

Use of Oncotype DX for guiding adjuvant chemotherapy decisions in early stage invasive breast cancer patients in Alberta

A Health Technology Assessment

Simrandeep K Tiwana, Alison Smith, Laura Leggett, Gail MacKean, Diane Lorenzetti,
Fiona Clement

On behalf of the Health Technology Assessment Unit, University of Calgary

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1 ABBREVIATIONS

BC Breast Cancer

BMI Body Mass Index

BRCA Breast Cancer Susceptibility Protein

CI Confidence Interval

CLS Calgary Lab Services

CPF Clinical Pathological Features

CT Chemotherapy

DCIS Ductal Carcinoma In Situ

EAG Expert Advisory Group

ER Estrogen Receptor

FFPE Formalin-Fixed Paraffin-Embedded

GEP Gene Expression Profiling

HER2 Human Epidermal Growth Factor Receptor 2

HT Hormone Therapy

ICER Incremental Cost-Effectiveness

IDC Invasive Ductal Carcinoma

IHC Immunohistochemistry

LCIS Lobular Carcinoma In Situ

LN- Lymph node negative

LN+ Lymph node positive

MeSH Medical Subject Heading

NPI Nottingham Prognostic Index

mRNA Messenger Ribonucleic Acid

NICE National Institute for Clinical Excellence

NOS Newcastle Ottawa Scale

PgR Progesterone Receptor

QALY Quality Adjusted Life Year

RS Recurrence Score

WTP Willingness to Pay

2 INTRODUCTION

Breast cancer is the most common cancer in Canadian women, accounting for an estimated 26% of all cancer cases¹. An estimated 1 in 9 Canadian women will develop breast cancer in their lifetime and 1 in 29 will die of the disease¹.

Gene expression profiling (GEP) is an emerging technology that may be able to successfully divide breast cancer patients into prognostic groups based on genes that increase in proliferating cells¹². Oncotype DX (Genome Health Inc.) is one commercially available GEP in Canada. However, there are concerns about the value-added merit of this testing as some reports find that the Oncotype- DX will report over 40% of ER+ patients as “indeterminate”¹⁰. In addition, the genetic material used for the assay derives from a tissue sample that contains both tumour and non-tumour cells. As the relative proportion of non-tumour cell “contamination” increases, Oncotype DX displays a random pattern of mis-classification¹¹. This has raised questions about the accuracy of this testing in a given patient⁵.

2.1 Objectives

The primary *policy question* to be answered by this assessment is:

Should Oncotype DX be publicly funded in Alberta?

The primary *research questions* to be answered in this review are:

- I. To determine the burden of illness, patterns of care and capacity in Alberta as it relates to Oncotype DX and other relevant comparators (e.g. IHC4) in terms of informing treatment decisions in breast cancer patients.
- II. To determine the safety and effectiveness/efficacy of Oncotype DX as a decision support tool for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer

- III. To determine the cost-effectiveness of Oncotype DX and other relevant comparators (e.g. IHC4) as decision support tools for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer
- IV. To determine the budget impact of Oncotype DX as a decision support tool for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer

3 BACKGROUND INFORMATION

3.1.1 Incidence and prevalence of breast cancer

Breast cancer is the most common cancer in Canadian women, accounting for an estimated 26% of all cancer cases¹. The 10 year prevalence of breast cancer in Canada is an estimated 147, 595⁶. An estimated 1 in 9 Canadian women will develop breast cancer in their lifetime and 1 in 29 will die of the disease¹. Furthermore, an estimated 22, 700 women in Canada will receive a breast cancer diagnosis in 2012 and an estimated 5, 100 will die of the disease^{7;8}. In Alberta, for the same time period, it is estimated that 1, 950 women will be diagnosed with breast cancer and another 390 will die of the disease⁹. Prevalence of breast cancer in Alberta women who had ever been diagnosed with the disease was 20, 200 in 2006¹⁰. Additionally, Alberta women living with breast cancer are expected to lose 7, 538 years of life to the disease¹⁰.

The 5-year survival rate for women diagnosed with breast cancer is approximately 88% in all of Canada and 89% in Alberta^{1;10}. Breast cancer mortality rates in Canada have decreased by an estimated 40% since 1986 due to improvements in screening, diagnosis, and treatment¹. This is also reflected in Alberta statistics where the age standardized incidence rates of breast cancer increased 13% between 1986 and 2006 and the mortality rates have showed a steady decrease of 36% over the same time period¹⁰.

3.1.2 Risk factors

Breast cancer is a disease where the breast is the primary location of a cancerous growth or tumour⁷. It is a complex disease with inherited and environmental causes⁷. Inherited causes, or internal factors, are associated with genes passed down from parents (an estimated 12% of women with breast cancer had one affected relative and 1% had two or more) and include genetic mutations, or malfunctioning DNA replication, that can lead to abnormal cell growth^{7;11}. Environmental causes, or external factors, are associated with lifestyle and the environment¹². For example, level of physical activity or exposure to carcinogenic chemicals are known to alter cell DNA¹².

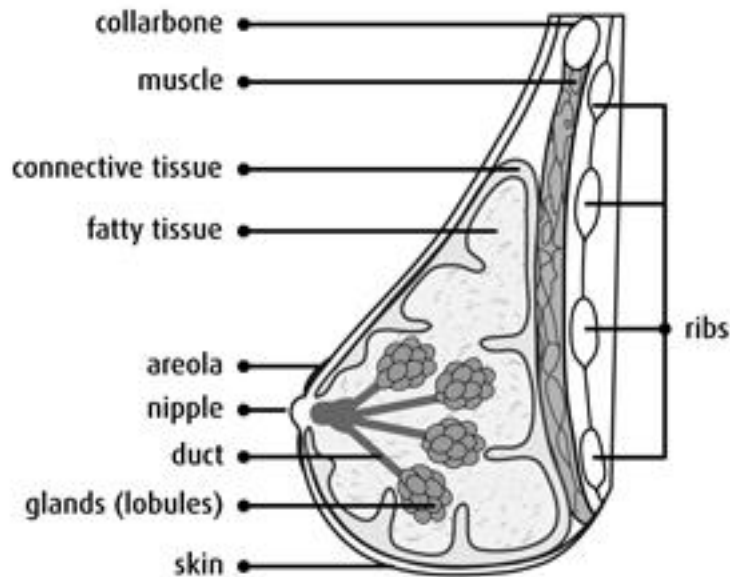
Factors that increase the chances of developing breast cancer are divided into non-modifiable and modifiable risk factors¹³. Non-modifiable risk factors are gender, age, personal history of cancer, family cancer history, early menstruation, late menopause, dense breast tissue, and non-cancerous breast conditions such as a proliferative condition¹³. Modifiable risk factors are excess weight, inactivity, alcohol, smoking, exposure to synthetic hormones found in oral contraceptives, fertility treatments, hormone replacement therapies, pregnancy, breastfeeding and radiation exposure to the chest, during radiation therapy, before the age of 30¹³.

3.1.3 Breast cancer progression

There are two major categories of early breast cancer, *in situ* and invasive¹⁴. *In situ* is cancer that has not spread and remains confined to a region such as ductal carcinoma *in-situ* (DCIS), which is confined to the milk ducts, and lobular carcinoma *in situ* (LCIS), which is confined to the milk producing glands (Figure 1). Breast cancer is considered invasive when it spreads to surrounding breast tissue¹⁴. Infiltrating ductal carcinoma (IDC), the most common type of invasive breast

cancer, occurs when cancer spreads beyond the milk ducts and into surrounding breast tissue¹⁴. Once IDC spreads beyond the ducts, it can metastasize to other parts of the body¹⁴.

