

Optical Coherence Tomography for Age-Related Macular Degeneration and Diabetic Macular Edema

An Evidence-Based Analysis

*Presented to the Ontario Health Technology
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The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

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List of Abbreviations

AMD	Age-related macular degeneration
AUC	Area under the curve
BM	Biomicroscopy
CCI	Canadian Classification of Health Interventions
CI	Confidence interval(s)
CNIB	Canadian National Institute for the Blind
DME	Diabetic macular edema
FA	Fluorescein angiography
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems 10th Revision (Canadian enhancement)
MAS	Medical Advisory Secretariat
OCCI	Ontario Case Costing Initiative
OCT	Optical coherence tomography
OHIP	Ontario Health Insurance Plan
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SFP	Stereo fundus photography
SROC	Summary receiver operating characteristic

Executive Summary

Objective

The purpose of this evidence-based review was to examine the effectiveness and cost-effectiveness of spectral-domain (SD) optical coherence tomography (OCT) in the diagnosis and monitoring of patients with retinal disease, specifically age-related macular degeneration (AMD) and diabetic macular edema (DME). Specifically, the research question addressed was:

- What is the sensitivity and specificity of spectral domain OCT relative to the gold standard?

Clinical Need: Target Population and Condition

The incidence of blindness has been increasing worldwide. In Canada, vision loss in those 65 years of age and older is primarily due to AMD, while loss of vision in those 18 years of age and older is mainly due to DME. Both of these conditions are diseases of the retina, which is located at the back of the eye. At the center of the retina is the macula, a 5 mm region that is responsible for what we see in front of us, our ability to detect colour, and fine detail. Damage to the macula gives rise to vision loss, but early detection of asymptomatic disease may lead to the prevention or slowing of the vision loss process.

There are two main types of AMD, ‘dry’ and ‘wet’. Dry AMD is the more prevalent of the two, accounting for approximately 85% of cases and characterized by small deposits of extracellular material called “drusen” that build up in Bruch’s membrane of the eye. Central vision loss is gradual with blurring and eventual colour fading. Wet AMD is a less prevalent condition (15% of all AMD cases) but it accounts for 90% of severe cases. It’s characterized by the appearance of retinal fluid with vision loss due to abnormal blood vessels/leakage within weeks to months of diagnosis. In 2003, the Canadian National Institute for the Blind (CNIB) prevalence estimate for AMD was 1 million Canadians, including approximately 400,000 affected Ontarians. The incidence in 2003 was estimated to be 78,000 new cases in Canada, with approximately one-third of these cases arising in Ontario (n=26,000). Over the next 25 years, the number of new cases is expected to triple.

DME is caused by complications of diabetes mellitus, both Type 1 and Type 2. It is estimated that 1-in-4 persons with diabetes has this condition, though it occurs more frequently among those with type 2 diabetes. The condition is characterized by a swelling of the retina caused by leakage of blood vessels at the back of the eye. In early stages of the disease, vision may still be normal but it can degrade rapidly in later stages. In 2003, the CNIB prevalence estimate for DME was 0.5 million Canadians, with approximately 200,000 Ontarians affected. The incidence of DME is more difficult to ascertain; however, based on an annual incidence rate of 0.8% (for those 20 years of age or older) and the assumption that 1-in-4 persons with diabetes is affected, the incidence of DME in Ontario is estimated to be 21,000 new cases per year.

Optical Coherence Tomography

Prior to the availability of OCT, the standard of care in the diagnosis and/or monitoring of retinal disease was serial testing with fluorescein angiography (FA), biomicroscopy (BM), and stereo-fundus photography (SFP). Each of these is a qualitative measure of disease based on subjective evaluations that are largely dependent on physician expertise. OCT is the first quantitative visual test available for the diagnosis of eye disease. As such, it allows for a more objective evaluation of the presence/absence of retinal disease and it is the only test that provides a measure of retinal thickness. The technology was developed at the Michigan Institute of Technology (MIT) in 1991 as a real-time imaging modality and is considered comparable to histology. It’s a light-wave based technology producing cross-sectional images with scan rates and resolution parameters that have greatly improved over the last 10 years. It’s also a

non-invasive, non-contact visual test that requires just 3 to 5 minutes to assess both eyes.

