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# Horizon Scanning Technology Prioritising Summary

# Optical coherence tomography for multiple sclerosis prognosis

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AHTA

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# PRIORITISING SUMMARY

**REGISTER ID:** **000354**

**NAME OF TECHNOLOGY:** **OPTICAL COHERENCE TOMOGRAPHY FOR MS PROGNOSIS**

**PURPOSE AND TARGET GROUP:** **PATIENTS WITH MULTIPLE SCLEROSIS BEING ASSESSED FOR DISEASE PROGRESSION**

**STAGE OF DEVELOPMENT (IN AUSTRALIA):**

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

**AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL**

- ☐ Yes — ARTG number
- ☒ No
- ☐ Not applicable

**INTERNATIONAL UTILISATION:**

| COUNTRY | LEVEL OF USE | | |
|---|---|---|---|
| | Trials Underway or Completed | Limited Use | Widely Diffused |
| United Kingdom | ✓ | | |
| United States of America | ✓ | | |
| Spain | ✓ | | |
| | | | |

**IMPACT SUMMARY:**

Optical coherence tomography (OCT) is a new non-invasive technique for the prognostic evaluation of multiple sclerosis patients. OCT is used to measure the thickness of the retinal nerve fibre layer (RNFL). A reduction in the RNFL is a marker of axonal loss and is related to the degree of damage seen in magnetic resonance imaging, neurological impairment scores, and the length of MS disease course. OCT may thus allow a simple, convenient and low cost measure of MS progression.

**BACKGROUND**

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system which has a wide variety of clinical manifestations. The exact cause of MS is

unknown, but the symptoms of the disease are a result of the demyelination of nerve axons. Demyelination prevents the proper signal transduction along the nerves and may also lead to nerve death. Accumulation of these lesions over time facilitates the progressive loss of function, such as numbness, weakness, incontinence, paralysis, tiredness, vision loss, memory and concentration problems, and mood swings. At onset, MS has two main forms: relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). RRMS can progress over time through multiple bouts of MS symptoms to secondary progressive MS. PPMS is the most severe form of MS and 20 per cent of MS cases have this form of the disease (AE 2005).

The lesions in the brain, among other factors, are used as a marker of disease progression. These lesions are normally visualised by magnetic resonance imaging (MRI) which is a limited health resource, expensive and time consuming. Additionally, as MRI measures inflammation and not axonal damage, the test results may not correlate well with symptomatic disease progression. While MRI visualised lesions are an invaluable surrogate marker for disease progression there is a need for other prognostic modalities to assess axonal damage.

Optical coherence tomography (OCT) uses near infrared light to measure the thickness of structures in the eye, including the retinal nerve fibre layer (RNFL). OCT is based on interferometry and can produce a cross-sectional image of the retina. The intensity of the reflected light is used to distinguish distinct layers of the retina. OCT can measure RNFL thickness and to locate retinal defects and thus provides a way of measuring the progression of several diseases such as glaucoma. OCT gives a value of the RNFL thickness in micrometres. In normal eyes the average thickness of the RNFL is around 110 micrometres, with thickness varying across the disc from 80 micrometres in the temporal quadrant to 145 micrometres in the inferior quadrant. There is some variation in normal RNFL with age and other factors (Tsai 2006). The optic nerve is a part of the CNS and therefore the detection of RNFL thinning is thought to be caused by axon damage. Current OCT research aims to determine whether retinal damage is a marker of MS disease progression.

### Clinical Need and Burden of Disease

Multiple sclerosis is an incurable, debilitating disease that has no known cause, yet it is associated with many factors such as being female, certain infectious agents, distance from the equator and other genetic and environmental factors. Onset of symptoms, and hence diagnosis, occurs in 70 per cent of cases between 20 and 40 years of age. Prevalence has been found to vary with increasing distance from the equator with southern Australia having a prevalence of over 30 cases per 100,000 population, whereas the rest of Australia has a prevalence of 5 to 25 cases per 100,000 population (AIHW 2001). It is estimated in 2005 that 16,000 Australians have MS (AE 2005).

The course of disease is extremely variable from almost asymptomatic to fully progressing, severely disabling disease. The fact that MS affects adults from the age of 20 onwards means that the cost impact to the patient and society is great as it affects the establishment of careers, relationships and families. A recent economic assessment of the economic costs of MS to Australian society reported that the annual cost of MS is $2 billion. This consists of $600 million of direct financial costs e.g. patient care, loss of productivity (3,195 people were prevented from working due to MS in 2005), and drug therapy and other costs. Additionally, the burden of disease was estimated to be 8,968 DALY[1]s lost in 2005 at a cost of $1.34 billion. The burden of MS disease was greater than DALYs lost due to chronic back pain, machinery accidents, rheumatic heart disease and the MS burden of disease was more than half that of diabetes (AE 2005; AIHW 2001).