Figure 1: Breast Anatomy



Source: Canadian Cancer Society¹⁵

3.1.4 Diagnosing early invasive breast cancer

The first sign of breast cancer is usually a painless lump in the breast or armpit that is usually discovered during a personal or clinical physical exam¹⁶. It may also be discovered after a routine screening mammogram¹⁶. Other signs and symptoms may include changes in breast size and shape, dimpling or puckering of the skin, redness, swelling, increased warmth, inverted nipple and nipple crusting or scaling¹⁶. If breast cancer is suspected, the patient will undergo a diagnostic mammogram which involves detailed imaging of the abnormal area¹⁷. Then, a biopsy is performed for a definitive diagnosis of breast cancer¹⁷. Cells removed during a biopsy

are assessed using a microscope to determine if they are cancerous¹⁷. If cancerous cells are found, the biopsy sample is sent for laboratory analysis to stage and grade the cancer¹⁷.

3.1.5 Staging and grading of invasive breast cancer

Once a diagnosis of breast cancer is made, the cancer is then staged and graded (Table 1 and Table 2). Staging is based on tumour size and whether or not the cancer has spread to the lymph nodes and surrounding tissue (LN+ if cancer has spread to lymph nodes or LN- if it has not spread)¹⁸. Cancer cells are graded by comparing their physical changes and speed of growth to normal cells¹⁸.

Table 1: Staging of Breast Cancer

Stage	Description
0	There are two kinds of stage 0 breast cancer:
	1. Ductal carcinoma <i>in situ</i> (DCIS): Abnormal cells are in the lining of a milk duct and have not spread outside the duct
	2. Lobular carcinoma <i>in situ</i> (LCIS): Abnormal cells are in the lining of a lobule
1	Tumour is 2 cm or smaller and the cancer has not spread outside the breast
2	Tumour is 2 to 5 cm, or cancer has spread to the lymph nodes, or both
3	Cancer has spread to the lymph nodes and may have spread to nearby tissues such as the muscle or skin
4	Cancer has spread to distant parts of the body

Source: Canadian Cancer Society¹⁸

Table 2: Grading of Breast Cancer

Grade	Description
1	Low grade – slow growing, less likely to spread
2	Moderate grade
3	High grade – tend to grow quickly, more likely to spread

Source: Canadian Cancer Society¹⁸

3.1.6 Treatment for invasive breast cancer

There are several treatment options for patients once they have received a breast cancer diagnosis. The most common primary treatment for early invasive breast cancer is surgery, followed by adjuvant therapies such as radiation therapy, chemotherapy, hormone therapy, and biological therapy¹⁹. Different types of breast cancer respond differently to the various types of adjuvant therapies.

High doses of radiation are used to destroy cancer cells¹⁹. The treatments are administered daily for several weeks and designed to continuously damage cancer cells and limit their ability to repair themselves¹⁹. Radiation therapy in patients with early invasive breast cancer is recommended if the patient has undergone a lumpectomy and the tumour removed was smaller than 4 cm, isolated to one site, and had clear margins²⁰. The treatment also damages normal cells leading to side effects such as tiredness, soreness in the radiated region, breast swelling, and changes in skin colour¹⁹. The side effects usually diminish with time after treatment¹⁹.

Chemotherapy is the use of pharmaceuticals to impede or stop the growth of cancer and prevent it from metastasizing¹⁹. The drugs are slowly administered intravenously, or orally, in a hospital setting^{19;21}. Treatments are usually given in cycles of two to three weeks followed by a recovery period and can last a total of three to six months^{19;21}. Chemotherapy can also damage normal cells leading to side effects such as nausea, vomiting, tiredness, mouth sores, increased risk of infection, loss of fertility, and hair loss^{19;22}. The side effects usually diminish with time after treatment¹⁹.

Hormone therapy blocks the receptor sites on hormone-receptor-positive cancer cells. Hormone therapy, often Tamoxifen, in this patient group is used to reduce the risk of cancer returning¹⁹. Hormone therapy is usually administered over a period of five years²³. The side effects of hormone therapy are drug specific and can include hot flashes, vaginal dryness, weight gain, early menopause, loss of libido, and/or muscle aches¹⁹. These side effects also usually diminish with time after treatment¹⁹.

Biological therapy works with the patient's immune system to limit the growth and spread of cancer cells¹⁹. The most common type of biological therapy used in women with early invasive breast cancer is trastuzumab (sold under the name Herceptin)¹⁹. Trastuzumab is only used in women with invasive breast cancers and who are HER2+. The medication works by blocking the HER2 protein in an effort to inhibit cancer cell growth¹⁹. Trastuzumab can be administered simultaneously or after chemotherapy¹⁹. Biological therapy is administered over a period of a year²⁴. The side effects of biological therapy are fever, chills, nausea, diarrhea, fatigue, headache, rash, and/or pain at the injection site¹⁹.

3.1.7 Technologies under assessment

Several tests have been developed to improve early invasive breast cancer patient triage for adjuvant therapies. There are 3 categories of tests: gene expression profiling (GEP), expanded immunohistochemistry (IHC) or protein expression, and tests that use pathologic parameters such as tumour size, grade, and lymph node status²⁵. The tests are designed to identify patients who will most benefit from chemotherapy and predict their risk of recurrence²⁵.

3.1.7.1 Gene Expression Profiling and Oncotype DX

GEP assesses the composition of messenger ribonucleic acid (mRNA) populations to inform cancer prognosis and treatment²⁶. The type and number of RNA transcripts (an RNA molecule with a transcribed DNA sequence) provide information on the genes producing them²⁶. The number of mRNA transcripts produced by a specific gene is a measure of the gene's expression²⁶. Eventually, mRNA molecules are translated into proteins; therefore, changes in mRNA populations are related to changes in a cell's protein composition²⁶. These changes at the cellular level alter the properties and functions of tissues in the body²⁶.

Oncotype DX (produced by Genomic Health) assesses the expression of 21-genes in breast cancer tissue using a real-time reverse transcription polymerase chain reaction assay²⁵. Oncotype DX provides information on ER, PgR, and HER2 status²⁵. The test predicts the likelihood of recurrence in women with early invasive (stage I and II), ER+, and LN± breast cancer who have been treated with tamoxifen²⁵. The test provides a breast cancer recurrence score (RS) and risk category (low $RS \leq 18$; intermediate $19 < RS < 30$; or high $RS > 31$)²⁵. However, there are concerns about the value-added merit of this testing as some reports find that the Oncotype DX will report over 40% of ER+ patients as “indeterminate”¹⁰. In addition, the genetic material used for the assay derives from a tissue sample that contains both tumour and non-tumour cells. As the relative proportion of non-tumour cell “contamination” increases, Oncotype DX displays a random pattern of mis-classification¹¹. This has raised questions about the accuracy of this testing in a given patient⁵.

3.1.7.2 Immunohistochemistry of four proteins

IHC is a staining process applied to fresh or frozen biopsy tissue²⁷. The IHC4 test is used to identify the presence and quantity of 4 key proteins on the surface of cancer cells: ER, PgR, HER2, and Ki-67 (a protein that increases in cells before cell division)^{25;28}. The IHC4 test for hormones can be reported in several different ways depending on the lab: a percentage of cells stained positive out of 100; a score between 0 (no receptors) and 3 (a large number of receptors); or an Allred score between 0 (no receptors) and 8 (a large number of receptors that are easily identifiable)²⁷. An algorithm is used to calculate a risk score for distant recurrence. The algorithm combines information gleaned from ER, PgR, HER2, and Ki-67 tests with clinicopathological variables to calculate a composite risk score or IHC4+C²⁵. IHC4+C provides a prediction of the 9 year residual risk of recurrence in postmenopausal women who are LN-, ER+, and have undergone 5 years of adjuvant treatment²⁹. The score is given as low (0%-10%), intermediate (>10%-20%) or high (>20%) risk of recurrence²⁹.