There are two main types of OCT system, both licensed by Health Canada as class II devices. The original patent was based on a time domain (TD) system (available from 1995) that had an image rate of 100 to 400 scans per second and provided information for a limited view of the retina with a resolution in the range of 10 to 20 μm . The newer system, spectral domain (SD) OCT, has been available since 2006. Improvements with this system include (i) a faster scan speed of approximately 27,000 scans per second; (ii) the ability to scan larger areas of the retina by taking six scans radially-oriented 30 degrees from each other; (iii) increased resolution at 5 μm ; and (iv) ‘real-time registration,’ which was not previously available with TD.

The increased scan speed of SD systems enables the collection of additional real-time information on larger regions of the retina, thus, reducing the reliance on assumptions required for retinal thickness and volume estimates based on software algorithms. The faster scan speed also eliminates image distortion arising from patient movement (not previously possible with TD), while the improvement in resolution allows for clearer and more distinguishable retinal layers with the possibility of detecting earlier signs of disease. Real-time registration is a new feature of SD that enables the identification of specific anatomical locations on the retina, against which subsequent tests can be evaluated. This is of particular importance in the monitoring of patients. In the evaluation of treatment effects, for example, this enables the same anatomic retinal location to be identified at each visit.

Methods

Literature Search

A literature search was performed on February 13, 2009 using Ovid MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 2003 to February 2009. The subject headings and keywords searched included AMD, DME, and OCT (the detailed search strategy can be viewed in Appendix 1). Excluded were case reports, comments, editorials, non-systematic reviews, and letters. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. In total, 542 articles were included for review.

Inclusion Criteria

- English-language articles and health technology assessments.
- RCTs and observational studies of OCT and AMD or DME.
- Studies focusing on either diagnosis or monitoring of disease.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies of pediatric populations.
- Studies on OCT as a screening tool.
- Studies that did not assess comparative effectiveness of OCT with a referent, as specified below in “Comparisons of Interest”.

Outcomes of Interest

- Studies of sensitivity, specificity.

Comparisons of Interest

Evidence exists for the following comparisons of interest:

- OCT compared with the reference “fluorescein angiography” for AMD.
- OCT compared with the reference “biomicroscopy” or “stereo or fundus photography” for DME.

Summary of Existing Evidence

No evidence for the accuracy of SD OCT compared to either FA, BM or SFP was published between January 2006 to February 2009; however, two technology assessments were found, one from Alberta and the other from Germany, both of which contain evidence for TD OCT. Although these HTAs included eight studies each, only one study from each report was specific to this review. Additionally, one systematic review was identified for OCT and DME. It is these three articles, all pertaining to time and not spectral domain OCT, as well as comments from experts in the field of OCT and retinal disease, that comprise the evidence contained in this review.

Upon further assessment and consultations with experts in the methodology of clinical test evaluation, it was concluded that these comparators could not be used as references in the evaluation of OCT. The main conclusion was that, without a third test as an arbiter, it is not possible to directly compare the sensitivity and specificity of OCT relative to either FA for AMD and stereo- or fundus – photography for DME. Therefore, in the absence of published evidence, it was deemed appropriate to consult a panel of experts for their views and opinions on the validity of OCT and its utility in clinical settings. This panel consisted of four clinicians with expertise in AMD and/or DME and OCT, as well as a medical biophysicist with scientific expertise in ocular technologies. This is considered level 5 evidence, but in the absence of an appropriate comparator for further evaluation of OCT, this may be the highest level of evidence possible.

Summary of Findings

The conclusions for SD OCT based on Level 5 evidence, or expert consultation, are as follows:

1. OCT is considered an essential part of the diagnosis and follow-up of patients with DME and AMD.
2. OCT is adjunctive to FA for both AMD and DME but should decrease utilization of FA as a monitoring modality.
3. OCT will result in a decline in the use of BM in the monitoring of patients with DME, given its increased accuracy and consistency.
4. OCT is diffusing rapidly and the technology is changing. Since FA is still considered pivotal in the diagnosis and treatment of AMD and DME, and there is no common outcome against which to compare these technologies, it is unlikely that RCT evidence of efficacy for OCT will ever be forthcoming.

