To read all new materials from MAS and OHTAC, be sure to visit the "What's New" section of our websites. You can subscribe to the e-Bulletin and other OHTAC/MAS releases via our RSS feed. To find out more, click on the icon to the right or visit:

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OHTAC and MAS wish all their colleagues the best of the holiday season.

NEW REPORTS FROM MAS & OHTAC

The following recommendations and MAS report have been completed recently, and are available for download or will be shortly, at the **Ontario Health Technology Assessment Series** (OHTAS) website.

1. Clinical Utility of Serologic Testing for Celiac Disease in Ontario (Symptomatic Patients)

Celiac disease is an autoimmune disorder characterized by a chronic inflammatory state of the proximal small bowel mucosa and triggered by the ingestion of gluten - a protein present in wheat, rye and barley. The structural and functional changes in the small bowel result in impaired digestion and absorption of nutrients and the treatment consists of strict, lifelong adherence to a gluten-free diet. The diagnosis of celiac disease is confirmed by characteristic abnormalities in small bowel biopsy. Serologic tests aid in the diagnosis of celiac disease.

MAS has conducted a systematic review of evidence in order to evaluate the sensitivity, specificity, clinical validity, clinical utility, and cost-effectiveness of serologic celiac disease tests used in Ontario in subjects with symptoms consistent with the disease. An expert panel was struck to contextualize the evidence. OHTAC made recommendations in regard to gastrointestinal indications, unexplained anemia unresponsive to iron supplementation, and dermatitis herpetiformis. OHTAC made the following recommendations in regards to gastrointestinal indications, unexplained anemia unresponsive to iron supplementation, and dermatitis herpetiformis.

1. Based on moderate quality evidence for IgA tTG¶, OHTAC supports the use of this serologic test in the diagnosis of celiac disease in subjects with suspicion of celiac disease (see * below).

2. Patients with a negative IgA tTG serologic test with strong suspicion of celiac disease (see * below) with or without IgA deficiency should be referred to a gastroenterologist for consideration of a small bowel biopsy.

3. Individuals with type 1 diabetes mellitus, autoimmune thyroid disease, and first degree relatives of individuals with celiac disease are reported to be at a higher risk of developing celiac disease and there should be a heightened awareness in testing for celiac disease if they meet the criteria listed at * below.

4. In people with a positive serologic test for celiac disease it is recommended that a confirmatory small bowel biopsy be performed.

5. Repeat serologic testing for patients diagnosed with celiac disease is reasonable for those patients who remain symptomatic despite strict adherence to a gluten-free diet. In this case, serologic testing for celiac disease should not be repeated more that once a year for each patient.

* In Adults: chronic diarrhea especially in the presence of weight loss, abdominal pain, and/or unexplained iron-deficiency anemia unresponsive to iron supplementation.
In Pediatrics: Chronic diarrhea especially in the presence of failure to thrive or weight loss; severe constipation especially with poor weight gain.
In Adults and Pediatrics: Unexplained iron deficiency anemia unresponsive to iron supplementation, or subjects with dermatitis herpetiformis.

¶ IgA tTG refers to the immunoglobulin A (IgA) anti-tissue transglutaminase antibody serologic test.

Please note: OHTAC will make recommendations regarding IgA tTG testing for possible non-gastrointestinal indications and for asymptomatic high risk individuals once the evidence-based analysis for these indications is provided for its consideration.

2. Negative Pressure Wound Therapy

In 2006 OHTAC concluded that there was insufficient evidence of effectiveness of Negative Pressure Wound Therapy (NPWT) and recommended that no additional funding be provided. In 2010 OHTAC reviewed the results of recent Randomized Control Trials (RCTs) and based on the new evidence, OHTAC has revised its previous recommendations.

A total of four Randomized Control Trials were reviewed to assess the safety and effectiveness of NPWT. Two of these trials included patients who had a diabetic foot ulcer and two trials included patients who were hospitalized for skin grafting. The studies of diabetic foot ulcer compared NPWT with advanced or standard moist wound therapy. The studies of skin grafting compared NPWT with standard wound care without using NPWT.

OHTAC's revised finding based on new evidence is that NPWT is an effective option in the management of diabetic foot ulcers, and an appropriate option for use following skin grafting of medium-sized (around 30 cm^2) vascular ulcers and burns. To optimize patient outcomes and safety, appropriate guidelines should be adhered to in the application of this technology.

3. Neuroimaging for the Evaluation of Chronic Headaches

Headache disorders are generally classified as either primary or secondary with further sub-classifications into specific headache types. Primary headaches are those not caused by a disease or medical condition and include i) tension-type headache, ii) migraine, iii) cluster headache and, iv) other primary headaches. Secondary headaches are those caused by an underlying medical condition. While primary headache disorders are far more frequent than secondary headache disorders, there is a willingness to carry out neuroimaging studies (CT and/or MRI scans) out of concern for missing uncommon secondary causes and often to relieve patient anxiety. The evidence of the clinical utility of neuroimaging studies to detect uncommon secondary causes of headache was examined and the quality of evidence was found to be low. Given the low quality of evidence, an expert panel met in the early fall to advise on the use of neuroimaging in persons with chronic headache.