3.1.7.3 Adjuvant! Online

Adjuvant! Online (Adjuvant! Inc.) is a computer program designed to estimate the benefits of adjuvant hormone therapy and chemotherapy after surgery³⁰. The program aids clinicians in estimating the 10 year survival probability and/or negative outcomes without adjuvant therapy, risk reduction with therapy, and the risk of side effects with therapy^{30;31}. The risk estimates are calculated using patient information and clinico-pathological tumour features such as tumour stage, tumour grade, and LN status³⁰. The test's parameters are based on Early Breast Cancer Trialists' Collaborative Group meta-analyses on the efficacy of various therapy options and do not include HER2, Ki-67, or the benefits of trastuzumab³²⁻³⁶.

3.1.7.4 Clinico-pathological features (CPF)

Clinico-pathological features include tumour size, grade, hormone receptor status, spread to lymph nodes, and whether the cancer has metastasized to other organs. Often, these features, along with the patient's individual characteristics and risk profile are used to assess the severity of the cancer and the probability of recurrence ¹⁸.

4 SAFETY AND EFFICACY OF ONCOTYPE DX IN COMPARISON TO STANDARD CLINICAL PRACTICE

4.1 Research Objective

- To determine the safety and effectiveness/efficacy of Oncotype DX as a decision support tool for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer.

4.2 Methods

A systematic review was conducted to gather evidence on the clinical effectiveness of Oncotype DX as a means of guiding the use of adjuvant chemotherapy in early breast cancer patients. The review built upon a previous clinical review conducted by the National Institute of Health and Clinical Excellence (NICE) in 2011. Given the quality and comprehensive nature of the NICE assessment, the current report incorporates the evidence from the NICE report replicating the literature search to update the evidence. NICE considered all evidence relating to 9 different GEP tests; the current review is limited to Oncotype DX and Immunohistochemistry (IHC4), compared to Adjuvant! Online (AOL) or clinico-pathological features (CPF) thus the NICE literature search was restricted when replicated. All papers identified in the NICE assessment were screened at full text according to this restricted criterion before inclusion in the final analysis, together with those papers identified in the updated review.

4.2.1 Identification of studies

Relevant studies were identified by searching the following electronic databases:

- MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE) 1946 to December 2012
- EMBASE 1974 to December 2012
- CINAHL Plus with full text 1982 to December 2012
- Cochrane Central Register of Controlled Trials December 2012
- Cochrane Database of Systematic Reviews 2005 to December 2012
- NHS Database of Abstracts of Reviews of effectiveness (DARE) 4th Quarter 2012
- Health Technology Assessment Database 4th Quarter 2012
- NHS Economic Evaluation Database (EED) 4th Quarter 2012
- Web of Science (WOS) December 2012
- BIOSIS Previews 1980 to December 2012

The search strategies adopted were formulated by adapting the MEDLINE example search strategy referenced in the NICE report³⁷. A total of four strategies were applied (see Appendix A): (i) the MEDLINE search strategy (also used for DARE, EED and HTA databases); (ii) the EMBASE search strategy; (iii) the WOS search strategy (also used for BIOSIS); and (iv) the CINAHL search strategy. Each involved conducting a Boolean search combining MeSH (medical subject heading) terms and title/abstract terms relating to the condition (breast cancer) and the intervention (nine GEP and expanded IHC tests). For example, the search strategy adopted for MEDLINE consists of first identifying those reports relating to the condition using the following searches:

1. Explode MeSH terms “breast neoplasms” “mammary neoplasms” and “neoplasms, ductal, lobular and medullary”
2. Combine MeSH terms “breast” and “neoplasms”
3. Combine title/abstract terms relating to breast (“breast” and “mammar”) with those relating to cancer (“neoplasm”, “carcinoma” etc.) using the 5-word distance proximity operator (“adj5”)

The searches were subsequently combined using the Boolean term “or” to generate a set containing all citations. All searches were restricted by date of publication (post January 2011). An overlap in dates was used to ensure that any reports published before May 2011 (NICE date of search) but not yet indexed in the system (and therefore missed by the NICE search) would be captured. Searches were not limited by publication type or language.

4.2.2 Inclusion criteria

The abstracts retrieved were screened in duplicate. Abstracts were included for full-text review if they reported original data on invasive early breast cancer adults and reported on the efficacy of Oncotype DX or IHC4 for breast cancer. All abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was conducted using broad criteria to ensure that all relevant literature was captured.

Full text review was completed in duplicate. Studies were included if they met all the inclusion criteria presented in Table 3. Studies were excluded if any one of the exclusion criteria were met.

Agreement between reviewers' selection of papers at full text was assessed using the Kappa statistic; a measure of agreement above and beyond that expected by chance alone³⁸.

Table 3: Inclusion/Exclusion Criteria for the Clinical Systematic Review

Inclusion Criteria	Exclusion Criteria
Population: Invasive early breast cancer patients; Adults (age ≥ 18 years); post-surgical, adjuvant chemotherapy setting	Not invasive early breast cancer Not adult population Not original data
Intervention: Oncotype DX or IHC4	Not Oncotype DX or IHC4 technology
Comparator: Adjuvant! Online or clinicopathological features	Not appropriate comparator Animal models
Outcomes (at least one): Use of chemotherapy as a treatment option Change in treatment Confidence in treatment decisions Risk of 10-year distant cancer recurrence Disease-free progression or survival Overall survival	Preclinical and biological studies Studies applied only to breast cancer biology Studies reported only in abstract or as poster presentations
Study Design: Observational, Controlled clinical trials, Randomized controlled trials Post January 2011 publication date	

4.2.3 Data Abstraction

Data from the included studies were extracted in duplicate using a standard data abstraction form (Appendix B). Discrepancies were resolved through consensus and discussion. Patient characteristics, study design, procedure information, outcomes, and adverse events were extracted from each included study. Quality of non-randomized studies was assessed using the Newcastle Ottawa Scale (Appendix C). The Newcastle Ottawa Scale categorizes studies into low quality (scores of <7), medium quality (scores of 7-8) and high quality (scores of 9) based on 8 questions assessing study design, bias and outcome assessment³⁹.

4.2.4 Statistical Analysis

Using a random-effects model, meta-analysis was conducted on four outcomes. The random effects model assumes a different underlying effect for each study, allowing for between-study variation in the calculation⁴⁰. A priori it was anticipated that most studies would be observational rather than randomized in design, and therefore the random effects model was most appropriate since it allows for between-study variance⁴⁰. All analyses were completed in STATA (STATA/IC 12.0).

4.3 Results for Technology Effects and Effectiveness (T)

Summary of Effects and Effectiveness: Based on 2 ad hoc retrospective analyses of RCTs in each of LN+ and LN- population, the survival difference between those treated with chemotherapy and those treated with hormones is greater in those with a high risk Oncotype DX score than those with a low risk Oncotype DX score. Based on 10 observational studies of low to medium quality, Oncotype DX results lead to a change in adjuvant chemotherapy decision in 32% (95% CI : 24%-40%) of cases. There was no evidence assessing the use of ICH4 and its impact on chemotherapy use.