In addition to the accuracy of OCT in the detection of disease, assessment of the clinical utility of this technology included a rapid review of treatment effects for AMD and DME. The treatment of choice for AMD is Lucentis®, with or without Avastin® and photodynamic therapy. For DME the treatment of choice is laser photocoagulation, which may be replaced with Lucentis® injections (Expert consultation). The evidence, as presented in systematic reviews and other health technology assessments, indicates that there are effective treatments available for both AMD and DME.

Considerations for the Ontario Health System

OCT testing is presently an uninsured service in Ontario with patients paying approximately \$150 out-of-pocket per test. Several provinces do provide funding for this procedure, including British Columbia, Alberta, Saskatchewan, Newfoundland, Nova Scotia, Prince Edward Island, and the Yukon Territory. Provinces that do not provide such funding are Quebec, Manitoba and New Brunswick.

The demand for OCT is expected to increase with aging of the population.

Background

Objective

The purpose of this evidence-based analysis was to examine the effectiveness and cost-effectiveness of spectral-domain (SD) optical coherence tomography (OCT) in the diagnosis and/or monitoring of patients with retinal disease, specifically age-related macular degeneration (AMD) and diabetic macular edema (DME), relative to the gold standard. Specifically, the research question addressed was:

- What is the sensitivity and specificity of spectral domain OCT relative to the gold standard?

Clinical Need and Target Population

The incidence of blindness has been increasing worldwide. In Canada, vision loss in those 65 years of age and older is primarily due to AMD, while loss of vision in those 18 years of age and older is mainly due to DME. Both of these conditions are diseases of the retina, which is located at the back of the eye. At the center of the retina is the macula, a 5 mm region that is responsible for what we see in front of us, our ability to detect colour, and fine detail. Damage to the macula gives rise to vision loss, but early detection of asymptomatic disease may lead to the prevention or slowing of the vision loss process.

Age-related macular edema (AMD) is the leading cause of vision loss in those 65 years of age or older. There are two main types of AMD, 'dry' and 'wet'. Dry AMD is the more prevalent of the two, accounting for approximately 85% of cases and characterized by small deposits of extracellular material called "drusen" that build up in Bruch's membrane of the eye. Central vision loss is gradual with blurring and eventual colour fading. Wet AMD is a less prevalent condition (15% of all AMD cases) but it accounts for 90% of severe cases. It is characterized by the appearance of retinal fluid with vision loss due to abnormal blood vessels/leakage within weeks to months of diagnosis. In 2003, the Canadian National Institute for the Blind (CNIB) prevalence estimate for AMD was 1 million Canadians, including approximately 400,000 affected Ontarians. (1) The incidence in 2003 was estimated to be 78,000 new cases in Canada, with approximately one-third of these cases arising in Ontario (n=26,000). Over the next 25 years, the number of new cases is expected to triple. (2)

DME is caused by complications of both Type 1 and Type 2 diabetes mellitus. It is estimated that 1-in-4 persons with diabetes has this condition, though it occurs more frequently among those with type 2 diabetes. (3) The condition is characterized by a swelling of the retina caused by leakage of blood vessels at the back of the eye. In early stages of the disease, vision may still be normal but it can degrade rapidly in later stages. In 2003 the CNIB prevalence estimate for DME was 0.5 million Canadians, with approximately 200,000 Ontarians affected. (1) The incidence of DME is more difficult to ascertain; however, based on an annual incidence rate of 0.8% (for those 20 years of age or older) (4) and the assumption that 1-in-4 persons with diabetes is affected, the incidence of DME in Ontario is estimated to be 21,000 new cases per year.

If these retinal conditions are not detected and treated early, the resulting loss of vision will have considerable health care and social costs (3).

Optical Coherence Tomography

Prior to the availability of OCT, the standard of care for the diagnosis and/or monitoring of retinal disease was serial testing with fluorescein angiography (FA), biomicroscopy (BM), and/or stereo-fundus photography (SFP). Each of these is a qualitative measure of disease, based on subjective evaluations that

are largely dependent on physician expertise.

