Optical Coherence Tomography

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

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

The advice in this report was noted by the Minister for Health and Ageing on 8 December 2008.

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Optical coherence tomography (OCT) is a non-contact, non-invasive high resolution imaging technique that provides cross-sectional tomographic images of the ocular microstructure through the thickness of the retina (McNaught 2007). It is analogous to ultrasound, measuring the back-reflection intensity of infrared light rather than sound. An OCT image is a two-dimensional data set that represents differences in optical backscattering or back-reflection in a cross-sectional plane. For the purpose of visualisation, OCT data are acquired by computer and displayed as a two-dimensional grey scale or false colour image. OCT images can be analysed qualitatively or quantitatively to detect retinal abnormalities. Time domain OCT instruments (Stratus OCT) have an axial resolution of 10 μm and a transverse resolution of 20 μm. Spectral/Fourier domain OCT is capable of higher resolutions of 5–7 μm (axial) and 10–20 μm (transverse). Reconstruction of two-dimensional data into a three-dimensional image is possible with this version of the technology.

As a result of providing detailed information on the architectural morphology of the retina on the level of individual retinal layers, OCT has been proposed to detect early pathological changes, even before clinical signs or visual symptoms occur (Drexler et al. 2008). OCT has been proposed as a new 'gold standard' structural test for retinal abnormalities.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government 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 National Health and Medical Research Council (NHMRC) Clinical Trials Centre was engaged to conduct a systematic review of literature on OCT. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of OCT

This report focuses on an assessment of OCT performed for the diagnosis and monitoring of macular diseases and glaucoma. OCT is intended to be used for diagnosis and monitoring of retinal diseases and glaucoma in a specialist ophthalmological setting; it is not intended to be applied for screening purposes. The specific research questions to be addressed are:

- What is the value of optical coherence tomography compared with fundus fluorescein angiography or a clinical observation strategy in the diagnosis of macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy, tractional diseases of the macula, macular oedema and neovascularisation?

- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and fundus fluorescein angiography in the monitoring of patients with macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy and macular oedema?

- What is the additional value of optical coherence tomography over that of computerised perimetry and clinical examination in the diagnosis of glaucoma, in patients with risk factors for glaucoma with questionable clinical examination (glaucoma-like optic discs)?

- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and computerised perimetry in the monitoring of patients treated or with risk factors for glaucoma?

A systematic review was conducted to identify evidence to August 2008 to answer these questions.

Clinical need

Macular diseases

The term 'macular disease' incorporates a conglomerate of conditions affecting the macula—the specialised area of the retina dedicated to high resolution visual acuity, defined anatomically as the central part of the posterior retina containing xanthophyll pigment and two or more layers of ganglion cells (Arevalo et al. 2006). The macula has the densest concentration of photoreceptors in the retina and enables the perception of fine detail (for example, reading or recognising faces) (Do et al. 2007). According to World Health Organisation (WHO) data, macular diseases comprised two of the three most common causes of blindness in Australia in 2002. Age-related macular degeneration (AMD) was the cause of 50% of cases of blindness, while 17% of cases were attributable to diabetic retinopathy (Resnikoff et al. 2004). (The other major cause of blindness in Australia—glaucoma—is discussed below.) Among the sequelae of both conditions are macular oedema (abnormal capillary permeability, resulting in the leakage of fluid into retinal tissue, collecting around the macula) and neovascularisation (the proliferation of new fibrovascular tissue on, into or below the retina) (Weisz et al. 2006; Williams et al. 2004). Both are major causes of vision loss due to these conditions.

Glaucoma

Glaucoma is a group of ocular diseases characterised by optic neuropathy, leading to progressive loss of the visual field (Allingham et al. 2005). If not managed, progressive glaucomatous optic neuropathy can lead to total, irreversible blindness. Risk factors include raised intraocular pressure (IOP), age and family history. The presence of systemic diseases such as diabetes mellitus has also been implicated as a risk factor, but this remains unclear (Australian Institute of Health and Welfare 2008a; Gupta 2005;

Mitchell et al. 1996; Mitchell et al. 1997a). Glaucoma is the second most common cause of blindness in Australia (18%), behind AMD (Resnikoff et al. 2004).

Glaucoma may be classified as either primary (not related to any other underlying condition) or secondary (resulting from other ocular or systemic disease, trauma or use of certain drugs), and further by the anatomy of the anterior chamber of the eye (open angle or closed angle). Glaucoma 'suspects' are individuals with clinical findings or risk factors that indicate a high risk of developing glaucoma (American Academy of Ophthalmology 2005c). Such clinical findings may include optic disc or retinal nerve fibre layer (RNFL) appearance suspicious for glaucomatous damage; visual field suspicious for glaucomatous damage; or consistently elevated IOP in the presence of normal visual fields, RNFL and optic disc appearance (otherwise termed 'ocular hypertension'). (Risk factors have been described above.) In 'preperimetric' glaucoma, patients are diagnosed with glaucomatous structural change in the optic disc, prior to functional impairment.

Safety

OCT is considered a safe procedure. No studies were identified which reported any adverse events with the use of OCT.

Effectiveness: Macular diseases

The main potential role of OCT in the diagnosis of macular diseases is to identify additional cases of disease, leading to the initiation of treatment in patients who would not have been treated in the absence of OCT. Additionally, for non-tractional macular diseases, a negative OCT may result in the avoidance of fundus fluorescein angiography (FFA) in many patients.

Direct evidence

No direct evidence was found reporting the health outcomes of patients with macular diseases, assessed with and without OCT.

Linked evidence

In the absence of direct evidence for the effectiveness of OCT, evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes is presented to evaluate the effectiveness of OCT using a linked evidence approach.

Diagnostic accuracy

Due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of macular abnormalities could not be assessed.

OCT was found to have a similar diagnostic yield to FFA for the detection of macular oedema. A proportion of patients who are positive for the presence of macular oedema on OCT would be negative on FFA; conversely, a proportion of patients who are negative on OCT would be positive on FFA. In the absence of verification of 'true'

disease status in patients with discordant test results, the accuracy of these results is uncertain.

Evidence for the comparative yield of OCT and FFA for the detection of other non-tractional macular abnormalities was not found.

OCT appears to provide an incremental yield over prior clinical examination for the detection of tractional diseases (epiretinal membrane, macular holes, vitreomacular traction syndrome). In the absence of verification of 'true' disease status in the additional patients diagnosed by OCT, the accuracy of these results is uncertain.

Impact on patient management

No studies reported the impact of OCT on patient management for non-tractional macular diseases compared with FFA. However, as a replacement test in first line diagnosis, it is reasonable to assume that management will be changed by the OCT result in the same manner as by FFA.

A prospective study in patients with epiretinal membranes or vitreomacular traction reported that 17% (95% confidence interval [CI]: 10.2–26.1%) of patients had their management plan altered from observation (prior to OCT) to surgery (after the addition of OCT information). The extent to which the post-OCT management plan was consistent with the management patients actually received was not reported. There is some uncertainty regarding the magnitude of this effect due to biases inherent in this study.

Impact on health outcomes

In the absence of conclusions regarding the accuracy of discordant OCT and FFA findings for the presence or absence of macular oedema, or of the additional OCT-detected cases of tractional disease not detected on prior clinical examination, it is not possible to draw conclusions regarding the clinical significance or impact of OCT on health outcomes using a linked evidence approach.

Monitoring of treated or untreated patients

No randomised controlled trials (RCTs) were identified which compared a monitoring strategy involving OCT to a strategy involving FFA in patients with treated or untreated macular disease.

A single small, non-randomised, low quality Level III-2 study found that eyes with AMD treated with photodynamic therapy (PDT) experienced non-significant decrements in best corrected distance acuity at 12 months when monitored by FFA alone relative to monitoring with OCT plus FFA. The proportion of eyes with a loss of distance acuity of more than three lines was significantly higher in the group monitored with FFA alone. The precision of these estimates is limited by biases inherent in this study; therefore the effectiveness of OCT for monitoring of PDT in patients with AMD remains uncertain.

Other considerations

Expert opinion

The introduction of OCT examination of the macula has revolutionised diagnosis and management of retinal disease by ophthalmic specialists, through giving a qualitative and quantitative measure of cross-sectional anatomical change in the macula. OCT has become an essential part of the standard of care, and so apparent is its utility to specialists and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination.

Despite the widespread diffusion of this technology into retinal ophthalmology at every level, establishing the utility of OCT for macular disease in the MSAC report has been difficult due to a lack of published evidence in the literature with an appropriate comparator.

In the estimation of ophthalmologist members of the Advisory Panel, this report, therefore, fails to convey the high utility of OCT and the fundamental role that OCT now plays in the management of patients with macular disease. The ophthalmologist members of the Advisory Panel strongly support appropriate application of this essential technology, carried out and interpreted by specialist ophthalmologists to allow early detection and intervention in blinding macular diseases.

Effectiveness: Glaucoma

The main potential role of OCT in the diagnosis of glaucoma is to identify additional cases of disease, leading to the initiation of treatment in patients who would not have been treated in the absence of OCT (or initiating management earlier than would have occurred in the absence of OCT).

Direct evidence

No direct evidence was found reporting the health outcomes of patients with glaucoma, assessed with and without OCT.

Linked evidence

Diagnostic accuracy

Due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of glaucomatous damage could not be assessed.

Evidence for the incremental yield of OCT over clinical examination for the detection of glaucomatous damage was not found.

Impact on patient management

Evidence for the impact of OCT on patient management for patients with glaucoma was not found.

Impact on health outcomes

In the absence of evidence demonstrating the diagnostic accuracy of OCT and its impact on patient management, conclusions regarding the impact of OCT on health outcomes are not possible using a linked evidence approach.

Monitoring of treated or untreated patients

Evidence for the effectiveness of OCT in monitoring treated or untreated patients with glaucoma was not found.

Other considerations

Expert opinion

With many forms of innovative technology, particularly when it is rapidly evolving, published literature lags behind its clinical acceptance and uptake.

In glaucoma, structural optic nerve head changes precede detectable changes in visual field sensitivity (Weinreb et al. 2004). Changes in optic nerve head structure are now relied upon to determine diagnosis and to detect progression of glaucoma. Digital methods to measure and to record optic nerve head structural abnormality should be standard tools in the management of glaucoma in 2008. OCT is one such method.

As well as its role in the diagnosis and in the detection of progression, OCT contributes significantly to a patient's understanding of the disease, thereby greatly increasing the likelihood of patient acceptance of, adherence to and perseverance with lifelong therapy.

The ophthalmologist members of the Advisory Panel strongly support appropriate clinical application of digital technology as, increasingly, optic nerve head imaging will be critical to the effective management of patients with glaucoma.

Economic considerations

A modelled economic evaluation has not been undertaken. Instead, the financial implications of unconditional public funding for OCT were estimated in terms of potential total costs to the Medicare Benefits Scheme (MBS). These costs represent fees for Medicare benefit for the use of OCT only (not discounted for the 75–85% rate of MBS reimbursement to patients); they do not incorporate potential costs to government associated with treatment undertaken based on OCT findings, or potential cost offsets associated with discontinuation or modification of therapy due to OCT results.

Macular diseases

If OCT were reimbursed in Australia using the cost estimates supplied by the applicant, and assuming potential utilisation derived from epidemiological estimates, the total annual cost to the MBS of OCT for diagnosis of macular disease is estimated to be approximately $4.4 million; for monitoring of therapy, total annual cost to the MBS is estimated to range between $6.7 and $17.3 million. Therefore, the total annual cost of OCT for macular diseases is estimated to range between $11.1 and $21.7 million.

Using past utilisation of FFA as an indication of potential OCT utilisation, the total annual cost of OCT for macular diseases is estimated to range between $6.1 and $10.1 million. This is considered to represent a lower bound of potential costs.

Glaucoma

If OCT were reimbursed in Australia using the cost estimates supplied by the applicant, total annual cost to the MBS of OCT for diagnosis of glaucoma is estimated to be approximately $1.2 million; for monitoring of therapy, total annual cost to the MBS is estimated to range between $7.1 and $12.6 million. Therefore, the total annual cost of OCT for glaucoma is estimated to range between $8.3 and $13.8 million.

Conclusions

The use of OCT in the diagnosis and monitoring of macular disease and glaucoma is considered to be safe.

The accuracy of OCT for the diagnosis of macular diseases and glaucoma could not be established, and therefore the effectiveness of OCT in improving health outcomes could not be demonstrated using a linked evidence approach.

Evidence for the use of OCT in monitoring treated or untreated patients with macular disease or glaucoma was not found.

Advice

Optical Coherence Tomography (OCT) is a non-invasive ophthalmic imaging technique, which provides high-resolution cross-sectional images of the macula, which in turn allows identification of changes due to ophthalmologic conditions. OCT is intended to be used for diagnosis and monitoring of retinal diseases and glaucoma in a specialist ophthalmologic setting.

The MSAC finds that OCT is a safe procedure.

MSAC finds that there is currently insufficient evidence to recommend public funding for the assessment of macular disease or glaucoma.

— The Minister for Health and Ageing noted this advice on 8 December 2008 —

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of optical coherence tomography (OCT), which is a diagnostic technology for macular diseases and glaucoma. MSAC evaluates new and existing diagnostic technologies and procedures for which funding is sought under the Medicare Benefits Scheme (MBS) in terms of their 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 health and health administration.

This report summarises the assessment of current evidence for OCT for macular diseases and glaucoma.

Background

Optical coherence tomography

Optical coherence tomography (OCT) is a non-contact, non-invasive high resolution imaging technique that provides cross-sectional tomographic images of the ocular microstructure through the thickness of the retina (McNaught 2007). It is analogous to ultrasound, measuring the back-reflection intensity of infrared light rather than sound. OCT operates based on an optical technique known as Michelson low coherence interferometry, which measures the echo delay and intensity of back-reflected or backscattered infrared light (approximately 800 nm) from internal tissue microstructure (Chen et al. 2007). The OCT machine generates an imaging beam which is split into two, with one beam being projected into the retina and the other to a moving reference mirror. Interference from the beams reflected from the retina and the reference mirror generates a signal which is detected by an interferometer. These signals correspond to optical interfaces within the retina. Scans of the retina at a single point (A-scans) are repeated at neighbouring points to construct a scan across the retina (B-scans) (McNaught 2007).

An OCT image is a two-dimensional data set that represents differences in optical backscattering or back-reflection in a cross-sectional plane. For the purpose of visualisation, OCT data are acquired by computer and displayed as a two-dimensional grey scale or false colour image. The grey scale tomographic picture differentiates microstructure in the retina including intraretinal layers and the retinal nerve fibre layer (RNFL). However, as the human eye has a limited ability to differentiate grey levels, an OCT image may also be displayed in a false colour representation which enhances differentiation of different microstructures within the image (Fujimoto 2002).

OCT images can be analysed qualitatively or quantitatively to detect retinal abnormalities. Quantitative analyses are processed automatically using computerised algorithms to extract features such as retinal or RNFL thickness (Fujimoto 2002). These quantitative features can then be compared to an internal reference database of 'normal' measurements, to allow the diagnosis of structural abnormalities according to different thresholds. The interpretation of OCT images requires specialist ophthalmological expertise.

Several generations of OCT technology have become available. Time domain OCT instruments (Stratus OCT) use superluminescent diode (SLD) light sources emitting light with 20–30 nm bandwidths centred at a wavelength of 820 nm. A maximum of 512 A-scans per B-scan can be acquired at a rate of 400 A-scans per second, with 10 μm axial and 20 μm transverse image resolution in the retina. Ultrahigh-resolution (UHR) OCT is reported to achieve superior axial image resolutions of 2–3 μm, but has a longer acquisition time, and is currently not widely used in clinical practice (Drexler et al. 2008). More recently, spectral/Fourier domain OCT has become available in Australia; this system uses a broader bandwidth than Stratus OCT centred at a wavelength of 840 nm. Spectral/Fourier domain OCT is capable of acquiring between 4,000 and 8,000 A-scans per B-scan at a rate of 18,000 to 40,000 A-scans per second. Resolutions of 5–7 μm (axial) and 10–20 μm (transverse) have been reported. Reconstruction of two-

dimensional data into a three-dimensional image is possible with this version of the technology.

As a result of providing detailed information on the architectural morphology of the retina on the level of individual retinal layers, OCT has been proposed to detect early pathological changes, even before clinical signs or visual symptoms occur (Drexler et al. 2008). OCT has been proposed as a new 'gold standard' structural test for retinal abnormalities.

Expert opinion

The following sections were prepared by ophthalmologist members of the Advisory Panel and reflect expert opinion regarding the role, uptake and value of OCT for the diagnosis and monitoring of macular diseases and glaucoma.

Macular diseases

The introduction of OCT examination of the macula has revolutionised diagnosis and management of retinal disease by ophthalmic specialists, through giving a qualitative and quantitative measure of cross-sectional anatomical change in the macula. OCT has become an essential part of the standard of care, and so apparent is its utility to specialists and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination. An indication of the fundamental role that OCT now plays is apparent, for instance, in recent guidelines for managing age-related macular degeneration published by the British Royal College of Ophthalmologists which state that OCT is essential to treat this disease, or the fact that many clinical trials of treatments of macular diseases are now designed with OCT measurements as the primary outcome measure. Detecting and managing macular problems without OCT is now obsolete and unacceptable.

Despite the widespread diffusion of this technology into retinal ophthalmology at every level, establishing the utility of OCT for macular disease in the MSAC report has been difficult due to a lack of published evidence in the literature with an appropriate comparator. The true comparator for OCT is clinical examination of the macula by a specialist (slit lamp biomicroscopy); however, the report has had to rely on comparisons with fluorescein angiography, the main prior retinal diagnostic technique. These tests are not, however, directly comparable, since OCT gives an indication of anatomy, whilst fluorescein angiography is frequently physiological. One major usage for OCT has been in the monitoring of intravitreal therapies (such as ranibizumab) which have been universally introduced into clinical practice using OCT assessment to guide treatment, and there is a corresponding absence of evidence to allow a comparison of treatment with and without OCT.

In the estimation of ophthalmologist members of the Advisory Panel, this report, therefore, fails to convey the high utility of OCT and the fundamental role that OCT now plays in the management of patients with macular disease. The ophthalmologist members of the Advisory Panel strongly support appropriate application of this essential technology, carried out and interpreted by specialist ophthalmologists to allow early detection and intervention in blinding macular diseases.

Glaucoma

In its assessment of OCT's usefulness for the diagnosis and management of glaucoma, this final draft of the MSAC report is handicapped by the lack of identifiable studies with an appropriate level of evidence. This is not surprising.

With many forms of innovative technology, particularly when it is rapidly evolving, published literature lags behind its clinical acceptance and uptake.

In glaucoma, structural optic nerve head (ONH) changes precede detectable changes in visual field sensitivity (Weinreb et al. 2004).

Visual field testing by white-on-white Static Automated Perimetry has in the past been one of the 'gold standards' for glaucoma diagnosis. Changes in ONH structure are now relied upon to determine diagnosis and to detect progression of glaucoma; the prior 'gold standard' is an imperfect comparator for OCT.

Digital methods to measure and to record ONH structural abnormality should be standard tools in the management of glaucoma in 2008. OCT is one such method.

As well as its role in the diagnosis and in the detection of progression, OCT contributes significantly to a patient's understanding of the disease. The clear demonstration of an anatomical abnormality with this instrument is easily comprehended, thereby greatly increasing the likelihood of patient acceptance of, adherence to and perseverance with lifelong therapy.

The ophthalmologist members of the Advisory Panel strongly support appropriate clinical application of digital technology as, increasingly, ONH imaging will be critical to the effective management of patients with glaucoma, thereby reducing the personal tragedy of avoidable visual disability and the burden it imposes on families and the community.

The procedure

Dilation of the pupil is undertaken prior to OCT scanning to optimise image quality. The patient is positioned in front of the OCT machine, and height adjustments are made to maximise the comfort of the patient. The scan is then performed, with the possibility of additional repeated scans if initial scans are of suboptimal quality (for example, if ocular motion artefacts are present or if the image is not appropriately centred). OCT takes approximately three to five minutes to perform per eye by a trained operator.

The patient's viewpoint

Patients' views about OCT have not been systematically investigated in the context of health technology assessment (HTA). Expert opinion suggests that the following concerns are important to patients:

- The safety and effectiveness of the technology, and communication to patients of the potential benefits and risks associated with OCT.
- Access to OCT services across socioeconomic groups. There is evidence that conditions such as diabetes which increase the risk of developing macular diseases and glaucoma disproportionately affect lower socioeconomic groups (Australian Institute of Health and Welfare 2008b); such groups are less able to pay for OCT examinations.
- Access to OCT services outside of major population centres. Specifically, access to OCT machines in rural and remote areas, training for those performing the scan and the availability of specialist expertise in interpreting OCT images are of concern to patients.

Expert opinion suggests that patients value the information provided by OCT examinations.

Intended purpose

This report focuses on an assessment of OCT performed for the evaluation of patients with macular diseases or glaucoma. OCT is intended to be used for diagnosis and monitoring of retinal diseases and glaucoma in a specialist ophthalmological setting; it is not intended to be applied for screening purposes. The specific research questions to be addressed in this assessment are:

- What is the value of optical coherence tomography compared with fundus fluorescein angiography or a clinical observation strategy in the diagnosis of macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy, tractional diseases of the macula, macular oedema and neovascularisation?
- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and fundus fluorescein angiography in the monitoring of patients with macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy and macular oedema?
- What is the additional value of optical coherence tomography over that of computerised perimetry and clinical examination in the initial diagnosis of glaucoma, in patients with risk factors for glaucoma with questionable clinical examination (glaucoma-like optic discs)?
- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and computerised perimetry in the monitoring of patients treated or with risk factors for glaucoma?

Macular diseases

The term 'macular disease' incorporates a conglomerate of conditions affecting the macula—the specialised area of the retina dedicated to high resolution visual acuity, defined anatomically as the central part of the posterior retina containing xanthophyll pigment and two or more layers of ganglion cells (Arevalo et al. 2006). The macula has the densest concentration of photoreceptors in the retina and enables the perception of fine detail (for example, reading or recognising faces) (Do et al. 2007). According to World Health Organisation (WHO) data, macular diseases comprised two of the three most common causes of blindness in Australia in 2002. Age-related macular degeneration (AMD) was the cause of 50% of cases of blindness, while 17% of cases were attributable to diabetic retinopathy (Resnikoff et al. 2004). (The other major cause of blindness in Australia—glaucoma—is discussed elsewhere in this report; see page 18.) Among the sequelae of both conditions are macular oedema (abnormal capillary permeability, resulting in the leakage of fluid into retinal tissue, collecting around the macula) and neovascularisation (the proliferation of new fibrovascular tissue on, into or below the retina) (Weisz et al. 2006; Williams et al. 2004). Both are major causes of vision loss due to these conditions. AMD and diabetic retinopathy are described below along with other macular diseases; however, this list is not intended to represent the totality of conditions that comprise 'macular disease' as an umbrella term.

Macular degeneration

Typically, the first clinical sign of macular degeneration is the presence of drusen (acellular, polymorphous debris between the retinal pigment epithelium and Bruch's membrane) (Jager et al. 2008). The appearance of drusen is considered to be a normal consequence of ageing; however, excess drusen can result in damage to the retinal pigment epithelium, either by retinal atrophy, the expression of vascular epithelial growth factor (VEGF) or both. Choroidal neovascularisation (CNV) may develop as a consequence. CNV refers to the proliferation of fibrovascular tissue from the choroid into or under the retina, leading most commonly to fibrotic scars, but also subretinal haemorrhage, fluid exudation, lipid deposition and detachment of the pigment epithelium. CNV is responsible for 85% of severe vision loss associated with AMD (Weisz et al. 2006). Importantly, CNV is not particular to AMD—it can be caused by other conditions, such as ocular histoplasmosis syndrome, multifocal choroiditis, pathological myopia and choroidal rupture due to trauma.

AMD is classified as either early or intermediate according to the number and size of drusen present. The presence of a few medium sized drusen indicates early AMD; intermediate AMD involves the presence of at least one large druse (Jager et al. 2008). Advanced AMD is classified according to the presence or absence of CNV—the former is commonly called 'wet' or 'exudative' AMD, while the latter is known as 'dry' or 'non-exudative' AMD. Early AMD typically involves only mild vision loss, and may be asymptomatic. Progression to more advanced vision loss evolves gradually over months to years when non-exudative AMD is present. In contrast, the development of severe vision loss may occur suddenly in the presence of neovascular AMD.

The incidence and prevalence of macular degeneration increase sharply with age. Other risk factors include family history, smoking and obesity (Jager et al. 2008).

Current treatment

Current treatment for patients with neovascular AMD in Australia includes a course of monthly injections of ranibizumab (0.3 mg) into the affected eye. Ranibizumab is an anti-VEGF drug, and thus acts to reduce and prevent abnormal blood vessel growth. Recent systematic reviews of four RCTs have demonstrated improved vision with this treatment compared with photodynamic therapy (PDT) or sham injections (Colquitt et al. 2008; Vedula et al. 2008). Significantly more patients receiving ranibizumab (0.3 mg) lost less than 15 letters of visual acuity at 12 months (94.3%–95.4%) compared with sham injections (62.2%, $p<0.001$) or PDT (64.3%, $p<0.001$) (Colquitt et al. 2008). Across all trials (using 0.3 mg or 0.5 mg formulations) the pooled relative risk of gaining 15 letters or more at 12 months was 5.81 (95% CI: 3.29–10.26) for ranibizumab compared with sham injections; 6.79 (95% CI: 3.41–13.54) for ranibizumab/sham PDT compared with PDT/sham ranibizumab; and 4.44 (95% CI: 1.40–14.08) for ranibizumab plus PDT versus PDT (Vedula et al. 2008). The proportion of patients gaining 15 letters or more was also significantly higher (24.8%–35.7%) in patients treated with 0.3 mg ranibizumab compared with sham injection (4.6%, $p<0.001$) or PDT (5.6%, $p<0.001$) (Colquitt et al. 2008). Adverse events were reported to be common but typically mild to moderate.

Ocular PDT may be considered for patients with subfoveal neovascular AMD (American Academy of Ophthalmology 2006), though it has largely been replaced by ranibizumab in Australian practice. PDT involves the intravenous administration of a light-sensitive dye (verteporfin) which preferentially accumulates in new blood vessels. The dye is activated by a 698 nm laser beam concentrated on the macula, causing selective damage to the neovacularisation (Jager et al. 2008). Risk ratios from a meta-analysis of three trials comparing verteporfin with 5% dextrose in water were 0.77 (95% CI: 0.69–0.87) for a loss of vision at 24 months of three or more lines and 0.62 (95% CI: 0.50–0.76) for six or more lines (Wormald et al. 2007). The most serious adverse event was acute, severe visual acuity decrease (approximately 2% of treated patients).

Thermal laser photocoagulation therapy may be considered for patients with extrafoveal classic CNV or juxtafoveal classic CNV. Photocoagulation involves focussing a green light laser onto the neovascularisation, which seals the vessels and prevents further leakage. A Cochrane systematic review of 15 trials concluded that laser photocoagulation slows the progression of visual loss in people with neovascular AMD in the medium to long term; however, it is associated with an increased risk of vision loss immediately after treatment (Virgili et al. 2007a).

Lifestyle modification—including smoking cessation, blood pressure control and maintenance of healthy weight—remains an important intervention to reduce the risk of early, intermediate and advanced non-exudative AMD and its progression (Guymer 2007; Jager et al. 2008). The American Academy of Ophthalmology recommends this management for patients with early AMD or advanced AMD with bilateral subfoveal geographic atrophy or disciform scars (American Academy of Ophthalmology 2006). Antioxidant or vitamin supplementation may be considered for patients with intermediate AMD or unilateral advanced AMD. Evidence for the effectiveness of antioxidants in slowing the progression of AMD comes from one large RCT, with smaller trials showing inconsistent results (Evans 2006). A Cochrane review of antioxidant or vitamin supplementation could not rule out the potential for long-term harm, and pointed to the need for further research.

Diabetic retinopathy

Diabetic retinopathy (DR) is a microvascular complication of diabetes caused by damage to the capillaries in the retina (Australian Institute of Health and Welfare 2008b). In the early stages, the retinal blood vessels swell and leak fluid into the retina; in later stages, abnormal neovascular growth may occur. At any stage of retinopathy, the leakage of fluid from retinal vessels can result in macular oedema, which is the most common cause of vision impairment in diabetic patients (Girach et al. 2007).

The Early Treatment of Diabetic Retinopathy Study (ETDRS) has classified diabetic macular oedema depending on the size of the lesion and its proximity to the macula. Clinically significant macular oedema (CSMO) is considered to be present when there is thickening of the retina within 500 μm of the centre of the macula; or if there are hard exudates within 500 μm of the centre of the macula associated with thickening of the adjacent retina; or if there is a zone or zones of thickening one disc diameter or larger within one disc diameter of the macula. Clinically non-significant macular oedema is present when the macular oedema does not meet these conditions. Patients with CSMO have an increased risk of progressive visual damage (Girach et al. 2007).

Current treatment

Treatment guidelines for DR in Australia have recommended laser photocoagulation as first line therapy for patients with high risk proliferative DR (ie where there is the formation of new abnormal blood vessels) and for earlier stages of proliferative DR after maculopathy is stabilised (National Health and Medical Research Council 2008). For patients with severe non-proliferative DR, consideration for laser photocoagulation was recommended, particularly in patients with type 2 diabetes mellitus, poor follow-up compliance, impending cataract surgery, renal disease, pregnancy, severe disease in the fellow eye or evidence of retinopathy progression. Where retinopathy is less severe, it was recommended that the benefits of laser photocoagulation be balanced against the (small) risk of damage to vision from treatment. For eyes with CSMO, laser treatment was recommended to areas of focal leak and capillary non-perfusion. These recommendations were based on Level II evidence (Early Treatment Diabetic Retinopathy Study Research Group 1987; Early Treatment Diabetic Retinopathy Study Research Group 1991; Ferris III 1987; Lovestam-Adrian et al. 2003).

Australian management guidelines also recommend that vitrectomy be considered within three months for type 1 diabetes mellitus patients with severe vitreous haemorrhage in eyes suspected to have very severe proliferative DR; additionally, consideration for vitrectomy was recommended for patients with severe proliferative DR not responding to aggressive and extensive laser treatment (National Health and Medical Research Council 2008). These recommendations were based on Level II evidence (Feman et al. 1990; Smiddy et al. 1999; The Diabetic Retinopathy Vitrectomy Study Research Group 1985). Consideration for vitrectomy was also recommended to relieve traction in advanced proliferative DR cases, or in cases of chronic or diffuse macular oedema not responding to laser treatment or associated with vitreomacular traction.