OHTAC found that while the current Ontario utilization of CT and MRI for the evaluation of headaches is not excessive, it recommends that the implementation of an electronic ordering system to capture data concerning the specific headache indications utilizing neuroimaging, may improve the efficient use of neuroimaging for the evaluation of headaches.

4. Personalized Medicine Technologies

Cancer Care Ontario asked MAS to provide evidence-based analyses on the effectiveness and cost-effectiveness of three oncology pharmacogenetic tests currently in use in Ontario:

- Gene Expression Profiling for Guiding Adjuvant Chemotherapy Decisions in Women with Early Breast Cancer
- Epidermal Growth Factor Receptor Mutation (EGFR) Testing for Prediction of Response to EGFR-Targeting Tyrosine Kinase Inhibitor (TKI) Drugs in Patients with Advanced Non-Small-Cell Lung Cancer
- Kristen-RAS (KRAS) Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer

These evidence-based analyses have been completed in conjunction with internal and external stakeholders including a Provincial Expert Panel on Pharmacogenetics (PEPP). Within the PEPP, subgroup committees were

developed for each disease area. For each technology, a budget impact analysis was also completed by the Toronto Health Economics and Technology Assessment Collaborative (THETA) and appears within the reports.

a) OHTAC recommended the following for **Multi-Gene Expression Profiling for Guiding Adjuvant Chemotherapy Decisions in Women with Early Breast Cancer**:

1) In women with newly diagnosed early breast cancer that is estrogen receptor (ER) positive and/or progesterone receptor (PR) positive, HER-2/*neu* negative, and lymph node (LN) negative, who are being treated with tamoxifen (or an aromatase inhibitor such as anastrozole for postmenopausal women) OHTAC recommended:

- Access to Oncoytpe-DX should be made available to patients in the above population within the context of a field evaluation.
- Field evaluation should be established in Ontario to evaluate further correlations between Oncotype-DX and Adjuvant! Online and other clinical variables, as well as the clinical impact of Oncotype-DX on patient and practitioner decision-making.
- Patients should be properly informed by their treating clinician of the uncertainties in current available evidence in regards to Oncotype-DX testing if testing is being considered. Patients should also receive assurances relating to the privacy and security of their genetic information. A patient-decision aid or tool should be made available to improve the ability of patients to make informed adjuvant therapy decisions with greater confidence and clarity.
- Evidence should continue to be monitored as it emerges; further validation studies may change the above recommendations.

2. In women with newly-diagnosed, early breast cancer that is ER and/or PR positive, HER-2/*neu* negative, and LN positive, who are being treated with tamoxifen or an aromatase inhibitor such as anastrozole:

- There is insufficient evidence to make a recommendation for or against the use of Oncotype-DX testing for this population.
- Patients of this population should be properly informed by their treating clinician of the lack of evidence regarding the predictive value of Oncotype-DX if requesting Oncotype-DX testing.
- Evidence should continue to be monitored as it emerges. Further validation studies may change the above recommendations.

b) OHTAC recommended that **Epidermal Growth Factor Receptor Mutation (EGFR)** testing should be a prerequisite for the first-line treatment of advanced non-small cell lung cancer (NSCLC) with gefitinib. Given the uncertainty (i.e. low quality of evidence) regarding the effectiveness of EGFR Mutation testing for erlotinib use in the second- or third-line treatment of advanced NSCLC, patient outcomes data should be collected and reported through a field evaluation.

c) OHTAC recommended that **Kristen-RAS, (KRAS)** testing has predictive value in the treatment of advanced colorectal cancer patients with cetuximab and Panitumumab monotherapy, or cetuximab-irinotecan combination therapy. Therefore, these treatment options should be given to patients with KRAS wildtype mutation status.

OHTAC wishes to point out that any test that overall avoids unnecessary exposure to potentially harmful effects should be a welcome addition to patient care.

COMING SOON

1. Endovascular Radiofrequency Ablation for Varicose Veins

This study examines the safety and effectiveness of endovascular radiofrequency treatment for varicose veins (VV). Endovascular techniques such as radiofrequency ablation (RFA) and endovascular laser therapy (ELT) are

image guided procedures within the vein that are increasingly being offered as alternatives to surgery for VV reflux. The overall summary of the evidence reviews showed that there were fewer complications, less pain and a quicker recovery after RFA than surgery. RFA was also as effective as surgery in the short term although longer term follow-up is needed to assess recurrence after both treatments. OHTAC recommended that patients with varicose vein reflux should be offered endovascular ablation [endovascular laser therapy (EVLT) or radiofrequency ablation (RFA)].

The April 2010 review and OHTAC recommendation on **Endovascular Laser Treatment for Varicose Veins** are already available on the website.

2. Robotic-Assisted Minimally Invasive Surgery for Gynecologic and Urologic Oncology

For both gynecology and prostate cancer, two comparisons were made:

- Robotic-assisted laparoscopic radical/total hysterectomy vs. laparotomy and laparoscopy; and,
- Robotic-assisted laparoscopic radical prostatectomy vs. retropubic radical prostatectomy and laparoscopic radical prostatectomy.