4.3.1 Health Canada Licensing

Oncotype DX is a reverse transcription polymerase chain reaction test which is considered a routine laboratory service, therefore, it does not require Health Canada licensing⁴¹.

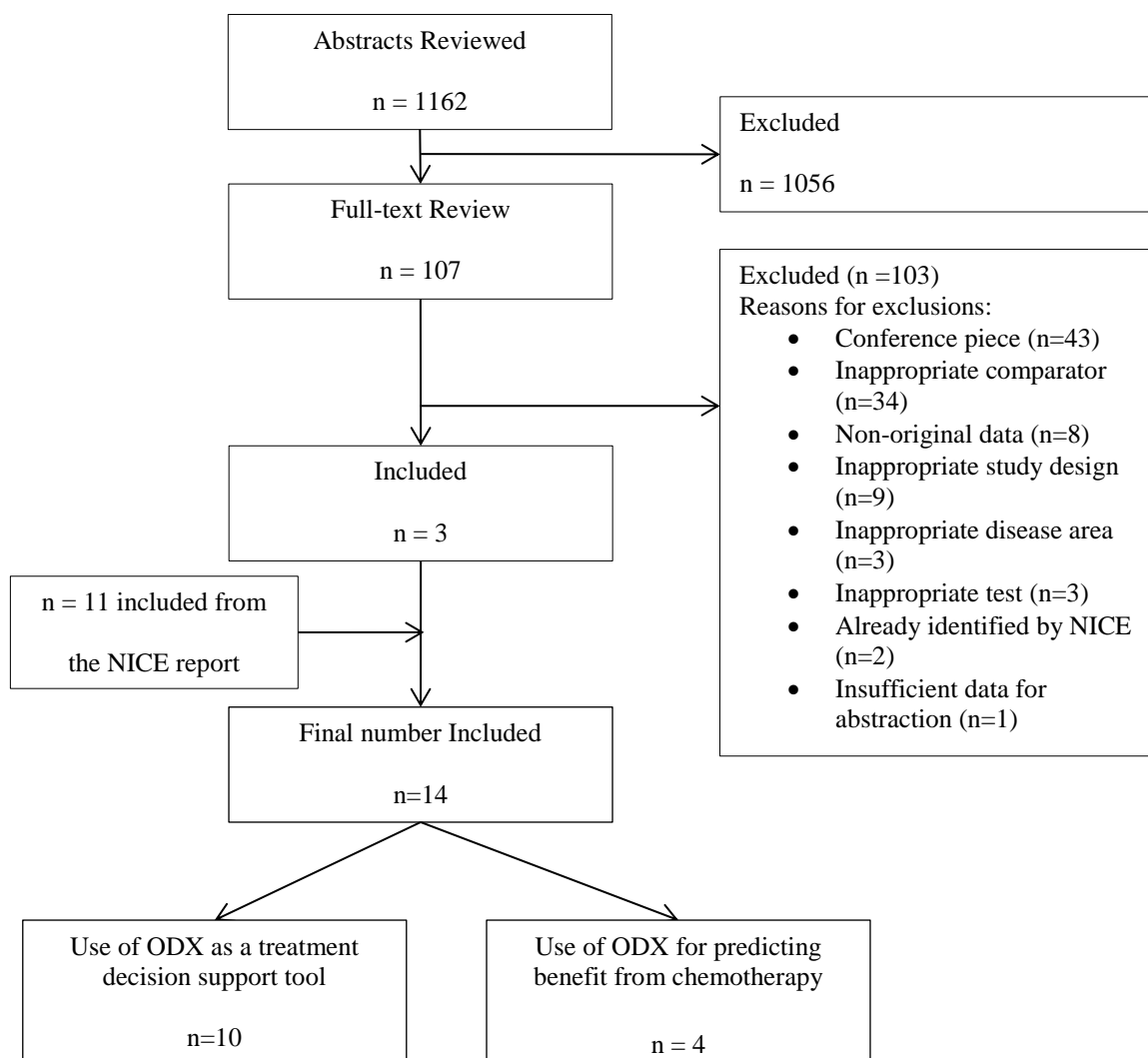
4.3.2 Effectiveness/Efficacy

4.3.2.1 Identification of studies

A total of 1162 citations were identified from the literature search. Of those, 1056 were excluded in the abstract review and 106 were included for full-text analysis. In full-text review, 103 studies were excluded; the remaining 3 papers were included in the final analysis. In addition, 11

articles were identified for inclusion from the NICE review. Together with the identified report from the current search, a total of 14 studies were included in the final analysis (see Figure 2).

Figure 2: Flow diagram for studies included in clinical effectiveness review



4.3.2.2 Summary of evidence on the prognostic utility of Oncotype DX to predict survival

The NICE report outlines the evidence assessing the ability of Oncotype DX to predict survival²⁵. In LN- patients, based on 5 studies of medium quality (3 ad-hoc retrospective analyses of large RCTs⁴²⁻⁴⁴, 2 small retrospective cohorts^{45;46}), Oncotype DX appears to be an independent predictor of survival, disease-free survival and risk of distant recurrence.

4.3.2.3 Clinical evidence on the prognostic utility of Oncotype DX to predict chemotherapy benefit in lymph node positive patients

Two studies were identified that assessed the ability of Oncotype DX to predict chemotherapy benefit in LN+ patients (Table 4). Both studies are ad-hoc retrospective analysis of RCTs assessing the benefit of chemotherapy. The first study uses a subset of data from a RCT conducted by the South Western Oncology Group analyzing 367 specimens from post-menopausal ER+, LN+ patients⁴⁷. The study compared tamoxifen to chemotherapy followed by tamoxifen. Women were followed for 5 years to assess for survival and disease-free survival. Among women subsequently classified as low risk using the Oncotype DX risk score, there was no survival difference observed between those treated with chemotherapy and those treated with tamoxifen. However, among women subsequently classified as high risk, there is an association between treatment with chemotherapy and survival at 5 years.

The second study, also an ad-hoc retrospective analysis of a RCT, used a subset of data from the Eastern Cooperative Oncology Group (ECOG)⁴⁸. Study subjects were treated with one of the two adjuvant chemotherapy regimens. Neither Oncotype DX nor tumour biologic subtype had a significant association with 10-year rates of local recurrence ($P > 0.12$).

Table 4: Overview of studies included for prognostic utility of Oncotype DX to predict chemotherapy benefit among lymph node positive (LN+) patients

Author (Year) Country	Study design	Study population	Comparators	Main findings	Limitations	Source of funding
Albain ⁴⁷ 2010 USA	Ad-hoc retrospective analysis of RCT (SWOG-8814)	Study population was a subset (n=367) of a RCT of postmenopausal women who were stratified by number of positive nodes, PR status and interval from surgery. The tumour sizes ranged from <2 cm to >5 cm. Disease-free survival and overall survival were the primary outcomes.	Tamoxifen Cyclophosphamide and fluorouracil, followed by Tamoxifen (CAF-T)	Oncotype-DX risk scores were predictive of benefit from chemotherapy vs. Tamoxifen, especially among patients in high risk category (HR = 0.59, 95% CI 0.35-1.01). The predictive benefit was primarily seen in the first 5 years, with little added gain in the next 5 years.	Ad hoc retrospective analysis of a RCT; patients were randomized to treatment and followed to assess for outcomes then Oncotype DX risk scores were calculated and the association between treatment, survival and risk score is established retrospectively. This study design is associated with large bias. Study results have large variance, as seen in the large confidence intervals.	National Cancer Institute, Genomic Health Inc.
Solin ⁴⁸ 2012 USA	Ad-hoc retrospective analysis of RCT (ECOG-E-2197)	Study population was a subset (n=388) of a larger RCT of women with 1-3 affected lymph nodes, or no affected lymph nodes but a tumour size >1.0 cm. Local recurrence or local regional recurrence was the main outcomes of interest.	Doxorubicin plus cyclophosphamide Doxorubicin plus docetaxel	Neither biologic subtype nor 21 gene recurrence scores were predictive of local or local regional recurrence	Ad hoc retrospective analysis of a RCT; patients were randomized to treatment and followed to assess for outcomes then Oncotype DX risk scores were calculated and the association between treatment, survival and risk score is established retrospectively. This study design is associated with large bias.	Public Health Service Grants, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Sanofi Aventis, Breast Cancer Research Foundation

