-thickness macular holes |
| G | glaucoma |
| IDDM | insulin-dependent diabetes mellitus |
| IDDM-er | IDDM with early retinopathy |
| I-CSNB | incomplete CSNB |
| ION | ischaemic optic neuropathy |
| IRF | intensity response function |
| ISCEV | International Society of Clinical Electrophysiology of Vision |
| LMH | lamella macular holes |
| LR | likelihood ratio |
| LR- | negative likelihood ratio |
| LR+ | positive likelihood ratio |
| M | male |
| MBS | Medicare Benefits Schedule |
| MD | macular disease |
| MERG | multifocal ERG |
| MH | macular holes |

| | |
|---|---|
| mmHg | millimetre of mercury |
| M/P | macular paramacular ratio |
| ms | milliseconds |
| MCS | macular chorioretinal scars |
| MSAC | Medical Services Advisory Committee |
| n | number |
| NE-AMD | non-exudative age-related macular disease |
| NHMRC | National Health and Medical Research Council |
| NIDDM | non-insulin-dependent diabetes mellitus |
| NPDR | non-proliferative diabetic retinopathy |
| NPG | normal pressure glaucoma |
| OA | optic atrophy |
| OAG | open-angle glaucoma |
| OHT | ocular hypertension |
| OMD | occult macular disease/dystrophy/degeneration |
| OP | oscillatory potentials |
| P | patients |
| PD | pattern dystrophy |
| PERG | pattern electroretinography |
| PFS | psychophysical flicker sensitivity |
| POAG | primary open-angle glaucoma |
| RAC | response assymetry coefficient |
| RG | at risk for glaucoma |
| RI | retinal ischaemia |
| RP | retinitis pigmentosa |
| RPE | retinal pigment epithelium |
| SA | strabismic amblyopia |
| SD | standard deviation |
| SD | Stargardt's disease |
| SG | suspected glaucoma |
| SMD | Stargardt's macular dystrophy |
| STR | scotopic threshold response |
| UEVS | unexplained visual symptoms |
| VD | vitelliform degeneration |
| VED | visual electrodiagnosis |
| VEP | visual evoked potential |
| VER | visual evoked response |
| XLR | X-linked congenital retinoschisis |

# References


Arden G.B., Vaegan and Hogg C.R. 1982, 'Clinical and experimental evidence that the pattern electroretinogram (PERG) is generated in more proximal retinal layers than the focal electroretinogram (FERG)', *Annals of the New York Academy of Sciences*, 388**:** 580–607.

Attebo K., Mitchell P. and Smith W. 1996, 'Visual acuity and the causes of visual loss in Australia: The Blue Mountains Eye Study', *Ophthalmology*, 103**:** 357–64.

Attebo K., Mitchell P., Cumming R. et al 1998, 'Prevalence and causes of amblyopia in an adult population', *Ophthalmology*, 105**:** 154–9.

Bankes J.L. 1967, 'The foveal electroretinogram', *Transactions of the Ophthalmological Societies of the United Kingdom*, 87**:** 249–62.

Birch D.G. and Fish G.E. 1988, 'Focal cone electroretinograms: ageing and macular disease', *Documenta Ophthalmologica*, 69**:** 211–20.

Carr R.E. and Siegel I.M. 1990, *Electrodiagnostic testing of the visual system: a clinical guide*, F.A. Davis Company, Philadelphia.

Chan H.L. and Brown B. 1998, 'Investigation of retinitis pigmentosa using the multifocal electroretinogram', *Ophthalmic & Physiological Optics*, 18**:** 335–50.

Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests: Recommended Methods 1996, Available from: http://www.cochrane.org.au.

Finger J. and Stasche M. 2000, *Basics and general description of generating the multifocal ERG with RETIscan*, Roland Consult, Wiesbaden.

Graham S.L. and Vaegan 1991, 'High correlation between absolute psychophysical threshold and the scotopic threshold response to the same stimulus', *British Journal of Ophthalmology*, 75**:** 603–7.

Jaeschke R., Guyatt G.H. and Sackett D.L. 1994, '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**:** 389–91.

Korth M. and Koca M. 1993, 'Clinical electrophysiology relevant for early glaucoma diagnosis', *Current Opinion in Ophthalmology*, 4**:** 22–8.

Kretschmann U., Seeliger M., Ruether K. et al 1998, 'Spatial cone activity distribution in diseases of the posterior pole determined by multifocal electroretinography', *Vision Research*, 38**:** 3817–28.

Lijmer J.G., Mol B.W., Heisterkamp S. et al 1999, 'Empirical evidence of design-related bias in studies of diagnostic tests', *Journal of the American Medical Association*, 282**:** 1061–6.

Mathers C., Vos T. and Stevenson C. 1999, 'The burden of disease and injury in Australia', *Australian Institute of Health and Welfare*, Canberra.

Mitchell P., Smith W., Attebo K. et al 1995, 'Prevalence of age-related maculopathy in Australia: The Blue Mountains Eye Study', *Ophthalmology*, 102**:** 1450–60.

Mitchell P., Smith W., Attebo K. et al 1996, 'Prevalence of open-angle glaucoma in Australia: The Blue Mountains Eye Study', *Ophthalmology*, 103**:** 1661–9.

Mitchell P., Hayes P. and Wang J.J. 1997, 'Visual impairment in nursing home residents: The Blue Mountains Eye Study', *Medical Journal of Australia*, 166**:** 73–6.

Mitchell P., Smith W., Wang J.J. et al 1998, 'Prevalence of diabetic retinopathy in an older community: The Blue Mountains Eye Study', *Ophthalmology* 105**:** 406–11.

National Health Service Research and Development Centre for Evidence-Based Medicine 1999, *Levels of evidence and grades of recommendations*, available from: http://cebm.jr2.ox.ac.uk/docs/levels.html.

Roecker E.B., Pulos E., Bresnick G.H. et al 1992, 'Characterization of the electroretinographic scotopic B-wave amplitude in diabetic and normal subjects', *Investigative Ophthalmolology and Visual Science*, 33**:** 1575–83.

Sackett D.L., Strauss S.E., Richardson W.S. et al 2000, *Evidence-Based Medicine: How to Practice and Teach EBM*, Churchill Livingstone, Edinburgh.

Sandberg M.A., Berson E.L. and Ariel M. 1977, 'Visually evoked response testing with a stimulator-ophthalmoscope. Macular scars, hereditary macular degenerations, and retinitis pigmentosa', *Archives of Ophthalmology*, 95**:** 1805–8.

Seiple W.H., Siegel I.M., Carr R.E. et al 1986, 'Evaluating macular function using the focal ERG', *Investigative Ophthalmology & Visual Science*, 27**:** 1123–30.

Vaegan, Billson F., Kemp S. et al 1984, 'Macular electroretinograms: their accuracy, specificity and implementation for clinical use', *Australian Journal of Ophthalmology*, 12**:** 359–72.