Central serous retinopathy

Central serous retinopathy (CSR) is characterised by serous detachment of the neurosensory retina and/or the retinal pigment epithelium (RPE) (Wang et al. 2008). It is

a common cause of mild to moderate visual impairment. In active or acute CSR, detachment of the neurosensory retina is caused by the accumulation of serous fluid between the photoreceptor outer segments and the RPE, combined with monofocal or multifocal changes in the RPE. Involvement of the fovea is typical. This disease does not include detachment due to retinal holes or tears, neovascularisation, neoplasia or specific hereditary disease. Chronic CSR involves multifocal or diffuse RPE depigmentation combined with serous retinal detachment. Symptoms include blurred vision with a relative central scotoma, metamorphosia, dyschromatopsia, micropsia, hypermetropization and reduced contrast sensitivity (Wang et al. 2008). Serous detachment often resolves spontaneously, particularly in acute CSR.

Current treatment

The evidence base for treatment of CSR is poor, and largely derived from non-controlled studies (Wang et al. 2008). The high rate of spontaneous resolution means that conservative treatment is favoured initially, focussing on lifestyle counselling and discontinuation of glucocorticoid medications. The rate of resolution of detachment with this strategy has been reported to be approximately 90%, with a return to visual acuity of 20/25 or better. Photocoagulation or photodynamic therapy is considered for patients with persistence of CSR for more than three months.

Uveitis

Uveitis is a diverse collection of conditions grouped together due to their involvement of the uveal tract (iris, ciliary body and choroid) (Smith 2004). These diseases may also affect the retina, optic nerve and vitreous (Durrani et al. 2004). Anterior uveitis involves the iris and/or pars plicata, and spares the retina; intermediate uveitis involves inflammation of pars plana and/or adjacent peripheral retina; and posterior uveitis refers to inflammation of the choroid and/or overlying retina. Panuveitis involves inflammation of the entire uvea. The most common form is anterior uveitis (76% in Australia), followed by posterior uveitis (18%) (Wakefield et al. 2005). Panuveitis (4%) and intermediate uveitis (2%) are relatively rare. Uveitis can also be classified as granulomatous or non-granulomatous, depending on the presence or absence of granulomatous-like collections of inflammatory cells. In the majority of cases, the cause of inflammation is unknown, but systemic conditions such as sarcoidosis, Behcet's disease and the HLA B27-related diseases and infectious agents such as *Toxoplasma gondii* and herpes viruses are known causes. The most common cause of vision loss related to uveitis is cystoid macular oedema (Durrani et al. 2004). Other complications include band ketratopathy, secondary glaucoma, secondary cataract, vitreous opacities, optic neuropathy, retinal scars and phthisis.

Current treatment

Treatment of uveitis affecting the retina varies according to the specific diagnosis. For toxoplasmic chorioretinitis, antimicrobial treatment (eg sulfadiazine, pyrimethamine) may be instituted. For immune-mediatied uveitis, corticosteroid treatment (injected either periocularly or intravitreally), with or without systemic immunosuppression, may be undertaken for cystoid macular oedema. It has been noted that the evidence base for treatment of uveitis is poor (Durrani et al. 2004).

There has been recent interest in intraocular drug delivery systems (implants which deliver a sustained dose of corticosteroids) for the treatment of macular oedema due to uveitis. One RCT has reported positive visual outcomes in patients with persistent macular oedema randomised to a dexamethasone implant compared with observation; however, these are short-term results (six months follow-up), and patients with uveitis comprised only a small proportion of the study population (4%) (Kuppermann et al. 2007). Additionally, an implant releasing flucinolone is currently being trialled in Australia. These implants are not currently listed on the Pharmaceutical Benefits Scheme (PBS).

Tractional diseases

Epiretinal membranes

The formation of epiretinal membranes—sometimes known as cellophane maculopathy, macular pucker or surface wrinkling maculopathy, among others—occurs due to retinal glial cell proliferation along the surface of the internal limiting membrane. The resulting membrane usually has a thin, cellophane appearance, but over time can thicken and contract (Chan et al. 2000; McCarty et al. 2005). In the early stages, patients may be asymptomatic or have only mild reduction in visual acuity (McCarty et al. 2005). However, epiretinal membranes can cause wrinkling or distortion of the macular surface, leading to symptomatic visual disturbances (Khaja et al. 2008; Kwok et al. 2005). When the foveal centre is involved, symptoms include metamorphosia, central blurring and distortion of the Amsler grid (a test for central visual field abnormalities). Contraction of the membrane may exert tangential traction on the macula, causing severe vision loss. Spontaneous resolution has been reported in a small proportion of cases. The development of epiretinal membranes may be idiopathic; however, they may also occur in association with other retinal diseases, as well as after ocular trauma, or following laser photocoagulation or intraocular surgery.

Vitreomacular traction syndrome

Vitreomacular traction syndrome (VMT) is a complication of partial posterior vitreous detachment. It occurs when the vitreous separates partially from the retina, but remains adherent to the macula (Johnson 2005). This can result in traction across the macula, and subsequent visual disturbances. Prior to the advent of OCT, there was no diagnostic test available for the reliable objective detection of VMT. Other findings which may co-exist with VMT include macular oedema, epiretinal membranes and macular detachment.

Macular holes

A macular hole is a full thickness defect of the retinal tissue involving the anatomic fovea (Ho et al. 1998). There are a number of theories concerning the pathophysiology of macular holes; however, these theories are considered to be controversial (Kang et al. 2003). The process of tangential traction of the vitreous cortex at the foveolar edges has been implicated in macular hole formation (Altaweel et al. 2003). It has been proposed that Muller cells in the fovea or retina can migrate through the internal limiting membrane, resulting in the development of a prefoveolar vitreoglial membrane. The contraction of this membrane may result in tangential traction on the retina resulting in foveolar detachment (Altaweel et al. 2003). Gass and colleagues have described a biomicroscopic classification of macular holes and precursor lesions based on this

hypothesis. Stage 1A holes present as a yellow spot, and stage 1B as a yellow ring on biomicroscopy. Stage 1B is further subclassified as occult or impending holes, the former being characterised by separation of retinal elements. Stage 2 includes full thickness holes less than 400 microns in width; stage 3 holes are 400 microns in diameter or greater. Stage 4 constitutes full-thickness macular holes with complete posterior vitreous detachment (Gass 1997). It has been estimated that 40% of patients with stage 1 holes will progress within two years, and macular hole formation will abort in 60% (De Bustros et al. 1994). It has been reported that 67% to 96% of patients with stage 2 holes will progress (Ho et al. 1998); however, it is possible for untreated stage 2–4 holes to spontaneously resolve, and it is estimated that this occurs in up to 10% of cases (Ezra 2001).

Current treatment

Treatment for patients with tractional diseases typically involves pars plana vitrectomy with epiretinal membrane removal (Johnson 2005; Kwok et al. 2005). Internal limiting membrane peeling may also be undertaken. Intraocular gas tamponade is used, and postoperative face-down positioning is generally used. Complications of surgery include retinal tears, rhegmatogenous retinal detachment, macular hole enlargement and late hole re-opening (Ho et al. 1998). There is also a high rate of reported nuclear cataract progression (81% after two years).

Patients with stage 1 macular holes are typically observed due to a high rate of spontaneous resolution (Altaweel et al. 2003). Vitrectomy may be offered to patients with stage 2 holes or above. Initial case series reported an anatomical success rate of 58%, with visual improvement of two or more lines in 42% (Kelly et al. 1991). More recently, a non-meta-analytic review which pooled data across non-comparative studies has reported a success rate of approximately 80%, with visual improvement of two or more lines in 60% (Kang et al. 2000).

Clinical need

Two major epidemiological studies have estimated the incidence and prevalence of macular diseases in Australia. The Blue Mountains Eye Study (BMES) examined a cohort of 3,654 residents of western Sydney who were aged 50 years or over, while the Melbourne Visual Impairment Project (MVIP) studied a cohort of 3,271 Melbourne residents aged 40 years and over. Findings from these studies are described below, and are used to derive estimates of the potential utilisation of OCT in Australia. Additional epidemiological studies for individual conditions are also described, where applicable.

Macular degeneration

In the BMES, the 10 year incidence of AMD was estimated to be 3.7% of people with no macular degeneration evident at baseline. In addition, the 10 year incidence of early age-related maculopathy (ARM) was estimated to be 14.1% (Wang et al. 2007). Age- and gender-adjusted estimates of the total number of incident cases of AMD and early ARM in Australia in 2007 are presented in Table 1. The MVIP estimated cumulative five year incidence of AMD and early ARM, and found rates of 0.49% and 17.3%, respectively (Mukesh et al. 2004). Table 1 also describes age- and gender-adjusted estimates of incident cases in 2007 based on these figures. Using this approach, it is estimated that there were between 16,100 and 35,400 incident cases of AMD. The lower figure derived from the MVIP has been attributed to an underestimation of incidence in the over 80

years age group, and hence the estimate of 35,400 incident cases is considered more representative. Estimates of incident cases of ARM are also presented in Table 1, and vary widely (between 97,800 and 264,700 cases). The definition of early ARM used in the MVIP was more inclusive than that employed in the BMES (either soft distinct drusen or retinal pigmentary abnormalities alone were considered indicative of ARM in the MVIP; in the BMES, ARM was considered to be present when these characteristics coexisted), and is therefore likely to include higher numbers of asymptomatic patients. Hence, the lower observed incidence in the BMES (97,800 cases) is considered more representative of the incident population who would be considered for further testing with OCT. However, as asymptomatic patients are included in this figure, only a proportion of these incident cases of early ARM are likely to present for ophthalmological evaluation.

Table 1 Age- and gender-adjusted estimates of the number of incident cases of early ARM and AMD in Australians aged 40 years and over, 2007

		AMD ('000s)		Early ARM ('000s)	
		BMES	MVIP	BMES	MVIP
2007	Males	15.1	4.2	44.8	121.9
	Females	20.3	11.9	53.0	142.8
	Total	35.4	16.1	97.8	264.7

Abbreviations: BMES, Blue Mountains Eye Study; MVIP, Melbourne Visual Impairment Project

Table 2 presents age- and gender-adjusted estimates of the prevalence of AMD and early ARM derived from the BMES and MVIP. In the BMES, the prevalence of AMD was estimated to be 1.9%, and 7.2% for early ARM (Mitchell et al. 1995). The MVIP estimated the prevalence of AMD and early ARM to be 0.68% and 15.1%, respectively (VanNewkirk et al. 2000). Based on these figures, the number of prevalent cases of AMD in Australia at the end of 2007 is estimated to range between 95,400 and 130,200 cases. Again, the upper estimate derived from the BMES is considered to be more representative of the true prevalence of AMD. Due to different definitions of early ARM between studies, estimates of the prevalence of early ARM vary widely—between 451,900 and 1,436,100 cases. The lower estimate derived from the BMES is considered to more closely represent the prevalent population of patients with early ARM who may be symptomatic, although this is still likely to overestimate the number of patients who would be diagnosed with the condition.

Table 2 Age- and gender-adjusted estimates of the number of prevalent cases of early ARM and AMD in Australians aged 40 years and over, 2007

		AMD ('000s)		Early ARM ('000s)	
		BMES	MVIP	BMES	MVIP
2007	Males	36.8	39.6	198.6	636.8
	Females	93.4	55.9	253.3	799.3
	Total	130.2	95.4	451.9	1,436.1

Abbreviations: AMD, age-related macular degeneration; ARM, age-related maculopathy; BMES, Blue Mountains Eye Study; MVIP, Melbourne Visual Impairment Project

Diabetic retinopathy

The MVIP study estimated the five year incidence of DR to be 11% (95% CI: 3.8–18.1) of diabetic patients with no retinopathy at baseline (McCarty et al. 2003). Proliferative retinopathy was observed in 2.9% (95% CI: 0–6.4), and macular oedema was evident in

8.0% (95% CI: 2.7–13.3). Of all diabetics in the cohort who were available for follow-up, the cumulative five year incidence of DR was 6.6%. All of the incident cases of DR had macular oedema. In the BMES, the cumulative five year incidence of DR in diabetic patients with no retinopathy at baseline was 22.2% (95% CI: 14.1–32.2) (Cikamatana et al. 2007). This represented an incidence of 13.3% in all diabetic patients who were followed up. The Australian Diabetes, Obesity and Lifestyle study (AusDiab) included younger patients (25 years or older, compared with 40 years or over in the MVIP and 49 years or over in the BMES) and found a five year incidence of retinopathy among known diabetes cases consistent with the higher estimate reported by the BMES (13.9%) (Tapp et al. 2008).

These figures have been converted to annual incidence, and applied to estimates of the prevalence of self-reported cases of diabetes in Australia (Australian Institute of Health and Welfare 2008b) to estimate the number of people developing DR per year (Table 3). Using this approach, it is estimated that between 9,100 and 19,600 people will develop DR annually. Given the inclusion of younger patients in the AusDiab study, the upper estimate of incident cases (19,600) is considered to be more indicative of the true incidence of retinopathy in diagnosed cases of diabetes. However, since incidence figures have been applied to self-reported prevalent cases of diabetes, undiagnosed incident cases of DR will not be included in these estimates. Using an estimate of prevalence that includes undiagnosed cases of diabetes (approximately 880,000 cases), the true incidence of DR (diagnosed and undiagnosed) may be as high as 24,600 cases per year (Australian Institute of Health and Welfare 2008b). The incidence of DR is expected to increase over time as diabetes becomes even more prevalent.

Table 3 Estimated number of annual incident cases of diabetic retinopathy in Australia

	Source	Estimate
Annual incidence	Cikamatana et al. (2007); McCarty et al. (2003); Tapp et al. (2008)	1.3–2.8%
Prevalence of diabetes	Australian Institute of Health and Welfare (2008b)	700,000
Total		9,100–19,600

The BMES estimated the prevalence of DR to be 32.4% of patients with diabetes; this was similar to the estimate reported by the MVIP (35.7%) (McCarty et al. 2003; Mitchell et al. 1998). The AusDiab study included younger patients, and consequently reported a lower estimate of 24.5% of patients with known diabetes mellitus (Tapp et al. 2003). These figures have been applied to estimates of the prevalence of diabetes in Australia (Australian Institute of Health and Welfare 2008b) to estimate the number of prevalent cases of DR (Table 4). Using this approach, it is estimated that between 171,500 and 249,900 Australians diagnosed with diabetes had DR at the end of 2007. Given the more generalisable sample of the AusDiab study in terms of the age of participants, the lower estimate (171,500) is more representative of Australian prevalence. Including potentially undiagnosed cases, the prevalence of DR may be as high as 314,200 cases. The number of prevalent cases of DR is expected to increase over time as the prevalence of diabetes increases.

Table 4 Estimated number of prevalent cases of diabetic retinopathy in Australia

	Source	Estimate
Prevalence of DR	McCarty et al. (2003); Mitchell et al. (1998); Tapp et al. (2003)	24.5–35.7%
Prevalence of diabetes	Australian Institute of Health and Welfare (2008b)	700,000
Total		171,500–249,900

Abbreviation: DR, diabetic retinopathy

Central serous retinopathy

There have been no Australian epidemiological studies conducted to investigate the incidence or prevalence of CSR, and systematically obtained international evidence on the epidemiology of this disease is lacking (Wang et al. 2008). Wang et al. have posited that CSR may rank fourth in incidence of non-surgical retinopathies behind AMD, DR and branch retinal vein occlusion, and that CSR may be second only to macular degeneration as a cause of subretinal neovascularisation; however, the basis for these statements is unclear. A recent population based study from the United States estimated the annual incidence to be 9.9 per 100,000 for men and 1.7 per 100,000 for women (Kitzmann et al. 2008). Applying age- and gender-specific incidence figures from this study to Australian population statistics, it is estimated that approximately 700 Australians develop CSR annually. However, the applicability of these estimates to the Australian setting is unclear.

There are insufficient epidemiological data to estimate the number of prevalent cases of CSR in Australia.

Uveitic maculopathy

No epidemiological studies of the incidence or prevalence of uveitis in Australia have been conducted. International data suggest that incidence is between 17 and 52 cases per 100,000 population (Wakefield et al. 2005); expert opinion is that Australian incidence is at the lower end of this range. Furthermore, international prevalence data provide a wide range of estimates (between 38 and 714 per 100,000 population) (Wakefield et al. 2005). Expert opinion is that Australian prevalence is again at the lower end of this range, with an estimate of 70 per 100,000 population considered to be representative. Cystoid macular oedema has been reported to occur in approximately 33% of patients with uveitis (Lardenoye et al. 2006). Table 5 and Table 6 apply these estimates to Australian population data. Using the lower range of the epidemiological data, it is estimated that the annual incidence of cystoid macular oedema associated with uveitis is approximately 1,200 cases; using expert opinion on the prevalence of uveitis in Australia, the prevalence of cystoid macular oedema associated with uveitis is estimated to be approximately 4,900 cases.

Table 5 Estimated number of incident cases of uveitic maculopathy in Australia

	Source	Estimate
Incidence of uveitis	Wakefield et al. (2005)	17–52 per 100,000
Cystoid macular oedema	Lardenoye et al. (2006)	33%
Australian population (2007)	Australian Bureau of Statistics (2008)	21,181,000
Total		1,200–3,650

Table 6 Estimated number of prevalent cases of uveitic maculopathy in Australia

	Source	Estimate
Prevalence of uveitis	Wakefield et al. (2005)	38–714 per 100,000
Cystoid macular oedema	Lardenoye et al. (2006)	33%
Australian population (2007)	Australian Bureau of Statistics (2008)	21,181,000
Total		2,650–49,900

Tractional diseases

The BMES investigated the cumulative five year incidence of epiretinal membranes in a population aged 50 years or older, and observed an incidence of 4.6% of all patients available for follow-up (Fraser-Bell et al. 2003). A gender-adjusted estimate of the number of Australians aged 50 and above developing epiretinal membranes in 2007 is provided in Table 7, based on Australian population statistics (Australian Bureau of Statistics 2008). This methodology suggests that approximately 58,650 Australians developed epiretinal membranes in 2007.

Table 7 Estimated number of incident cases of epiretinal membranes in Australians aged 50 years and over, 2007

	Source	Males	Females	All
Annual incidence	Fraser-Bell et al. (2003)	0.8%	1.0%	–
Population ≥ 50 years	Australian Bureau of Statistics (2008)	3,105,834	3,379,885	–
Total		24,850	33,800	58,650

Overall estimates of the prevalence of epiretinal membranes were similar in the MVIP (6.0%) and the BMES (7.0%), though prevalence in those aged 70 years or older appeared to be greater in the MVIP (McCarty et al. 2005; Mitchell et al. 1997b). Based on these studies and Australian population statistics (Australian Bureau of Statistics 2008), age-adjusted estimates of the number of prevalent cases of epiretinal membranes in Australia at the end of 2007 range between 429,100 and 527,000.

No Australian epidemiological studies of macular holes have been conducted. International data suggest that prevalence is approximately 30 per 100,000 population, and that macular holes typically manifest in the sixth and seventh decades of life (Ezra 2001). If applied to the Australian population, this results in an estimated 6,350 prevalent cases at the end of 2007.

There are insufficient epidemiological data relating to vitreomacular traction syndrome to estimate incidence and prevalence.

Potential utilisation of OCT

The following sections estimate the potential utilisation of OCT in the Australian setting using epidemiological data, and by extrapolation from utilisation data of fundus fluorescein angiography (FFA). These estimations are predicated on the use of OCT as a diagnostic test in the specialist ophthalmological setting. Expert opinion is that the use of OCT for screening asymptomatic patients in not appropriate, and is not considered in this assessment.

Epidemiological data

The estimation of potential utilisation of OCT for the diagnosis of macular disease based on epidemiological data is problematic, given that the incidence and prevalence figures derived from epidemiological data capture both symptomatic and asymptomatic patients. Asymptomatic patients would not undergo OCT in routine clinical practice. However, expert opinion suggests that summing incidence data across individual diseases, adjusted by the proportion of cases expected to be eligible for OCT, is the most valid estimate of potential utilisation for diagnosis based on epidemiological data. Such estimates could be expected to provide an upper range for the potential utilisation of OCT.

Table 8 summarises incidence figures for the macular diseases considered in this assessment, including incidence for AMD, early ARM, DR, CSR, uveitis and epiretinal membranes. Summing these figures, and adjusting for the proportion of cases expected to undergo OCT based on the expert opinion of Advisory Panel members, provides a potential estimated annual utilisation of diagnostic OCT for macular disease of approximately 43,690 scans per year (OCT performed bilaterally is included as a single scan in these estimates.) Epidemiological data do not allow for an estimation of the number of patients who will be eligible for a diagnostic OCT scan for macular holes or vitreomacular traction. Expert opinion suggests that, as an upper limit, the estimate presented would reflect utilisation with these indications included.

Table 8 Estimated potential utilisation of OCT for diagnosis of macular disease

	Source	Incident cases	Proportion tested [a]	Scans / year
Macular degeneration				
AMD	Wang et al. (2007)	35,400	50%	17,700
Early ARM	Wang et al. (2007)	97,800	2%	1,960
Diabetic macular oedema	Cikamatana et al. (2007) Australian Institute of Health and Welfare (2008b); Tapp et al. (2008)	19,600	50%	9,800
Central serous retinopathy	Kitzmann et al. (2008)	700	100%	700
Uveitis	Wakefield et al. (2005)	3,600	50%	1,800
Epiretinal membrane	Fraser-Bell et al. (2003)	58,650	20%	11,730
Macular hole	N/A	unknown	–	unknown
Vitreomacular traction	N/A	unknown	–	unknown
Total				43,690

Abbreviations: AMD, age-related macular degeneration; ARM, age-related maculopathy

[a] Expert opinion of Advisory Panel members

A similar approach has been adopted for the estimation of utilisation of OCT for monitoring macular disease, using estimates of the number of prevalent cases for individual conditions to describe patients who would be monitored as part of ongoing therapy. Expert opinion has been used to estimate the proportion of prevalent cases (derived from the epidemiological literature) that would present and be treated in routine clinical practice. Table 9 summarises these estimates, and also describes the number of scans likely to be performed per patient per year for each indication (again, derived from expert opinion). Summing the figures results in an estimate of between 110,880 and 288,540 OCT scans per year for monitoring of therapy. The number of scans for

monitoring treatment for CSR could not be estimated; expert opinion is that the upper estimate would reflect utilisation with this indication included.

Table 9 Estimated potential utilisation of OCT for monitoring of treatment for macular disease

	Prevalent cases	Proportion tested [a]	Scan frequency [a]	Number of scans per year
Macular degeneration	130,200	10%	4–12 / year	52,080–156,240
Diabetic retinopathy	171,500	10–15%	2–4 / year	34,300–102,900
Central serous retinopathy	unknown	–	2–3 / year	unknown
Uveitic maculopathy	4,900	100%	5–6 / year	24,500–29,400
Total				110,880–288,540

[a] Expert opinion of Advisory Panel members

Therefore, the total potential utilisation of OCT (diagnosis and monitoring combined) based on epidemiological data is estimated to range between 154,570 and 332,230 scans annually. This is considered to be an upper range of potential utilisation.

Utilisation data

Data concerning the past utilisation of FFA may be used to provide an indication of the likely utilisation of OCT for macular diseases. MBS and Department of Veterans' Affairs (DVA) claims data for item numbers 11215 and 11218 (retinal photography, multiple exposures with intravenous dye injection) between 2004 and 2007 are presented in Table 10. It is not possible to estimate specific utilisation data for diagnostic and monitoring uses of the test; these figures therefore represent overall utilisation. The number of services claimed over this period has declined, which may be attributed to the uptake of OCT in clinical practice. The maximum number of services claimed was 50,702 (in 2005).

Expert opinion is that FFA is performed in a more restricted patient group than that proposed for OCT (approximately 50–70% of patients undergoing OCT would previously have undergone FFA; see Appendix C, page 79); furthermore, the frequency with which OCT is conducted for monitoring purposes is proposed to be greater than that of FFA due to its non-invasive nature (see Appendix C, page 80). In addition, reliance on MBS and DVA claims data for FFA will not capture public hospital patients. Therefore, data on past utilisation of FFA will underestimate the potential utilisation of OCT. Expert opinion has been used to adjust FFA utilisation estimates to take the various sources of underestimation into account. Expert opinion from the Advisory Panel suggests that multiplying past utilisation of FFA by a factor of two will provide an indicative estimate of potential utilisation of OCT. Therefore, based on the maximum number of FFA services claimed between 2004 and 2007, potential annual utilisation of OCT is estimated to be approximately 101,400 scans. This is considered to represent a lower range of potential utilisation.

Table 10 MBS and DVA claims for FFA services (items 11215 and 11218), 2004–June 2008

Year	MBS claims	DVA claims	Total
2004	43,102	7,419	50,521
2005	43,321	7,381	50,702
2006	41,491	6,779	48,270
2007	38,447	5,415	43,862

Abbreviations: DVA, Department of Veterans' Affairs; FFA, fundus fluorescein angiography; MBS, Medical Benefits Scheme

Glaucoma

Glaucoma is a group of ocular diseases characterised by optic neuropathy, leading to progressive loss of the visual field (Allingham et al. 2005). If not managed, progressive glaucomatous optic neuropathy can lead to total, irreversible blindness. Risk factors include raised intraocular pressure (IOP), age and family history. The presence of systemic diseases such as diabetes mellitus has also been implicated as a risk factor, but this remains unclear (Australian Institute of Health and Welfare 2008a; Gupta 2005; Mitchell et al. 1996; Mitchell et al. 1997a). Glaucoma is the second most common cause of blindness in Australia (18%), behind AMD (Resnikoff et al. 2004).

Glaucoma may be classified as either primary (not related to any other underlying condition) or secondary (resulting from other ocular or systemic disease, trauma or use of certain drugs), and further by the anatomy of the anterior chamber of the eye (open angle or closed angle). Primary open angle glaucoma (POAG) is a chronic, progressive disease characterised by acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons, adult onset and open anterior chamber angles. Contributors to damage may include IOP or other (potentially unknown) factors, in the absence of other identifiable causes (American Academy of Ophthalmology 2005b). Where other causes are implicated, open angle glaucoma is considered to be secondary. Evidence of optic nerve damage consists of optic disc or retinal nerve fibre layer (RNFL) structural abnormalities (eg diffuse thinning, focal narrowing or notching of the optic disc; progression of optic disc cupping; diffuse or localised abnormalities of the peripapillary RNFL; disc rim or RNFL haemorrhages; optic disc neural rim asymmetry) and/or reproducible visual field abnormalities in the absence of other known explanations. Many POAG patients present with elevated IOP; however, a significant minority of patients presenting with damage consistent with POAG have IOP within the normal range. While elevated IOP has been shown to be associated with progressive optic neuropathy in POAG, other factors may also contribute to this damage (eg blood supply to the optic nerve, substances toxic to the optic nerve or retina, axonal or ganglion cell metabolism, the lamina cribrosa extracellular matrix) (American Academy of Ophthalmology 2005b).

In primary angle closure (PAC), pupillary block causes resistance of aqueous humour flow through the pupil, resulting in a pressure gradient between the posterior and anterior chambers (American Academy of Ophthalmology 2005a). This in turn causes bowing of the peripheral iris, covering the filtration portion of the trabecular meshwork, and potentially resulting in elevated IOP. Contact between the iris and trabecular meshwork may result in peripheral anterior synechiae and residual functional damage. Angle closure may or may not result in elevated IOP and glaucomatous optic neuropathy (primary angle closure glaucoma, PACG); however, angle closure does increase the risk of glaucomatous optic disc damage, particularly when IOP is elevated. In secondary angle closure glaucoma, angle closure is induced by other causes (eg subluxed lens) (American Academy of Ophthalmology 2005a). In addition to those risk factors already mentioned,

hyperopia, female gender, Asian descent and shallow peripheral anterior chamber are considered to be risk factors for PAC and PACG.

Glaucoma 'suspects' are individuals with clinical findings or risk factors that indicate a high risk of developing glaucoma (American Academy of Ophthalmology 2005c). Such clinical findings may include optic disc or RNFL appearance suspicious for glaucomatous damage; visual field suspicious for glaucomatous damage; or consistently elevated IOP in the presence of normal visual fields, RNFL and optic disc appearance (otherwise termed 'ocular hypertension'). (Risk factors have been described above.) In 'preperimetric' glaucoma, patients are diagnosed with glaucomatous structural change in the optic disc, prior to functional impairment. In a systematic review of the literature as part of a guideline for the management of glaucoma, Tuulonen et al. concluded that it is possible to observe glaucomatous RNFL abnormalities prior to the development of defects in the optic disc or visual field (Tuulonen et al. 2003). RNFL abnormalities were observed with photography in these studies.

Current treatment

Intraocular pressure (IOP) is the only risk factor for glaucoma known to be amenable to treatment (American Academy of Ophthalmology 2005c). Hence, the focus of treatment for glaucoma is lowering IOP to inhibit progression of glaucomatous optic neuropathy (Tuulonen et al. 2003). IOP reduction can be achieved by medical, surgical and/or laser therapy.

Medications aim to either increase drainage or decrease the production of intraocular fluid, thereby lowering IOP. The most commonly used topical agents are beta-adrenergic agonists and prostaglandin analogues; less frequently used medications include alpha$_2$ adrenergic agonists, topically or orally administered carbonic anhydrase inhibitors, and parasympathomimetics (American Academy of Ophthalmology 2005b). A meta-analysis of 10 studies comparing topical therapies with placebo or no treatment has shown a reduction in the onset of visual field defects in treated patients with ocular hypertension (Odds Ratio = 0.62; 95% CI: 0.47–0.81) (Vass et al. 2007). No significant protective effect was found for any individual drug, but a borderline protective effect for beta-blockers was evident. Adherence to therapy is critical for successful medical management of IOP; this may not be achieved in upwards of one-third of patients (American Academy of Ophthalmology 2005b).

Trabeculectomy is the surgical removal of parts of the trabecular meshwork to improve aqueous humour drainage, and therefore lower IOP. Evidence from one RCT suggests that surgery reduces IOP more than medical treatment; however, the risk of glaucoma progression up to five years is not significantly different between the treatments in patients with mild open angle glaucoma (Burr et al. 2004). Surgery is required in many moderate or advanced glaucoma patients. Although long-term IOP control may be achieved via incisional filtration surgery, some patients still require medications or re-operation (which has a higher failure rate) (American Academy of Ophthalmology 2005b). Trabeculectomy has been noted to increase the risk of undergoing cataract surgery in phakic eyes; additionally, the use of intraoperative or postoperative antifibrotic agents to reduce scarring is associated with elevated risk of complications including hypotony, hypotony maculopathy, late-onset bleb leak and late-onset infection (American Academy of Ophthalmology 2005b).

Laser surgery to the trabecular meshwork (trabeculoplasty) may be undertaken to improve drainage and thereby reduce IOP, particularly as an alternative to medical treatment where adherence to therapy is not maintained (American Academy of Ophthalmology 2005b). A meta-analysis of three trials comparing trabeculoplasty and trabeculectomy found an increased risk of uncontrolled IOP in laser-treated patients at six months, although there was significant heterogeneity at 24 months follow-up (Rolim-de et al. 2007). The same review reported a higher risk of IOP progression in patients managed medically compared with laser-treated patients; however, the medications used were not current, and conclusions about the relative effectiveness of contemporary treatments was not possible. It has been reported that the IOP-lowering effect of laser trabeculoplasty diminishes by approximately 8% per year and, in the long term, most patients require medical treatment (American Academy of Ophthalmology 2005b; Tuulonen et al. 2003).