OCT is the first quantitative visual test available for the diagnosis of eye disease. As such, it allows for a more objective evaluation of the presence or absence of retinal disease and it is the only test that provides a measure of retinal thickness. The technology was developed at the Michigan Institute of Technology (MIT) in 1991 as a real-time imaging modality and is considered comparable to histology. It's a light-wave based technology producing cross-sectional images with scan rates and resolution parameters that have greatly improved over the last 10 years. It's also non-invasive, non-contact visual test that requires just 3 to 5 minutes to assess both eyes.

There are two main types of OCT systems. The original patent was based on a time domain (TD) system (available from 1995) that had an image acquisition rate of 100 to 400 scans per second and provided information for a limited view of the retina with a resolution is in the range of 10 to 20 μm . The newer OCT system, spectral domain (SD), has been available since 2006. Improvements with this system include (i) a faster scan speed of approximately 27,000 scans per second; (ii) the ability to scan larger areas of the retina by taking six scans, radially oriented 30 degrees from each other; (iii) increased resolution at 5 μm ; and (iv) 'real-time registration,' which was not previously available with TD. (5)

The increased scan speed of SD systems enables the collection of additional real-time information on larger regions of the retina, thus, reducing the reliance on assumptions required for retinal thickness and volume estimates based on software algorithms. The faster scan speed also eliminates image distortion arising from patient movement (not previously possible with TD), while the improvements in resolution allows for clearer and more distinguishable retinal layers with the possibility of detecting earlier signs of disease. Real-time registration is a new feature of SD that enables the identification of specific anatomical locations on the retina, against which subsequent tests can be evaluated. This is of particular importance in the monitoring of patients. In the evaluation of treatment effects, for example, this enables the same anatomic retinal location to be identified at each visit (6).

Regulatory Status

OCT systems, whether TD or SD, are licensed by Health Canada as class II devices.

Evidence-Based Analysis

Research Question

The research question specifically addressed was:

What is the sensitivity and specificity of spectral domain OCT relative to the gold standard?

Methods

Literature Search

A literature search was performed on February 13, 2009 using Ovid MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 2003 to February 2009. The subject headings and keywords searched included AMD, DME, and OCT (the detailed search strategy can be viewed in Appendix 1). Excluded were case reports, comments, editorials, non-systematic reviews, and letters.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. For the purposes of the review of evidence for SD OCT, articles from 2006 onwards were included, for a total of 542 publications.

Inclusion Criteria

- English-language articles and health technology assessments.
- RCTs and observational studies of OCT and AMD or DME.
- Studies focusing on either diagnosis or monitoring of disease.

Exclusion Criteria

- Studies in which outcomes were not specific to those of interest in this report.
- Studies of pediatric populations.
- Studies on OCT as a screening tool.
- Studies that did not assess comparative effectiveness of OCT with a referent, as specified below in “Comparisons of Interest”.

Outcomes of Interest

- Studies of sensitivity, specificity.

Comparisons of Interest

Evidence exists for the following comparisons of interest:

- OCT compared with the reference “fluorescein angiography” for AMD.
- OCT compared with the reference “biomicroscopy” or “stereo or fundus photography” for DME.

Summary of Existing Evidence

No evidence for the accuracy of SD OCT compared to either FA, BM or SFP was published between January 2006 to February 2009; however, two technology assessments were found, one from Alberta (7) and the other from Germany (8), both of which contain evidence for TD OCT (see Table 1). Although these HTAs included eight studies each, only one study from each report was specific to this MAS review. Additionally, one systematic review was identified for OCT and DME. It is these three articles, all pertaining to time and not spectral domain OCT, as well as comments from experts in the field of OCT and retinal disease, that will comprise the evidence for this review.

Table 1: Focus of Previous Health Technology Assessments on Optical Coherence Tomography

Year	Author	Focus of Assessment
2007	German Agency for HTA of the German Institute of Medical Documentation and Information (8)	<ul style="list-style-type: none"> ▪ To determine the efficacy and efficiency of OCT compared to FA in the diagnosis of AMD. ▪ Included in this review : 1 study of 8 relevant to this review of AMD.
2003	Alberta Heritage Foundation for Medical Research (7)	<ul style="list-style-type: none"> ▪ To evaluate the evidence of the use of OCT in diagnosing retinal disease. ▪ Included in this review: 1 study of 8 relevant to this review of DME.

