OHTAC Recommendation

Multi-gene expression profiling for guiding adjuvant chemotherapy decisions in women with early breast cancer

Presented to the Ontario Health Technology Advisory Committee in August 2010

December 2010

OHTAC
Ontario
Health Technology
Advisory Committee

Issue Background

Breast Cancer

Breast cancer is the most common cancer among Canadian women. In 2007, breast cancer represented 28.9% of all new cancer cases (first among cancers) as well as 15.5% of all deaths due to cancer (second only to lung cancer) in Canada. In Ontario, this translated to 8,500 new cases of breast cancer per year (in 2007).

Early breast cancer is subdivided into two major categories, *in situ* disease, mainly in the form of ductal carcinoma in situ (DCIS), and invasive cancer. Breast cancer that is *in situ* has confined itself to the ducts or lobules of the breast and has not spread to the surrounding tissues in the breast or to other parts of the body. Breast cancer that is *in situ*, however, may become invasive. Invasive (infiltrating) breast cancers spread outside the membrane that lines a duct or lobule, invading the surrounding tissues. Invasive cancers may spread cancer to other parts of the body through the bloodstream and lymphatic system. Invasive cancer is far more prevalent than *in situ* disease and was the focus of an evidence-based assessment by the Medical Advisory Secretariat.

The majority of women newly diagnosed with invasive breast cancer will receive some form of adjuvant therapy. Options include chemotherapy, hormonal therapy, combined chemotherapy plus hormonal therapy, or observation alone (i.e., no therapy). Treatment recommendations have traditionally been based upon a woman's risk of recurrence and the estimated or perceived benefits of therapy weighted against the potential adverse events of therapy. Chemotherapy is by far the most harmful of available adjuvant treatment options for women.

Unfortunately, far more women currently receive chemotherapy than can benefit. For these women, the harms of chemotherapy are incurred without any benefit. Better estimators of baseline risk (i.e., prognostic risk) and response to chemotherapy (i.e., predictive response) could ensure that more women receive the appropriate treatment. Gene expression profiling is an example of an emerging technology with the potential to improve decision-making for adjuvant treatment decisions in women with early breast cancer.

Gene Expression Profiling

Gene expression profiling refers to a process of identifying genes whose activity within tumours may provide insight towards appropriately assessing disease prognosis and guiding therapy. Gene expression profiling examines the composition of cellular messenger ribonucleic acid (RNA) within tumours providing information about the global activity of genes that give rise to them.

Over the past decade, a number of gene expression profiling assays have seen development in breast cancer research; however, very few assays have progressed through development to commercial availability. While the Medical Advisory Secretariat's review sought to identify all gene expression profile assays relevant to Ontario, only the Oncotype-DX assay (Genomic Health, Redwood City, CA) was identified as being commercially available and of current relevance to the Ontario breast cancer population and this review therefore focuses on this assay alone.

Oncotype-DX

The Oncotype-DX Breast Cancer Assay quantifies gene expression for 21 genes in breast cancer tissue by RT-PCR using formalin-fixed paraffin-embedded tumour blocks that are obtained during initial surgery (lumpectomy, mastectomy, or core biopsy). The panel of 21 genes include genes associated with tumour proliferation and invasion, as well as other genes related to HER-2/*neu* expression, estrogen receptor expression, and progesterone receptor expression. The expression of these 21 genes is used to generate a recurrence score that ranges from 0 to 100. A higher score refers to a higher risk of a woman developing a breast cancer recurrence.

Because Oncotype-DX is not indicated for all women with early breast cancer, the target population of the Medical Advisory secretariat's review was women with newly diagnosed early stage (stage I–IIIa) invasive breast cancer that is estrogen-receptor positive and/or progesterone-receptor positive. This population still compromises more than half of all new breast cancers in Ontario.

Taking into consideration the scale of the population involved as well as the potential benefits of gene expression profiling, the Medical Advisory Secretariat sought to review all the available clinical evidence on Oncotype-DX. An economic analysis that included a cost-effectiveness model of Oncotype-DX was also undertaken as well as qualitative research on the ethical and societal implications of gene expression profiling. This qualitative research component also incorporated the views and opinions of a Citizen's Panel of Ontario citizens.

Please note that the recommendations below are segregated by the population for which Oncotype-DX testing research had been carried out. Please refer to the recommendations for greater clarity regarding the differences in population.

Decision Determinants

OHTAC has developed a decision-making framework that consists of seven guiding principles for decision making and a decision-making tool, called the Decision Determinants (DD) tool. The evaluation of the four explicit main criteria (overall clinical benefit, value for money, feasibility of adoption into health system, and consistency with expected societal & ethical values) are reported in using 1 of 4 symbols. For more information on the Decision-Making Framework and the meaning of the symbols below, please refer to the Decision Determinants Guidance Document or visit: www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html

	Lymph-Node Negative	Lymph-Node Positive
Effectiveness		
Safety		
Burden of Illness		
Need		
Overall Clinical Effectiveness		

OHTAC Recommendations

In considering the above ratings, OHTAC weighted all factors of the above decision determinants equally to arrive at its recommendations. The recommendations were based on a systematic review of the available clinical evidence, an economic analysis that included a cost-effectiveness model of Oncotype-DX, as well as qualitative research on the ethical and societal implications of gene expression profiling. This qualitative research component also incorporated the views and opinions of a Citizen's Panel of Ontario citizens.

OTHAC's recommendations are as follows:

1. In women with newly diagnosed early breast cancer that is ER and/or PRpositive, HER-2/*neu* negative, and LN negative, who are being treated with tamoxifen (or an aromatase inhibitor such as anastrozole for postmenopausal women):
    a) Access to Oncoytpe-DX should be made available to patients in the above population within the context of a field evaluation.
    b) 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.
    c) 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.
    d) 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:
    a) There is insufficient evidence to make a recommendation for or against the use of Oncotype-DX testing for this population.
    b) 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.
    c) Evidence should continue to be monitored as it emerges; further validation studies may change the above recommendations.