4.3.2.4 Clinical evidence on the prognostic utility of Oncotype DX to predict chemotherapy benefit in lymph node negative patients

Two studies were identified that assessed the ability of Oncotype DX to predict chemotherapy benefit in LN- patients (Table 5). Paik et al⁴⁹ reported an ad hoc retrospective analysis of a RCT comparing tamoxifen to chemotherapy in addition to tamoxifen. An association was reported between treatment with chemotherapy and Oncotype DX risk score; those treated with chemotherapy and then subsequently classified as high risk based on their Oncotype DX score had improved distant recurrence-free survival compared to those treated with tamoxifen alone. The difference in observed benefit was less clear in low to intermediate Oncotype DX risk categories.

A 2011 study by Tang⁵⁰ also reported an ad hoc retrospective analysis of a RCT comparing tamoxifen to chemotherapy in addition to tamoxifen. The study reported a significant predictive ability of chemotherapy benefit among Oncotype DX tested patients ($p=0.031$). The study also compared the relative benefits of Oncotype DX and Adjuvant! Online and concluded that Adjuvant! Online! was marginally better at predicting overall survival.

Table 5: Overview of studies included for prognostic utility of ODX to predict chemotherapy benefit among lymph node negative (LN-) patients

Author (Year) Country	Study design	Study population	Comparators	Main findings	Limitations	Source of funding
Paik 2006	Ad-hoc retrospective analysis of RCT (NSABP B- 20)	Study population was a subset (n=651) of a RCT of LN -patients with tumour blocks available for Oncotype DX testing Primary outcome was distant recurrence-free survival.	Tamoxifen Tamoxifen plus chemotherapy	A significant improvement in distant- recurrence free survival was reported in the high risk group receiving Tamoxifen plus chemotherapy (as compared to the group with Tamoxifen alone). Chemotherapy benefit in low and intermediate risk groups was not as clear.	Ad hoc retrospective analysis of a RCT; patients were randomized to treatment and followed to assess for outcomes then Oncotype DX risk scores were calculated and the association between treatment, survival and risk score is established retrospectively. This study design is associated with large bias.	Public Health Service Grants, National Cancer Institute, national Institutes of Health, and Genomic Inc.
Tang 2011	Ad-hoc retrospective analysis of RCT (NSABP-B- 14 and NSABP B- 20)	Study population was a subset (n=651) of a RCT of LN -patients with tumour blocks available for Oncotype DX testing Predictive ability of Adjuvant! Online was obtained from a separate subset of 1952 patients. Primary outcomes were Distant recurrence-free survival, overall survival, disease free survival and breast cancer specific mortality	Tamoxifen Tamoxifen plus chemotherapy	Oncotype DX risk scores were predictive of chemotherapy benefit, expressed in distant-recurrence free survival, overall survival, and disease free survival. The benefit was more pronounced in higher risk score patients. Significant predictive ability was observed for Adjuvant! Online in terms of overall survival, but not distant recurrence free survival, or disease free survival	Ad hoc retrospective analysis of a RCT; patients were randomized to treatment and followed to assess for outcomes then Oncotype DX risk scores were calculated and the association between treatment, survival and risk score is established retrospectively. This study design is associated with large bias. Cut offs for Adjuvant! Online risk categories were chosen to match Oncotype DX risk scores, which may have led to some misallocation of patients.	Public Health Service Grants, National Cancer Institute, Department of Health and Human Services

4.3.2.5 Clinical evidence on utility of Oncotype DX as a decision support tool

All included studies on the use of Oncotype DX as a decision support tool were non-randomized studies published between 2009 and 2012 (Table 6). Sample size varied from 29 to 7375, and the majority of included patients were women with LN-, ER+, HER2- early stage breast cancer. Nine studies were conducted in the United States⁵¹⁻⁵³ and one were conducted in Israel^{54;55}. None of the studies were conducted in Canada. All studies recruited patients by consecutive retrospective selection or prospective enrollment. In general follow-up was short or not reported and the primary outcome was recommendation/ treatment informed by Oncotype DX. Included studies had either clinic-pathological features or Adjuvant! Online as a comparator for Oncotype DX. In general the articles stated that Adjuvant! Online was used alongside traditional clinico-pathological data (and other tools such as the Nottingham Prognostic Index (NPI)) to produce pre-Oncotype DX treatment recommendations.

Table 6: Overview of studies included in effectiveness of ODX as a treatment decision support tool

Author (Year) Country	Study Design	Setting	Recruitment Dates	No. of patients (exclusions)	% Male	Age (years) Mean/ Median	% LN-	% ER+	Tumour size (cm) Mean/Median	% HER2-	Stage	% Grade	AOL risk	Source of funding
Oratz ⁵⁶ 2007 USA	Retrospective Study – medical records	Rocky Mountain Cancer Centers	January 2004 - April 2005	72 (4) Subset that used Oncotype DX: 68	1.5	NR/54 Range: 35- 77	100	100	1.2/NR Range: NR	NR	Early Stage (negative stage I or II)	I: 44 II: 35 III: 21	Low risk 47% Intermediate risk 32% High risk 21%	NR.
Asad ⁵⁷ 2008 USA	Retrospective Study - medical records	St. Luke's– Roosevelt Hospital and Beth Israel Medical Center	Feb 2006- Jan 2008	85	0	54/NR Range: NR	100	100	1.5/NR Range: NR	94	Early stage	Well: 4 Moderate: 75 Poorly: 17 Unknown: 4	NR	NR
Rayhanabad ⁵⁸ 2008 USA	Retrospective study - medical records	Southern California Kaiser Permanente	Jan – Dec 2006	61 (3) Subset that used Oncotype DX: 58	0	54/NR Range: 26- 78	100	100	NR	NR	NR	NR	NR	NR
Geffen ⁵⁴ 2009 Israel	Prospective Cohort - tumour samples	Soroka University medical Centre	Nov. 2002- Dec. 2006	328 Subset that used Oncotype DX: 25	0.6 Subset: NR	NR/ 59 Range: 28-87 Subset: NR	100	88	All ≤2 cm	93.6	Stage I	Elston & Ellis Low: 21 Int.: 44 High: 19 Unknown: 16 Subset: NR	NR	Unfunded