Clinical need

The BMES and MVIP studies (described previously, page 11) have estimated the incidence and prevalence of glaucoma in Australia. In both the BMES (Mitchell et al. 1996) and the MVIP (Wensor et al. 1998), glaucoma was defined as the presence of matching optic disc cupping, rim thinning and glaucomatous visual field defects on automated perimetry. The BMES estimated the prevalence of open angle glaucoma to be 3% (95% CI: 2.5–3.6). Only 50% of glaucoma cases had been previously diagnosed. The reported prevalence of definite POAG was 1.7% (95% CI: 1.2–2.2). The prevalence of PACG was 0.1%, and the prevalence of secondary glaucoma was 0.2%. A similar proportion of people with a previous diagnosis of glaucoma was observed when compared with the BMES (49%).

Results from these studies, combined with demographic figures about the Australian population (Australian Bureau of Statistics 2008), have been used to calculate age- and gender-adjusted estimates of the prevalence of probable or definite glaucoma in Australians over the age of 50 years in 2007 (Table 11). Based on these figures, there were between 178,000 and 210,000 people with glaucoma in Australia in 2007. In addition, published projections for the number of Australians with glaucoma in 2030 are also provided in Table 11 (Rochtchina et al. 2000). It was projected that there will be between 304,000 and 347,000 Australians living with glaucoma in 2030.

In addition, the MVIP estimated the prevalence of possible glaucoma to be approximately 1.2% overall (Wensor et al. 1998). Applying age- and gender-specific estimates to Australian population data (Australian Bureau of Statistics 2008), it is estimated that there were approximately 117,300 prevalent cases of possible glaucoma at the end of 2007.

Table 11 Age- and gender-adjusted estimates of the number of Australians over 50 with glaucoma in 2007, and projected to 2030

		Probable ('000s)		Definite ('000s)		All glaucoma ('000s)	
		BMES	MVIP	BMES	MVIP	BMES	MVIP
2007	Males	8.3	14.1	51.2	68.9	59.5	83.0
	Females	31.0	34.4	87.6	92.6	118.6	127.0
	Total	39.3	48.5	138.8	161.5	178.1	210.0
2030 [a]	Total	67.3	66.4	239.4	271.2	303.9	346.6

Abbreviations: BMES, Blue Mountains Eye Study; MVIP, Melbourne Visual Impairment Project

[a] Source: Rochtchina et al. (2000)

The MVIP also estimated the incidence of glaucoma, diagnosed by IOP measurement, visual field assessment, cup-to-disc ratio measurement and stereo optic disc photography over a follow-up period of five years (Mukesh et al. 2002). The five year incidence was 0.5% (95% confidence limit [CL]: 0.3–0.7) for definite open angle glaucoma; 1.1% (95% CL: 0.8–1.4) for definite or probable open angle glaucoma; and 2.7% (95% CL: 1.8–3.7) for definite, probable or possible open angle glaucoma. These figures, combined with Australian population statistics (Australian Bureau of Statistics 2008), have been used to calculate age- and gender-adjusted estimates of the number of incident cases of glaucoma in the Australian population aged 40 and over in 2007 (Table 12). Using this methodology, it is estimated that there were approximately 16,200 definite, 14,900 probable and 30,400 possible incident glaucoma cases in 2007. However, since incidence in the MVIP was determined by routine follow-up, these figures represent overestimates of the rate of detection of glaucoma in clinical practice.

Table 12 Age- and gender-adjusted estimates of the number of incident cases of glaucoma in Australians aged 40 years and over, 2007

	Definite ('000s)	Probable ('000s)	Possible ('000s)	Total ('000s)
Males	7.2	7.3	14.2	28.7
Females	9.0	7.6	16.2	32.8
Total	16.2	14.9	30.4	61.5

Potential utilisation of OCT

Based on an estimated annual incidence of 30,400 cases of possible glaucoma (the patient group most closely approximating those who would undergo OCT) (Table 12), and an estimation that approximately 50% of these cases are diagnosed in clinical practice (Mitchell et al. 1996; Wensor et al. 1998), it is therefore estimated that the potential annual utilisation of diagnostic OCT for glaucoma will be approximately 15,200 scans.

Based on a prevalence of probable and definite glaucoma of between 178,100 and 210,000 cases, an estimation that approximately 50% of these cases are diagnosed in clinical practice (Mitchell et al. 1996; Wensor et al. 1998), and expert advice which suggests that all diagnosed patients are treated, it is estimated that between 89,000 and 105,000 patients per year will be eligible for OCT examination for monitoring of therapy. Expert advice indicates that monitoring OCT scans in treated patients will occur with a frequency of between once per year and once every eight months (an average of 1.5

scans per year). This corresponds to a range of expected utilisation of between 89,000 and 157,500 scans per year.

Therefore, the total potential utilisation of OCT (diagnosis and monitoring combined) based on epidemiological data is estimated to range between 104,200 and 172,700 scans annually.

Existing procedures

Fundus fluorescein angiography

Fundus fluorescein angiography (FFA) is a procedure for studying retinal and choroidal circulation and has been used to assess chorioretinal disorders since the early 1960s (Novtny et al. 1961). It is now one of the most commonly performed investigations in ophthalmology (Musa et al. 2006). The procedure involves the intravenous injection of sodium fluorescein ($C_{20}H_{12}O_5Na$) dye, which diffuses through the choriocapillaris but does not cross the retinal pigment epithelium or retinal vascular endothelium. The dye emits a yellow-green light (fluorescence) of wavelength 520–530 nm after a blue light of wavelength 465–490 nm is projected into the eye (Jumper et al. 2006). These frequencies are within the visible spectrum, thus allowing conventional photographic techniques to capture angiographic images. Digital image acquisition is also possible, and digital angiographic systems may contain software that aids in image interpretation. Conditions that affect the intact blood–retinal barrier, blood flow or the pigmentation of the retina or pigment epithelium can cause abnormalities which are visible on FFA. Angiographic abnormalities are broadly categorised as increased fluorescence (hyperfluorescence) or decreased fluorescence (hypofluorescence).

Protocols for conducting FFA may differ between centres, but a common protocol involves the positioning of the patient at the retinal camera, where stereoscopic colour and red-free photographs centred on the macula are taken before injection (Benjamin 2007). The patient is then rapidly (<6 seconds) injected with 5 ml of 10% sodium fluorescein (Jumper et al. 2006). Image capture through a yellow filter then begins at the time when it is anticipated that the dye will reach the eye (typically 8–12 seconds) and at intervals thereafter. Late stereophotographs may be taken at between 5 and 10 minutes after injection.

Adverse events related to FFA have been reported in the literature. A recent Australian study of nearly 12,000 patients undergoing the procedure found nausea to be the most common adverse reaction (0.7%), followed by vomiting (0.4%) and dizziness (0.3%) (Kwan et al. 2006). These reactions were categorised as 'mild' and were noted to be transient (lasting for seconds to minutes). 'Moderate' adverse reactions included fainting (0.1%), localised reactions such as pain and oedema (0.1%) and urticaria (0.2%). There were no severe reactions (eg seizure, myocardial infarction, anaphylactic attack) or deaths. However, mortality has been reported in the international literature, and Kwan et al. (2006) note two (unpublished) deaths associated with FFA in Australia. The risk of death associated with FFA has previously been estimated at 1 in 220,000 (Yannuzzi et al. 1986).

Computerised perimetry

Perimetry, or visual field testing, involves the non-invasive measurement of the field of perception of the eye. The two major types of perimetry are static and kinetic perimetry (though the latter is now seldom performed in practice). Static perimetry involves gradually increasing the brightness of an object within the visual field until it becomes perceptible; in kinetic perimetry, an object of fixed size and brightness is moved slowly from outside towards the centre of the visual field until the patient can see it (James 2007a). Both approaches allow the mapping of the patient's visual field.

Computerised or (standard) automated perimetry (eg the Humphrey field analyser) has largely replaced older perimetry technology (eg the Goldmann perimeter) for visual field testing (James 2007a). Computerised perimetry typically involves static visual field assessment, with a 'staircase' approach undertaken to determine thresholds. Algorithms such as the Swedish interactive testing algorithm (SITA) may also be used to determine thresholds with fewer steps, thus reducing testing time (and therefore patient fatigue and, potentially, test reliability). Test strategies may be employed to concentrate on particular areas of the visual field, typically the central 24 degrees, 30 degrees or (for those with severe glaucoma) 10 degrees. The advent of computerised perimetry has also allowed for patient data to be compared against a normal population database. Short wave automated perimetry (SWAP) and frequency doubling technology (FDT) perimetry are more recent iterations of computerised perimetry.

Slit-lamp biomicroscopy

The slit-lamp is one of the most fundamental examination tools in ophthalmology, and has been in use in various forms for over a century. It utilises an illuminator, which projects a thin slit of light into the eye, and a binocular microscope through which the examiner observes light reflected from ocular structures (James 2007b). The illuminator can be adjusted in terms of the intensity, height, width, angle and colour of the slit-beam. The magnification of the microscope may also be adjusted (up to 25x in most microscopes in common use, although greater magnification is possible). The greater the magnification used, the less the depth of focus.

The attachment of additional equipment to the slit-lamp allows for a range of other investigations to be undertaken. Contact lenses allow three-dimensional viewing of the iridocorneal angle (gonioscopy); contact or non-contact lenses allow three-dimensional viewing of the retina (fundoscopy); and the attachment of a tonometer allows for the measurement of IOP (James 2007b).

Recent technologies

Confocal scanning laser ophthalmoscopy

The scanning laser ophthalmoscope (SLO) was first introduced into clinical practice in the early 1980s as a technique for imaging the optic nerve head (Bartsch et al. 2006). The scanner focuses a laser beam on the retina, with reflected light being focussed onto a photodetector and recorded on either video tape or a computer (Sharp et al. 2004). The laser beam scans across the retina one line at a time at high speed; between 20 and 30 frames per second are captured by the SLO, with between 256 and 1,536 lines per frame.

The reflected light is quantified, allowing for the construction of two-dimensional images of the posterior segment of the eye (McNaught 2007). The introduction of confocal scanning laser ophthalmoscopy (CSLO) in 1987 improved image contrast and allowed for the construction of three-dimensional images (Sharp et al. 2004). Confocal (a contraction of 'conjugate' and 'focal') imaging reduced the amount of reflected light detected from retinal areas outside the focal plane by introducing a narrow aperture, through which the reflected light must pass before being detected by the machine.

There are a number of companies that manufacture CSLO instruments; however, the most widely available CSLO is the Heidelberg retinal tomograph (HRT), and specifically the HRT II (there are three types of CSLO produced by Heidelberg) (McNaught 2007; Sharp et al. 2004). The HRT II includes diagnostic software to aid in image interpretation; in particular, there are a number of algorithms available for discriminating glaucomatous from normal subjects.

Scanning laser polarimetry

Scanning laser polarimetry (SLP) is performed by the GDx or (more recently) the GDx VCC (variable corneal compensation) technologies to measure the thickness of the RNFL (McNaught 2007). Infrared laser light with a wavelength of 780 nm is sent to the posterior retina, and the change in polarisation (retardation) of the reflected beam is assessed. The retardation of the scanning beam results from the birefringent properties of the neurotubules contained within ganglion cell axons. A high resolution image of 256 by 256 pixels is created of the optic nerve and peripapillary retina. Three serial scans are obtained in one test. SLP measures RNFL thickness throughout the entire image. However, RNFL thickness for the double hump is determined along a 3.2-mm-diameter 8-pixel-wide circle, centred on the calculation circle. The double hump (or temporal-superior-nasal-inferior-temporal [TSNIT] graph) is a graphic plot of the RNFL thickness around the optic nerve, with superior and inferior poles having the greatest RNFL thickness as opposed to the nasal and temporal poles. Some of the parameters presented are based on the RNFL thickness measurements within the calculation circle, but the nerve fibre indicator (representing the likelihood of glaucomatous RNFL loss) is based on the entire RNFL thickness map (Lin et al. 2007). In the anterior segment, the cornea and lens are also birefringent and may affect measurements. Therefore, anterior segment birefringence needs to be neutralised by a so-called corneal compensator (Lemij et al. 2008). The updated device, GDx with VCC, incorporates individualised compensation for the corneal component (Lin et al. 2007). More recently, an alternative algorithm known as enhanced corneal compensation (ECC) has been introduced, and has been proposed to increase accuracy compared with VCC by reducing the signal-to-noise ratio (Saito et al. 2008).

Potential impact of OCT on patients

In patients with suspected macular disease, OCT is expected to increase sensitivity for detecting macular abnormalities, leading to the initiation of treatment in patients who would otherwise be observed. In addition, high specificity of OCT would lead to the avoidance of unnecessary invasive testing with FFA in some patients.

In patients with suspected glaucoma, OCT is expected to increase sensitivity for detecting glaucomatous damage, leading to the initiation of treatment in patients who would otherwise be observed.

Reference standard

For macular diseases, clinical follow-up was considered the most valid reference standard to determine true disease status of patients for assessment of OCT accuracy in this review. For glaucoma, a composite of one or more of clinical follow-up, ophthalmoscopy, photography, and computerised perimetry was considered the most valid reference standard for the determination of diagnostic accuracy.

Comparator

Macular diseases

The comparator for OCT in initial diagnosis of macular diseases (other than tractional diseases) is standard clinical examination plus FFA. OCT is considered as a replacement test for FFA in first line diagnosis (although some patients with a positive OCT will still proceed to FFA to guide therapy).

The comparator for OCT in initial diagnosis of tractional diseases is standard clinical examination plus observation. OCT is considered an additional test to standard clinical examination.

The comparator for OCT in monitoring macular diseases is standard clinical examination plus FFA. OCT is considered an additional test to FFA and clinical examination in the monitoring strategy (with FFA being undertaken with reduced frequency).

Glaucoma

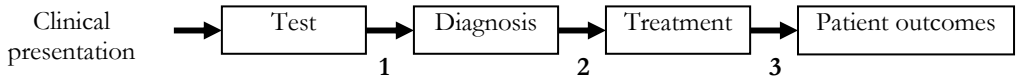
The comparator for OCT in initial diagnosis of glaucoma is standard clinical examination plus computerised perimetry. OCT is considered an additional test to clinical examination and computerised perimetry.

The comparator for OCT in monitoring glaucoma is standard clinical examination plus computerised perimetry. OCT is considered an additional test to clinical examination and computerised perimetry in the monitoring strategy.

Methodological considerations

The clinical value of a test depends on whether its use improves patient outcomes (Figure 1). This is determined by its ability to accurately detect or exclude disease, whether this information influences treatment decisions, and the effectiveness of the treatment selected.

Figure 1 Causal pathway and determinants of the clinical value of a test



1. Diagnostic accuracy
2. Therapeutic impact
3. Treatment effectiveness

If RCTs are not available to assess whether adopting a new test improves patient outcomes compared to standard testing practice, evidence from studies assessing test accuracy and therapeutic impact can be linked to evidence about treatment efficacy or improved prognosis to infer effectiveness in some situations.

There are guidelines for designing, conducting, reporting and appraising studies of test accuracy, treatment efficacy and patient prognosis (National Health and Medical Research Council 1999); however, the methods for designing and interpreting therapeutic impact studies are less well established. The role of these studies is to provide evidence that the test information has an impact on clinical decision-making, for example, by demonstrating changes in clinician diagnostic certainty, test ordering and/or treatment plans. This evidence is interpreted with evidence about the benefits or harms of these decisions, either through a simple descriptive assessment or quantitatively using decision-analytic methods, for a judgement about the potential clinical value of the test or the need for further research to demonstrate effectiveness.

Demonstrating a change in diagnosis and/or treatment does not by itself provide evidence of effectiveness; therefore, therapeutic impact studies need to be carefully designed to address a clearly defined question about the potential benefits of the test on clinical decision-making with an explicit statement about existing evidence for the effectiveness or cost-effectiveness of these decisions (for example, improved patient outcomes through reduction of invasive testing, increase in effective treatment, reduction in patient anxiety). Therapeutic impact studies can be designed as randomised trials to assess clinician diagnostic certainty, diagnosis and treatment selection with and without the new test, or as observational studies including pre-and-post test studies where clinicians are asked to record their provisional diagnosis, diagnostic certainty and proposed management plan before and after testing. Data are analysed to report on change in diagnostic thinking and therapeutic plans and interpreted with information about the accuracy of the test and the true disease state of the subject to assess the benefits or harms of the test information.

Marketing status of the technology

The Australian Register of Therapeutic Goods (ARTG) number for OCT is 96556.

It is the expert opinion of the Advisory Panel that OCT machines are located in every Australian state capital city and in the Australian Capital Territory. Machines are also located in some major population centres outside capital cites. Wide dissemination of the technology has occurred across Australia, and as such it not possible to accurately describe the number of machines around the country. Expert opinion suggests that the technology will become increasingly widespread.

Current reimbursement arrangement

There are currently no specific MBS item numbers that cover OCT for the diagnosis and monitoring of macular diseases or glaucoma.

Approach to assessment

Research question

Specific research questions addressing the value of OCT as a diagnostic test for the assessment and monitoring of macular diseases and glaucoma were developed by the evaluators working in consultation with members of the Advisory Panel. These questions were formulated *a priori* based on information about the characteristics of macular diseases and glaucoma, current practice and the intended purpose of the technology using the PICO criteria (population, intervention, comparator and outcomes) (Table 13–Table 16).

Flow charts (see Appendix C) depicting the clinical pathways for diagnosing, monitoring and treating macular diseases and glaucoma were developed with the Advisory Panel. These flow charts were used to define the potential role of OCT in patient management.

The research questions were:

- What is the value of optical coherence tomography compared with fundus fluorescein angiography or a clinical observation strategy in the diagnosis of macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy, tractional diseases of the macula, macular oedema and neovascularisation?

- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and fundus fluorescein angiography in the monitoring of patients with macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy and macular oedema?

- What is the additional value of optical coherence tomography over that of computerised perimetry and clinical examination in the diagnosis of glaucoma, in patients with risk factors for glaucoma with questionable clinical examination (glaucoma-like optic discs)?

- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and computerised perimetry in the monitoring of patients treated or with risk factors for glaucoma?

Table 13 PICO criteria and clinical questions: Optical coherence tomography (OCT) for diagnosis of macular diseases

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Diagnoses: • Macular degeneration • Diabetic maculopathy • Other (non-diabetic) retinal vascular diseases • Uveitic maculopathy • Central serous retinopathy • Tractional disease of the macula (macular holes, epiretinal membrane, vitreomacular traction syndromes) • Macular oedema • Neovascularisation	Clinical examination	OCT (+ FFA in non-tractional OCT positives)	FFA Observation	Clinical examination (follow-up over time)	Diagnostic accuracy [a] • Sensitivity • Specificity • NPV • PPV • Accuracy Impact on patient management Health Outcomes • Visual acuity • QoL Safety

Abbreviations: FFA, fundus fluorescein angiogram; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; QoL, quality of life

[a] Yield may be used when accuracy cannot be calculated

Table 14 PICO criteria and clinical questions: Optical coherence tomography (OCT) for monitoring of macular diseases

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Macular diseases: • Macular degeneration Diabetic maculopathy • Other (non-diabetic) retinal vascular diseases Uveitic maculopathy • Central serous retinopathy • Macular oedema	Clinical examination	OCT +/– FFA	FFA	Clinical examination (follow-up over time)	Diagnostic accuracy [a] • Sensitivity • Specificity • NPV • PPV • Accuracy Impact on patient management Health Outcomes • Visual acuity • QoL Safety

Abbreviations: FFA, fundus fluorescein angiogram; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; QoL, quality of life

[a] Yield may be used when accuracy cannot be calculated

Table 15 PICO criteria and clinical questions: Optical coherence tomography (OCT) for diagnosing glaucoma

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with risk factors for glaucoma with questionable clinical examination (glaucoma-like optic discs)	Clinical examination	OCT +/– computerised perimetry	Computerised perimetry	Composite of one or more: • Clinical examination (follow-up over time) • Ophthalmoscopy • Photography Computerised perimetry	Diagnostic accuracy [a] • Sensitivity • Specificity • NPV • PPV • Accuracy Impact on patient management Health Outcomes • Visual acuity • QoL Safety

Abbreviations: NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; QoL, quality of life
[a] Yield may be used when accuracy cannot be calculated

Table 16 PICO criteria and clinical questions: Optical coherence tomography (OCT) for monitoring glaucoma

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with risk factors for glaucoma (eg family history) (not actively treated) Patients with treatment initiated for glaucoma	Clinical examination	OCT + computerised perimetry	Computerised perimetry	Composite of one or more: • Clinical examination (follow-up over time) • Ophthalmoscopy • Photography Computerised perimetry	Diagnostic accuracy [a] • Sensitivity • Specificity • NPV • PPV • Accuracy Impact on patient management Health Outcomes • Visual acuity • QoL Safety

Abbreviations: NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; QoL, quality of life
[a] Yield may be used when accuracy cannot be calculated

Assessment framework

Types of evidence

In the absence of any direct evidence for the effectiveness of OCT, effectiveness evidence is presented with a linked approach, considering the evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes.

Review of the literature

A systematic review of the medical literature was conducted to identify relevant studies. Websites of international health technology assessment (HTA) agencies were searched for existing HTA reports (see Appendix D) and electronic databases of published research (Table 17) were searched for original research papers, including systematic reviews. Initially, the literature search period extended between January 1990 and April 2008. However, due to the publication of a relevant paper after completion of the initial search, the literature search was updated to August 2008.

A search of clinical trial databases (Table 18) was undertaken, supplemented by information provided by the applicant, to identify ongoing studies.

Table 17 Electronic databases searched

Database	Period covered
EMBASE.com (includes EMBASE and MEDLINE)	January 1990–August 2008
Premedline	January 2005–August 2008
All-EBM databases (includes The Cochrane Library, Database of Abstracts of Reviews of Effects, ACP Journal Club, NHS Economic Evaluation Database, Health Technology Assessment Database)	Up to August 2008

Table 18 Databases searched to identify ongoing studies

www.controlled-trials.com
www.clinicaltrials.gov
www.actr.org.au
www.acrin.org
www.cancer.gov/search/clinical_trials/
www.ncchta.org/ProjectData/1_project_select.asp

Search strategy

The search strategy was developed using the key elements of the clinical question. The search strategy shown in Table 19 was used to identify papers in Embase.com. This search was adapted for the other databases described in Table 17.

Table 19 Search strategy for EMBASE.com (containing MEDLINE and EMBASE)

Element of clinical question	Search terms
Population	1 'retina macula degeneration'/syn OR 'retina macula degeneration'
	2 'diabetic macular edema'/syn OR 'diabetic macular edema'
	3 'retina blood vessel'/syn OR 'retina blood vessel'
	4 'central serous retinopathy'/syn OR 'central serous retinopathy'
	5 'retina macula hole'/syn OR 'retina macula hole'
	6 'epiretinal membrane'/syn OR 'epiretinal membrane'
	7 (('vitreous disease'/exp OR 'vitreous disease') AND traction*:ti,ab) OR 'vitreomacular traction':ab,ti
	8 'retina macula edema'/syn OR 'retina macula edema'
	9 'retina neovascularization'/syn OR 'retina neovascularization'
	10 'glaucoma'/syn OR 'glaucoma'
	11 or/1-10
Index test	1 'optical coherence tomography'/syn OR 'optical coherence tomography'
	2 1 AND [Population search string]
Comparator (if applicable)	nil
Outcomes (if applicable)	nil

Reference lists of included publications were also checked and experts in the field were contacted for relevant citations that may have been inadvertently missed in the searches of major databases.

Search results

Existing health technology assessment reports

Four HTA reports or systematic reviews on the value of OCT for the investigation of macular diseases or glaucoma were identified by the search (see Appendix F). Two of these reports evaluated the use of OCT for macular diseases only (McDonald et al. 2007; Virgili et al. 2007b); one report considered glaucoma only (Lin et al. 2007); and one considered both indications (Alberta Heritage Foundation for Medical Research 2003).

Eligibility criteria for studies

The search strategy retrieved a total of 2,490 non-duplicate citations. The citations were evaluated by one reviewer, who determined whether the retrieved studies met the eligibility criteria outlined in Table 20. A sample of 605 citations (24%) was checked by a second reviewer and discrepancies in the results of the screening process were resolved by discussion.

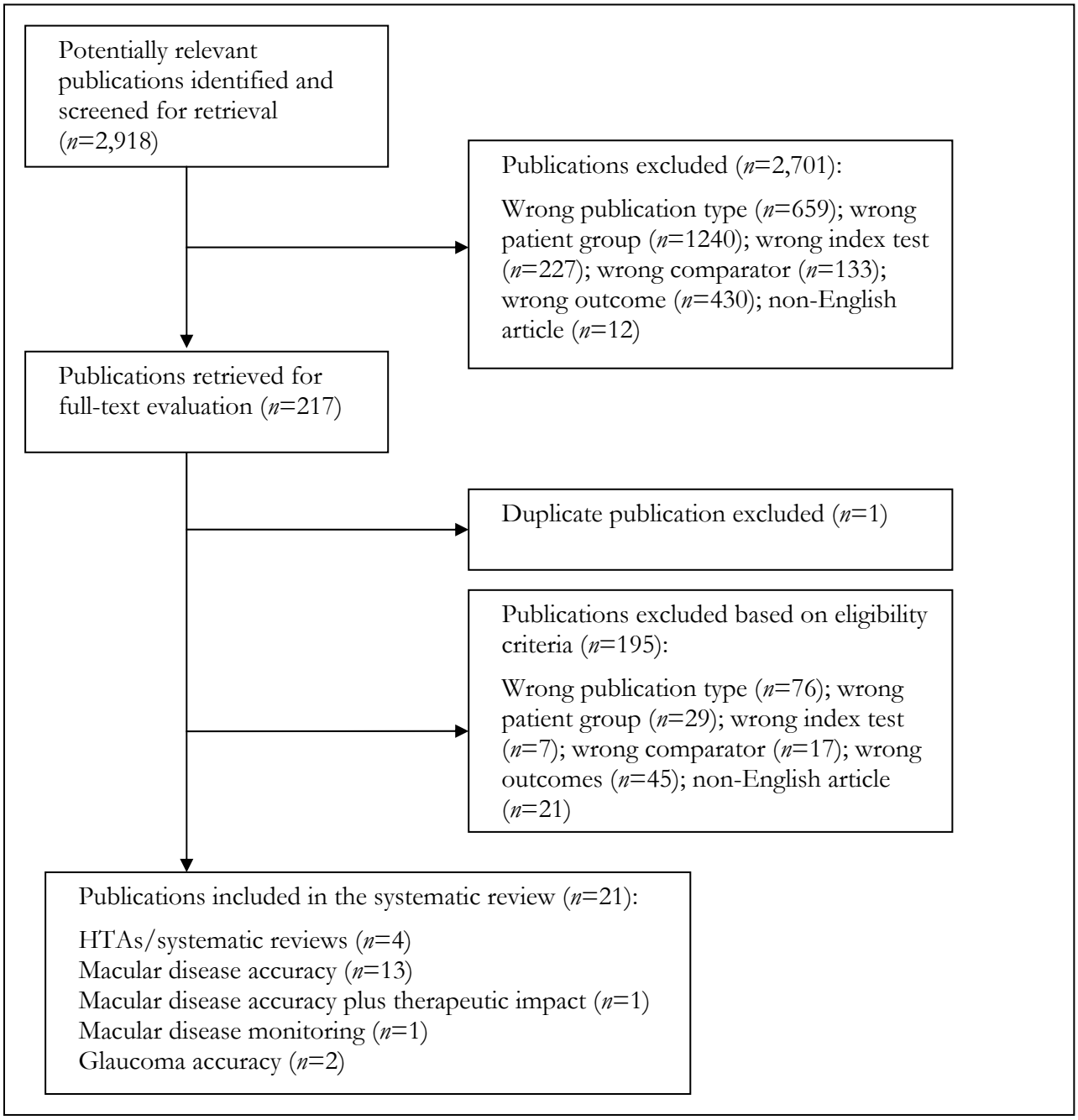
Table 20 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Non-comparative studies will be excluded for glaucoma. Non-systematic reviews, letters, editorials, animal, in-vitro, laboratory studies, conference abstracts and technical reports will be excluded **Systematic reviews** Systematic reviews that have been superseded will be excluded **Primary studies** Primary studies published during the search period of included systematic reviews will be excluded Accuracy studies will be excluded if: • patients were selected for inclusion in the study based on their known disease (case-referent, case-control studies) Change in patient management studies will be excluded if: • reported outcomes are a subjective rating of physician's perceived usefulness of the test without actual changes in management plan
Patient	≥ 70% of patients with suspected macular diseases, including: • Macular degeneration • Diabetic maculopathy • Other retinal vascular disease • Uveitic maculopathy • Central serous retinopathy • Tractional disease of the macula • Macular oedema • Neovascularisation ≥ 70% of patients with suspected glaucoma Studies with <20 patients undergoing OCT for the indication of interest will be excluded
Index test	OCT (macular diseases diagnosis) OCT + FFA (macular diseases monitoring) OCT + computerised perimetry (glaucoma diagnosis and monitoring)
Comparator	FFA Computerised perimetry Observation
Outcome	Studies must report on at least one of the following outcomes: • Diagnostic accuracy: sensitivity and specificity (or data enabling calculation); diagnostic odds ratios or ROC curves; Q* • Yield (may be used when accuracy cannot be calculated) • Impact of OCT results on clinical management • Patient outcomes (visual acuity, adverse events, quality of life)
Language	Non-English language articles will be excluded

Abbreviations: FFA, fundus fluorescein angiography; OCT, optical coherence tomography; ROC, receiver operating characteristic

Based on these criteria, 2,474 citations were excluded from the review. The QUOROM (Quality of Reporting of Meta-analyses) flowchart (Figure 2) summarises the results of the literature search and the application of the study exclusion criteria.

Figure 2 QUOROM flowchart summarising the results of the literature search and the application of entry criteria



In addition to the four HTAs and systematic reviews identified, 17 primary studies met the criteria for inclusion in this assessment; 15 were studies of macular diseases, including 13 studies of diagnostic test accuracy, 1 study of therapeutic impact (also reporting accuracy information) and 1 monitoring study. Two further glaucoma accuracy studies meeting the inclusion criteria for glaucoma were identified. No ongoing studies were found.

Evidence appraisal

Assessment of eligible studies

The evidence presented in the selected studies was appraised and classified using the NHMRC Dimensions of Evidence (National Health and Medical Research Council 1999, 2005) and the MSAC Diagnostic Test Guidelines (Medical Services Advisory Committee 2005). These dimensions (Table 21) consider important aspects of the evidence supporting a particular diagnostic test and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular diagnostic test. The last two require expert clinical input as part of their determination.

Table 21 Dimensions of evidence [a]

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

[a] Adapted from NHMRC (1999) and MSAC (2005)
[b] See Table 22

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 22.