AMD

German Agency for HTA of the German Institute of Medical Documentation and Information, 2007

Evaluation of optical coherence tomography in the diagnosis of age-related macular degeneration compared with fluorescein angiography. (8)

Objective: To investigate the efficacy and efficiency of OCT compared to FA. Ethical, societal and legal aspects are also considered.

Search Date: To November 2005.

Studies Included	Comments	Conclusions
8 observational studies, only 1 was relevant to this MAS review	<ul style="list-style-type: none"> ▪ Number of studies is very limited and quality generally very low. ▪ Patient groups and objectives of studies very heterogeneous. 	<ul style="list-style-type: none"> ▪ All publications uniformly show that OCT cannot replace FA. ▪ OCT yields additional diagnostic findings and may verify unclear findings of FA.

This HTA included eight observational studies, only one of which was relevant to the present review. The seven other studies were excluded because they did not provide data on sensitivity and specificity, the main outcomes of interest. The included study was a UK case series by Sandhu et al. (9), which assessed the diagnostic accuracy of OCT, with and without SFP, in predicting FA findings. Over a 6 month period, a consecutive series of 128 patients suspected of having choroidal neovascularization (CNV) and who had undergone imaging by TD OCT, SFP, and FA, were assigned a diagnosis by two masked observers, one examining OCT alone and then OCT plus SFP, and one examining FA alone. Included in the analysis were 131 eyes (118 patients), the results of which are presented in Table 2. (9)

Compared to FA, OCT alone was found to be better than OCT plus SFP at detecting the presence of CNV in patients suspected of being new cases. (9) The sensitivity of OCT alone was 96.4% compared to that of OCT with SFP (94.0%). The specificity of OCT, however, was much lower (66.0%) than for OCT with SFP (89.4%). With respect to identifying the exact components of CNV, OCT alone was less accurate (sensitivity=78.6%, specificity=82.7%) than OCT with SFP (sensitivity=82.1%, specificity=89.3%). The authors thus concluded that OCT cannot replace FA in accurately diagnosing disease Components; however, it may have a role as a screening tool to help prioritise FA requests.

Table 2: Results from Sandhu et al. 2005

	Sensitivity	Specificity
New AMD, treatable CNV lesions		
OCT	96.4%	66.0%
OCT + SFP	94.0%	89.4%
CNV with Classic Component		
OCT	78.6%	82.7%
OCT + SFP	82.1%	89.3%

DME

Alberta Heritage Foundation for Medical Research, 2003

Optical coherence tomography for diagnosing retinal disease (7)

Objective: To evaluate the evidence of the use of OCT to diagnose retinal disease.

Search Date: 1995 to 2003.

Studies Included	Comments	Conclusions
8 observational studies; only 1 was relevant to the MAS review	<ul style="list-style-type: none"> ▪ Although on retinal disease, most studies reviewed were based on glaucoma. ▪ 1 of 8 studies on DME. 	<ul style="list-style-type: none"> ▪ OCT cannot be used as a sole diagnostic test, ▪ There is uncertainty in OCT performance in mild/moderate disease. ▪ Accuracy of OCT may be biased by using a single comparator.

This HTA included eight observational studies, only one of which was relevant to this review. The seven other studies were excluded as they focused on OCT use in glaucoma. As we were informed by an expert consultant that OCT is not particularly effective in glaucoma, we elected to exclude this condition from the MAS review.

A cross-sectional study of 136 eyes with diabetic retinopathy and 30 normal eyes (on BM) was conducted by Goebel et al. in Germany. (10) The sensitivity and specificity of TD OCT were compared to those of FA or BM alone for average retinal thickness measures (results reported in Table 3), as measured on OCT. Of importance is that the referent for this study was defined as the presence/absence of leakage as seen on FA, or clinically significant macular edema.