Author (Year) Country	Study Design	Setting	Recruitment Dates	No. of patients (exclusions)	% Male	Age (years) Mean/ Median	% LN-	% ER+	Tumour size (cm) Mean/Median	% HER2-	Stage	% Grade	AOL risk	Source of funding
Henry ⁵⁹ 2009 USA	Prospective Cohort (tumour characteristics, Adjuvant! Online! and Oncotype risk scores collected)	National Capital Area Breast Care Center	Dec. 2004- Dec. 2006	139 (110) Subset that used Oncotype DX: 29	3.5	NR/ 51 Range: 31- 74	100	100	NR/ 1.2 Range: 0.2- 2.3	0: 10 1+: 62 2+: 28 3+: 0	NR	Nottingham Score Low: 41 Int.: 48 High: 10	Median relapse risk (range): 18% (11-45%)	NR
Lo ⁵³ 2010 USA	Prospective Cohort - (tumour samples collected)	1 community and 3 academic practices	Dec 2005- Aug. 2006	93 (4) Subset that used Oncotype DX: 89		55/ NR Range: 35- 77	100	100	1.7/ NR Range: 0.6- 3.5	93	I: 66% II: 35%	Low: 21 Int.: 65 High: 14	NR	Genomic Health Inc.
Ademuyiwa ⁵¹ 2011 USA	Retrospective Cohort –(Using medical records)	Two cancer centers	2005- 2009	276	0	54.8/55 Range: 29- 82	100	100	1.6/ 1.4 Range: 0.3- 4.5	100	Early stage	I: 38 II: 50 III: 12	10-yr mortality 1-10: 80%; 11-20: 15%; >20: 5% Median:8	Unfunded
Kama ⁶⁰ 2011 USA	Retrospective Cohort (using stored tissue samples)	Mayo Clinic	2006	31	0	NR/53 Range: 42- 82	100	100	1.4/1.2 Range: 0.6-3.6	94	Early stage	I: 29 II: 58 III:13	NR	NR
Oratz ⁶¹ 2011 USA	Retrospective Cohort (using stored tissue samples)	Genomic Health Database	April 2009 – June 2009	160	0	60/61 Range: 34- 82	100	100	NR	NR	NR	I: 62 II: 35 III: 3 Unknown: 1	NR	Genomic Health Inc.
Schneider ⁶² 2012 USA	Retrospective Cohort – (using medical records)	single community medical oncology practice	July 2005 - June 2010	89	0	NR/NR Range: NR	100	100	NR	NR	NR	I: 31 II: 56 III: 13	10-yr mortality 1-10: 44%; 11-20: 49%; >20: 7%	NR

4.3.2.6 Quality of included studies

Study quality assessment is presented in Table 7. Four of the included studies were medium quality (7 stars) and the remaining six were of low quality (5-6 stars). The most common pitfalls were: the medical oncologists who gave initial AOL- or CPF-based recommendations subsequently gave the post-Oncotype DX recommendations potentially leading to recall bias, studies failed to report how treatment recommendations were made making an assessment of reproducibility challenging, and lack of representativeness of the exposed cohort making the generalizability of the findings difficult to assess.

Table 7: Quality assessment of studies included in clinical systematic review

Author Year	Representative- ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at the start of the study	Comparability of cohorts on the basis of design or analysis	Was the follow- up long enough	Adequacy of follow- up cohorts	Number of stars
Oratz⁵⁶ 2007	1	No control group-N/A	1	1	2	1	1	7
Asad⁵⁷ 2008	1	No control group-N/A	1	1	1	1	0	5
Rayhanabad⁵⁸ 2008	1	No control group-N/A	1	1	1	1	1	6
Geffen⁶³ 2009	1	No control group-N/A	1	1	1	1	1	6
Henry⁵⁹ 2009	1	No control group-N/A	1	1	1	1	1	6
Lo⁵³ 2010	1	No control group-N/A	1	1	1	1	1	6
Ademuyiwa⁵¹ 2011	1	No control group-N/A	1	1	2	1	1	7
Kamal⁶⁰ 2011	1	No control group-N/A	1	1	2	1	1	7

Author Year	Representative- ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at the start of the study	Comparability of cohorts on the basis of design or analysis	Was the follow- up long enough	Adequacy of follow- up cohorts	Number of stars
Oratz ⁶¹ 2011	1	No control group-N/A	1	1	1	1	0	5
Schneider ⁶² 2012	1	No control group-N/A	1	1	2	1	1	7

4.3.2.7 Meta-analysis

Four outcomes were analyzed all related to change in treatment decisions. Table 8 shows the summary results for each meta-analysis. Varying outcomes were reported in each study thus a varying number of studies are included in each meta-analysis. The forest plots for each analysis are shown below (Figures 3-6). In the forest plot, each study is represented horizontally with the author and publication year listed. The individual study point estimate is represented by the dot with the horizontal line representing the 95% confidence interval of the study. The weight of each study, calculated based on sample size, carries in the pooled estimate is represented by the size of the box surrounding the point estimate. The pooled estimate is visually presented by the dotted vertical line and the diamond at the bottom of the plot.

Table 8: Meta-analysis summary results

Outcome	Studies (n)	Heterogeneity (I^2)	Pooled estimate (95% Confidence interval)	Interpretation
Total proportion of change (Figure 3)	9	86.1%	0.319 (0.238 - 0.401)	31.9% of patients experience a change in treatment recommendation using Oncotype DX in comparison to standard AOL-informed recommendations. There is a significant heterogeneity across studies.
Proportion of net change (CT to No CT) (Figure 4)	10	93.8%	0.182 (0.110 - 0.254)	Oncotype DX testing results in an 18.2% reduction in CT treatment recommendations. There is a significant heterogeneity across studies.
Change from CT to No CT as a proportion of those originally assigned to CT (Figure 5)	6	89.5%	0.423 (0.297 – 0.550)	42.3% of patients originally recommended CT move to a no CT recommendation after Oncotype DX testing. There is a significant heterogeneity across studies.
Change from No CT to CT as a proportion of those originally assigned to No CT (6)	5	83.7%	0.146 (0.068 – 0.225)	14.6% of patients originally recommended no CT move to a CT recommendation after Oncotype DX testing. There is a significant heterogeneity across studies.

CT=chemotherapy, CI= Confidence Interval

Total proportion of change in treatment recommendation

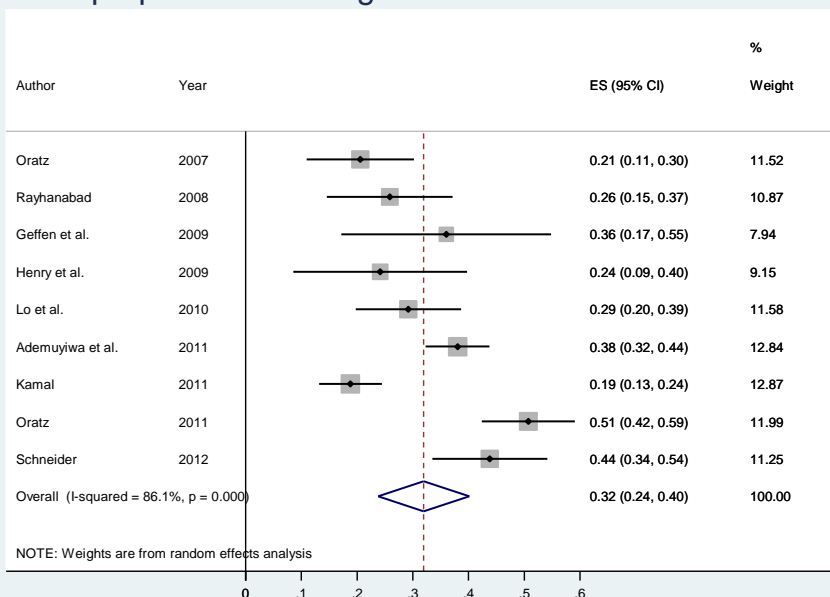


Figure 3: Total proportion of change in adjuvant chemotherapy recommendations after Oncotype DX testing