Table 22 Designations of levels of evidence (pilot)

Level	Intervention	Diagnosis
I	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III-1	A pseudo-randomised controlled trial (ie alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study
IV	Case series with either post-test or pretest/post-test outcomes	Study of diagnostic yield (no reference standard)

Source: National Health and Medical Research Council (2005)

Quality appraisal

The quality of a study refers to the extent to which it has been designed and conducted to reduce bias in the estimation of the outcome. The potential sources of bias vary according to whether the study is designed to estimate the impact of the test on health outcomes (where the ideal is a randomised trial of alternative tests) or to estimate the diagnostic accuracy of the test (for which the ideal is a cross-sectional analytic study of consecutive patients tested using both the test of interest and a valid reference standard).

A structured appraisal was performed to assess the quality of all included studies. The quality of studies of diagnostic test accuracy was assessed using a checklist of 12 items adapted from the QUADAS (Quality Assessment of studies of Diagnostic Accuracy included in meta-analyseS) tool developed by Whiting et al. (2003) (Appendix E, Table 31). This tool was developed recently by experts in the field following a systematic review of the evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy. Studies were required to meet all 12 criteria to be assessed as high quality. In addition, only prospective diagnostic test accuracy studies were assessed as high quality. Studies that did not use a valid reference standard in all patients were classified as low quality.

Seven criteria were applied to assess the quality of systematic reviews, as outlined below (Appendix E, Table 32). For the criterion addressing heterogeneity, systematic reviews that did not undertake a meta-analysis were rated 'not applicable' (N/A), unless heterogeneity was specifically mentioned. Studies were required to meet all seven criteria to be assessed as high quality. A study with four or fewer 'yes' or 'N/A' ratings was considered to be of low quality.

Criteria for appraising the quality of therapeutic impact studies were not available. Therefore a checklist was developed based on criteria discussed by Guyatt et al. (1986) (Appendix E, Table 33).

Quality criteria for interventions were applied to studies investigating the effectiveness of monitoring strategies (Appendix E, Table 31). For RCTs, studies were required to meet

all 10 criteria to be assessed as high quality. A study with five or fewer 'yes' or 'N/A' ratings was considered to be of low quality. In addition, studies without true randomisation, allocation concealment or blinded outcome assessment were classified as low quality. For cohort study designs, studies were required to meet all nine criteria to be assessed as high quality. A study with five or fewer 'yes' or 'N/A' ratings was considered to be of low quality.

Data analysis

The characteristics of the study population, type of diagnostic test, reference standard, comparator, study quality and relevant endpoints were extracted for each included study.

Ninety-five per cent confidence intervals were calculated where these were not presented. Comparisons of proportions were conducted using Pearson's χ^2 test, the Fisher exact test or McNemar's test for correlated proportions.

Measurement of test accuracy

The accuracy of a test is determined by its ability to identify the target condition compared to a reference standard test that is used as a proxy for true disease status. Subjects who test positive using the reference standard are classified as having the disease and those who test negative are classified as disease-free.

Results of the index test and reference standard for a group of tested subjects were summarised in a two-by-two table as shown in Figure 3.

Figure 3 Two-by-two table displaying the data used to determine test accuracy

		Reference standard	
		disease +	disease –
Index test		true positive (TP)	false positive (FP)
		false negative (FN)	true negative (TN)
		TP + FN	TN + FP

Total number of subjects tested = TP + TN + FP + FN
Number of subjects with disease = TP + FN
Number of subjects without disease = TN + FP

As shown, subjects who test positive for the disease of interest by both the index test and the reference standard were recorded as true positives (TP). Subjects without the target condition who test negative by both tests were recorded as true negatives (TN). The index test result was recorded as a false positive (FP) if it detected the target condition and the reference standard did not. A false negative (FN) was recorded if the reference standard confirmed the target condition and the index test did not.

Sensitivity and specificity

The sensitivity of a test is the probability of a positive test in subjects with the disease of interest. The specificity of a test is the probability of a negative result in subjects without the disease. The sensitivity and specificity of a test are always considered together and vary according to the threshold used to define a positive test. Sensitivity and specificity are known to vary according to the spectrum of disease (for example, variation in disease

severity) in the patient group tested. High sensitivity is particularly important if the penalty for missing disease is high. However, high specificity is particularly important if a false positive result can harm the patient.

Calculation of sensitivity and specificity is as follows:

- sensitivity = TP/(TP + FN)
- specificity = TN/(TN + FP).

Likelihood ratios and diagnostic odds ratio

Measures that combine estimates of sensitivity and specificity may be useful for the comparison of multiple tests, particularly in a scenario where a new test outperforms an existing test on one test characteristic but not the other (eg increased sensitivity, but reduced specificity). Likelihood ratios (LRs) combine sensitivity and specificity to describe the ratio of a positive or negative test result in patients with the disease to the same result in those without the disease.

Calculation of LRs is as follows:

- positive likelihood ratio = sensitivity / (1 – specificity)
- negative likelihood ratio = (1 – sensitivity) / specificity.

The diagnostic odds ratio (DOR) is a single estimate of test performance, and describes the ratio of the odds of a positive test result in those with disease to the odds of the same result in those without disease. The greater the value of the DOR, the higher is the discriminatory power of the test.

Calculation of the DOR is as follows:

- diagnostic odds ratio = positive LR / negative LR.

Positive and negative predictive value

In studies reporting the additional value of a test, only patients testing positive may receive follow-up with the reference standard. In this case the proportion of positive test results that were correct (positive predictive value, PPV) was calculated. Where patients with discordant negative results also receive the reference standard, the proportion of negative test results that were correct (negative predictive value, NPV) was calculated.

Calculation of positive and negative predictive value is as follows:

- positive predictive value = TP/(TP + FP)
- negative predictive value = TN/(TN + FN).

Data extraction

Data were extracted using a standardised instrument designed for this review. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion. The data extraction tables are provided in

Appendices G through J. Where possible, two-by-two tables were reconstructed from study data to estimate sensitivity, specificity and associated 95 per cent confidence intervals for each test.

Expert advice

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

Results of assessment

Is it safe?

OCT is considered to be a safe procedure. It is a non-invasive, non-contact technique that involves a low coherent, infrared light source (approximately 800 nm) (Chen et al. 2007). Dilatation of the pupil is undertaken as part of the routine clinical examination. An HTA review conducted by the Alberta Heritage Foundation for Medical Research (2003) concluded that it is unlikely that patients would suffer any adverse effects as a consequence of undergoing an OCT scan. There were no studies identified in the current assessment which reported any adverse events associated with the use of OCT.

Macular diseases: Is it effective?

OCT for diagnosing macular disease

No studies were identified which provided direct evidence of the impact of OCT on patient outcomes in patients with macular disease.

Ten Level IV studies reported the comparative yield of OCT and FFA in diagnosing macular oedema. A meta-analysis of these data found that a similar number of patients would be diagnosed with macular oedema by either test (incremental yield of OCT = 1% [95% CI: –1 to 2%; p=0.39]). However, some patients positive on OCT would be negative on FFA (median = 9%; range: 0 to 21%) and some patients negative on OCT would be positive on FFA (median = 4%; range: 0 to 26%). In the absence of a reference standard to determine 'true' disease state in patients with discordant test results, the clinical significance of these results is uncertain.

Four Level IV studies reported the incremental yield of OCT over prior clinical examination in diagnosing tractional diseases. One of two studies reported an incremental yield of 33% to 37% for OCT in diagnosing epiretinal membrane (0% in the other study); two of two studies investigating vitreomacular traction reported an incremental yield of OCT (range: 12% to 23%); and a single study reported an OCT incremental yield of between 5% and 7% for the diagnosis of macular holes. In the absence of a reference standard to determine 'true' disease state in 'extra' diagnosed patients, the clinical significance of these results is uncertain.

One study reported a change in management plan from observation (pre-OCT) to surgery (post-OCT) in 17% (95% CI: 10.2–26.1%) of patients with epiretinal membranes or vitreomacular traction.

Due to uncertainties regarding the accuracy of OCT, and in the absence of prognostic studies of patients with discordant test results, a linked evidence approach to demonstrate the effectiveness of OCT is not possible.

OCT for monitoring treated or untreated patients with macular disease

No RCTs were identified which compared a monitoring strategy involving OCT to a strategy involving FFA in patients with treated or untreated macular disease.

A single small, non-randomised, low quality Level III-2 study found that eyes with AMD treated with photodynamic therapy (PDT) experienced non-significant decrements in best corrected distance acuity at 12 months when monitored by FFA alone relative to monitoring with OCT plus FFA. The proportion of eyes with a loss of distance acuity of more than three lines was significantly higher in the group monitored with FFA alone. The precision of these estimates is limited by biases inherent in this study; therefore the effectiveness of OCT for monitoring of PDT in patients with AMD remains uncertain.

Existing HTAs and systematic reviews

A search for existing HTA reports and published systematic reviews on OCT in the assessment of macular diseases yielded three reports published between 1990 and 2008 (Alberta Heritage Foundation for Medical Research 2003; McDonald et al. 2007; Virgili et al. 2007b) (see Appendix F). The reports focused primarily on OCT in diagnosing macular oedema, though one report included other patient groups (McDonald et al. 2007). None of the three reviews reported the comparative accuracy of OCT and FFA. The characteristics and quality assessment of these reports are presented in Table 23. The results of these reports are discussed in more detail in the following sections.

American Academy of Ophthalmology (2007)

This HTA reports a systematic review of OCT for diagnosing macular disease, prepared by the American Academy of Ophthalmology (McDonald et al. 2007). The aim of the review was to investigate the accuracy of laser scanning imaging (including OCT, but also HRT and retinal thickness analyser [RTA] technologies) to assess macular diseases compared with a reference standard of slit-lamp biomicroscopy or stereoscopic fundus photography. The accuracy of these technologies was not compared with that of FFA (the relevant comparator defined by this assessment for patients with non-tractional macular disease). This review was assessed to be of 'fair' quality, due to inadequate description of the process by which studies were selected for inclusion in the review. It is noted that a panel reviewed abstracts and determined studies that were 'sufficiently clinically relevant', but the criteria for doing so were not specified.

McDonald et al. (2007) searched the English language literature from 2000 to August 2006. A total of 50 studies examining OCT were included and classified by study design and quality. Level I studies considered a blinded comparison of OCT and a reference standard in a consecutive cohort of an appropriate spectrum of patients (4 studies); Level II studies were non-consecutive and/or included a restricted spectrum of patients, or did not apply the reference standard to all patients (8 studies); and Level III studies used diagnostic case-control designs, employed differential verification or did not apply OCT and the reference standard in an independent, masked manner (38 studies). Level III studies were summarised descriptively. Only one study (classified as Level I) reported measures of the diagnostic accuracy of OCT (in diagnosing macular oedema against a reference standard of stereoscopic fundus photographs)—sensitivity was 92% and specificity was 73%. Other Level I and II studies reported agreement between OCT and other tests, measures of repeatability/reliability or incremental yield over other tests for the detection of postoperative macular oedema, macular holes or epiretinal membrane. Study populations included previously treated and untreated patients. The review concluded that OCT is accurate, reproducible and reliable, and provides additional information that aids in the management of macular disease. However, conclusions

relating to accuracy are based on a single study, and the comparative accuracy of OCT and FFA is not addressed.

Virgili et al. (2007b)

This systematic review was undertaken to estimate the accuracy of OCT in diagnosing macular oedema associated with diabetic retinopathy, using a reference standard of fundus stereophotography or biomicroscopy (Virgili et al. 2007b). The review was assessed to be of fair quality, due to a lack of explicit inclusion and exclusion criteria (all other quality criteria were met). Although the review reported that 15 studies met eligibility criteria for inclusion in the review, only six studies reported the outcome of diagnostic accuracy. Two of the six accuracy studies (Brown et al. 2004; Goebel et al. 2006) were also included in the review by McDonald et al. (2007).

Results of a summary ROC curve analysis indicated that OCT had a sensitivity of 0.79 (95% CI: 0.71–0.86), a specificity of 0.88 (95% CI: 0.80–0.93), a positive likelihood ratio of 6.5 (95% CI: 4.0–10.7) and a negative likelihood ratio of 0.24 (95% CI: 0.17–0.32). The pooled diagnostic odds ratio was 27.7 (95% CI: 17.0–45.3). The accuracy of OCT for detecting macular oedema was not compared with that of FFA.

The authors note that the reference standard adopted in their review was 'imperfect', thereby distorting the reported accuracy of OCT. Furthermore, the use of healthy 'control' subjects in some studies was noted to be problematic, as was the within-patient correlation between eyes (ie analysis of both eyes from single patients) in all studies. It was reported that such issues would inflate the estimates of accuracy of OCT and the precision of these estimates in the included studies. Furthermore, the reporting of uninterpretable results or study withdrawals in the primary studies was considered to be poor. The review concluded that OCT performs well compared with fundus stereophotography or biomicroscopy, but that reporting of diagnostic accuracy studies of OCT should be improved, including the cross tabulation of OCT and reference standard test results.

Alberta Heritage Foundation for Medical Research (2003)

This rapid HTA ('Technote') report was conducted to investigate the value of OCT in diagnosing retinal diseases; however, data were only reported for the indications of cystoid macular oedema and glaucoma (results for the latter indication are discussed on page 62). The review was assessed to be of 'fair' quality. Explicit review questions and eligibility criteria were specified, and a comprehensive literature search was undertaken; however, a structured assessment of quality for included studies was not performed. The review included two studies which investigated the accuracy of OCT using standard diagnostic tests as the reference standard (FFA, slit-lamp biomicroscopy). The accuracy of OCT for detecting macular oedema was not compared with that of FFA. Neither study was included in the reviews by McDonald et al. (2007) or Virgili et al. (2007b).

The sensitivity of OCT (using FFA as the reference standard) was reported to range between 73% and 89%; specificity ranged between 94% and 100%. Methodological issues in the included studies led the authors to conclude that these are overestimates of OCT's diagnostic accuracy. However, the studies included in this review predominantly used a now-obsolete version of the technology (OCT 2000), and more recent generations of OCT could be expected to have superior accuracy. It was concluded that OCT was capable of diagnosing macular oedema in a select group of patients with relatively severe

disease, but its diagnostic performance in mild or moderate disease was uncertain. No studies reporting patient outcomes were presented, and it was concluded that further studies were necessary to establish the clinical impact of OCT on the management and outcomes of patients. OCT as a replacement for FFA was not recommended (Alberta Heritage Foundation for Medical Research 2003).

Table 23 Characteristics and appraisal of included HTA reports (macular disease)

Author (year) Country	Objective & methods	Included studies	Quality assessment of review
American Academy of Ophthalmology McDonald et al. (2007) United States	**Objectives:** 1) To determine whether OCT is a sensitive and specific tool for detecting macular disease when compared with the current standard technique of slit-lamp biomicroscopy or stereoscopic fundus photography **Literature review:** Databases: PubMed, Cochrane Library Time period: 2000–August 2006. Inclusion/exclusion criteria: • Study design not stated *a priori*. Studies not excluded by quality rating • Population: macular disease • Intervention: OCT. Also considered RTA and SLP • Outcomes: not stated *a priori*, but reported accuracy measures and macular thickness parameters • Language: English language articles	4 Level I studies 8 Level II studies 38 Level III studies summarised qualitatively	**Quality: fair** Explicit review questions: yes Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes
Virgili et al. (2007b) Italy	**Objectives:** To review systematically the sensitivity and specificity of OCT for diagnosing macular oedema attributable to diabetic retinopathy compared with fundus stereophotography or contact and non-contact fundus biomicroscopy **Literature review:** Databases: Medline, Embase, hand searching (journals, reference lists) Time period: Medline (1966–September 2006); Embase (2002–September 2006); journal hand search (1998–2006) Inclusion/exclusion criteria: • Studies of OCT accuracy (reference standard: stereoscopic fundus photography, biomicroscopy) • Population: diabetes (use of glucose-lowering medication); clinically significant macular oedema • Intervention: OCT • Outcomes: sensitivity/specificity • Language: no restriction specified	15 included studies 6 described accuracy of OCT	**Quality: fair** Explicit review questions: yes Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: yes Summary of results clear and appropriate: yes
Alberta Heritage Foundation for Medical Research (2003) Canada	**Objectives:** To evaluate the evidence on the use of OCT to diagnose retinal disease **Literature review:** Databases: PubMed, Cinahl, Embase, Cochrane Library, Science	**Macular disease** 2 studies compared OCT against FFA and/or biomicroscopy **Glaucoma** 6 studies compared OCT with perimetry or other tests (SLP,	**Quality: fair** Explicit review questions: yes Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search

Author (year) Country	Objective & methods	Included studies	Quality assessment of review
	Citation Index, Clinical Trials registries, HTA Databases, FDA website, world wide web searches Time period: 1995–July/August 2003. Inclusion/exclusion criteria: • Prospective RCTs or nonrandomised comparative studies, n≥10 per arm • Population: symptoms suggestive of retinal pathology (untreated by surgery) • Intervention: OCT • Outcomes: Area under ROC, sensitivity/specificity, technical failures, patient discomfort, adverse effects • Language: English language articles	CSLO, photography)	strategy: yes Quality of included studies appraised: no Methods of study appraisal reproducible: N/A Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes

Abbreviations: CSLO, confocal scanning laser ophthalmoscope; FDA, Food and Drug Administration; HTA, health technology assessment; N/A, not applicable; OCT, optical coherence tomography; ROC, receiver operating characteristics; RCT, randomised controlled trial; RTA, retinal thickness analyser; SLP, scanning laser polarimetry

Direct evidence

This review did not identify any studies reporting the health outcomes of patients with macular diseases, assessed with and without OCT. Furthermore, no ongoing RCTs were identified. In the absence of direct evidence for the effectiveness of OCT, the evidence for test accuracy, changes in management arising from the test and the expected benefit of changes in management on health outcomes is presented for conclusions about the effectiveness of OCT using a linked evidence approach.

Indirect evidence

Is it accurate?

For all indications except tractional diseases, the comparator test of interest was FFA. No studies were identified which assessed the accuracy of OCT and FFA against clinical follow-up (identified as the most appropriate reference standard to establish the 'true' presence or absence of disease). The absence of such studies reflects the difficulty in validating disease status by clinical follow-up in patients where test results are used to initiate treatment (Rutjes et al. 2008). Theoretically it may be possible to follow up 'negatives' (eg on OCT or FFA, or both, depending on which test or tests inform the decision to initiate treatment) to validate true disease status in these patients. However, where treatment is undertaken in 'positive' patients, this confounds the findings on follow-up (ie the absence of disease may represent a false positive, or a true positive in whom treatment was effective). Therefore, a reference standard of clinical follow-up applied in the above scenario will not produce a valid estimate of the diagnostic accuracy of OCT.

For the indication of tractional diseases (epiretinal membrane, vitreomacular traction syndrome, macular holes), expert advice indicated that FFA was not indicated where there was clinical suspicion of such conditions. Hence, the non-comparative accuracy of OCT in this patient group (or the incremental accuracy over clinical examination) was of interest. However, as for other macular diseases, no studies were identified which reported the accuracy of OCT against a reference standard of clinical follow-up.

Studies exist which compare the test results of OCT against the results of a test (or tests) specified as the comparator in this assessment (ie FFA, or a range of tests undertaken as part of routine clinical examination). It is possible to derive measures of diagnostic accuracy for OCT using the comparator or prior tests as a reference standard; however, since the diagnostic claim of OCT is for greater accuracy than these tests, misclassification by the comparator will distort the reported diagnostic accuracy of OCT. If misclassification by OCT and the comparator are independent (ie they tend to misclassify different patients), the diagnostic accuracy of OCT will be underestimated. Conversely, if misclassification by OCT and the comparator are not independent (ie they tend to misclassify the same patients), the diagnostic accuracy of OCT will be overestimated (Medical Services Advisory Committee 2005). The MSAC *Guidelines for the assessment of diagnostic technologies* state that when the best available reference standard is 'imperfect', and that reference standard is also the comparator, direct (RCT) evidence of the test's impact on patient outcomes is required. However, the examination of discordant test results may provide some additional information about the clinical utility of the test (Lord et al. 2006; Rutjes et al. 2008).

Studies reporting the accuracy of OCT using comparator tests as the 'imperfect' reference standard are described below as the best available evidence. In accordance with MSAC guidelines, these studies are considered to be of low methodological quality in their estimation of test characteristics (Medical Services Advisory Committee 2005). The yield of OCT and comparator tests, and discrepant results of these tests, are also provided. Data extraction and quality assessment of these studies is presented in Appendix G.

A common methodology employed in ophthalmological studies is to include both eyes from a single participant in the analysis. Some studies also include multiple sets of data from re-examination of individual patients. In interpreting the data provided by these studies, it should be recognised that these methodological features have the potential to distort estimates of diagnostic accuracy or yield, since within-patient variance in test results is likely to be less than between-patient variance. Essentially, eyes from the same patient are more likely to have a congruent test result (or results) than are eyes from different patients. The impact on observed test characteristics may be unpredictable; however, the use of such correlated data without statistical adjustment is likely to result in overly precise results.

Included studies: Non-tractional macular disease

The following sections report results of studies comparing OCT and FFA in the evaluation of patients with macular degeneration, other retinovascular disease, diabetic retinopathy, uveitis and central serous retinopathy. Macular oedema and neovascularisation due to causes other than those already specified are also included.

Macular oedema

This section reports the detection by OCT of macular oedema in all patient groups with suspected macular disease (including diabetic retinopathy, uveitis and macular degeneration as specified by this assessment as patient groups of interest). Seven studies reported both sensitivity and specificity of OCT (or sufficient data to enable their calculation) with FFA as the reference standard. The sensitivity of OCT ranged from 47% to 100%, and specificity ranged from 0% to 100%. These estimates will be distorted by the imperfect nature of the reference standard, and are not considered to be valid estimates of test characteristics. Therefore, these studies have been interpreted as Level IV studies of the comparative yield of OCT and FFA.

Comparative yield

Table 24 reports the comparative yield of OCT and FFA for 10 Level IV studies where this information could be extracted. Six studies used Stratus OCT; the remaining four studies used older versions of the technology. By far the largest study used Stratus OCT and included 654 retrospectively enrolled patients (1,272 eyes, which were unit of analysis) (Kozak et al. 2008). Patients were included if they had positive results for macular oedema (due to a variety of aetiologies) on OCT and/or FFA. As a result, this study did not include patients who were eligible for these tests for the assessment of suspected macular oedema, but who were negative on both OCT and FFA; therefore, the yields reported by this study will be overestimates of those that would be obtained in clinical practice. The yield of OCT (96% [95% CI: 95–97%]) was significantly lower than the yield of FFA (99% [95% CI: 98–99%]) ($p<0.001$), though the difference was small in absolute terms. This corresponds to 27 fewer positive tests (ie more negative tests) for macular oedema per 1,000 patients tested by OCT instead of FFA. The large proportion of patients contributing two eyes to this analysis (94%) means that the estimates of yield are likely to be overly precise; it is possible that a per-patient analysis of these data (or statistical adjustment for correlated data) would result in the observed differences not reaching statistical significance, but this cannot be explored further from the data presented.

One further (smaller) study in patients with diabetic retinopathy reported either equal or lower yield of OCT 2000, depending on the test threshold used (Goebel et al. 2002). When a threshold of mean retinal thickness greater than 271 μm was applied, OCT would yield 204 fewer positive tests (ie more negative tests) for macular oedema than would FFA per 1,000 patients tested; when a threshold of foveal retinal thickness greater than 183 μm was used, there was no statistically significant difference in yield.

In five of the remaining studies, there were no significant differences in the yield reported for the two tests (Table 24). Three of these studies used Stratus OCT (Espinoza et al. 2004; Monnet et al. 2007; Tran et al. 2008); OCT 2000 was used in the other two studies (Antcliff et al. 2000; Catier et al. 2005). In two studies defining positivity for macular oedema by the presence of cystoid spaces (in patients with diabetic retinopathy or age-related macular degeneration), the yield of Stratus OCT was higher than for FFA (Iranmanesh et al. 2007; Ozdek et al. 2005), corresponding to between 97 and 330 extra positives for every 1,000 patients tested. One additional small study reported a higher yield for OCT in a mixed patient group (Varano et al. 1999), but the definition of OCT positivity is unclear in this study, and this finding is therefore of little clinical utility. The generation of OCT was not reported in this study, but given the dates of patient

enrolment (November 1997 to February 1998), an obsolete version of the machine is likely to have been used.

When the results of these studies are pooled (using the mean retinal thickness threshold of 271 μm from Goebel et al.), there was no statistically significant incremental yield of OCT (1% [95% CI: –1 to 2%]) (Figure 4). Using the lower test threshold from Goebel et al. did not substantially alter this result (incremental OCT yield of 0% [95% CI: –1 to 2%]; forest plot not shown). However, there was significant heterogeneity observed among the studies, reflecting the different populations and test interpretations applied.

An additional analysis was conducted which restricted studies to those using Stratus OCT (6 studies), and excluded those studies using superseded versions of the technology (OCT 2000 or older: 4 studies). There was no evidence for a difference in effect in this subgroup. There was no statistically significant incremental yield of Stratus OCT (0% [95% CI: –1 to 2%]; forest plot not shown). Significant heterogeneity was still evident among the studies.

Discordant OCT and FFA results

Table 24 also reports discordant results between OCT and FFA. The proportion of cases of macular oedema that would be detected on OCT, but which would not be detected on FFA, ranged between 0% and 21% (median = 9%). This is the proportion of patients who would not have been treated for macular oedema in clinical practice based on FFA, but would now be considered for treatment based on their OCT result. There is also a proportion of patients—ranging between 0% and 26% (median = 4%) in these studies—in whom macular oedema was identified by FFA, but not diagnosed by OCT. These patients represent those who would have been considered for treatment if FFA had been performed, but who would not be treated based on their OCT result.

The largest study addressing this question (Kozak et al. 2008) reported that 1% of patients were Stratus OCT positive and FFA negative, and 4% were OCT negative and FFA positive for macular oedema (it was reported that most discordant cases occurred in patients with AMD or diabetes). However, despite the sample size, there are features of this study which suggest that discordance between OCT and FFA was underestimated. Most significantly, reinterpretation of each retrospectively obtained OCT and FFA image was undertaken by four trained retina specialists, in two groups of two. The process whereby discrepancies in image evaluation between groups was resolved is unclear; however, it is likely that image interpretation by multiple graders would reduce the number of discordant results between OCT and FFA compared with what might be observed in routine clinical practice (where image interpretation is usually undertaken by a single grader). Secondly, images from 35 eyes were discarded due to image quality retrospectively considered to be poor in one or both tests. Again, this would plausibly contribute to increased concordance between OCT and FFA, although the effect is likely to be small given the total sample size. Finally, 94% of patients contributed two eyes to the analysis. If the proportion of patients with both eyes included in the analysis is greater in those who are positive on both tests compared with those who have discordant OCT/FFA results, this could result in overestimates of concordance between the tests. It is not possible to determine the extent to which this is the case from the data presented in this study.

Table 24 Studies reporting comparative yield of OCT and FFA for macular oedema

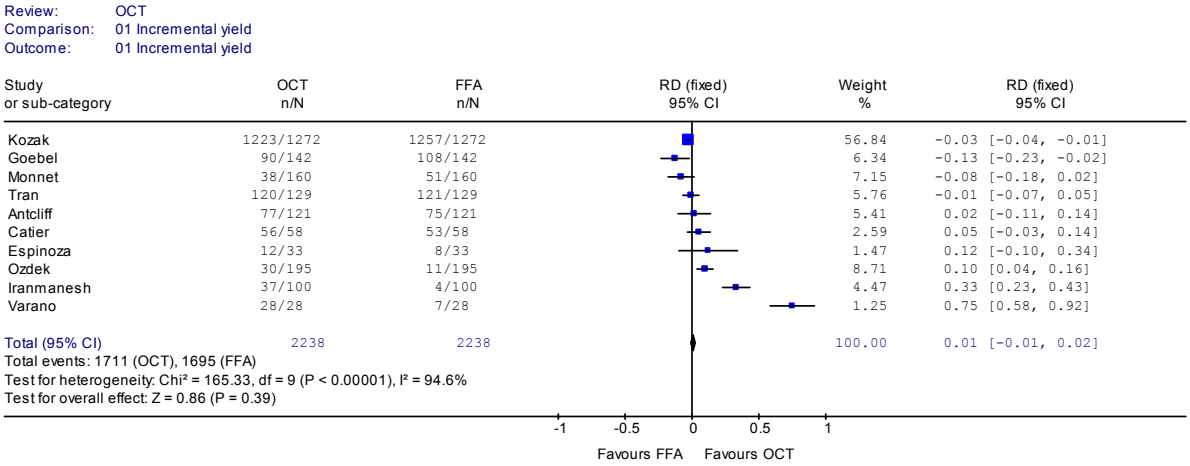
Author (year)	*N* (eyes)	Population	OCT positivity	OCT+ FFA–	OCT– FFA+	Yield % [95% CI]		Extra cases / 1,000	
						OCT Yield	FFA yield	[95% CI]	*p*
Yield of OCT < FFA									
Kozak et al. (2008)	654 (1,272)	Suspected or confirmed macular oedema (mixed aetiologies)	Loss of central foveal contour, intraretinal cysts, subretinal fluid, or foveal and perifoveal thickness ≥ 250 µm	1%	4%	96% [95–97%]	99% [98–99%]	–27 [–19 to –37]	<0.001
Goebel et al. (2002)	142 [a] (142)	Diabetic retinopathy	Mean retinal thickness ≥ 271 µm	2%	18%	56% [47–64%]	76% [68–82%]	–204 [–271 to –138]	<0.001
			Foveal retinal thickness ≥ 183 µm	0%	26%	63% [55–71%]	76% [68–82%]	-	ns
Yield of OCT = FFA									
Monnet et al. (2007)	80 (160)	Uveitis (birdshot chorioretinopathy)	Cystoid spaces or macular thickness ≥ 250 µm	9%	17%	24% [18–31%]	32% [25–39%]	-	ns
Tran et al. (2008)	90 (129)	Uveitis	Diffuse macular oedema, cystic changes or serous retinal detachment	6%	7%	93% [87–96]	94% [88–97]	-	ns
Antcliff et al. (2000)	58 (121)	Uveitis	Cystic spaces or subretinal fluid	4%	2%	64% [55–72%]	62% [53–70%]	-	ns
Catier et al. (2005)	58 (58)	Macular oedema (thickening on biomicroscopy) (mixed aetiologies)	Cystic spaces	9%	3%	97% [88–100%]	91% [81–97%]	-	ns
Espinoza et al. (2004)	33 (33)	Choroidal melanocytic tumours	Subretinal fluid	18%	6%	36% [21–55%]	24% [12–43%]	-	ns
Yield of OCT > FFA									
Ozdek et al. (2005)	110 (195)	Diabetic retinopathy	Cystoid spaces	10%	0%	15% [11–21%]	6% [3–10%]	97 [56–139]	<0.001
Iranmanesh et. al (2007)	93 (100)	Neovascular age-related macular degeneration	Cystoid changes	ne	ne	37% [28–47%]	4% [0–10%]	330 [ne]	<0.05 [b]
Varano et al. (1999)	27 (28)	Suspected macular oedema (mixed aetiologies)	Unclear	21%	0%	100% [85–100%]	25% [13–43%]	750 [590–910]	<0.001

Abbreviations: CI, confidence interval; FFA, fundus fluorescein angiography; ne, not estimable; ns, not significant; OCT, optical coherence tomography

[a] Includes 30 normal control patients (diagnostic case-control design), and therefore accuracy will be overestimated. Study eligible for inclusion in this review since ≥70% of patients had suspected macular disease

[b] Insufficient information reported to determine discordant test results, exact *p* value or CI for extra OCT positives per 1,000

Figure 4 Meta-analysis of OCT yield versus FFA yield



Macular degeneration

One study reporting the comparative yield of OCT and FFA for macular oedema in patients with macular degeneration has been presented previously. No additional studies were identified which assessed OCT and FFA for detecting neovascularisation in previously untreated patients with suspected macular degeneration. OCT for monitoring treated patients with macular degeneration is discussed elsewhere in this report (see 'OCT in monitoring of treated or untreated patients with macular disease', page 57).