It is noted that surgical expertise is critical to maximize patient outcomes and minimize complication rates with the use of this technology.

Recognizing the low quality evidence for robotic-assisted minimally invasive surgery and its current diffusion, the following OHTAC recommendations were made:

- Due to the low quality of evidence, OHTAC is unable to make a recommendation on the effectiveness of robotic-assisted laparoscopic radical/total hysterectomy or robotic-assisted laparoscopic radical prostatectomy at this time.

For gynecology:

- Recognizing the rapid diffusion of this technology, OHTAC recommends a field evaluation using administrative datasets to address the residual uncertainty of this technology prior to definitive OHTAC recommendations regarding its wide adoption. In this context, OHTAC recommends that a subcommittee be formed to report back to OHTAC regarding the ongoing conduct of the field evaluation.

For prostate cancer:

- Recognizing the rapid diffusion of this technology, OHTAC recommends a field evaluation to address the residual uncertainty of this technology prior to definitive decisions regarding its wide adoption.
- OHTAC recommends a subcommittee be formed and report back to OHTAC regarding the feasibility of undertaking a field evaluation that addresses relevant outcomes for prostate cancer including the complex measurement of erectile dysfunction and urinary incontinence.

3. Emerging Pharmacogenomic Tests

As part of the Provincial Pharmacogenomics Expert Panel (PEPP), two subgroup committees were established to determine a preliminary list of emerging pharmacogenetic tests and to scan the pharmacogenetic horizon to recommend priorities for health technology assessment (HTA) from specialties outside of oncology.

PEPP concluded that genetic testing to determine response to Carbamazepine, Warfarin, Abacavir and Azathioprine were considered ready for HTA evaluation. Genetic tests for response to Isoniazid (INH), Codeine and Allopurinol were not deemed ready for examination at this time. Pharmacogenetic tests associated with clopidogrel and statins were identified as potential tests that could be examined when more evidence becomes available.

In terms of determining biomarkers which are considered emerging markers for pharmacogenetic testing, PEPP identified the following tests which will present a real pressure to the health care system in the next 12 months.

These include:

1. Warfarin
2. Carbamazepine
3. Abacavir
4. Azathioprine
5. HER-2 /neu in Gastric Cancer
6. B-Raf mutations/B-Raf inhibitors in Melanoma
7. BRCA 1 and 2 in Ovarian Cancer
8. for ALK mutation/ ALK inhibitors in Lung Cancer and Neuroblastoma

Note: Tests 1-4 include paediatrics and Azathioprine includes paediatrics for Inflammatory Bowel Disease (IBD)

OHTAC supports the PEPP recommendation that there is a need in Ontario for a mechanism to be established to identify and determine which pharmacogenetic tests are emerging, and to ensure that these are assessed and prioritized for health technology assessment appropriately.

CURRENTLY UNDER REVIEW

The following topics are currently **under review**:

Chronic Obstructive Pulmonary Disease (COPD) – COPD is a leading cause of mortality, morbidity and health care utilization. This mega analysis will synthesize the clinical and economic evidence around a variety of interventions to treat COPD in order to determine best evidence for improving patient outcomes. Interventions to be studied include: smoking cessation; multidisciplinary care; influenza and pneumococcal vaccinations; pulmonary rehabilitation; long-term oxygen therapy; telemonitoring; ventilation; hospital-at-home care for acute exacerbations, and palliative care. *Anticipated Completion of All Components: Winter 2011*

Continuous Glucose Monitoring - This review will examine the role of Continuous Glucose Monitors (CGM) in the management of diabetes. *Anticipated Completion: Winter 2011*

Diurnal Tension Curve for Intraocular Pressure Management - This review will examine the validity of this test for screening for glaucoma in selected populations and the test's clinical utility in a post-diagnosis treatment situation. *Anticipated Completion: Winter 2011*

Remote Monitoring of Cardiovascular Implantable Electronic Devices (CIED) - This review will assess the effectiveness of internet-assisted, device-based remote monitoring systems (RMS) which provide physicians with data from implanted cardiac devices. *Anticipated Completion: Winter 2011*

Genetic Testing for Dilated Cardiomyopathy (DCM) – This review will assess the effectiveness of genetic testing in the diagnosis of Dilated Cardiomyopathy. *Anticipated Completion Spring 2011*

Serologic Testing for Celiac Disease: Non-Gastro-Intestinal Indications and High Risk Asymptomatics – This review will review IgA tTG testing for possible non-gastrointestinal indications and for asymptomatic individuals at high risk for celiac disease. *Anticipated Completion Spring 2011*

Study of Improving Multiple Infusion Line Safety - As requested by OHTAC, the Healthcare Human Factors Laboratories at the University Health Network is investigating the safety, effectiveness and usability of multiple line infusions. *Anticipated Completion: 2011*

OHTAC and MAS welcome your questions and comments. Please contact us at OHTACinfo.moh@ontario.ca