Proportion of net change in recommendation (CT to No CT)

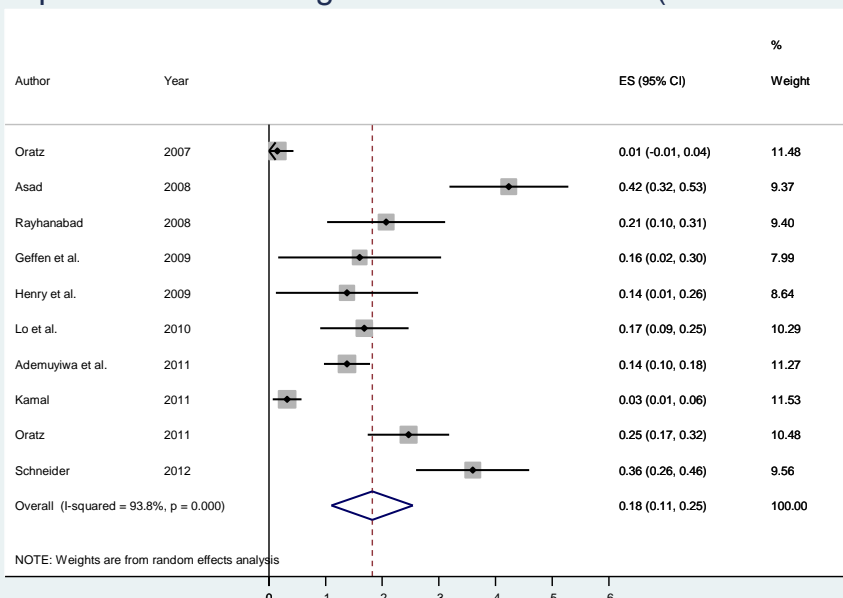


Figure 4: Proportion of net change in adjuvant chemotherapy recommendations after Oncotype DX testing

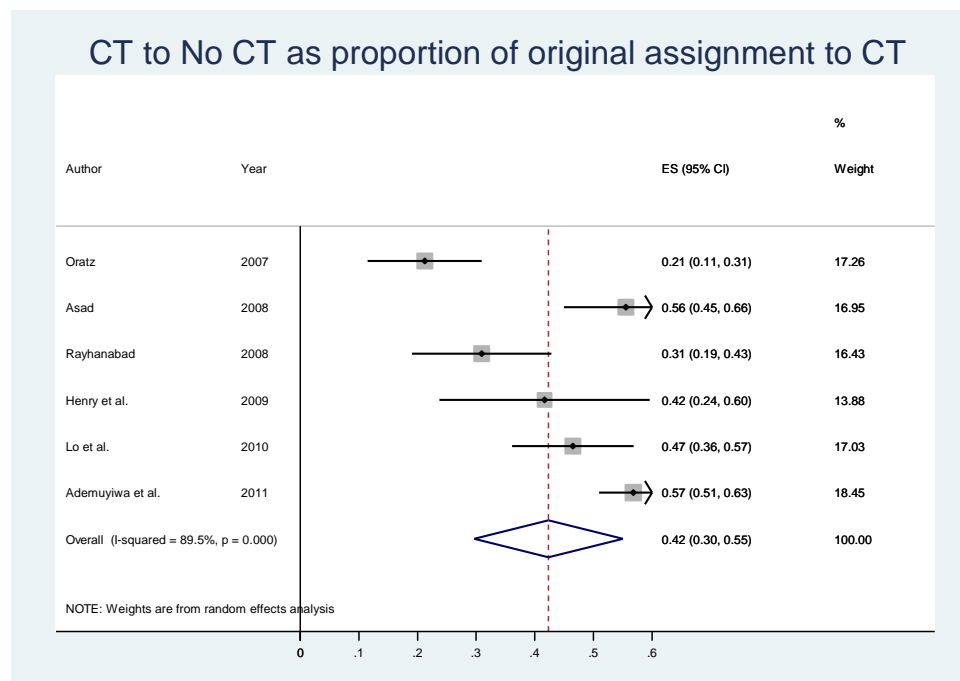


Figure 5: Change in treatment decision of chemotherapy to no chemotherapy

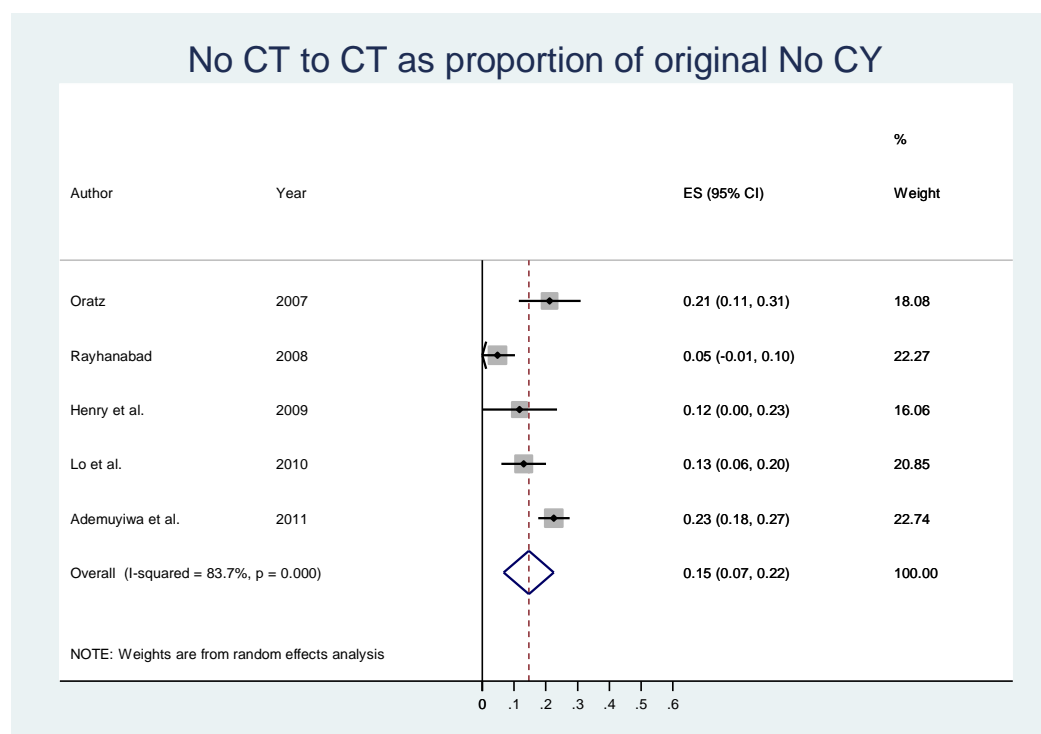


Figure 6: Change in treatment decision of no chemotherapy to chemotherapy

4.4 Discussion

The clinical systematic review identified 14 relevant articles. Of the selected studies, 10 reported the effect of Oncotype DX risk score on chemotherapy treatment decisions, and 4 reported the utility of Oncotype DX in predicting benefit from chemotherapy.

Based on 2 ad hoc retrospective analyses of RCTs in each of LN+ and LN- population, the survival difference between those treated with chemotherapy and those treated with hormones is greater in those with a high risk Oncotype DX score than those with a low risk Oncotype DX score. These studies represent limited, low quality evidence supporting the clinical utility of Oncotype DX to predict benefit from chemotherapy. In addition, this study design has a high risk of bias; 1) the studies are not powered to detect differences among risk subgroups as the subgroup analysis is not part of the original design, 2) ad-hoc analyses are likely to identify spurious relationships due to chance alone, 3) the treatment received and outcome of the women is known and may influence the Oncotype DX risk score classification and finally 4) the generalizability of the population is compromised as the ad-hoc analyses utilized a subset of the original RCT population.