Other indications

No studies were identified which evaluated OCT and FFA in the pre-treatment assessment of central serous retinopathy, neovascularisation or other retinovascular disease (eg vascular occlusion).

Summary

Data from 10 included studies suggest that, overall, a similar number of patients will be diagnosed with macular oedema by OCT as by FFA. OCT will detect some cases that would not have been diagnosed on FFA; OCT will also 'miss' some cases that would otherwise have been diagnosed if FFA had been performed. In the absence of a reference standard to define 'true' disease state, the accuracy of these results is unknown. It is not possible to determine whether 'extra' cases of macular oedema represent true 'consequential' cases which will benefit from being treated; true cases of early or mild disease for which the benefits of treatment have not been established; or false positive cases for whom therapy is unnecessary. Equally, it cannot be determined whether 'missed' cases represent true negatives for which therapy is unnecessary, or false negatives for which therapy may be of benefit. The clinical significance of these results is therefore unclear. This is further discussed under 'Does change in management improve patient outcomes?' on page 56.

Included studies: Tractional diseases

The following sections report studies investigating the incremental value of OCT over routine clinical examination in the diagnosis of epiretinal membrane, vitreomacular traction syndrome and macular hole. Due to the imperfect nature of clinical examination

as a reference standard for the presence or absence of tractional diseases, sensitivities and specificities from these studies are not considered to be valid estimates of test characteristics. These studies are therefore interpreted as Level IV studies of the incremental yield of OCT over clinical examination.

Epiretinal membrane

Two studies were identified which reported the accuracy of OCT for identifying epiretinal membrane against a reference standard of clinical examination (Table 25). One study used Stratus OCT (Do et al. 2007), and the other used OCT 1 (Markomichelakis et al. 2004). Clinical examination in both studies included slit-lamp biomicroscopy (in addition to other unspecified ophthalmic investigations). Sensitivity ranged from 81% to 100%; specificity ranged from 63% to 100%.

In one study (Do et al. 2007), clinical diagnoses from two of 84 eyes are not described—consistent with the vitreomacular traction results presented in this study (see the following section), these patients are assumed to have had equivocal clinical examination results. Test characteristics therefore depend on whether these patients are considered positive or negative for epiretinal membrane on clinical examination. This study reported that the range of possible incremental yields of OCT (ie epiretinal membrane identified by OCT in eyes with a negative clinical examination) was 33% to 37%. OCT did not identify the presence of epiretinal membranes in either patient with an equivocal clinical examination.

In the second study, OCT identified no cases of epiretinal membrane in eyes with a negative clinical examination (ie no incremental yield) (Markomichelakis et al. 2004). Epiretinal membranes were not detected in 8 of 42 patients (19%) with epiretinal membranes diagnosed on slit-lamp biomicroscopy. However, the use of an obsolete version of OCT in this study is likely to underestimate its incremental yield when compared with more recent generations of the technology.

Vitreomacular traction syndrome

One study reported the sensitivity and specificity of Stratus OCT against clinical examination (slit-lamp biomiscroscopy and other unspecified ophthalmic investigations) for the diagnosis of vitreomacular traction (Do et al. 2007) (Table 25). Clinical examination was equivocal for the presence of vitreomacular traction in six of 84 eyes, and test characteristics depend on whether these patients are considered positive or negative. The range of possible sensitivities is 82% to 100%; the range of possible specificities is 82% to 88%. The range of possible incremental yields reported by this study was 12% to 16%.

One further study examined the accuracy of OCT in identifying vitreoretinal adhesions associated with partial vitreous separation; however, it is unclear if these adhesions were associated with traction (Gallemore et al. 2000) (Table 25). Only five of the 132 eyes in this study were diagnosed with vitreomacular traction on prior clinical examination (including contact lens slit-lamp biomicroscopy, plus photography, FFA and B-scan ultrasonography in selected cases). Using biomicroscopy as the reference standard, the sensitivity and specificity of OCT in identifying adhesions were 100% and 77%, respectively. The incremental yield of OCT over biomicroscopy was 23%. However, considering the results of biomicroscopy in isolation from other prior tests is likely to overestimate the incremental yield, as indicated by the fact that only three of five clinical diagnoses of vitreomacular traction had adhesions diagnosed by biomicroscopy alone.

The generation of OCT was not specified in this study, but the dates of patient recruitment (August 1997 to May 1998) indicate that a superseded version of the technology is likely to have been used.

Macular holes

One study was identified which reported sufficient data for the determination of sensitivity and specificity of OCT for the detection of a full thickness macular hole against clinical examination (Hee et al. 1995) (Table 25). Clinical examination consisted of indirect and contact lens slit-lamp biomicroscopy, fundus photography, FFA, Amsler grid testing and visual acuity testing. Of 51 eyes, six did not have a definitive clinical diagnosis prior to OCT (five were referred for the possible existence of a macular hole on clinical examination, and there was disagreement about the clinical diagnosis in one patient). Test characteristics therefore depend on whether these patients are considered positive or negative for a full thickness macular hole on clinical examination. The range of possible sensitivities is between 76% and 90%; the range of specificities is 65% to 93%. The range of possible incremental yields (the proportion of patients in whom OCT identified a full thickness macular hole not evident on clinical examination) is 5% to 7%. In all six patients with an equivocal clinical examination, OCT did not confirm the existence of a full-thickness macular hole. Given the recruitment period of this study (January to October 1994), it is likely that an early version of OCT was used in this study. As such, the incremental yield of OCT is likely to be underestimated compared with newer iterations of the technology.

Summary

Three of four studies of OCT in tractional diseases reported that OCT identified patients with epiretinal membrane, vitreomacular traction or a full thickness macular hole that were not identified by prior clinical examination. In the absence of a reference standard to define 'true' disease state, the accuracy of these results is unknown. It is not possible to determine whether 'extra' cases represent true 'consequential' cases which will benefit from being treated; true cases of early or mild disease for which the benefits of treatment have not been established; or false positive cases for which therapy is unnecessary. The clinical significance of these results is therefore unclear. This is further discussed under 'Does change in management improve patient outcomes?' on page 56.

Table 25 Studies reporting incremental yield of OCT over clinical examination for the detection of epiretinal membrane, vitreomacular traction or macular hole

Author (year)	*N* (eyes)	Population	OCT positivity	Incremental Yield % [95% CI]	Extra cases / 1000 [95% CI]
Epiretinal membrane					
Do et al. (2007)[a]	73 (84)	Macular disorders	Highly reflective membrane with partial separation or wrinkles (equivocal clinical exam considered positive)	37% [16–64%]	375 [163–641]
			(equivocal clinical exam considered negative)	33% [14–59%]	333 [143–588]
Markomichelakis et al. (2004)	60 (84)	Uveitis	Unclear	0% [0–8%]	0 [0–80]
Vitreomacular traction					
Gallemore et al. (2000)	119 (132)	Clinical diagnosis of idiopathic epiretinal membrane, idiopathic full thickness macular hole, vitreomacular traction syndrome, cystoid macular oedema or diabetic retinopathy	Vitreoretinal adhesions associated with partial posterior vitreous separation of the macula	23% [17–31%]	231 [165–314]
Do et al. (2007)[a]	73 (84)	Macular disorders	Separation on posterior hyaloid, adherent vitreous causing traction (equivocal clinical exam considered positive)	12% [6–23%]	123 [61–226]
			(equivocal clinical exam considered negative)	16% [10–26%]	165 [98–261]
Macular holes					
Hee et al. (1995)	51 (51)	Clinical diagnosis of full thickness macular hole, impending macular hole, history of macular hole, epimacular membrane with macular pseudohole or lamellar hole	Stage 2–4 macular hole (equivocal clinical exam considered positive)	7% [0.2–34%]	71 [2–338]
			(equivocal clinical exam considered negative)	5% [0.1–25%]	50 [1–249]

Abbreviations: CI, confidence interval; OCT, optical coherence tomography

[a] Incremental yield depends on whether equivocal clinical exam results are considered positive or negative

Does it change patient management?

The detection of macular conditions by OCT can lead to changes in management by initiating treatment that would not otherwise have been undertaken. Additionally, for patients with non-tractional macular diseases, a negative OCT result will result in the avoidance of FFA. However, the proportion of patients in whom these management changes will occur cannot be predicted from accuracy data alone as decisions regarding management will be influenced by factors other than the OCT result (for example, the health status of the patient, or patient preferences) (Guyatt et al. 1986).

When a new test is intended to directly replace an existing test in the diagnostic pathway, it may be reasonable to assume that management decisions will be altered similarly by the new and old test. However, when the new test supplements rather than replaces other tests in the diagnostic pathway, inference about the potential impact of the test on management decisions requires studies which demonstrate this impact. Therefore, evidence that OCT, when used as an additional test, leads to a change in patient management is a necessary but not sufficient condition for concluding that it leads to an improvement in health outcomes. On the other hand, if OCT cannot be shown to affect patient management, its effectiveness is disproven.

Potential sources of bias in therapeutic impact studies are described in Guyatt et al. (1986). To minimise bias and maximise applicability of the results, studies should:

- be conducted prospectively in a routine clinical setting using patient eligibility criteria that reflect the intended use of the test in practice and target test population
- document what proportion of consecutive eligible patients were included in the study and reasons for exclusion of eligible patients
- include all patients enrolled in data analysis
- include independent assessment of the influence of test results on reported treatment decisions; document actual treatment received for comparison with clinician recorded planned treatment
- include an assessment of test accuracy per patient and adequate follow-up of included subjects to capture potential false negatives.

Included studies

One primary study was identified which reported the impact of Stratus OCT in determining treatment decisions for patients with macular disease (Do et al. 2007). Data extraction and quality assessment of this study are presented in Appendix H. This prospective study evaluated the degree to which OCT altered plans for management in patients with epiretinal membranes or vitreomacular traction. Surgeons were required to generate a pre-OCT management plan (either surgery or clinical observation) based on information from a complete clinical evaluation (including history and stereoscopic slit-lamp biomicroscopy after pharmacological dilation). OCT findings were then combined with those from clinical examination, and surgeons generated a new management plan. The plans were compared to determine whether OCT influenced the decision to instigate

surgical management. However, the extent to which planned management was concordant with the management the patient actually received was not described. Furthermore, health outcomes in these patients were not reported.

Prior to OCT, 19/84 eyes (23%) were planned for surgery; after the addition of OCT information, surgical intervention was planned in 33/84 eyes (39%). No eyes planned for surgery pre-OCT had a management plan for observation post-OCT. Hence, a total of 14/84 patients (17%) (95% CI: 10.2–26.1%) had their management plan changed from observation to surgery based on OCT information. Of just the patients planned for observation pre-OCT, management plans changed to surgery in 14/65 (22%) (95% CI: 13.3–33.0%).

Reasons that planned management changed from observation to surgery were described. These were: detection of vitreomacular traction by OCT not observed on clinical examination (7/14); detection of macular oedema by OCT not observed on clinical examination (4/14); detection of epiretinal membrane by OCT not observed on clinical examination (2/14); and detection of more extensive macular oedema by OCT than observed on clinical examination (1/14). The individual incremental yields of OCT over clinical examination for epiretinal membranes, vitreomacular traction and macular oedema are higher than the number of patients whose management plan was changed due to the detection of these abnormalities (see page 51 for epiretinal membranes and vitreomacular traction; the macular oedema results did not meet the inclusion criteria for this assessment). This is not unexpected, given that these abnormalities may co-exist.

Although this study was conducted prospectively, it did not enrol consecutive patients eligible for examination with OCT (potentially eligible patients were only included in the study if a chief investigator was available to identify the patient before examination by the retina specialist). Therefore, the sample may not be representative of patients who would routinely undergo OCT in clinical practice. The absence of baseline characteristics of the patients studied (combined with a lack of explicit inclusion and exclusion criteria) means that the generalisability of the sample cannot be explored further.

The pre-OCT management plan in this study was not independently assessed. This is a key quality feature for this study design, since a change in management plan may be falsely attributed to a new test when prior workup is poorly conducted or otherwise inadequate (Guyatt et al. 1986). Independent review of the pre-test plan helps to ameliorate this bias. A further limitation of this study is that it reports changes in management plans, but does not report the actual management received. 'Planned' therapy may not reflect 'actual' therapy for a number of reasons (eg patient preference). Additionally, limitations in the reporting of data in this study preclude the linkage of management change to the OCT result—there may be some patients with abnormalities detected by OCT whose management plan was unchanged.

This study was conducted in the United States, and as such may not reflect management practice in Australia. Different patterns of referral may further reduce the applicability of the sample enrolled in this study to the Australian setting. Furthermore, in the absence of clearly described criteria for surgical eligibility, it is not possible to assess whether the reported changes in management are likely to be generalisable.

Does change in management improve patient outcomes?

The main role of OCT in macular diseases is to identify additional cases of disease, leading to the initiation of treatment in patients who would not have been treated in the absence of OCT. Additionally, for non-tractional macular diseases, a negative OCT will result in the avoidance of FFA in some patients (expert advice suggests that a minority of patients may still undergo FFA after a negative OCT).

In general, the studies included in this assessment suggest that at least as many patients will be diagnosed with macular oedema by OCT as by FFA. As a replacement test, it is reasonable to assume that management will be changed by the OCT result in the same manner as by FFA. However, OCT will detect some cases that would not have been diagnosed on FFA; OCT will also 'miss' some cases that would otherwise have been diagnosed if FFA had been performed. Whether these extra or missed cases represent 'consequential' cases of disease is unknown. For example, extra cases of macular oedema detected by OCT may represent false positives, early or mild cases of disease for which the benefits of treatment have not been established (for example, if spontaneous resolution of the condition may occur without treatment) or 'consequential' cases who will benefit from being treated. Equally, missed cases may be false negatives who would not receive treatment that is potentially of benefit or true negatives who will avoid unnecessary treatment. Given these uncertainties, the clinical significance of these results is therefore unclear.

Expert opinion suggests that some (but not all) patients positive for macular oedema on OCT will then undergo FFA to guide therapy (see clinical flowchart in Appendix C); a minority of patients negative for macular oedema may also undergo subsequent FFA. Therefore, it is possible that some of the theoretically discordant OCT and FFA results may become evident in clinical practice. However, since it is not known which test result more accurately reflects the 'true' presence or absence of disease, it cannot be assumed that FFA will 'correct' an erroneous OCT result to guide management in these patients. Furthermore, since FFA will not be performed in all patients after OCT, it is likely that many theoretically discordant test results will not become apparent.

Studies of OCT for the diagnosis of tractional diseases suggest that OCT will diagnose extra cases over and above those diagnosed by clinical examination. There is also some evidence that the information provided by OCT will lead to the initiation of surgery in a proportion of these patients. However, the clinical significance of a positive OCT result is unclear—as above, it is unknown whether additional cases represent 'consequential' cases of disease.

RCTs of treatment or prognostic studies of OCT in patients with discordant test results could potentially provide evidence of the clinical significance of the extra cases detected by OCT (see the following section, 'Future research'). No studies of the prognostic value of OCT, or RCTs of treatment in patients with discordant test results, were identified in the current assessment (although a systematic review answering this specific question was not attempted). In the absence of such information, conclusions about the effectiveness of OCT in improving patient outcomes are not possible using a linked evidence approach.

Future research

RCTs of treatment which enrol patients with discordant test results could provide evidence of the clinical significance of the extra cases detected by OCT (Lord et al. 2006). In an RCT design, patients with positive OCT and negative FFA or prior test results would be randomised to receive treatment or no treatment. For the clinical significance of a positive OCT result to be demonstrated, outcomes would be improved in the treated group relative to the untreated group. A similar trial could be conducted to demonstrate the clinical significance of a negative OCT result for non-tractional macular diseases, in the presence of positive FFA (in which case there would be no observed benefits of treatment, and potentially worse health outcomes in treated patients). RCTs to investigate such questions may be impractical and may not be necessary if there is evidence that the OCT result provides more accurate prognostic information than FFA or prior clinical examination.

In a prognostic study, patients who are either OCT positive/FFA negative or OCT negative/FFA positive for macular oedema would be followed for a period of time without treatment to assess disease progression. A finding that OCT positive/FFA negative patients show worse outcomes than OCT negative/FFA positive patients would demonstrate that OCT provides more accurate prognostic information than FFA to guide treatment decisions. This would support conclusions that OCT could improve patient outcomes by identifying extra patients who may benefit from treatment for macular oedema and avoiding unnecessary treatment in OCT negative patients who would otherwise have been treated. For tractional diseases, patients who are negative on clinical examination could be followed without treatment, regardless of their OCT result. For evidence of the prognostic value of a positive OCT result, outcomes observed in OCT positive patients should be worse than those in OCT negative patients.

OCT in monitoring of treated or untreated patients with macular disease

In patients with non-tractional macular diseases, OCT has a proposed role in the monitoring of therapy and in the ongoing monitoring of untreated patients with suspected macular disease. The evaluation of the effectiveness of a monitoring test involves consideration of more than just the test itself; it also includes consideration of the monitoring procedure and other actions based on monitoring (Bossuyt 2008). As such, assessment of the effectiveness of monitoring requires evaluation of a specific monitoring strategy— 'a planned and organised system of repeated assessments and subsequent decisions about additional interventions, such as starting, stopping, or modifying treatment' (Bossuyt 2008, p.161)—and its impact on health outcomes, relative to a comparator strategy.

The effectiveness of a monitoring strategy is ideally demonstrated by RCT designs. For such studies to be interpreted properly, all elements of the monitoring strategy (or strategies) must be pre-specified, including protocols for repeated testing, monitoring intervals, decision limits and the nature and extent of subsequent interventions (Bossuyt 2008).

Included studies

No RCTs comparing a monitoring strategy involving OCT to a strategy involving FFA in patients with treated or untreated macular disease were identified by the systematic review.

One non-randomised, low quality Level III-2 study was identified which compared a monitoring strategy involving OCT plus FFA against a strategy involving FFA alone (Krebs et al. 2005). Given the recruitment period of this study (April 2000–June 2002), a pre-Stratus OCT version of the technology is likely to have been used. Data extraction and quality assessment of this study are presented in Appendix I. Forty eyes of 38 patients with predominantly classic choroidal neovascularisation (CNV) as a result of AMD were included in this study. Patients were treated with photodynamic therapy (PDT). One subgroup of patients (n=27 [28 eyes]) was monitored and retreated based on detection of active leaking membrane by a combination of OCT and FFA; a second subgroup (n=11 [12 eyes]) was monitored and retreated based on leakage detected by FFA alone. The first follow-up examination occurred at six weeks after initial treatment with PDT; subsequent follow-up examinations were three monthly after initial treatment. Best corrected distance acuity was tested with standard ETDRS charts at all follow-up examinations in both groups. After 12 months, the mean best corrected distance acuity remained unchanged in the OCT plus FFA group (0.2 at baseline vs 0.2 at 12 months). Distance acuity decreased in the group monitored by FFA alone (0.25 at baseline vs 0.16 at 12 months), although it was reported that this difference did not reach statistical significance. The proportion of eyes with a loss of distance acuity of more than three lines was 18% (95% CI: 7.9–35.6%) in the group monitored by OCT plus FFA; this proportion was 67% (95% CI: 39.1–86.2%) in the group monitored by FFA alone ($p<0.01$).

This study suffers from several methodological flaws which hinder its interpretation. First and foremost, this is a non-randomised study, and hence there is the strong likelihood of selection bias being present, reflected in differences in patient demographics and baseline visual acuity between the treatment groups. It is not clear how patients were allocated to either the intervention or control group. Furthermore, although the control group was noted to be consecutively enrolled, it is unclear whether this was also the case for the intervention group—if only some eligible patients were enrolled in the OCT monitoring group, this would exacerbate the potential for bias in the observed outcomes. Also, it is unclear from the description of methods whether OCT was in fact performed in the group supposedly managed according to FFA results alone. If so, it may not be possible to conclude that the comparator strategy reflected FFA alone, even if clinicians were instructed to ignore the OCT results. It is also likely that the assessment of visual acuity was not masked to the monitoring strategy, and this may contribute to bias in outcome assessment. Finally, this is a small study (the group monitored by FFA alone consisted of just 11 patients), and as such, the measures of effectiveness are likely to be imprecise. The authors concluded that this study requires replication by adequately powered RCTs.

Summary

One small, low quality, non-randomised study in AMD patients treated with PDT reported non-significant decrements in visual acuity in eyes monitored with FFA alone, relative to eyes monitored with OCT in addition to FFA. The proportion of eyes with a

loss of distance acuity of more than three lines was significantly higher in the group monitored with FFA alone. The precision of these estimates is limited by biases inherent in this study; therefore the effectiveness of OCT for monitoring of PDT in patients with AMD remains uncertain.

Other considerations

The following section describes expert opinion by the Advisory Panel, and is presented separately from the results of this assessment. The studies referenced in this section were not identified through a systematic review of the literature and have not been subjected to formal critical appraisal, quality assessment or data extraction.

Expert opinion

Intended role of OCT

It is the expert opinion of the Advisory Panel that OCT should not be used in a screening setting. The intended role of OCT is for diagnosis and monitoring of patients in a specialist ophthalmological setting.

OCT for diagnosis of macular disease

The introduction of OCT examination of the macula has revolutionised diagnosis and management of retinal disease by ophthalmic specialists, through giving a qualitative and quantitative measure of cross-sectional anatomical change in the macula. OCT has become an essential part of the standard of care, and so apparent is its utility to specialists and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination.

Despite the widespread diffusion of this technology into retinal ophthalmology at every level, establishing the utility of OCT for macular disease in the MSAC report has been difficult due to a lack of published evidence in the literature with an appropriate comparator. The true comparator for OCT is clinical examination of the macula by a specialist (slit lamp biomicroscopy); however, the report has had to rely on comparisons with fluorescein angiography, the main prior retinal diagnostic technique. These tests are not, however, directly comparable, since OCT gives an indication of anatomy, whilst fluorescein angiography is frequently physiological.

In the estimation of the ophthalmologist members of the Advisory Panel, this report, therefore, fails to convey the high utility of OCT and the fundamental role that OCT now plays in the management of patients with macular disease. The ophthalmologist members of the Advisory Panel strongly support appropriate application of this essential technology, carried out and interpreted by specialist ophthalmologists to allow early detection and intervention in blinding macular diseases.

OCT for monitoring of therapy

It is the expert opinion of the Advisory Panel that monitoring of therapy in patients with macular disease is a major potential use of OCT.

Expert opinion suggests that ranibizumab (Lucentis) has become standard management in Australia for the treatment of most patients with CNV due to macular degeneration.

Ranibizumab was listed on the PBS in August 2007. Trials demonstrating the effectiveness of ranibizumab employed a 'forced treatment' strategy, whereby patients underwent repeated monthly or three monthly injections (Brown et al. 2006; Heier et al. 2006; Regillo et al. 2008; Rosenfeld et al. 2006). Patients in these RCTs were monitored clinically at regular intervals, but monitoring did not inform decisions about continuing or discontinuing ranibizumab therapy. Monitoring of therapy is not mentioned in the PBS listing for ranibizumab (Australian Government Department of Health and Ageing 2008), and expert opinion suggests that a forced treatment strategy of monthly injections is standard management in the absence of monitoring with OCT. However, since the research questions defined *a priori* for this assessment specified a monitoring strategy involving FFA as the relevant comparator, a comparison of an OCT monitoring strategy versus no monitoring for patients with macular degeneration treated with ranibizumab has not been undertaken.

A recent, single-arm case series study (Level IV) investigated OCT-guided treatment of AMD with ranibizumab (Fung et al. 2007). A total of 40 patients with neovascular AMD and central retinal thickness of at least 300 μm received three consecutive monthly injections of ranibizumab, followed by additional injections if specific criteria were met at monthly monitoring intervals. Monitoring consisted of monthly OCT, fundus photography, visual acuity testing and ophthalmoscopic examinations, and three monthly FFA. Retreatment was undertaken if any of the following criteria were met: 1) visual acuity loss of at least five letters with OCT evidence of fluid in the macula; 2) increase in OCT central retinal thickness of at least 100 μm; 3) new macular haemorrhage; 4) new area of classic CNV; or 5) OCT evidence of persistent fluid at least one month after previous injection. After 12 months, mean visual acuity improved by 9.3 letters ($p<0.001$), and visual acuity improved by 15 letters or more in 35% of patients. Patients had an average of 5.6 injections over 12 months.

Fung et al. (2007) note that these visual acuity outcomes were comparable to the ranibizumab treatment arms of RCTs employing a fixed monthly dosing regimen, and were achieved with approximately half the mean number of injections over 12 months. The authors acknowledge that there are important methodological differences between studies that render such comparisons problematic. It is also acknowledged that direct head-to-head trials are necessary to conclude that an OCT monitoring strategy is as effective as fixed monthly dosing; however, the authors argue that such studies are unlikely to be undertaken.

In the Australian context, OCT monitoring of treatment with ranibizumab is expected to reduce the frequency of FFA monitoring examinations, and therefore potentially to reduce the incidence of adverse events associated with FFA in these patients. In addition, OCT is expected to reduce the utilisation of ranibizumab; this could be expected to reduce the risks of treatment and improve quality of life for patients. This is also a potential cost offset.

New therapies for macular disease are continuously in development. Expert opinion suggests that OCT will be used to monitor response to future treatments.

Glaucoma: Is it effective?

OCT for diagnosing glaucoma

No studies were identified which provided direct evidence of the impact of OCT on patient outcomes in patients with glaucoma.

Two studies reported detection of RNFL defects by OCT in glaucoma suspects with normal visual fields on computerised perimetry. However, these RNFL defects were observed on prior clinical examination in at least some patients in one study, and in all patients in the second study. The incremental yield of OCT is therefore not known.

No studies reported changes in patient management due to OCT results.

In the absence of evidence of accuracy and therapeutic impact, a linked evidence approach to demonstrate the effectiveness of OCT is not possible.

OCT for monitoring treated or untreated patients with glaucoma

No studies were identified which compared a monitoring strategy involving OCT with a strategy involving computerised perimetry for patients with glaucoma. The effectiveness of OCT for monitoring patients with glaucoma remains uncertain.

Existing HTAs and systematic reviews

A search for existing HTA reports and published systematic reviews on OCT in the assessment of glaucoma yielded two reports published between 1990 and 2008 which met the eligibility criteria for this review (Alberta Heritage Foundation for Medical Research 2003; Lin et al. 2007) (see Appendix F). The characteristics and quality assessment of these reports are presented in Table 23 and Table 26. The results of these reports are discussed in more detail in the following sections.

American Academy of Ophthalmology (2007)

This HTA, prepared by the American Academy of Ophthalmology, was conducted to examine the diagnostic performance of OCT in addition to a complete ophthalmological examination, including perimetry (Lin et al. 2007). In addition, the effectiveness of OCT to detect glaucomatous progression in a monitoring capacity was also examined. The quality of this review was assessed to be 'fair'. Explicit review questions were not defined *a priori*, particularly in terms of the specific patient group and outcomes of interest. Furthermore, the process by which studies were deemed (in)eligible for inclusion in the review is not explicitly described. It is noted that a panel reviewed abstracts and determined studies that were "sufficiently clinically relevant", but the criteria for doing so were not specified.

Lin et al. (2007) searched the literature from 2003 to update a previous (non-systematic) review of the literature conducted by the American Academy of Ophthalmology (Lee 1999) and an unpublished review of the literature by the American Academy of Ophthalmology and the American Glaucoma Society Work Group. Therefore, while the search strategy for the period 2003–2006 appears to be comprehensive, research published prior to this time period is not included in the review.

Eighteen studies were included: 13 assessed the accuracy of OCT for diagnosis; one examined OCT for monitoring; and the remaining four studies reported differences in RNFL or macular parameters, and thus are not relevant to the current assessment. From the studies addressing the accuracy of OCT for the diagnosis of glaucoma, RNFL thicknesses in the superior and inferior quadrants were found to have the highest areas under the receiver operating characteristic (ROC) curve (AUCs). For distinguishing patients with glaucomatous visual field loss from normal controls, AUCs ranged between 0.79 and 0.952 for the superior quadrant and between 0.863 and 0.971 for the inferior quadrant. AUCs for distinguishing perimetrically normal glaucoma suspects and normal controls were lower, ranging between 0.591 and 0.840 for the superior quadrant and 0.694 and 0.810 for the inferior quadrant. ONH parameters were found to have similar AUCs to RNFL parameters for distinguishing glaucoma from controls. Both RNFL and ONH parameters were found to have superior AUCs than macular parameters for distinguishing glaucoma and glaucoma suspects from normal controls.

All of the included accuracy studies were of a diagnostic case-control design, whereby series of 'normal' patients without glaucoma (eg no visual field defects, normal IOP, normal disc appearance, no history of ocular disease) and patients with glaucoma (varying degrees of abnormality on these parameters) were enrolled, and the ability of OCT to discriminate between the groups was assessed. Seven studies enrolled patients with glaucomatous visual field loss on standard automated perimetry and normal controls, while the remaining six included glaucoma suspects or ocular hypertensives who did not have visual field defects on standard automated perimetry. The measures of diagnostic accuracy obtained from such studies are artificially inflated by the limited spectrum of patients included, and are therefore not considered to represent valid estimates of test characteristics. This issue is discussed further in the section 'Is it accurate?' (page 45).

Alberta Heritage Foundation for Medical Research (2003)

This 'fair' quality report has been described previously in its consideration of macular diseases (see 'Existing HTAs and systematic reviews', page 42; Table 23). For the indication of glaucoma, the review included six studies which investigated the accuracy of OCT compared to standard diagnostic tests (clinical examination, measurement of IOP, stereoscopic photography of the ONH, standard automated perimetry). All studies were published prior to the search period of Lin et al. (2007), and hence were not included in that review.