Table 3: Results from Goebel et al. 2002

	Sensitivity	Specificity
Average retinal thickness		
OCT vs. FA	73.1%	100.0%
OCT vs. BM	80.2%	100.0%

These results demonstrate the dependence of OCT accuracy on the assumption that FA and BM are the gold standards. Furthermore, they illustrate the need for a common third measure against which both technologies can be compared. It is, therefore, questionable whether any published studies of the accuracy of OCT compared to FA, BM, or SFP, can be considered valid.

Also identified by the MAS literature search was a systematic review by Virgili et al. (11), conducted in Italy. Its purpose was to determine the sensitivity and specificity of OCT in diagnosing DME compared with SFP or BM. In total, 15 studies published from 1998 to 2006 (11 prospective, four retrospective, one with unclear directionality) were included in the systematic review, although only six studies had sufficient data on sensitivity and specificity. The range of OCT sensitivity in these six studies was from 0.74 (95%CI: 0.62 to 0.83) to 1.00 (95%CI: 0.93 to 1.00), while specificity ranged from 0.77 (95%CI: 0.62 to 0.88) to 0.96 (95%CI: 0.91 to 0.96). As demonstrated in the study by Goebel et al. (10), these results (summarized in Table 4) also illustrate the variability in the accuracy of OCT based on comparators that cannot be considered gold standards.

Table 4: Results of 6 studies on Accuracy of OCT relative to BM or SFP.

	Sensitivity (95%CI)	Specificity (95%CI)
Hee 1996 (12)	0.74 (0.62 - 0.83)	0.91 (0.85 – 0.96)
Brown 2004 (13)	0.67 (0.48 - 0.82)	0.96 (0.91 – 0.98)
Browning 2004 (14)	0.84 (0.71 - 0.93)	0.82 (0.72 – 0.89)
Gaucher 2005 (15)	1.00 (0.93 - 1.00)	0.96 (0.85 – 0.99)
Goebel 2006 (16)	0.83 (0.71 - 0.91)	0.77 (0.62 – 0.88)
Sadda 2006 (17)	0.89 (0.73 - 0.97)	0.86 (0.67 – 0.96)

Source: Modified from Virgili et al. (11)

Methodologic Issue

In the published literature, FA, BM and SFP were identified as comparators for the evaluation of OCT. Upon further review and consultations with experts in the field of clinical test evaluation, however, it was concluded that these comparators should not be considered as gold standards. OCT is a novel technology that is superior to FA, BM and SFP (from expert opinion) and, as the only means of measuring retinal thickness, it lacks an adequate reference for comparison. Nevertheless, studies have been published and in the absence of an established gold standard and a third test as an arbiter, it is questionable whether any published studies of the accuracy of OCT compared to FA, BM, or SFP, can be considered valid. Therefore, on the basis of Level 5 evidence, i.e., conclusions based on expert consultations, as presented in the following section.

Conclusions from Expert Consultations

The overall conclusions regarding SD OCT are as follows:

1. OCT is considered an essential part of the diagnosis and follow-up of patients with DME and AMD.
2. OCT is adjunctive to FA for both AMD and DME but should decrease utilization of FA as a monitoring modality.
3. An increased use of OCT will result in a decline in the use of BM for the monitoring of patients with DME, given OCT's superior accuracy and consistency.
4. OCT is diffusing rapidly and the technology is changing. Since FA is still considered pivotal in the diagnosis and treatment of AMD and DME and there is no common outcome against which to compare these technologies, it's unlikely that RCT evidence of efficacy for OCT will ever be forthcoming.

Clinical Utility of OCT

In addition to the accuracy of OCT in the detection of disease, assessment of the clinical utility of this technology included a rapid review of evidence for treatment effects. The treatment of choice for AMD is Lucentis® injections, with or without Avastin® and photodynamic therapy. The treatment of choice for DME is laser photocoagulation, which may be replaced with Lucentis® injections (from expert consultation). The evidence, as presented in systematic reviews and other health technology assessments, indicates that there are effective treatments available for both AMD (18) and DME. (19;20)

Ontario Health System Health Impact Analysis

OCT testing is presently an uninsured service in Ontario with patients paying approximately \$150 out-of-pocket per test. Several provinces do provide funding for this procedure, including British Columbia, Alberta, Saskatchewan, Newfoundland, Nova Scotia, Prince Edward Island, and the Yukon Territories. Provinces that do not provide such funding are Quebec, Manitoba and New Brunswick. The demand for OCT is expected to increase with aging of the population.