There has been demonstrated clinical efficacy for the early identification and intervention with pharmaceuticals in patients with MS. Early intervention has been shown to be effective in limiting the progression of MS. In addition, early intervention has been shown to be cost effective in that the early expenditure prevents a greater, later expenditure and allows the patient to participate productively in normal activities (AE 2005).

The fact that MS affects otherwise productive adults in the prime of their life makes it a very significant problem for Australian society, both socially and financially. The ability of the disease course to be modified by existing treatments raises the need of accurately identifying the appropriate subjects for early intervention therapies.

### DIFFUSION

OCT is used in Australia for indications other than MS prognosis, such as age-related macular degeneration, but no evidence was found for its use for MS management.

### COMPARATORS

MRI visualised lesions are a widely used surrogate marker for MS disease progression. In the absence of better techniques MRI is currently the best available assessment for disease status in a MS patient. However, evidence shows MRI, as a surrogate marker, lacks the ability to elucidate important MS related disease parameters such as underlying pathology and clinically relevant damage to the grey and white matter. A recent review of MRI usage in MS management found that while MRI is very useful in diagnosing and managing patients there are many areas where current MRI application in MS patients goes beyond the limits of scientific evidence. New research in the field of MRI for MS is closing the gap between evidence and application, yet additional new measures are needed to accurately assess patient status (Neema et al 2007).

[1] disability adjusted life year

A systematic review of 29 studies found that many were of poor quality and that wide ranging efficacy was reported for MRI diagnosis of MS (Whiting et al 2006). Studies which followed patients for longer periods (>10 years) reported that MRI had a lower sensitivity and higher specificity than studies that monitored for shorter time periods. The exact sensitivity and specificity was, as expected, dependent on the cut-off values used. In the two studies that followed patients for greater than 10 years, sensitivity and specificity varied with the number of MRI visualised lesions that were designated as diagnostic for MS (Figure 1).

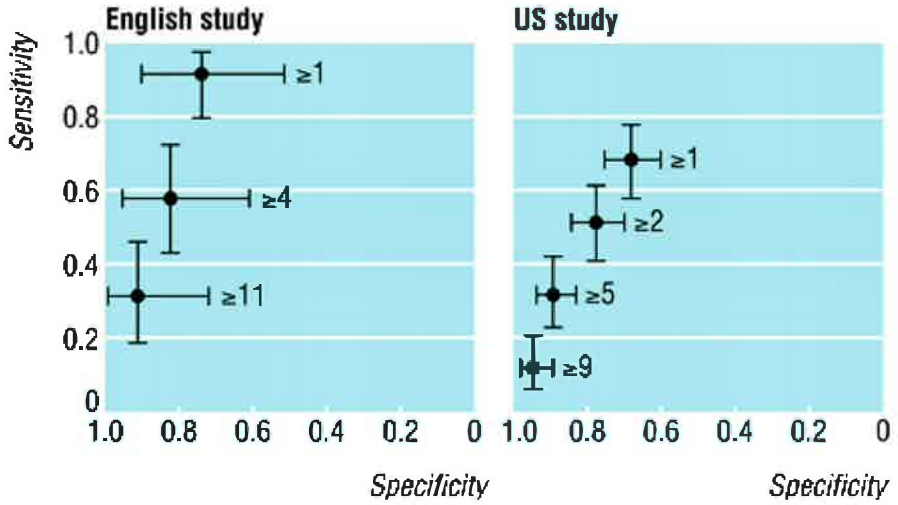


**Figure 1 Sensitivity plotted against specificity (95% confidence intervals) for different thresholds (number of lesions shown next to plots) reported in English and US studies. Source: (Whiting et al 2006)**

Overall, MRI is a useful yet limited tool for the diagnosis and management of MS. Further research is expected to define parameters which more accurately predict MS status and progression. There exists a definite need for more tools to diagnose and manage MS patients.

## Safety and Effectiveness Issues

OCT for has been used in several studies on patients with a variety of MS manifestations including patients with or without active optic neuritis (ON), RRMS, SPMS and PPMS.

Ninety MS patients of varying disease stages and 36 disease free controls were assessed using OCT and visual acuity tests to investigate the potential links between RNFL thickness, MS disease status and visual acuity. Significant correlations were found between RNFL thinning and MS status. The eyes of MS patients (average thickness = 92±16μm) had significantly ($p<0.001$) thinner RNFL than normal controls (average thickness = 105±12μm). In addition, the eyes of MS patients who had a history of ON, showed significantly ($p<0.001$) thinner RNFL compared to both non-ON MS eyes and normal eyes. The RNFL thickness in MS-ON eyes averaged 85±17μm, while in MS non-ON eyes RNFL thickness averaged 96±14μm. RNFL

thinning also correlated with visual acuity, being thinner in patients with lower visual acuity (Fisher et al 2006) (prognostic evidence level IV).