The sensitivity of OCT was reported to range between 71% and 82%; specificity ranged between 80% and 90%. It was concluded based on likelihood ratios from the included studies that OCT provided 'strong but not conclusive diagnostic evidence for detecting glaucoma' (Alberta Heritage Foundation for Medical Research 2003). However, the studies included in this review were all of diagnostic case-control design, and thus have the same limitations outlined previously. All studies compared normal patients and those with glaucoma to determine accuracy. Although two studies did include groups of glaucoma suspects with normal visual fields on standard automated perimetry (SAP), the incremental accuracy of OCT in these patients could not be derived from the data reported. Therefore, the conclusions of this review do not relate to the incremental diagnostic accuracy of OCT over SAP in diagnosing glaucoma suspects.

No studies reporting patient outcomes were presented. The review concluded that 'randomised controlled trials are also needed to establish the clinical impact of OCT

diagnostic imaging on the management, treatment options, and outcomes of patients' (Alberta Heritage Foundation for Medical Research 2003).

Table 26 Characteristics and appraisal of included HTA reports

Author (year) Country	Objective & methods	Included studies	Quality assessment of review
American Academy of Ophthalmology Lin et al. (2007) United States	**Objectives:** 1) To determine how well OCT aids in glaucoma diagnosis, particularly as an adjunctive test to a complete ophthalmological examination including perimetric testing. 2) To determine whether glaucoma progression can be detected with OCT **Literature review:** Databases: PubMed, Cochrane Library Time period: January 2003–February 2006 (Update of previous non-systematic review) Inclusion/exclusion criteria: • Study design not stated *a priori*. Studies not excluded by quality rating • Population: glaucoma • Intervention: OCT. Also considered CSLO and SLP • Outcomes: not stated *a priori*, but reported accuracy measures and RNFL parameters • Language: English language articles	**Diagnosis:** 17 studies 10 studies compared healthy eyes and eyes with glaucomatous visual field loss 7 studies included glaucoma suspect and/or ocular hypertensive patients **Monitoring:** 1 study	**Quality: fair** Explicit review questions: no Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes

Abbreviations: CSLO, confocal scanning laser ophthalmoscopy; HTA, health technology assessment; N/A, not applicable; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; ROC, receiver operating characteristics; SLP, scanning laser polarimetry

Direct evidence

This review did not identify any studies reporting the health outcomes of patients with glaucoma, assessed with and without OCT. Furthermore, no ongoing RCTs were identified. In the absence of direct evidence for the effectiveness of OCT, the evidence for test accuracy, changes in management arising from the test and the expected benefit of changes in management on health outcomes is presented for conclusions about the effectiveness of OCT using a linked evidence approach.

Indirect evidence

Is it accurate?

For glaucoma, OCT is an additional test to computerised perimetry and clinical examination. Expert advice identified clinical follow-up, ophthalmoscopy, photography or computerised perimetry (or a composite of these) as the most valid reference standard for the determination of diagnostic accuracy. Clinical follow-up is problematic as a reference standard, since treatment implemented based on the test result confounds the

assessment of 'true' disease state, and is therefore unlikely to provide valid estimates of test characteristics (Rutjes et al. 2008). (For further discussion of this issue, refer to the section 'Is it accurate?', page 45.) No studies were identified which used clinical follow-up as a reference standard, which is indicative of this problem.

Furthermore, a reference standard comprised of a composite of other tests is problematic, as such tests represent those over which OCT is proposed to provide incremental diagnostic value. Misclassification by an 'imperfect' reference standard will therefore result in distorted estimates of diagnostic accuracy (Medical Services Advisory Committee 2005). (See page 45 for further discussion.)

Studies exist which report the accuracy of OCT in discriminating patients known to have glaucoma (as diagnosed by prior tests) from controls. In these diagnostic case-control studies, a series of 'normal' patients without glaucoma (eg no visual field defects, normal IOP, normal disc appearance, no history of ocular disease) and patients with glaucoma (varying degrees of abnormality in these parameters) are enrolled, and the accuracy of OCT in detecting patients with glaucoma and excluding those without glaucoma is calculated. Such studies are not applicable to the current assessment as these patient groups do not represent 'glaucoma suspects'. Normal patients (from whom specificity is derived in these studies) would not undergo OCT in routine clinical practice. Furthermore, patients with a definitive diagnosis of glaucoma on prior tests (from whom sensitivity is calculated) would not undergo OCT. These studies are likely to inflate the accuracy of OCT, and are thus considered to provide invalid estimates of test characteristics.

The incremental value of OCT over computerised perimetry is derived from those cases where perimetry does not detect a visual field defect, but a diagnosis of glaucomatous damage is made based on the OCT result. Therefore, this incremental value cannot be estimated from studies enrolling patients with visual field defects present on computerised perimetry. Where diagnostic case control studies have included a subset of perimetrically normal 'glaucoma suspect' patients, and the sensitivity of OCT for this patient group can be calculated from the data presented, this information can be interpreted as the incremental yield of OCT over computerised perimetry. These studies are described in the following section. In accordance with MSAC guidelines, they have been classified as low quality studies for the assessment of diagnostic accuracy (Medical Services Advisory Committee 2005). Data extraction and quality assessment of these studies are presented in Appendix J.

Included studies

Two studies were identified which reported the incremental diagnostic yield of Stratus OCT over perimetry (Bagga et al. 2006; Kim et al. 2007). Bagga et al. (2006) enrolled 25 patients (one eye per patient) with glaucomatous optic neuropathy (normal results on SAP, in the presence of cupping asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation or RNFL defect on clinical examination). An RNFL defect on Stratus OCT was defined as mean or quadrantic thickness values outside 95% of normal limits, confirmed on at least 2 of 3 repeat scans. The yield of OCT in this study was 12/25 (48%). Kim et al. (2007) performed Stratus OCT in 49 eyes of 49 patients with preperimetric localised RNFL defects (no glaucomatous visual field loss on SAP, in the presence of a localised wedge-shaped RNFL defect on red-free photography). The yield of OCT ranged from 1/49 (2%) to 20/49 (41%), depending on

the OCT parameter used to define an RNFL defect. The parameters with the highest yield were ≥1 clock hours abnormal at the 5% level (20/49 [41%]), and the greatest value in the inferior quadrant abnormal at the 5% level (16/49 [33%]).

Although both studies report RNFL defects observed by OCT in patients without perimetric visual field defects, an undefined number of patients in the study by Bagga et al. (2006) and all patients in the study by Kim et al. (2007) had RNFL defects observed on prior tests. Hence, the incremental yield of OCT over prior testing remains uncertain, as does the clinical significance of a positive OCT result.

Does it change patient management?

The diagnosis of glaucoma by OCT can lead to changes in management by initiating treatment that would not otherwise have been undertaken (or initiating management earlier than would have occurred in the absence of OCT). However, the proportion of patients in whom these management changes will occur cannot be predicted from accuracy data alone as decisions regarding management will be influenced by factors other than the OCT result (for example, the health status of the patient, or patient preferences) (Guyatt et al. 1986). When a new test supplements existing tests in clinical practice, evidence of the new test's impact on management decisions is required as a necessary (but not sufficient) condition for concluding that it leads to an improvement in health outcomes. (For further discussion, refer to the section 'Does it change patient management?', page 54.)

Included studies

No primary studies were identified which reported the impact of OCT in determining treatment decisions for patients with glaucoma.

Does change in management improve patient outcomes?

In the absence of evidence which defines the incremental yield of OCT over prior tests in detecting RNFL defects, or studies which document a change in management due to the information provided by OCT, it is not possible to draw conclusions of the impact of OCT on health outcomes for patients with glaucoma using a linked evidence approach.

Future research

Study designs which would enable conclusions regarding the incremental yield of OCT over prior clinical examination, and the clinical significance of these results include:

- studies enrolling glaucoma suspects or patients with risk factors for glaucoma (ideally prospectively and consecutively), who do not have perimetric abnormalities diagnostic for glaucoma or structural defects detectable on prior standard clinical examination, to quantify the proportion of patients with structural defects detected by OCT (incremental yield of OCT in target population).

A systematic review of the prognostic value of detecting early structural damage as a predictor of the development of glaucomatous visual field defects has not been

attempted. If there was convincing evidence about the natural history of glaucoma to indicate that structural abnormalities detected by other tests (eg photography) progress to glaucomatous visual field defects, and if it is considered reasonable to assume that structural abnormalities detected only by OCT will also progress to glaucomatous visual field defects, then assumptions could be made regarding the clinical significance of any incremental OCT yield. If convincing evidence was not available, and/or it was not considered reasonable to assume that OCT-detected and conventionally-detected abnormalities progress similarly, studies would be required to demonstrate the clinical significance of these results, for example:

- prognostic studies enrolling patients without perimetric abnormalities or structural defects observed on prior tests to compare outcomes in patients with and without structural defects detected on OCT with treatment based on existing test results only (see 'Future research', page 57, for further discussion of this study design).

Information on the therapeutic impact of OCT, collected as part of a study of diagnostic yield, could provide information on the use of OCT in Australian clinical practice to influence management decisions. However, such information alone is not sufficient to demonstrate the impact of OCT on patient outcomes. This requires studies demonstrating the effectiveness of early intervention in this patient group in preventing, reducing or delaying progression to glaucomatous visual field damage, compared to intervention based on standard evaluation without, or blinded to the results of, OCT.

A systematic review of the evidence for the benefit of early treatment to prevent or delay glaucomatous progression has not been undertaken. If there exists convincing evidence for the effectiveness of early versus late treatment, and it was considered reasonable to assume similar treatment benefit in patients with structural damage observed only on OCT, then a linked evidence approach could be used to describe the potential effectiveness of OCT in improving patient outcomes. If such evidence was not available, and/or the assumption of the applicability of treatment benefit to patients with structural damage detected only by OCT was not considered reasonable, studies of treatment effectiveness in this patient group would be required.

OCT in monitoring of treated or untreated patients with glaucoma

OCT has a proposed role in the monitoring of therapy in patients treated for glaucoma, and in the ongoing monitoring of untreated patients with risk factors for glaucoma. The assessment of OCT in monitoring requires evaluation of the testing strategy as a whole and its impact on health outcomes, compared with an alternative strategy or strategies (Bossuyt 2008). RCTs are the ideal study design to provide this evidence. The evaluation of monitoring strategies is further discussed on page 56.

Included studies

No primary studies of a monitoring strategy involving OCT compared with a strategy involving computerised perimetry were identified which met the inclusion criteria for this assessment.

Excluded studies

One study was identified which reported the comparative yield of OCT and computerised perimetry in monitoring for glaucomatous progression. The study did not report health outcomes related to different monitoring strategies; the monitoring interval is of limited applicability to Australian clinical practice; and the OCT machine used is not commercially available. This study is presented for completeness only, in the absence of studies meeting the inclusion criteria for this review. It does not contribute to the conclusions of this assessment.

Wollsetin et al. retrospectively examined rates of glaucomatous progression in 37 patients (64 eyes) monitored with a comprehensive clinical assessment, standard automated perimetry and prototype OCT (Wollstein et al. 2005). The monitoring interval was six months, with a median follow-up of 4.7 years. Study participants consisted of 32 patients (55 eyes) with glaucoma and 5 glaucoma suspects (9 eyes) with normal visual fields. Perimetric progression was defined as a decrease in mean visual field mean deviation of 2 dB from baseline in two of three consecutive follow-up visits. OCT progression was defined as mean RNFL thinning of at least 20 μm compared with baseline in two of three consecutive follow-up visits. The yield of OCT for progression over the follow-up period was 16/64 eyes (25%) compared with 8/64 eyes (13%) in which progression was identified by perimetry. Progression was detected in two eyes (3%) by both tests. The authors note that is not known whether progression identified by OCT alone represents true, early glaucomatous progression or 'hypersensitivity' (false positives) by OCT.

Other considerations

The following section describes expert opinion by the Advisory Panel, and is presented separately from the results of this assessment. The studies referenced in this section were not identified through a systematic review of the literature and have not been subjected to formal critical appraisal, quality assessment or data extraction.

Expert opinion

Intended role of OCT

It is the expert opinion of the Advisory Panel that OCT should not be used in a screening setting. The intended role of OCT is for diagnosis and monitoring of patients in a specialist ophthalmological setting.

OCT in the diagnosis and monitoring of patients with glaucoma

It is the expert opinion of the Advisory Panel that digital methods to measure and to record optic nerve head (ONH) structural abnormality should be standard tools in the management of glaucoma in 2008. OCT is one such method.

In glaucoma, structural ONH changes precede detectable changes in visual field sensitivity (Weinreb et al. 2004).

Visual field testing by white-on-white static automated perimetry has in the past been one of the 'gold standards' for glaucoma diagnosis. Changes in ONH structure are now relied

upon to determine diagnosis and to detect progression of glaucoma; the prior 'gold standard' is an imperfect comparator for OCT.

As well as its role in the diagnosis and in the detection of progression, OCT contributes significantly to a patient's understanding of the disease. The clear demonstration of an anatomical abnormality with this instrument is easily comprehended, thereby greatly increasing the likelihood of patient acceptance of, adherence to and perseverance with lifelong therapy.

The ophthalmologist members of the Advisory Panel strongly support appropriate clinical application of digital technology as, increasingly, ONH imaging will be critical to the effective management of patients with glaucoma.

What are the economic considerations?

The evidence from the systematic review did not allow for any conclusions regarding the effectiveness of OCT in the diagnosis and monitoring of macular diseases or glaucoma. A modelled economic evaluation has therefore not been undertaken. Instead, the financial implications of unconditional public funding for OCT were estimated in terms of potential total costs to the MBS. These costs represent fees for Medicare benefit for the use of OCT only (not discounted for the 75–85% rate of MBS reimbursement to patients); they do not incorporate potential costs to government associated with treatment undertaken based on OCT findings, or potential cost offsets associated with discontinuation or modification of therapy due to OCT results.

Macular diseases

Estimates of potential annual utilisation of OCT for macular disease derived from epidemiological data (see 'Potential utilisation of OCT', page 15) were combined with the proposed MBS fees for OCT specified by the applicant to derive estimates of the potential annual cost of OCT to the MBS for diagnosis and monitoring of macular diseases. The proposed fee differed for unilateral and bilateral examinations, and for diagnostic scans and scans used for monitoring of therapy.

For diagnosis, the estimated total annual cost to the MBS using both proposed fees is presented in Table 27. Expert opinion is that the majority of diagnostic OCT examinations in Australian clinical practice will be bilateral; if OCT was to be reimbursed at the bilateral rate, the total annual cost to the MBS is estimated to be approximately $4.4 million.

Table 27 Estimated annual cost to the MBS of unrestricted funding for OCT for diagnosis of macular disease (epidemiological estimate)

	Scans / year	Proposed fee	Total cost / year ($millions)
Diagnosis	43,690	Unilateral: $60	$2.6
		Bilateral: $100	$4.4

Estimated total annual cost of OCT for monitoring is presented in Table 28. Expert opinion is that bilateral examination for monitoring of therapy and ongoing monitoring of untreated patients is standard practice for the majority of patients. Using the proposed rate of reimbursement for bilateral examinations, the total annual cost to the MBS for monitoring of therapy is estimated to range between $6.7 and $17.3 million.

Therefore, the total annual cost of OCT for macular diseases based on epidemiological data is estimated to range between $11.1 and $21.7 million.

Table 28 Estimated annual cost to the MBS of unrestricted funding for OCT for monitoring of macular disease (epidemiological estimate)

	Scans / year	Proposed fee	Total cost / year ($millions)
Monitoring of therapy	110,880–288,540	Unilateral: $40 Bilateral: $60	$4.4–$11.5 $6.7–$17.3

Potential utilisation of OCT was also estimated based on past utilisation of FFA (see Potential utilisation of OCT, page 15). This has been used as an alternative method for estimating total annual cost of OCT for diagnosis and monitoring for macular disease (Table 29). Since diagnostic and monitoring uses of the test cannot be disaggregated from past utilisation data, the proposed fees for bilateral diagnostic and monitoring scans have been applied to calculate a range of potential costs. Using this methodology, the total annual cost of OCT for macular diseases based on past utilisation of FFA is estimated to range between $6.1 and $10.1 million. This is considered to represent a lower bound of potential costs.

Table 29 Estimated annual cost to the MBS of unrestricted funding for OCT for diagnosis and monitoring of macular disease (based on past FFA utilisation)

Scans / year	Proposed fee	Total cost / year ($millions)
101,400	Bilateral (diagnosis): $100 Bilateral (monitoring): $60	$10.1 $6.1

Glaucoma

Estimates of potential annual utilisation of OCT for glaucoma derived from epidemiological data (see 'Potential utilisation of OCT', page 21) were combined with the proposed MBS fees for OCT specified by the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) to derive estimates of potential annual cost of OCT to the MBS for diagnosis and monitoring of glaucoma (Table 30). The proposed fee was per patient (ie the same fee for unilateral and bilateral examinations) and was for general use of OCT (ie different fees were not provided for diagnosis or monitoring uses of the test). The estimated annual cost for diagnosis of glaucoma is approximately $1.2 million; for monitoring of therapy, the estimated annual cost ranged between $7.1 and $12.6 million.

Therefore, the total annual cost of OCT for glaucoma is estimated to range between $8.3 and $13.8 million.

Table 30 Estimated annual cost to the MBS of unrestricted funding for OCT for diagnosis and monitoring of glaucoma

	Scans / year	Proposed fee	Total cost / year ($millions)
Diagnosis	15,200	$80	$1.2
Monitoring of therapy	89,000–157,500	$80	$7.1–$12.6
TOTAL	104,200–172,700	$80	$8.3–$13.8

Conclusions

The main potential role of OCT in the diagnosis of macular diseases is to identify additional cases of disease, leading to the initiation of treatment in patients who would not have been treated in the absence of OCT. Additionally, for non-tractional macular diseases, a negative OCT will result in the avoidance of FFA in some patients (expert advice suggests that a minority of patients may still undergo FFA after a negative OCT).

The main potential role of OCT in the diagnosis of glaucoma is to identify additional cases of disease, leading to the initiation of treatment in patients who would not have been treated in the absence of OCT (or initiating management earlier than would have occurred in the absence of OCT).

Safety

OCT is considered a safe procedure. No studies were identified which reported any adverse events with the use of OCT.

Effectiveness: Macular disease

The specific research questions for this review were:

- What is the value of optical coherence tomography compared with fundus fluorescein angiography or a clinical observation strategy in the diagnosis of macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy, tractional diseases of the macula, macular oedema and neovascularisation?

- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and fundus fluorescein angiography in the monitoring of patients with macular degeneration, diabetic maculopathy, other retinal vascular diseases, uveitic maculopathy, central serous retinopathy and macular oedema?

Diagnosis of macular disease

Diagnostic accuracy

Due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of macular abnormalities could not be assessed.

OCT was found to have a similar diagnostic yield to FFA for the detection of macular oedema. A proportion of patients who are positive for the presence of macular oedema on OCT would be negative on FFA; conversely, a proportion of patients who are negative on OCT would be positive on FFA. In the absence of verification of 'true' disease status in patients with discordant test results, the accuracy of these results is uncertain.

Evidence for the comparative yield of OCT and FFA for the detection of other non-tractional macular abnormalities was not found.

OCT appears to provide an incremental yield over prior clinical examination for the detection of tractional diseases (epiretinal membrane, macular holes, vitreomacular traction syndrome). In the absence of verification of 'true' disease status in the additional patients diagnosed by OCT, the accuracy of these results is uncertain.

Impact on patient management

No studies reported the impact of OCT on patient management for non-tractional macular diseases compared with FFA. However, as a replacement test in first line diagnosis, it is reasonable to assume that management will be changed by the OCT result in the same manner as by FFA.

A prospective study in patients with epiretinal membranes or vitreomacular traction reported that 17% (95% CI: 10.2–26.1%) of patients had their management plan altered from observation (prior to OCT) to surgery (after the addition of OCT information). The extent to which the post-OCT management plan was consistent with the management patients actually received was not reported. There is some uncertainty regarding the magnitude of this effect due to biases inherent in this study.

Impact on health outcomes

In the absence of conclusions regarding the accuracy of discordant OCT and FFA findings for the presence or absence of macular oedema, or of the additional OCT-detected cases of tractional disease not detected on prior clinical examination, it is not possible to draw conclusions regarding the clinical significance or impact of OCT on health outcomes using a linked evidence approach.

Monitoring of treated or untreated patients

No RCTs were identified which compared a monitoring strategy involving OCT to a strategy involving FFA in patients with treated or untreated macular disease.

A single small, non-randomised, low quality Level III-2 study found that eyes with AMD treated with photodynamic therapy experienced non-significant decrements in best corrected distance acuity at 12 months when monitored by FFA alone relative to monitoring with OCT plus FFA. The proportion of eyes with a loss of distance acuity of more than three lines was significantly higher in the group monitored with FFA alone. The precision of these estimates is limited by biases inherent in this study; therefore, the effectiveness of OCT for monitoring of PDT in patients with AMD remains uncertain.

Other considerations

Expert opinion

The introduction of OCT examination of the macula has revolutionised diagnosis and management of retinal disease by ophthalmic specialists, through giving a qualitative and quantitative measure of cross-sectional anatomical change in the macula. OCT has become an essential part of the standard of care, and so apparent is its utility to

specialists and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination.

Despite the widespread diffusion of this technology into retinal ophthalmology at every level, establishing the utility of OCT for macular disease in the MSAC report has been difficult due to a lack of published evidence in the literature with an appropriate comparator.

In the estimation of ophthalmologist members of the Advisory Panel, this report, therefore, fails to convey the high utility of OCT and the fundamental role that OCT now plays in the management of patients with macular disease. The ophthalmologist members of the Advisory Panel strongly support appropriate application of this essential technology, carried out and interpreted by specialist ophthalmologists to allow early detection and intervention in blinding macular diseases.

Effectiveness: Glaucoma

The specific research questions for this review were:

- What is the additional value of optical coherence tomography over that of computerised perimetry and clinical examination in the diagnosis of glaucoma, in patients with risk factors for glaucoma with questionable clinical examination (glaucoma-like optic discs)?
- What is the value of the addition of optical coherence tomography to a strategy of clinical examination and computerised perimetry in the monitoring of patients treated or with risk factors for glaucoma?

Diagnosis of glaucoma

Diagnostic accuracy

Due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of macular abnormalities could not be assessed.

Evidence for the incremental yield of OCT over clinical examination for the detection of glaucomatous damage was not found.

Impact on patient management

Evidence for the impact of OCT on patient management for patients with glaucoma was not found.

Impact on health outcomes

In the absence of evidence demonstrating the diagnostic accuracy of OCT and its impact on patient management, conclusions regarding the impact of OCT on health outcomes are not possible using a linked evidence approach.

Monitoring of treated or untreated patients

Evidence for the effectiveness of OCT in monitoring treated or untreated patients with glaucoma was not found.

Other considerations

Expert opinion

With many forms of innovative technology, particularly when it is rapidly evolving, published literature lags behind its clinical acceptance and uptake.

In glaucoma, structural optic nerve head changes precede detectable changes in visual field sensitivity (Weinreb et al. 2004). Changes in optic nerve head structure are now relied upon to determine diagnosis and to detect progression of glaucoma. Digital methods to measure and to record optic nerve head structural abnormality should be standard tools in the management of glaucoma in 2008. OCT is one such method.

As well as its role in the diagnosis and in the detection of progression, OCT contributes significantly to a patient's understanding of the disease, thereby greatly increasing the likelihood of patient acceptance of, adherence to and perseverance with lifelong therapy.

The ophthalmologist members of the Advisory Panel strongly support appropriate clinical application of digital technology as, increasingly, optic nerve head imaging will be critical to the effective management of patients with glaucoma.

Economic considerations

A modelled economic evaluation has not been undertaken. Instead, the financial implications of unconditional public funding for OCT were estimated in terms of potential total costs to the MBS. These costs represent fees for Medicare benefit for the use of OCT only (not discounted for the 75–85% rate of MBS reimbursement to patients); they do not incorporate potential costs to government associated with treatment undertaken based on OCT findings, or potential cost offsets associated with discontinuation or modification of therapy due to OCT results.

Macular diseases

If OCT were reimbursed in Australia using the cost estimates supplied by the applicant, and assuming potential utilisation derived from epidemiological estimates, the total annual cost to the MBS of OCT for diagnosis of macular disease is estimated to be approximately $4.4 million; for monitoring of therapy, total annual cost to the MBS is estimated to range between $6.7 and $17.3 million. Therefore, the total annual cost of OCT for macular diseases is estimated to range between $11.1 and $21.7 million.

Using past utilisation of FFA as an indication of potential OCT utilisation, the total annual cost of OCT for macular diseases is estimated to range between $6.1 and $10.1 million. This is considered to represent a lower bound of potential costs.

Glaucoma

If OCT were reimbursed in Australia using the cost estimates supplied by the applicant, total annual cost to the MBS of OCT for diagnosis of glaucoma is estimated to be approximately $1.2 million; for monitoring of therapy, total annual cost to the MBS is estimated to range between $7.1 and $12.6 million. Therefore, the total annual cost of OCT for glaucoma is estimated to range between $8.3 and $13.8 million.

Conclusions

The use of OCT in the diagnosis and monitoring of macular disease and glaucoma is considered to be safe.

The accuracy of OCT for the diagnosis of macular diseases and glaucoma could not be established, and therefore the effectiveness of OCT in improving health outcomes could not be demonstrated through a linked evidence approach.

Evidence for the use of OCT in monitoring treated or untreated patients with macular disease or glaucoma was not found.

Advice

Optical Coherence Tomography (OCT) is a non-invasive ophthalmic imaging technique, which provides high-resolution cross-sectional images of the macula, which in turn allows identification of changes due to ophthalmologic conditions. OCT is intended to be used for diagnosis and monitoring of retinal diseases and glaucoma in a specialist ophthalmologic setting.

The MSAC finds that OCT is a safe procedure.

MSAC finds that there is currently insufficient evidence to recommend public funding for the assessment of macular disease or glaucoma.

— The Minister for Health and Ageing noted this advice on 8 December 2008 —

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures
- 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 or affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Brendon Kearney (Deputy Chair)	health administration and planning
Dr William Glasson (Second Deputy Chair)	ophthalmology
Associate Professor John Atherton	cardiology
Associate Professor Michael Cleary	emergency medicine
Associate Professor Paul Craft	clinical epidemiology and oncology
Professor Geoff Farrell	gastroenterology
Dr Kwun Fong	thoracic medicine
Professor Richard Fox	oncology
Professor Jane Hall	health economics
Professor John Horvath	Department of Health and Ageing Chief Medical Officer
Associate Professor Terri Jackson	health economics
Associate Professor Frederick Khafagi	nuclear medicine
Associate Professor Ray Kirk	health research
Dr Ewa Piejko	general practice
Dr Ian Prosser	haematology
Ms Sheila Rimmer	consumer health issues
Dr Judy Soper	radiology

Member	Expertise or affiliation
Professor Ken Thomson	radiology
Dr David Wood	orthopaedics

Appendix B Advisory panel

Advisory panel for application 1116/reference 40: Optical coherence tomography

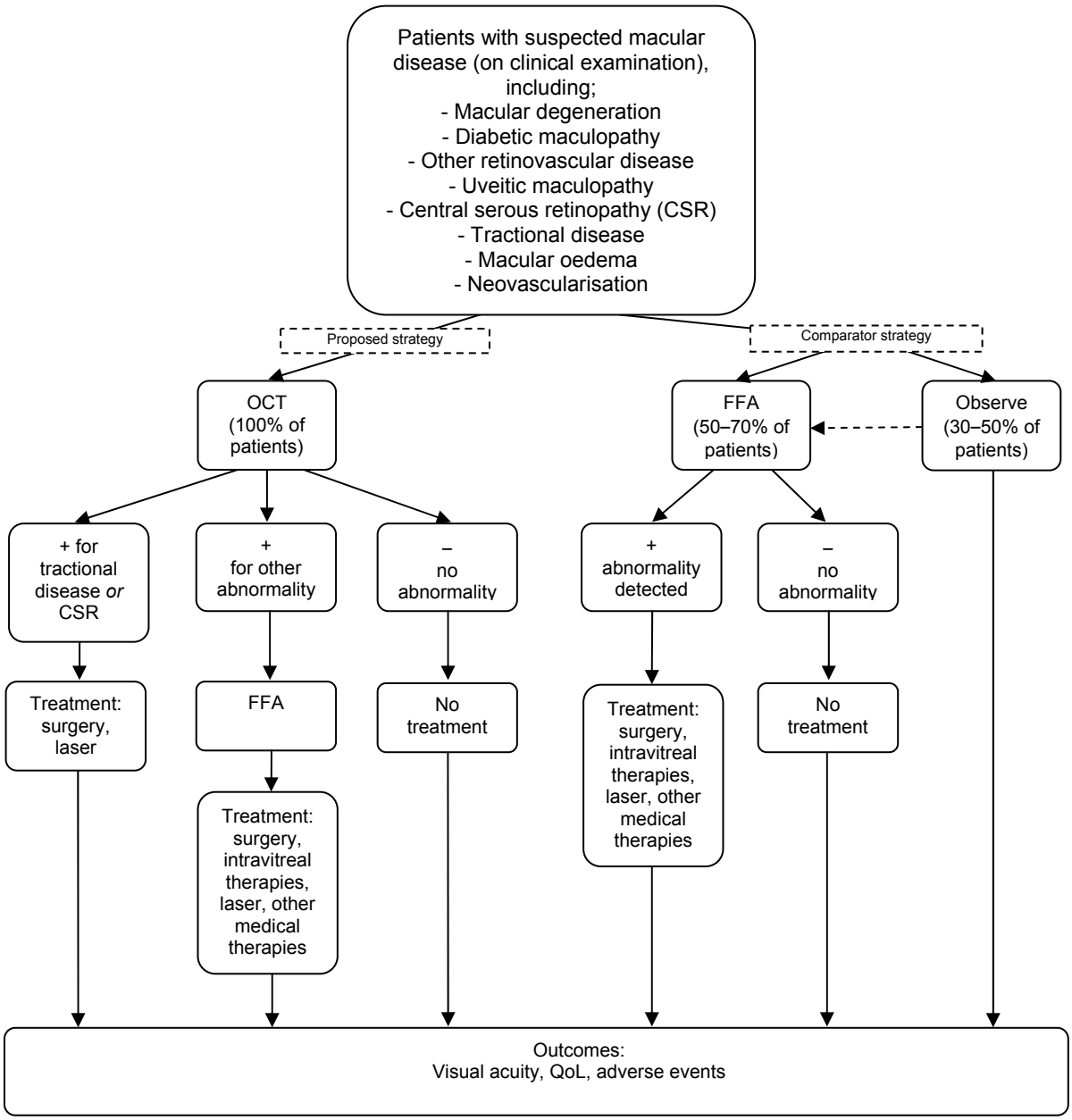
A/Professor Michael Cleary (Chair) Emergency Medicine	Member of MSAC
A/Professor Frederick Khafagi Nuclear Medicine	Member of MSAC
Dr William Glasson Ophthalmology	Member of MSAC
Dr Jennifer Joan Arnold Ophthalmology	Co-opted Ophthalmologist
Dr Guy Timothy Edwin D'Mellow Ophthalmology	Co-opted Ophthalmologist
Ms Barbara Daniels Consumer Health	Consumer Health Forum nominee
Dr Ivan Goldberg Ophthalmology	Co-opted Ophthalmologist
Dr Alex P Hunyor Ophthalmology	Co-opted Ophthalmologist
Dr Ehud Zamir Ophthalmology	Co-opted Ophthalmologist