Economic Analysis

Disclaimer: The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for all in-hospital stay costs for the designated International Classification of Diseases-10 (ICD-10) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits for physician fees, laboratory fees from the Ontario Laboratory Schedule of Fees, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effectiveness analyses, a discount rate of 5% is used as per the Canadian Agency for Drugs and Technologies in Health.

Downstream costs: All costs reported are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature. In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach. The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

A literature review was conducted, however, no published economic analyses on the use of OCT for the diagnosis of AMD and DME were identified.

Physician Costs for AMD and DME

Consultation with experts identified the type and number of tests conducted to diagnose AMD and DME using current OCT technology. This was compared to the previous standard of using FA for disease diagnosis and monitoring. Physician costs associated with the administration and interpretation of the tests were summarized in order to examine the economic impact of OCT testing on physician costs according to the Ontario Health Insurance (OHIP) Schedule of Benefits and Fees. Note that OCT tests are not currently insured by OHIP.

Diagnostic Tests

Traditionally, AMD has been diagnosed and monitored through the administration of five FA tests over a one year period (one administered initially, followed by one every three months thereafter), while for DME, a biomicroscopy test was performed alongside the initial FA test, followed by two further FA tests at 6 and 12 months.

With the availability of OCT to diagnose and monitor these two conditions, the diagnosis of AMD over a one year period currently involves the administration of three FA tests (one initially, and one at 6 and at 12 months) and five OCT tests (one initially, one every 3 months thereafter). The diagnosis of DME, however, may include a biomicroscopy test (administered initially), two FA tests (one initially and one at 6 months), and four OCT tests (one initially and one at 3, 6, and 12 months).

Cases of AMD and DME in Ontario

According to the CNIB, the incidence of AMD in Canada in 2003 for all age groups was approximately 78,000 cases. (1) Using the same incidence rate, the corresponding proportion in Ontario in 2006 was estimated as being 30,000. (21) The number of DME cases in Ontario was estimated in a similar way using the 2003 Ontario-specific incidence rate of diabetes of 0.0082% (4) and the approximation that 1-in-4 diabetics will develop DME; the number of DME cases in Ontario in 2006 was thus estimated to be 18,700.

Estimated Costs of AMD and DME in Ontario

Physician fees associated with the cost of performing and interpreting diagnostic procedures for AMD and DME were taken from provincial health insurance fee schedules. The procedure fee currently listed in the Ontario Schedule of Benefits from OHIP for FA was taken as \$46.35. (22) As no fee codes specific to biomicroscopy and OCT tests were found in the Ontario Schedule of Benefits, the procedure costs of these diagnostic tests were estimated from other provincial schedules of medical benefits and insurance plans. For biomicroscopy, an average fee of \$26.53 was estimated from the physician procedure fees in British Columbia and Alberta. (23;24) For OCT tests, an average fee of \$26.67 was estimated from the schedule of medical benefits and insurance plans of Alberta, Saskatchewan and Newfoundland and Labrador. (25;26)

The physician procedure cost of diagnostic tests for AMD, using current standards for diagnosis and monitoring, was approximately \$272.38 (three FA tests and five OCT tests) per patient. The corresponding cost for DME was estimated as being \$225.90 (one biomicroscopy, two FA tests and four OCT tests) per patient. As a result, the total cost of physician fees for diagnostic procedures for the estimated total number of cases of AMD and DME in Ontario are approximately \$8.2 million and \$4.2 million, respectively.

The current use of OCT in the diagnosis of AMD and DME was found to yield higher costs than the use of traditional testing involving only FA or biomicroscopy. For AMD physician costs, the use of OCT increased the cost per patient from \$231.75 to \$272.38, resulting in a total cost increase in Ontario from \$7.0 million to \$8.2 million. Similarly for DME physician costs, the use of OCT increased per-patient costs from \$165.58 to \$225.90, resulting in a total cost increase from \$3.1 million to \$4.2 million.