The investigation of the links between RNFL thickness and MS disease activity was carried out in a prospective cohort of 61 MS affected subjects with 29 matched controls. After baseline MRI scans were taken, ophthalmologic and neurologic evaluations of subjects were performed every three months and OCT performed at six month intervals. MS affected subjects had a range of disease severities, ranging from isolated episodes, through RRMS, SPMS to PPMS. There were significant correlations between RNFL thickness and MS disease parameters. MS patients had thinner RNFL than controls, the greatest thinning being in the temporal quadrant of the retina ($p=0.004$). All quadrants except the nasal quadrant showed thinning ($p<0.05$). Patients with MS and ON had greater RNFL thinning compared to controls except again in the nasal quadrant ($p<0.05$). RNFL thinning was greatest in MS patients with greatest disease severity, and RNFL thinning correlated with greater disability. RNFL thinning was moderately correlated with MRI determined white matter and grey matter volume. This demonstrates that OCT determined RNFL thinning is a marker of global brain atrophy. The authors concluded that OCT is a useful technique for assessing MS activity (Sepulcre et al 2007) (prognostic evidence level IV).

The relationship between OCT determined RNFL thinning and PPMS and SPMS was investigated in 23 PPMS, 27 SPMS and, 20 healthy subjects. Again RNFL thinning was significantly greater in MS subjects (91μm (SD=12.6)) versus healthy controls (98.8μm (SD=10.5)). Additionally, SPMS subjects (88.4μm(SD=10.9)) had a greater extent of RNFL thinning compare to PPMS subjects (93.9μm (SD=13.9)) (Henderson et al 2008) (prognostic evidence level IV). This demonstrates that OCT may be useful for not only determining disease progression versus normative controls, but may also allow objective distinctions to be drawn between MS patients with different disease progressions.

Whether OCT determined RNFL thinning can be used to predict global brain atrophy in MS patients was investigated in 40 MS and 15 control subjects. MS subjects had a variety of disease manifestations: RRMS, PPMS and SPMS. Brain atrophy was measured using MRI determined brain parenchyma fraction (BPF) and cerebrospinal fluid (CSF) volume. OCT determined RNFL thickness correlated with BPF (partial coefficient correlation when controlled for age of 0.46 ($p=0.003$)) in MS patients but not in normal controls, indicating the utility of OCT for monitoring MS disease status (Gordon-Lipkin et al 2007) (prognostic evidence level IV).

While the studies all presented here are small and are of low level of evidence, all demonstrate similar results and show that OCT holds great promise for rapid, cheap and convenient assessment of MS patient status. To establish the role of OCT determined RNFL as a valid MS disease predictor, larger longitudinal trials must be

conducted to show if it is efficacious. Future investigations will likely use it as a measure of the effectiveness of MS therapies. If, in future trials, OCT is not shown to produce information that is equivalent to MRI and other measures, its utility will still allow it to play an important role in MS patient management.

### Cost Impact

No information about cost was found during prioritising summary preparation.

### Ethical, Cultural or Religious Considerations

No issues were identified/raised in the sources examined.

### Other Issues

All the studies reviewed in this prioritising summary used an OCT system from a single supplier (Carl Zeiss Meditec, Dublin, CA, USA) to determine RNFL thickness. No conflicts of interest were reported, indeed most studies included a statement repudiating any conflicting interests. Although, one study did state that the researchers received an "unrestricted grant for OCT machine" from GlaxoSmithKline (Henderson et al 2008).

### Summary of findings

OCT determined RNFL thinning may be a valid surrogate marker of MS disease status in a patient. In small studies OCT RNFL thinning has shown correlation with several markers of MS progression and may be used to inform patients and clinicians about the likely future course of the disease. While no formal cost effectiveness evidence was found, most authors comment that OCT is cheaper, faster and more convenient that the current standard of care, MRI.

### HealthPACT action

Research into OCT I sin the early stages and there is a lack of large scale trials which utilise OCT RNFL measurements in MS patients. Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

### Number of included Studies

| | |
|---|---|
| Total number of studies | |
| Level IV prognostic evidence | 4 |

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Tsai, J. C. (2006). 'Optical coherence tomography measurement of retinal nerve fiber layer after acute primary angle closure with normal visual field', *Am J Ophthalmol,* 141 (5), 970-972.

Whiting, P., Harbord, R. et al (2006). 'Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review', *Bmj,* 332 (7546), 875-884.

**SEARCH CRITERIA TO BE USED**

Disease Progression

Multiple Sclerosis/complications/ pathology/physiopathology

Retina/ pathology/physiopathology

Retinal Degeneration/etiology/ pathology/physiopathology

Retinal Ganglion Cells/pathology

Tomography, Optical Coherence/methods