Health Technology Assessors

Mr Luke Marinovich, Manager	NH&MRC Clinical Trials Centre, University of Sydney

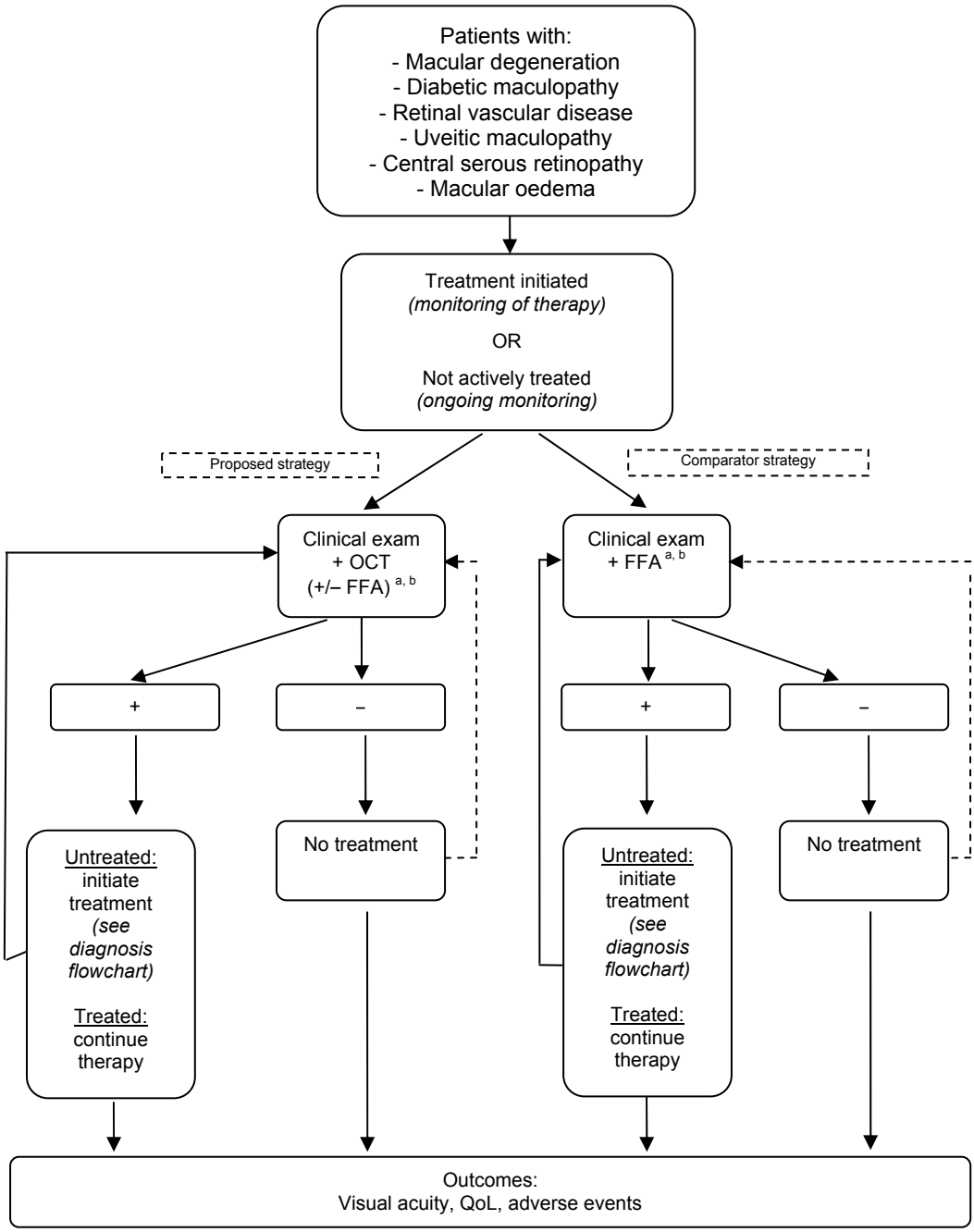
Appendix C Clinical flowcharts

Macular diseases (diagnosis)



Abbreviations: CSR, central serous retinopathy; FFA, fundus fluorescein angiography; OCT, optical coherence tomography; QoL, quality of life

Macular diseases (monitoring)



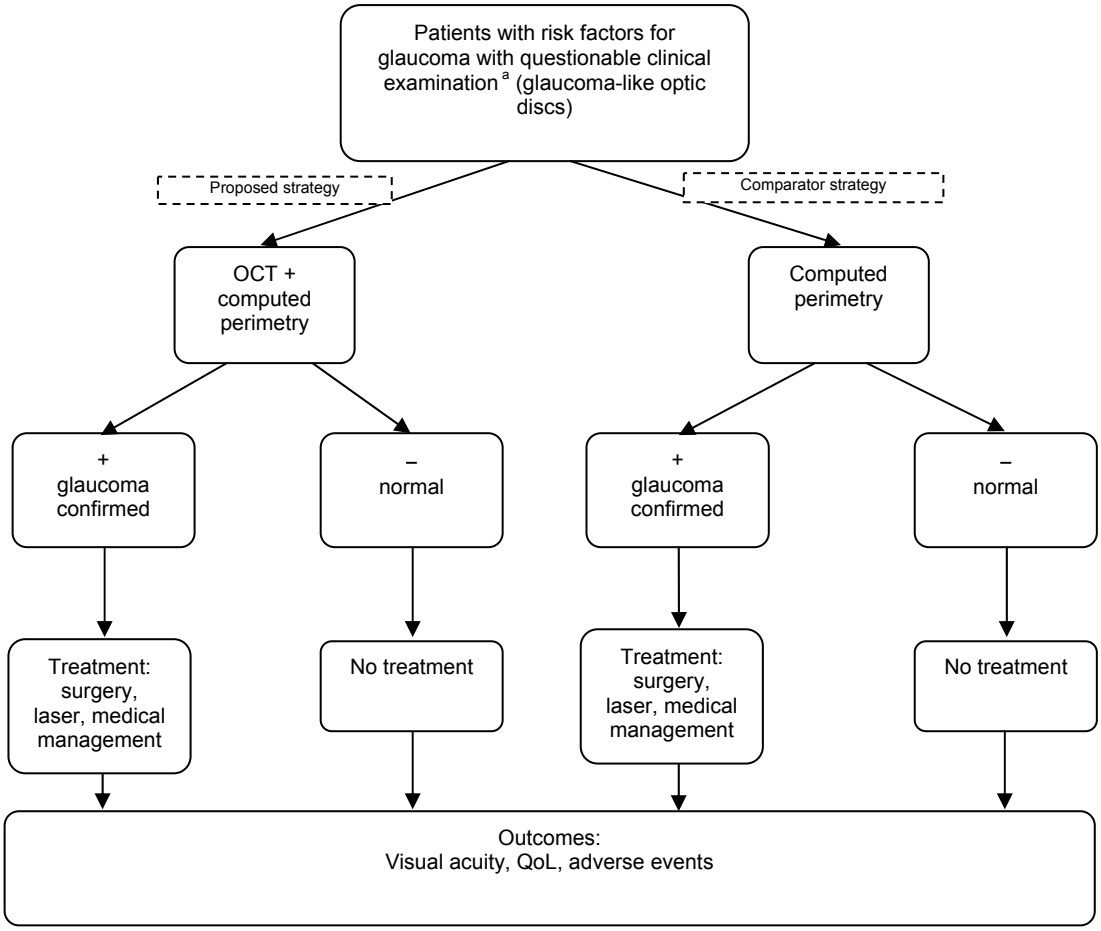
Abbreviations: FFA, fundus fluorescein angiography; OCT, optical coherence tomography; QoL, quality of life

[a] Table of monitoring frequency (monitoring of therapy)

	New test strategy (OCT +/– FFA)		Comparator arm
Disease/Indication	**OCT**	**FFA**	**FFA**
Macular degeneration	1–3 months	2 years	2–12 weeks
Diabetic maculopathy	6–12 weeks initially then episodic	2 years	6 months
Retinal vascular disease	6–12 months	2 years	3–6 months
Uveitic maculopathy	6 weeks	6 months	3–6 months
Macular oedema	6–12 weeks initially then episodic	12 months	3–6 months
Central serous retinopathy	Episodic	Episodic	4 weeks initially then episodic

[b] Ongoing monitoring with OCT is episodic (with a lower threshold than FFA); monitoring with FFA is also episodic (with a higher threshold)

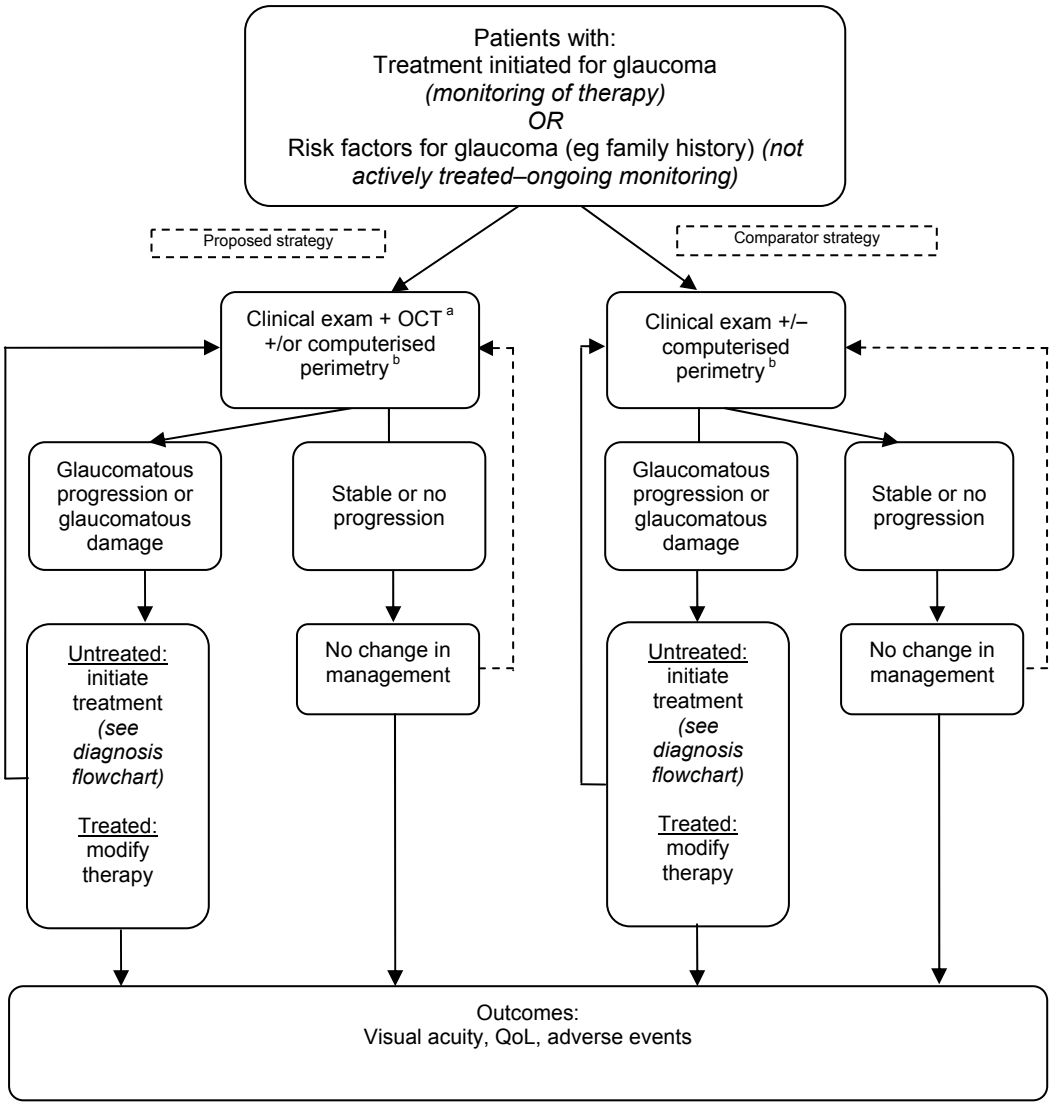
Glaucoma (diagnosis)



Abbreviations: OCT, optical coherence tomography; QoL, quality of life

[a] Clinical examination includes photography, visual acuity, risk factor assessment, intra-ocular pressure, disc assessment

Glaucoma (monitoring)



Abbreviations: OCT, optical coherence tomography; QoL, quality of life

[a] Where no prior OCT, the first OCT will be conducted for baseline purposes

[b] Table of monitoring frequency

Ongoing monitoring of 'suspects'	Monitoring of treatment
1–2 years (clinical, functional and structural assessments) More frequent if patient is rapidly progressing	Clinical exam every 4–6 months Functional test every second visit With addition of OCT, alternate between functional and structural (ie clinical exam and functional test one visit; clinical exam and structural test next visit)

Appendix D Electronic databases and HTA websites

1. International electronic databases
NHS Centre for reviews and Dissemination databases/ International Network of Agencies for Health Technology Assessment (INAHTA) Economic evaluation database (EED) Database of abstracts of reviews of effectiveness (DARE) Heath Technology Assessment (HTA) www.york.ac.uk/inst/crd/
Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register www.cochrane.org
2. Individual health technology assessment agencies
AUSTRALIA
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S) http://www.surgeons.org/open/asernip-s.htm
Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
AUSTRIA
Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm
CANADA
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/
Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html
Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html
Canadian Health Economics Research Association (CHERA/ACRES)—Cabot database http://www.mycabot.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
DENMARK
Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
FINLAND
FINOHTA http://www.stakes.fi/finohta/e/
FRANCE
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/
GERMANY
German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/en/hta/index.html

THE NETHERLANDS Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php
NEW ZEALAND New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
NORWAY Norwegian Centre for Health Technology Assessment (SMM) http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm
SPAIN Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud 'Carlos III'I/Health Technology Assessment Agency (AETS) http://www.isciii.es/aets/ Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html
SWEDEN Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/admin/index.asp Centre for Medical Health Technology Assessment http://www.cmt.liu.se/English/Engstartsida.html
SWITZERLAND Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/
UNITED KINGDOM Health Technology Board for Scotland http://www.htbs.org.uk/ National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/ University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/ National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm
UNITED STATES Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm Harvard School of Public Health—Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html U.S. Blue Cross/ Blue Shield Association Technology Evaluation Centre (TEC) http://www.bcbs.com/consumertec/index.html

Appendix E Quality criteria

Table 31 Criteria used to assess the quality of diagnostic accuracy studies—the QUADAS tool [a]

Item	
1	Were patients prospectively recruited?
2	Were patients consecutively recruited? That is, a consecutive group of patients presenting with a defined clinical presentation.
3	Were selection criteria explicitly described? That is, in enough detail to clearly define eligibility of patients and to be reproducible.
4	Is the reference standard likely to correctly classify the target condition? Valid/invalid/optimal.
5	Did all patients receive verification using a reference standard?
6	Is the time period between reference standard, comparator and index test short enough to be reasonably sure that the target condition did not change between the tests?
7	Was the execution of the index test described in sufficient detail to define applicability of the test?
8	Were OCT/comparator results interpreted blind to reference standard?
9	Were reference standard results interpreted blind to OCT/comparator results?
10	Were the same clinical data including conventional imaging available when test results were interpreted as would be available when the test is used in practice?
11	Were uninterpretable/intermediate test results reported?
12	Were withdrawals from the study explained?

Source: adapted from Whiting et al. (2003)

Abbreviation: OCT, optical coherence tomography

[a] High quality: Yes to 1, 3, 4, 5, 10, 11; other items required to be either Yes or Unclear. Low quality: No/Unclear for either 4, 5. Other studies are assessed as fair quality

Table 32 Criteria used to assess the quality of effectiveness studies

Study design	Quality checklist
Systematic review [a]	Was the research question specified?
	Was the search strategy explicit and comprehensive?
	Were the eligibility criteria explicit and appropriate?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were sources of heterogeneity explored?
	Was a summary of the main results clear and appropriate?
Studies evaluating effectiveness of an intervention on health outcomes	
Randomised controlled trial	Were the inclusion and exclusion criteria specified?
	Was the assignment to the treatment groups really random?
	Was the treatment allocation concealed from those responsible for recruiting subjects?
	Was there sufficient description about the distribution of prognostic factors for the treatment and control groups?
	Were the groups comparable at baseline for these factors?
	Were outcome assessors blinded to the treatment allocation?
	Were the care providers blinded?
	Were the subjects blinded?
	Were all randomised participants included in the analysis?
	Was a point estimate and measure of variability reported for the primary outcome?

Source: adapted from NHMRC (2000) and CRD (2001)

[a] High quality: yes or N/A to all seven criteria. Low quality: four or less yes or N/A. Other studies will be assessed as fair quality

Table 33 Criteria used to assess the quality of therapeutic impact studies

Item	
1	Was the study designed and conducted prospectively?
2	Explicit eligibility criteria reflecting specific presentation or clinical problem?
3	Consecutive recruitment of all patients eligible for testing?
4	Referring clinician determining management plan?
5	Test accuracy documented concomitantly?
6	Pretest plan independently assessed?
7	Blinding to study test results at pretest measurement?
8	Association between management change and study test result independently assessed?
9	Management changes reported for specific test use and patient presentation?
10	Management changes reported in adequate detail? For example, surgery avoided, additional investigations, etc.
11	Descriptive information about patient outcomes reported?
12	Physician experience reported?

Source: adapted from Guyatt et al. (1986)

Appendix F Characteristics, appraisal and results of included systematic reviews

Author (year) Setting	Objective of report	Number & publication dates of included studies	Population considered in included studies Test comparison	Conclusions/recommendation	Quality assessment
American Academy of Ophthalmology Lin et al. (2007) United States	1) To determine how well OCT aids in glaucoma diagnosis, particularly as an adjunctive test to a complete ophthalmological examination including perimetric testing 2) To determine whether glaucoma progression can be detected with OCT	Databases: PubMed, Cochrane Library Time period: January 2003–February 2006 (Update of previous non-systematic review) **Diagnosis:** 17 studies 10 studies compared healthy eyes and eyes with glaucomatous visual field loss 7 studies included glaucoma suspect and/or ocular hypertensive patients **Monitoring:** 1 study	**Diagnosis:** 10 studies compared healthy eyes and eyes with glaucomatous visual field loss 7 studies included glaucoma suspect and/or ocular hypertensive patients **Monitoring:** 1 study compared OCT and standard automated perimetry in glaucoma patients or glaucoma suspects Inclusion/exclusion criteria: English language journals Other inclusion/exclusion criteria not specified	**OCT for initial diagnosis** RNFL thickness in the inferior and superior quadrants, as well as the inferior/inferior-temporal and superior/superior-temporal clock hours, provided the best AUCs for glaucoma detection. Most studies included only patients with VF loss, and have limited applicability in clinical practice. When glaucoma suspects with normal VFs were included, observed AUCs were lower **OCT for detecting glaucomatous progression (monitoring)** In one study, OCT detected progression at a higher rate than perimetry. There is the need for long-term studies to determine whether OCT-detected progression predicts later VF progression	**Quality: fair** Explicit review questions: no Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes

Results:

Accuracy for diagnosis of glaucoma

OCT RNFL measurement in glaucoma vs control (5 studies):

- Mean RNFL (superior quadrant): AUC range = 0.790–0.952
- Mean RNFL (inferior quadrant): AUC range = 0.863–0.971

OCT RNFL measurement in glaucoma suspects vs control (3 studies):

- Mean RNFL (superior quadrant): AUC range = 0.591–0.840
- Mean RNFL (inferior quadrant): AUC range = 0.694–0.810

OCT macular parameters in glaucoma vs control (1 study):

- Macular nerve fibre layer and inner retinal complex parameters: AUC as high as 0.97 in glaucoma vs control (1 study)

OCT RNFL, OHN and macular parameters (7 studies):

- AUC of RNFL and OHN parameters reportedly comparable, and higher than macular parameters in glaucoma vs control (3 of 4 studies)
- AUCs of RNFL and OHN parameters comparable in glaucoma vs control (2 studies)
- AUCs of RNFL parameters higher than macular parameters in glaucoma vs control and in glaucoma suspect vs control (1 study)

Detection of glaucomatous progression

OCT-identified progression = 25%; SAP-identified progression = 12% (1 study)

Author (year) Setting	Objective of report	Number & publication dates of included studies	Population considered in included studies Test comparison	Conclusions/recommendation	Quality assessment
Virgili et al. (2007b) Italy	To review systematically the sensitivity and specificity of OCT for diagnosing macular oedema attributable to diabetic retinopathy compared with fundus stereophotography or contact and non-contact fundus biomicroscopy	Databases: Medline, Embase, hand searching (journals, reference lists) Time period: Medline (1966–September 2006); Embase (2002–September 2006); journal hand search (1998–2006) 15 included studies 6 described accuracy of OCT	Diabetes (defined as use of any glucose-lowering medication); CSME (by ETDRS definition) OCT (against reference standard of fundus stereophotography or contact and non-contact fundus biomicroscopy)	OCT can be used to diagnose CSME, particularly its central type or CDME, and decide on laser photocoagulation in patients with intermediate suspicion of disease The strength of this conclusion is limited by the fact that data could be extracted from only a fraction of the published literature due to limitations in reporting. The precision of estimates is inflated by the within-patient correlation between eyes in all studies	**Quality: fair** Explicit review questions: yes Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: yes Summary of results clear and appropriate: yes

Results:

- Sensitivity = 0.79 (95% CI: 0.71–0.86); specificity = 0.88 (95% CI: 0.80–0.93)
- Positive likelihood ratio = 6.5 (95% CI: 4.0–10.7); negative likelihood ratio = 0.24 (95% CI: 0.17–0.32)
- Pooled DOR = 27.7 (95% CI: 17.0–45.3)

Author (year) Setting	Objective of report	Number & publication dates of included studies	Population considered in included studies Test comparison	Conclusions/recommendation	Quality assessment
Alberta Heritage Foundation for Medical Research (2003) Canada	To evaluate the evidence on the use of OCT to diagnose retinal disease	Databases: PubMed, Cinahl, Embase, Cochrane Library, Science Citation Index, Clinical Trials registries, HTA Databases, FDA website, world wide web searches Time period: 1995–July/August 2003 **Diagnosis:** 8 studies 6 glaucoma studies 2 cystoid macular oedema studies	**Glaucoma diagnosis:** 6 studies compared OCT with perimetry or other tests (SLP, CSLO, photography) **Cystoid macular oedema diagnosis:** 1 study compared OCT with FFA in patients with uveitis 1 study compared OCT with FFA + slit-lamp biomicroscopy in patients with diabetic retinopathy	**Glaucoma diagnosis:** Likelihood ratios indicate that OCT provided strong but not conclusive diagnostic evidence for detecting glaucoma **Cystoid macular oedema diagnosis:** Likelihood ratios indicate that OCT provided strong to convincing diagnostic evidence for detecting cystoid macular oedema and retinal blood vessel leakage Sensitivity and specificity may be over-estimated in included studies	**Quality: fair** Explicit review questions: yes Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search strategy: yes Quality of included studies appraised: no Methods of study appraisal reproducible: N/A Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes

Results:

Accuracy for diagnosis of glaucoma

OCT in glaucoma vs control (4 studies):

- Sensitivity range = 71–82%
- Specificity range = 80–92%

Accuracy for diagnosis of macular oedema

OCT in patients with uveitis (FFA as reference standard) (1 study):

- Sensitivity = 89%; specificity = 100%

OCT in patients with diabetic retinopathy (FFA as reference standard) (1 study):

- Foveal retinal thickness: Sensitivity = 81.5%; specificity = 94.1% (FFA as reference standard)
- Average retinal thickness: Sensitivity = 73.1%; specificity = 100% (FFA as reference standard)
- Foveal retinal thickness: Sensitivity = 88.8%; specificity = 96.0% (slit-lamp biomicroscopy as reference standard)
- Average retinal thickness: Sensitivity = 80.2%; specificity = 100% (slit-lamp biomicroscopy as reference standard)

Author (year) Setting	Objective of report	Number & publication dates of included studies	Population considered in included studies Test comparison	Conclusions/recommendation	Quality assessment
American Academy of Ophthalmology McDonald et al. (2007) United States	To evaluate currently available data in the published literature to answer the question of whether laser scanning imaging is a sensitive and specific tool for detecting macular disease when compared with the current standard technique of slit-lamp biomicroscopy or fundus photography	Databases: PubMed, Cochrane Library Time period: 2000–August 2006 50 studies of OCT 4 Level I studies 8 Level II studies 38 Level II studies	OCT vs biomicroscopy and/or fundus photography Any macular disease One study in patients with diabetic retinopathy reported accuracy outcomes (Also considered HRT and RTA)	OCT measures retinal thickness with a high degree of accuracy and reproducibility. It provides accurate quantitative information about macular thickness changes over time, and provides information about the architecture of the retina along its depth that is not available with standard imaging modalities. The usefulness of OCT depends on the skill of the operator and is limited by media opacity and the cooperation of the patient	**Quality: fair** Explicit review questions: no Explicit & appropriate eligibility criteria: no Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of results clear and appropriate: yes (Level I & II); no (Level III)

Results:

Accuracy for diagnosis of macular oedema:

OCT in patients with diabetic retinopathy (stereoscopic fundus photography as reference standard) (1 study):

- Sensitivity = 92%
- Specificity = 73%

Appendix G Included accuracy studies (macular diseases)

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Antcliff et al. (2000) United Kingdom Single site Recruitment period: January 1997–March 1998 Number of participants: 58 (121 eyes) Including 7 patients examined twice	Objective: To compare OCT with FFA for the detection of cystoid macular oedema in patients with uveitis Study design: Prospective diagnostic accuracy study Index test: Humprey OCT 2000 Primary outcomes: Accuracy Reference standard: Fundus fluorescein angiography	Inclusion criteria: Suspected or known macular oedema on clinical examination Exclusion criteria: Not specified Patient characteristics (age, gender etc): Not reported	**Accuracy** Cystoid macular oedema or subretinal fluid: FFA OCT + 72 5 77 – 3 41 44 total 75 46 121 Sn / Sp (FFA as reference standard): 96% / 89% OCT yield: 64% [95% CI: 55–72%] FFA yield: 62% [95% CI: 53–70%] (no significant difference in yield at p=0.05)	**Quality: low** Prospective: yes Consecutive: unclear Explicit selection criteria: no OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: unclear Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: yes Routine clinical data available: yes Uninterpretable/intermediate results reported: no Study withdrawals explained: N/A Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: unclear relevant population: yes prior tests: yes Applicable comparator: yes Applicable intervention: yes

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Catier et al. (2005) France Single site Recruitment period: Not reported Number of participants: 58 (58 eyes) Subset of 78 patients (20 did not undergo FFA)	Objective: To use OCT to characterise the intraretinal changes associated with macular oedema according to its aetiology Study design: Retrospective diagnostic accuracy study Index test: Humphrey 2000 OCT Primary outcomes: Accuracy Reference standard: Fundus fluorescein angiography	Inclusion criteria: Patients with macular oedema who had undergone OCT (mixed aetiologies) Exclusion criteria: Lack of FFA examination. Patient characteristics (full sample, 78 patients): Age range: 23–83 years Gender: male (54%), female (46%)	**Accuracy** Cystoid macular oedema: FFA OCT + : 51 / 5 / 56 OCT – : 2 / 0 / 2 OCT total : 53 / 5 / 58 Sn / Sp (FFA as reference standard): 96% / 0% OCT yield: 97% [95% CI: 88–100%] FFA yield: 91% [95% CI: 81–97%] (no significant difference in yield at p=0.05)	**Quality: low** Prospective: no Consecutive: no Explicit selection criteria: no OCT protocol: no Reference standard not valid not applied to all participants Test interval: reference standard: unclear (months–years) Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: yes Uninterpretable/intermediate results reported: yes Study withdrawals explained: yes Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: unclear relevant population: yes prior tests: yes Applicable comparator: yes Applicable intervention: yes

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Do et al. (2007)
USA
Single centre
Recruitment period:
June–November 2004
Number of participants: 73 (84 eyes)</td>
<td>Objectives:
To compare retina surgeons' recommendations for management of epiretinal membranes and vitreomacular traction based on clinical assessment alone with management based on clinical evaluation supplemented by OCT
Study design:
Pre-OCT/post-OCT management plans
Index test:
Stratus OCT 3
Primary outcomes:
Management change
Other outcomes:
Accuracy
Reference standard:
History, slit-lamp biomicroscopy after pharmacological dilation</td>
<td>Inclusion criteria:
Patients with macular disorders such as ERM or VMT (referred, or found on clinical exam)
Management plan developed prior to OCT
Exclusion criteria:
Comorbid conditions not treatable by surgery (eg retinal vascular occlusions, diabetic retinopathy)
Patient characteristics (age, gender etc):
Not reported</td>
<td>Accuracy
<u>Epiretinal membranes</u>:
<table>
<tr><td></td><td></td><td colspan="4">Clinical exam</td></tr>
<tr><td></td><td></td><td>+</td><td>?</td><td>–</td><td>total</td></tr>
<tr><td>OCT</td><td>+</td><td>66</td><td>0</td><td>6</td><td>72</td></tr>
<tr><td></td><td>–</td><td>0</td><td>2</td><td>10</td><td>12</td></tr>
<tr><td></td><td>total</td><td>66</td><td>2</td><td>13</td><td>84</td></tr>
</table>
?Clinical exam considered positive:
Sn / Sp (clinical exam as reference standard): 97% / 67%
Incremental yield: 37% [95% CI: 16–64%]
Extra cases / 1000: 375 [95% CI: 163–641]
?Clinical exam considered negative:
Sn / Sp (clinical exam as reference standard): 100% / 63%
Incremental yield: 33% [95% CI: 14–59%]
Extra cases / 1000: 333 [95% CI: 143–588]
<u>Vitreomacular traction</u>:
<table>
<tr><td></td><td></td><td colspan="4">Clinical exam</td></tr>
<tr><td></td><td></td><td>+</td><td>?</td><td>–</td><td>total</td></tr>
<tr><td>OCT</td><td>+</td><td>5</td><td>4</td><td>6</td><td>18</td></tr>
<tr><td></td><td>–</td><td>0</td><td>2</td><td>64</td><td>66</td></tr>
<tr><td></td><td>total</td><td>5</td><td>6</td><td>73</td><td>84</td></tr>
</table>
?Clinical exam considered positive:
Sn / Sp: 82% / 88%
Incremental yield: 12% [95% CI: 6–23%]
Extra cases / 1000: 123 [95% CI: 61–226]
?Clinical exam considered negative:
Sn / Sp: 100% / 84%
Incremental yield: 16% [95% CI: 10–26%]
Extra cases / 1000: 165 [95% CI: 98–261]</td>
<td>Quality
Prospective: yes
Consecutive: no
Explicit selection criteria: no
OCT protocol: no
Reference standard
not valid
applied to all participants
Test interval: unclear
Tests reported blinded to reference standard: yes
Reference standard reported blinded to tests: yes
Routine clinical data available: yes
Uninterpretable/intermediate results reported: yes for clinical exam, no for OCT
Study withdrawals explained: unclear
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: unclear
relevant population: unclear
prior tests: yes
Applicable comparator: yes
Applicable intervention: yes</td>
</tr>
</table>