Comparison of Hospital Costs

The use of OCT in the diagnosis of AMD and DME resulted in a decrease in hospital costs as patients required fewer FA tests in day surgery settings. Traditionally, testing for AMD implied approximately five FA tests per patient over a one year period, compared to three FA tests when OCT was used for diagnosis and monitoring. The resulting avoided costs in providing two FA tests were estimated as approximately \$276 per patient for a total cost avoidance in Ontario of \$8.3 million. Similarly for DME, diagnosis traditionally required three FA tests compared to two FA tests over a one year period, resulting in a cost avoidance of \$138 per patient, with a total cost avoidance of \$2.6 million for Ontario.

Note that direct hospital costs for a FA test were estimated using fiscal 2007/08 OCCI data with the CCI diagnostic procedure code 2.CZ.70 under the procedure heading “eye inspection, not elsewhere classified”. The average direct cost for day surgery patients with an ICD-10-CA most responsible diagnosis of H35.3 (“degeneration of macula and posterior pole”) was found to be approximately \$138. (27-29) This cost was used to estimate the direct cost of FA for both AMD and DME patients in a day surgery setting.

Discussion

Compared to traditional diagnosis and monitoring using FA instead of OCT tests (i.e., using five FA tests for AMD, one biomicroscopy and three FA tests for DME), the current use of OCT implied the following increase in total physician procedure costs in Ontario: \$1.2 million for AMD and \$1.1 million for DME. In terms of direct hospital costs, the current use of OCT implied a cost avoidance of approximately \$8.3 million and \$2.6 million for AMD and DME, respectively. Costs associated with providing OCT in different care settings were not included in the current economic analysis.

Appendix: Literature Search Strategy

Search date: February 13, 2009

Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, OVID Cochrane Library, OVID EMBASE, Centre for Reviews and Dissemination (CRD)/International Agency for Health Technology Assessment (INAHTA)

Database: Ovid MEDLINE(R) <1996 to February Week 1 2009>

Search Strategy:

- 1 exp Tomography, Optical Coherence/ (3811)
- 2 (optical coherence adj5 tomograph*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4760)
- 3 ((spectral or fourier) adj2 domain).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (435)
- 4 (CIRRUS or SPECTRALIS or FD?OCT or 3D OCT?1000 or RTVue or SOCT or OCT?SLO or oct).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10650)
- 5 or/1-4 (13217)
- 6 exp Macular Degeneration/ (6984)
- 7 (age-related adj2 maculopath*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (430)
- 8 (macula* adj2 degeneration).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (6817)
- 9 exp Macular Edema/ (1704)
- 10 exp Diabetes Mellitus/ (115031)
- 11 9 and 10 (736)
- 12 (diabet* adj10 (macula* or retina*) adj2 (edema or oedema)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (958)
- 13 11 or 12 (1084)
- 14 6 or 7 or 8 or 13 (8733)
- 15 14 and 5 (1082)
- 16 limit 15 to (english language and humans and yr="2003 - 2009") (865)
- 17 limit 16 to (case reports or comment or editorial or letter) (280)
- 18 16 not 17 (585)

Database: EMBASE <1980 to 2009 Week 06>

Search Strategy:

- 1 exp Optical Coherence Tomography/ (4374)
- 2 (optical coherence adj5 tomograph*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4620)
- 3 (CIRRUS or SPECTRALIS or FD?OCT or 3D OCT?1000 or RTVue or SOCT or OCT?SLO or oct).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7404)
- 4 ((spectral or fourier) adj2 domain).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (398)
- 5 or/1-4 (10116)
- 6 exp Retina Macula Age Related Degeneration/ (5900)
- 7 (age-related adj2 maculopath*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (520)
- 8 (macula* adj2 degeneration).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7919)
- 9 exp Diabetic Macular Edema/ (459)
- 10 (diabet* adj10 (macula* or retina*) adj2 (edema or oedema)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1354)
- 11 or/6-10 (11013)

- 12 5 and 11 (796)
- 13 limit 12 to (human and english language and yr="2003 - 2009") (607)
- 14 limit 13 to (editorial or letter or note) (80)
- 15 Case Report/ (1024342)
- 16 13 not (14 or 15) (430)

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