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Espinoza et al. (2004)
United States
Single site
Recruitment period: August–December 2002
Number of participants: 33 (33 eyes)</td>
<td>Objective:
To investigate OCT in evaluating subretinal fluid in suspicious choroidal melanocytic tumours
Study design:
Retrospective diagnostic accuracy study.
Index test:
OCT 3
Primary outcomes:
Accuracy
Reference standard:
Fundus fluorescein angiography</td>
<td>Inclusion criteria:
Untreated choroidal melanocytic tumours and suspicion of subtle separation of the retina by slit-lamp biomicroscopy
Exclusion criteria:
Poor quality OCT, loss to follow-up.
Patient characteristics:
Mean age: 60 years (median 62, range 33–73)
Gender: male (52%), female (48%)</td>
<td>Accuracy
<u>Macular oedema</u>:
<table>
<tr><th></th><th></th><th>FFA
+</th><th>–</th><th>total</th></tr>
<tr><td rowspan="3">OCT</td><td>+</td><td>6</td><td>6</td><td>12</td></tr>
<tr><td>–</td><td>2</td><td>19</td><td>21</td></tr>
<tr><td>total</td><td>8</td><td>25</td><td>33</td></tr>
</table>
Sn / Sp (FFA as reference standard): 75% / 76%
OCT yield: 36% [95% CI: 21–55%]
FFA yield: 24% [95% CI: 12–43%]
(no significant difference in yield at p=0.05)</td>
<td>Quality: low
Prospective: no
Consecutive: no
Explicit selection criteria: yes
OCT protocol: no
Reference standard
not valid
applied to all participants
Test interval:
reference standard: unclear
Tests reported blinded to reference standard: unclear
Reference standard reported blinded to tests: unclear
Routine clinical data available: yes
Uninterpretable/intermediate results reported: yes
Study withdrawals explained: yes
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: yes
relevant population: yes
prior tests: yes
Applicable comparator: yes
Applicable intervention: yes</td>
</tr>
</table>

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Gallemore et al. (2000) United States Single site Recruitment period: August 1997–May 1998 Number of participants: 119 (132 eyes)	Objective: To compare the relative incidence of vitreoretinal adhesions associated with partial vitreous separation within the macula diagnosed with OCT and biomicroscopy Study design: Retrospective diagnostic accuracy study Index test: OCT Primary outcomes: Accuracy Reference standard: Slit-lamp contact lens biomicroscopy	Inclusion criteria: Clinical diagnosis of idiopathic epiretinal membrane, idiopathic full thickness macular hole, vitreomacular traction syndrome, cystoid macular oedema, or diabetic retinopathy Exclusion criteria: Not reported Patient characteristics: Not reported	**Accuracy** <u>Vitreoretinal adhesions associated with partial posterior vitreous separation of the macula</u>: Biomicroscopy OCT: + / 11 / 28 / 39 OCT: – / 0 / 93 / 93 OCT: total / 11 / 121 / 132 Sn / Sp (biomicroscopy as reference standard): 100% / 77% Incremental yield: 23% [95% CI: 17–31%] Extra cases / 1000: 231 [95% CI: 165–314]	**Quality: low** Prospective: no Consecutive: no Explicit selection criteria: no OCT protocol: no Reference standard not valid applied to all participants Test interval: reference standard: unclear Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: yes Uninterpretable/intermediate results reported: no Study withdrawals explained: N/A Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: unclear relevant population: yes prior tests: yes Applicable comparator: no (biomicroscopy only, rather than full clinical examination) Applicable intervention: unclear (likely older version of OCT)

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Goebel et al. (2002)
Germany
Single site
Recruitment period: 8 months (unspecified date range)
Number of participants: 142 (142 eyes)
Included 30 normal control eyes (21%)</td>
<td>Objective:
To evaluate the relationship between retinal thickness measured by OCT and standard methods of evaluating macular oedema
Study design:
Prospective diagnostic accuracy study
Index test:
OCT 2000
Primary outcomes:
Accuracy
Reference standard:
Fundus fluorescein angiography (or normal clinical exam in controls, assumed to have no leakage on FFA)</td>
<td>Inclusion criteria:
Diabetic retinopathy of any stage in at least one eye and absence of other retinal diseases (eg macular degeneration, retinal vein occlusion, hypertensive retinopathy)
Exclusion criteria:
Vitreous haemorrhage, advanced cataract, significant corneal opacities, intraocular inflammation
Patient characteristics:
Mean age:
Normal = 53 years (SD 20)
Diabetes = 64 years (SD 12)
Gender:
Normal–male (60%), female (40%)
Diabetes–male (48%), female (52%)
Diabetic patients include n=24 excluded from analysis due to uninterpretable FFA</td>
<td>Accuracy
<u>Macular oedema (foveal retinal thickness ≥ 183 µm)</u>:
<table>
<tr><td></td><td></td><td>FFA +</td><td>FFA –</td><td>total</td></tr>
<tr><td>OCT</td><td>+</td><td>88</td><td>2</td><td>90</td></tr>
<tr><td></td><td>–</td><td>20</td><td>32</td><td>52</td></tr>
<tr><td></td><td>total</td><td>108</td><td>34</td><td>142</td></tr>
</table>
Sn / Sp (FFA as reference standard): 81% / 94%
OCT yield: 63% [95% CI: 55–71%]
FFA yield: 76% [95% CI: 68–82%]
(no significant difference in yield at p=0.05)

<u>Macular oedema (mean retinal thickness ≥ 271 µm)</u>:
<table>
<tr><td></td><td></td><td>FFA +</td><td>FFA –</td><td>total</td></tr>
<tr><td>OCT</td><td>+</td><td>79</td><td>0</td><td>79</td></tr>
<tr><td></td><td>–</td><td>29</td><td>34</td><td>63</td></tr>
<tr><td></td><td>total</td><td>108</td><td>34</td><td>142</td></tr>
</table>
Sn / Sp (FFA as reference standard): 73% / 100%
OCT yield: 56% [95% CI: 47–64%]
FFA yield: 76% [95% CI: 68–82%]
(difference in yield, p<0.001)
Extra cases / 1000: –204 [95% CI: –271 to –138]</td>
<td>Quality: low
Prospective: yes
Consecutive: no
Explicit selection criteria: yes
OCT protocol: yes
Reference standard
not valid
not applied to all participants
Test interval:
reference standard: unclear
Tests reported blinded to reference standard: unclear
Reference standard reported blinded to tests: yes
Routine clinical data available: yes
Uninterpretable/intermediate results reported: no
Study withdrawals explained: yes (uninterpretable OCT, n=14; uninterpretable FFA, n=24)
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: yes
relevant population: yes
prior tests: yes
Applicable comparator: yes
Applicable intervention: yes</td>
</tr>
</table>

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Hee et al. (1995)
United States
Single site
Recruitment period:
January–October 1994
Number of participants: 49 (51 eyes)</td>
<td>Objective:
To assess the potential of OCT for diagnosing and monitoring macular holes
Study design:
Diagnostic accuracy study
Index test:
OCT
Primary outcomes:
Accuracy
Reference standard:
Indirect and contact lens slit-lamp biomicroscopy, fundus photography, fluorescein angiography, Amsler grid testing, visual acuity testing</td>
<td>Inclusion criteria:
Clinical diagnosis of full thickness macular hole, impending macular hole, history of macular hole, epimacular membrane with macular pseudohole, or lamellar hole
Exclusion criteria:
Not specified
Patient characteristics (age, gender etc.):
Not reported</td>
<td>Accuracy
<u>Full thickness macular holes</u>:
<table>
<tr><td></td><td></td><td colspan="4">Clinical exam</td></tr>
<tr><td></td><td></td><td>+</td><td>?</td><td>–</td><td>total</td></tr>
<tr><td>OCT</td><td>+</td><td>28</td><td>0</td><td>1</td><td>29</td></tr>
<tr><td></td><td>–</td><td>3</td><td>6</td><td>13</td><td>22</td></tr>
<tr><td></td><td>total</td><td>31</td><td>6</td><td>14</td><td>51</td></tr>
</table>
?Clinical exam considered positive:
Sn / Sp (clinical exam as reference standard): 76% / 93%
Incremental yield: 7% [95% CI: 0.2–34%]
Extra cases / 1000: 71 [95% CI: 2–338]
?Clinical exam considered negative:
Sn / Sp (clinical exam as reference standard): 90% / 65%
Incremental yield: 5% [95% CI: 0.1–25%]
Extra cases / 1000: 50 [95% CI: 1–249]</td>
<td>Quality: low
Prospective: unclear
Consecutive: unclear
Explicit selection criteria: yes
OCT protocol: no
Reference standard
not valid
not applied to all participants
Test interval:
reference standard: unclear
Tests reported blinded to reference standard: unclear
Reference standard reported blinded to tests: unclear
Routine clinical data available: yes
Uninterpretable/intermediate results reported: yes
Study withdrawals explained: N/A
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: unclear
relevant population: unclear
prior tests: yes
Applicable comparator: yes
Applicable intervention: unclear (likely older version of OCT)</td>
</tr>
</table>

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Iranmanesh et al. (2007) United States Single site Recruitment period: December 2003–August 2004 Number of participants: 93 (100 eyes)	Objective: To evaluate the frequency of neovascularisation in age-related macular degeneration using OCT and FFA Study design: Prospective diagnostic accuracy study.. Index test: Stratus OCT Primary outcomes: Accuracy Reference standard: None	Inclusion criteria: Newly diagnosed neovascular age-related macular degeneration using Macular Photocoagulation Study definitions Exclusion criteria: Other forms of neovascularised maculopathy (eg pathological myopia, infectious or inflammatory chorioretinal diseases, angioid streaks, trauma, hereditary disorders, tumours) Patient characteristics: Age: range 61-95 years Gender: male (32%), female (68%)	**Accuracy** Macular oedema: OCT yield: 37% [95% CI: 28–47%] FFA yield: 4% [95% CI: 0–10%] (difference in yield, $p<0.05$) Extra cases / 1000: 330 Insufficient data reported to allow calculation of exact significance level and CI around additional cases detected	**Quality: low** Prospective: yes Consecutive: yes Explicit selection criteria: yes OCT protocol: no Reference standard not valid applied to all participants Test interval: reference standard: unclear Tests reported blinded to reference standard: no Reference standard reported blinded to tests: unclear Routine clinical data available: yes Uninterpretable/intermediate results reported: no Study withdrawals explained: N/A Sufficient data for 2x2 table: no Applicability Applicable population: unclear relevant population: yes prior tests: yes Applicable comparator: yes Applicable intervention: yes

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Kozak et al. (2008) United States Single site Recruitment period: October 2005–October 2006 Number of participants: 654 (1,272 eyes)	Objective: To compare high-resolution OCT and FFA in detection of macular oedema of various aetiologies Study design: Retrospective diagnostic accuracy study. Index test: Stratus OCT Primary outcomes: Accuracy Reference standard: Fundus fluorescein angiography	Inclusion criteria: Patients with simultaneous OCT and FFA scans and a diagnosis of suspected or confirmed macular oedema (based on one or both tests) Exclusion criteria: Poor quality OCT or FFA studies Patient characteristics: Mean age: 54 years (SD 12.1)) Gender: male (47%), female (53%)	**Accuracy** Macular oedema: FFA OCT: + / 1,208 / 15 / 1,223 OCT: – / 49 / 0 / 49 OCT: total / 1,257 / 15 / 1,272 Sn / Sp (FFA as reference standard): 96% / – (NB: Negatives on both tests not included in study) OCT yield: 96% [95% CI: 95–97%] FFA yield: 99% [95% CI: 98–99%] (difference in yield, $p<0.001$) Extra cases / 1000: –27	**Quality: low** Prospective: no Consecutive: no Explicit selection criteria: yes OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: same day Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: unclear Uninterpretable/intermediate results reported: no Study withdrawals explained: yes (poor quality images = 35 eyes) Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: unclear relevant population: yes prior tests: unclear Applicable comparator: yes Applicable intervention: yes

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Markomichelakis et al. (2004)
Greece
Single site
Recruitment period: January 2000–January 2001
Number of participants: 60 (84 eyes)</td>
<td>Objective:
To describe the morphological characteristics of macular oedema by the use of OCT and to investigate the correlation between tomographic features and visual acuity
Study design:
Diagnostic accuracy study
Index test:
OCT 1
Primary outcomes:
Accuracy
Reference standard:
Slit-lamp biomicroscopy</td>
<td>Inclusion criteria:
Clinical diagnosis of macular oedema (confirmed by OCT), adequate media clarity
Exclusion criteria:
Other ocular diseases (eg optic nerve atrophy, macular holes, macular scars). Lack of confirmation of macular oedema on OCT
Patient characteristics:
Age: 35.8 ± 16.2 years (range 8–73)
Gender: male (50%), female (50%)</td>
<td>Accuracy
<u>Epiretinal membrane</u>:
<table>
<tr><th></th><th></th><th>Biomicroscopy
+</th><th>–</th><th>total</th></tr>
<tr><td rowspan="3">OCT</td><td>+</td><td>34</td><td>0</td><td>34</td></tr>
<tr><td>–</td><td>8</td><td>42</td><td>50</td></tr>
<tr><td>total</td><td>42</td><td>42</td><td>84</td></tr>
</table>
Sn / Sp (biomicroscopy as reference standard): 81% / 100%
Incremental yield: 0% [95% CI: 0–8%]
Extra cases / 1000: 0 [95% CI: 0–80]</td>
<td>Quality: low
Prospective: unclear
Consecutive: no
Explicit selection criteria: no
OCT protocol: no
Reference standard
not valid
applied to all participants
Test interval:
reference standard: unclear
Tests reported blinded to reference standard: unclear
Reference standard reported blinded to tests: unclear
Routine clinical data available: yes
Uninterpretable/intermediate results reported: yes
Study withdrawals explained: yes
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
applicable population: yes
relevant population: unclear (exclusion of OCT negatives for macular oedema)
prior tests: yes
Applicable comparator: yes
Applicable intervention: older version of OCT</td>
</tr>
</table>

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Monnet et al. (2007)
France
Single site
Recruitment period: November 2002 and November 2003
Number of participants: 80 (160 eyes)</td>
<td>Objective:
To describe OCT and FFA parameters in a cohort with birdshot chorioretinopathy
Study design:
Prospective diagnostic accuracy study
Index test:
OCT 3
Primary outcomes:
Accuracy
Reference standard:
Fundus fluorescein angiography</td>
<td>Inclusion criteria:
Clinical diagnosis of birdshot chorioretinopathy (bilateral involvement; no more than mild anterior unveitis or moderate vitreous inflammatory reaction; at least three hypopigmented choroidal lesions inferior or nasal to the optic disc)
Exclusion criteria:
Not specified
Patient characteristics:
Median age: 55.9 years (range 21–79)
Gender: male (36%), female (64%)</td>
<td>Accuracy
<u>Macular oedema</u>:
<table>
<tr><th></th><th></th><th>FFA +</th><th>FFA –</th><th>total</th></tr>
<tr><td rowspan="3">OCT</td><td>+</td><td>24</td><td>14</td><td>38</td></tr>
<tr><td>–</td><td>27</td><td>95</td><td>122</td></tr>
<tr><td>total</td><td>51</td><td>109</td><td>160</td></tr>
</table>
Sn / Sp (FFA as reference standard): 47% / 87%
OCT yield: 24% [95% CI: 18–31%]
FFA yield: 32% [95% CI: 25–39%]
(no significant difference in yield at p=0.05)</td>
<td>Quality: low
Prospective: yes
Consecutive: unclear
Explicit selection criteria: yes
OCT protocol: yes
Reference standard
not valid
applied to all participants
Test interval:
reference standard: Same day
Tests reported blinded to reference standard: yes
Reference standard reported blinded to tests: yes
Routine clinical data available: no
Uninterpretable/intermediate results reported: yes
Study withdrawals explained: N/A
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: yes
relevant population: yes
prior tests: yes
Applicable comparator: yes
Applicable intervention: yes</td>
</tr>
</table>

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Ozdek et al. (2005) Turkey Single site? Recruitment period: Not reported Number of participants: 110 (195 eyes)	Objective: To compare OCT and FFA in patients with diabetic retinopathy Study design: Retrospective diagnostic accuracy study Index test: Humphrey OCT 3000 Primary outcomes: Accuracy Reference standard: Fundus fluorescein angiography	Inclusion criteria: Diabetic retinopathy of any stage with clear media without any other ocular diseases Exclusion criteria: Other ocular diseases. Patient characteristics: Age range: 34–77 years Gender: male (51%), female (49%)	**Accuracy** Cystoid macular oedema: FFA OCT + : 11 / 19 / 30 OCT – : 0 / 165 / 165 OCT total: 11 / 184 / 195 Sn / Sp (FFA as reference standard): 100% / 90% OCT yield: 15% [95% CI: 11–21%] FFA yield: 6% [95% CI: 3–10%] (difference in yield, p<0.001) Extra cases / 1000: 97 [95% CI: 56–139]	**Quality: low** Prospective: no Consecutive: unclear Explicit selection criteria: yes OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: unclear Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: unclear Uninterpretable/intermediate results reported: yes Study withdrawals explained: N/A Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: yes relevant population: yes prior tests: yes Applicable comparator: yes Applicable intervention: yes

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Tran et al. (2008) France Single site Recruitment period: February 2004–November 2004 Number of participants: 90 (129 eyes)	Objective: To associate OCT patterns with particular FFA findings in uveitis patients with macular oedema Study design: Retrospective diagnostic accuracy study Index test: Stratus OCT Primary outcomes: Accuracy Reference standard: Fundus fluorescein angiography	Inclusion criteria: Patients with uveitis and known or suspected macular oedema; FFA of sufficient quality to allow assessment of macula in at least one early, midphase and late frame; OCT of sufficient quality in all six cross-section scans Exclusion criteria: Poor quality OCT or FFA studies Patient characteristics: Age: 49 years (unclear if mean or median) (range 7–78) Gender: male (41%), female (59%)	**Accuracy** Macular oedema: FFA OCT + / + : 112 + / – : 8 + / total : 120 – / + : 9 – / – : 0 – / total : 9 total / + : 121 total / – : 8 total / total : 129 Sn / Sp (FFA as reference standard): 93% / 0% OCT yield: 93% [95% CI: 87–96%] FFA yield: 94% [95% CI: 88–97%] (no significant difference in yield at p=0.05)	**Quality: low** Prospective: no Consecutive: no Explicit selection criteria: no OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: same day Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: unclear Uninterpretable/intermediate results reported: no Study withdrawals explained: yes (poor quality images = 30 patients) Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: unclear relevant population: yes prior tests: unclear Applicable comparator: yes Applicable intervention: yes

<table>
<tr><th>Author (year)
Setting
N</th><th>Study objective & design</th><th>Study population</th><th>Results</th><th>Study quality and applicability</th></tr>
<tr>
<td>Varano et al. (1999)
Italy
Single site?
Recruitment period: November 1997–February 1998
Number of participants: 27 (28 eyes)</td>
<td>Objective:
To compare and contrast the anatomical and functional data of OCT and FFA in patients with suspected macular oedema
Study design:
Diagnostic accuracy study
Index test:
OCT
Primary outcomes:
Accuracy
Reference standard:
Fundus fluorescein angiography</td>
<td>Inclusion criteria:
Suspected macular oedema
Exclusion criteria:
Not specified
Patient characteristics (age, gender etc):
Not reported.</td>
<td>Accuracy
<u>Macular oedema</u>:
<table>
<tr><td></td><td></td><td>FFA +</td><td>FFA –</td><td>FFA total</td></tr>
<tr><td rowspan="3">OCT</td><td>+</td><td>7</td><td>21</td><td>28</td></tr>
<tr><td>–</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>total</td><td>7</td><td>21</td><td>28</td></tr>
</table>
Sn / Sp (FFA as reference standard): 100% / 0%
OCT yield: 100% [95% CI: 85–100%]
FFA yield: 25% [95% CI: 13–43%]
(difference in yield, p<0.001)
Extra cases / 1000: 750 [95% CI: 590–910]</td>
<td>Quality: low
Prospective: unclear
Consecutive: unclear
Explicit selection criteria: no
OCT protocol: yes
Reference standard
not valid
applied to all participants
Test interval:
reference standard: unclear
Tests reported blinded to reference standard: unclear
Reference standard reported blinded to tests: unclear
Routine clinical data available: unclear
Uninterpretable/intermediate results reported: no
Study withdrawals explained: N/A
Sufficient data for 2x2 table: yes (yield); no (comparative accuracy)
Applicability
Applicable population: unclear
relevant population: yes
prior tests: yes
Applicable comparator: yes
Applicable intervention: unclear (likely older version of OCT)</td>
</tr>
</table>

Appendix H Included therapeutic impact studies (macular diseases)

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Do et al. (2007)	Objectives:	Inclusion criteria:	**Therapeutic impact**	Quality
USA	To compare retina surgeons' recommendations for management of epiretinal membranes and vitreomacular traction based on clinical assessment alone with management based on clinical evaluation supplemented by OCT	Patients with macular disorders such as ERM or VMT (referred, or found on clinical exam)	19/84 (23%) eyes planned for surgery pre-OCT	Was the study designed and conducted prospectively? yes
Single centre			33/84 (39%) eyes planned for surgery post-OCT	Explicit eligibility criteria reflecting specific presentation or clinical problem? no
Recruitment period: June–November 2004		Management plan developed prior to OCT	14/84 (17%) had plan changed from observation to surgery post-OCT	Consecutive recruitment of all patients eligible for testing? no
Number of participants: 73 (84 eyes)		Exclusion criteria: Comorbid conditions not treatable by surgery (eg retinal vascular occlusions, diabetic retinopathy)	0/84 (0%) had plan changed from surgery to observation post-OCT	Referring clinician determining management plan? yes
	Study design: Pre-OCT/post-OCT management plans	Patient characteristics (age, gender etc): Not reported.	Reasons for changed management plan: • detection of vitreomacular traction by OCT not observed on clinical examination (7/14) • detection of macular oedema by OCT not observed on clinical examination (4/14) • detection of epiretinal membrane by OCT not observed on clinical examination (2/14) • detection of more extensive macular oedema by OCT than observed on clinical examination (1/14)	Test accuracy documented concomitantly? yes
	Index test: Stratus OCT 3			Pretest plan independently assessed? no
	Primary outcomes: Management change			Blinding to study test results at pretest measurement? yes
	Other outcomes: Accuracy			Association between management change and study test result independently assessed? unclear
				Management changes reported for specific test use and patient presentation? no
				Management changes reported in adequate detail? (eg surgery avoided, additional investigations, etc) yes
				Descriptive information about patient outcomes reported? no
				Physician experience reported? no

Appendix I Included monitoring studies (macular diseases)

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Krebs et al. (2005) Austria Single site? Recruitment period: April 2000–June 2002 Number of participants: 38 (40 eyes)	Objective: To evaluate the results of a retreatment modality of photodynamic therapy based on OCT and FFA Study design: Monitoring study Index test: OCT Test comparison: OCT + FFA vs FFA Monitoring frequency: Baseline, 6 weeks, 3 months, then 3 monthly (both groups) Primary outcomes: Distance acuity Follow-up: 12 months	Inclusion criteria: Eyes with subfoveal predominantly classic choroidal neovascularisation due to age-related macular degeneration, previously treated with photodynamic therapy Exclusion criteria: Not specified Patient characteristics: OCT + FFA n = 27 (28 eyes) Mean age = 74 (range 53-87) Gender: male (44%), female (56%) FFA n = 11 (12 eyes) Mean age = 72 (range not reported) Gender: male (73%), female (27%)	Mean best corrected distance acuity at baseline vs 12 months **Baseline [95% CI] / 12 months [95% CI]** OCT + FFA: 0.20 [0.10–0.44] / 0.20 [0.08–0.70] FFA: 0.25 [0.10–0.60] / 0.16 [0.05–0.70] (no significant differences at p=0.05) Loss of distance acuity > 3 lines (after 12 months): OCT + FFA = 17.8% [95% CI: 7.9–35.6%] FFA = 66.7% [95% CI: 39.1–86.2%] p<0.01	**Quality: low** Prospective: unclear Intervention reliably ascertained: unclear Selection for groups described: no Comparable groups: no Controlled for confounders: no Unbiased measurement of outcomes: unclear Valid follow-up: yes Exclusions reported: N/A Drop-outs similar in both groups: N/A Applicability Applicable population: yes relevant population: yes prior tests: unclear Applicable comparator: no Applicable intervention: yes

Appendix J Included accuracy studies (glaucoma)

Author (year) Setting *N*	Study objective & design	Study population	Results	Study quality and applicability
Bagga et al. (2006) United States Single site Recruitment period: Not specified Number of participants: 25 (25 eyes) Additional 22 patients (22 eyes) enrolled as normal controls	Objective: To compare the prevalence of structural and psychophysical abnormalities in normal eyes and eyes with glaucomatous optic neuropathy and normal standard automated perimetry Study design: Diagnostic case control study Index test: Stratus OCT Primary outcomes: Accuracy Reference standard: Presence or absence of disease as defined by prior tests	Inclusion criteria: Patients with either cupping disc asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation, or RNFL defect; normal visual fields on standard automated perimetry Exclusion criteria: Visual acuity less than 20/40, peripapillary atrophy extending to 1.7 mm from the disc centre, retinal disease, unreliable or abnormal perimetry. OCT scans excluded if obtained during eye movement, or if unfocussed, poorly centred, or with a quality grade less than 8 Prior tests: Slit-lamp biomicroscopy, gonioscopy, pachymetry, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc and fundus, standard automated perimetry Patients also underwent SWAP, FDT and GDx for comparison of accuracy with OCT Age: 61 ± 14 years (range 28–83) Gender: male (24%), female (76%)	OCT yield (abnormal RNFL): 48% [95% CI: 30–67%]	**Quality: low** Prospective: unclear Consecutive: no Explicit selection criteria: yes OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: within 6 months Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: yes Routine clinical data available: unclear Uninterpretable/intermediate results reported: no Study withdrawals explained: no Sufficient data for 2x2 table: yes (yield); no (comparative accuracy) Applicability Applicable population: yes relevant population: no (RNFL defects previously diagnosed) prior tests: yes Applicable comparator: yes Applicable intervention: yes

Author (year) Setting *N*	Study objective & design	Study population	Results		Study quality and applicability
Kim et al. (2007) Korea Single site Recruitment period: May 2003 – October 2005 Number of participants: 49 (49 eyes) Additional 49 patients (49 eyes) enrolled as normal controls	Objective: To evaluate the ability of Stratus OCT to discriminate between healthy eyes and eyes with a localised RNFL defect not accompanied by a perimetric defect according to standardised automated perimetry Study design: Retrospective diagnostic case control study Index test: Stratus OCT Primary outcomes: Accuracy Reference standard: Presence or absence of disease as defined by prior tests	Inclusion criteria: Normal standard automated perimetry on at least two tests; localised wedge-shaped RNFL defect clearly visible on red-free photographs Exclusion criteria: Best-corrected visual acuity < 20/40, spherical refraction > ± 5 D, cylinder correction > ± 3 D, closed angles, history of ocular surgery other than cataract extraction, disease that may affect the peripapillary area Prior tests: Visual acuity, refraction, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc, red-free fundus photography, standard automated perimetry Age: 55.8 ± 11.5 years (range 34-82) Gender: male (53%), female (47%)	OCT yield (abnormal RNFL): ≥ 1 Clock hours abnormal at the 5% level 40.8% ≥ 1 Clock hours abnormal at the 1% level 16.3% ≥ 1 quadrants abnormal at the 5% level 26.5% ≥ 1 quadrants abnormal at the 1% level 10.2% I_{max}/S_{max} abnormal at the 5% level 26.5% S_{max}/I_{max} abnormal at the 5% level 6.1% S_{max}/T_{avg} abnormal at the 5% level 16.3% I_{max}/T_{avg} abnormal at the 5% level 20.4% S_{max}/N_{avg} abnormal at the 5% level 2.0% Max-min abnormal at the 5% level 22.5% S_{max} abnormal at the 5% level 16.3% I_{max} abnormal at the 5% level 32.7% Average RNFL thickness abnormal at the 5% level 14.3% Average RNFL thickness abnormal at the 1% level 4.1%	**Quality: low** Prospective: no Consecutive: no Explicit selection criteria: yes OCT protocol: yes Reference standard not valid applied to all participants Test interval: reference standard: within 6 months Tests reported blinded to reference standard: unclear Reference standard reported blinded to tests: unclear Routine clinical data available: unclear Uninterpretable/intermediate results reported: no Study withdrawals explained: N/A Sufficient data for 2x2 table: yes Applicability Applicable population: yes relevant population: no (RNFL defects previously diagnosed) prior tests: yes Applicable comparator: yes Applicable intervention: yes

Abbreviations

AIHW	Australian Institute of Health and Welfare
AMD	Age-related macular degeneration
ARM	Age-related maculopathy
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the curve
BMES	Blue Mountains Eye Study
CI	Confidence interval
CL	Confidence limit
CNV	Choroidal neovascularisation
CRD	Centre for Reviews and Dissemination
CSLO	Confocal scanning laser ophthalmoscope
CSMO	Clinically significant macular oedema
CSR	Central serous retinopathy
DOR	Diagnostic odds ratio
DR	Diabetic retinopathy
DVA	Department of Veterans' Affairs
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDT	Frequency doubling technology
FFA	Fundus fluorescein angiography
FN	False negative
FP	False positive
HRT	Heidelberg Retinal Tomograph
HTA	Health technology assessment
IOP	Intraocular pressure
MBS	Medicare Benefits Schedule/Medicare Benefits Scheme
MSAC	Medicare Services Advisory Committee
MVIP	Melbourne Visual Impairment Project
N/A	Not applicable
NHMRC	National Health and Medical Research Council
NPV	Negative predictive value
OCT	Optical coherence tomography
ONH	Optic nerve head
PACG	Primary angle closure glaucoma

PBS	Pharmaceutical Benefits Scheme
PDT	Photodynamic therapy
PICO	Patient, intervention, comparator, outcome
POAG	Primary open angle glaucoma
PPV	Positive predictive value
QoL	Quality of life
RANZCO	Royal Australian and New Zealand College of Ophthalmologists
RCT	Randomised controlled trial
RNFL	Retinal nerve fibre layer
ROC	Received operating characteristics
RPE	Retinal pigment epithelium
RTA	Retinal thickness analyser
SAP	Standard automated perimetry
SITA	Swedish interactive testing algorithm
SLD	Superluminescent diode
SLO	Scanning laser ophthalmoscope
SLP	Scanning laser polarimetry
SWAP	Short wave automated perimetry
TN	True negative
TP	True positive
UHR	Ultra-high resolution
VCC	Variable corneal compensation
VEGF	Vascular epithelial growth factor
VMT	Vitreomacular traction
WHO	World Health Organisation

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