All 10 studies on treatment decisions report that Oncotype DX testing results in a significant change in treatment recommendations. The pooled analysis resulted in a 31.0% change in treatment recommendations with Oncotype DX, with an overall decrease in CT recommendations of 18.2%. Of those initially recommended CT, 42.3% can be expected to have their recommendation changed to no CT; of those initially recommended no CT 14.6% can be

expected to have their recommendation changed to CT. However, significant heterogeneity exists between individual study estimates thus the pooled values must be interpreted with caution. Nonetheless, all studies reported that Oncotype DX results in a significant change to current clinical practice. Of particular interest is the fact that Oncotype DX produces an average 18.2% decrease in CT recommendations potentially saving a sizable number of patients from cost and risk intensive treatment.

Most of the included studies were conducted in the United States with one based in Israel. Therefore, the generalizability of our findings may not directly translate into the Canadian context. Nevertheless, all the reported results lie within similar ranges, and all indicate a decrease in CT recommendations, suggesting that it is the similarity between patient clinico-pathological data that is most relevant to the outcomes. All the included studies were of medium to low quality. The studies suffered from potential bias from lack of independent blind assessments, the lack of randomized studies, and the presence of significant heterogeneity.

The TAILORx trial is an ongoing RCT that aims to more accurately determine patient outcomes within various Oncotype DX risk profiles. The patients are stratified into low, intermediate and high Oncotype DX risk groups, and then assigned to hormonal therapy alone or a combination of chemotherapy and hormonal therapy. The primary objectives of the study focus on women in the intermediate risk profile (Oncotype DX risk score of 11-25) and aim to compare the disease free survival and overall survival of intermediate risk women assigned to the different treatment arms. The trial is due to complete primary outcomes in April 2014. The target recruitment number is 11,248, with patients recruited across centers in USA, Canada, Australia, and Peru.

The results are likely to have a significant influence on the extent to which Oncotype DX changes current clinical practice. The results of the trial will fill a major knowledge gap and inform the clinical utility of Oncotype DX using the reference standard study design (RCT).

5 SOCIAL IMPLICATIONS OF ONCOTYPE DX AND ITS COMPARATORS

5.1 Research question

- To determine the burden of illness, patterns of care and capacity in Alberta as it relates to Oncotype DX and other relevant comparators (e.g. IHC4) in terms of informing treatment decisions in breast cancer patients.

5.2 Methods

Key informant interviews were conducted to collect information that would inform and contextualize the policy questions. Of particular interest was an Alberta practice perspective on where Oncotype DX and IHC4 testing fit in the care pathway, the clinical utility of the test, the capacity in Alberta to offer genomic testing and the future of this kind of testing.

Two semi-structured interview guides (Appendix D) were developed to guide the key informant interviews; one for pathologists and one for oncologists. These guides evolved over the course of the interviews as questions were refined to reflect what had been learned through the previous interviews. All of the interviews were audiotaped with the consent of the interview participants and detailed notes were taken; some of the interviews were also transcribed. Individual interviews were confidential with no participants identified in the report.

Using constant comparative analysis, transcripts and notes were reviewed to identify key themes. Data management and analysis was facilitated through the use of mind-mapping software that supports the identification of key themes, and understanding the relationships between them.

5.3 Results

Summary of System capacity and care patterns in Alberta: Oncotype DX, as it is proprietary, must be outsourced. Provincial laboratory services are equipped to conduct IHC4 testing in Alberta. However, there is a lack of standardization in communication and interpretation of IHC4 test results. Oncotype DX results are easier to interpret, but the test causes significant economic burden for the patient. At least two pilot studies are ongoing in Alberta which may lead to a common understanding on interpretation and utilization of ICH4 test results.

5.3.1 Patterns of care in Alberta

5.3.1.1 Current standard of care in Alberta

Telephone interviews were conducted with eleven key informants between November 2012 and January 2013, ranging in length from 45 - 105 minutes. The eleven interview participants included six members of the Oncotype DX Expert Advisory Group (EAG) and five individuals identified through a snowball sampling method. The participants included individuals working in Edmonton, Calgary and Lethbridge. They represented a range of health care providers and administrators including pathologists, oncologists, and senior managers.

Based on interviews with oncologists, the current standard of care in Alberta is to use clinico-pathological features (i.e., age, tumour size, tumour grade, receptor status, nodal involvement) to determine risk of recurrence and the subsequent need for adjuvant chemotherapy for this subgroup of patients. Several oncologists stated they may use Adjuvant! Online to generate a risk of recurrence score based on these clinico-pathological criteria and that the results were presented in a helpful way to share with patients.

Currently, IHC3 is routinely ordered for breast cancer patients. The fourth protein in the IHC4 panel, Ki67, is rarely, if ever, ordered by oncologists in Southern Alberta. Oncologists in

Northern Alberta may be ordering it more frequently. Oncotype DX is not currently being ordered in Alberta because the test is not publicly funded; it was felt that the cost of the test is prohibitive to pay out of pocket and the test is rarely covered by private health insurance plans. It was noted that the “out of country funding” policy cannot be used to request public payment for Oncotype DX testing as in Alberta out-of-country funding will pay for consultation but not for pathological testing.

There are ongoing discussions in provincial breast tumor group meetings about Oncotype DX testing and whether patients should be made aware of genetic testing for adjuvant treatment decisions and the kind of information it provides. Some oncologists are discussing Oncotype DX with their patients and others are not. Some oncologists feel “...*that we are at a tipping point now where we have enough evidence that if you don’t do this test (or something like it), you had better be prepared to justify why you are recommending adjunct chemo. There are negative long term effects from chemo (e.g., leukemia, cardiac problems, in addition to the short term side-effects), so you do have to be sure there is likely to be a real benefit to patients before recommending it.*”

5.3.2 Current clinical practice guidelines

There are Alberta clinical practice guidelines for breast cancer. The guidelines do not include guidance around the use of Oncotype DX testing due to the funding situation. There is also no reference to the use of Ki67 test results in the guidelines. The provincial breast tumor group develops these guidelines with members of both the North and South tumor groups participating. The process of developing Alberta guidelines involves careful consideration of other guidelines

developed in North America, with the goal of ensuring that practice in Alberta fits with best and standard practice in other centers. Guidelines that are most commonly referred to include: the American Society of Clinical Oncology (ASCO); Cancer Care Ontario; the B.C cancer agency; and the European Society of Medical Oncology (ESMO). The Alberta guidelines are well known and routinely followed by the oncologists who formed our key informant group, and in their opinion, by all Alberta oncologists.

Despite the guidelines, the consensus of the key informants interviewed is that despite the shortcomings, Oncotype DX is the current standard of practice in North America, although this may change as results from ongoing research projects on gene expression profiling and comparable technologies become available.

5.3.3 Capacity of system to provide care

5.3.3.1 Current practice with respect to Oncotype DX testing

Oncotype DX is not currently being funded publicly in Alberta. Patients do not have access to this testing unless they are willing to pay out of pocket (approximately \$4175). There is a small feasibility study currently underway at the Cross Cancer Institute in Edmonton being done in partnership with Oncotype DX. Through this study, 30 patients will get access to the test with the test cost covered by Oncotype DX.

If Oncotype DX were funded in Alberta, all patients for whom the test would be of value should have the test discussed as an option. Oncologists felt that there would be no inequity regarding

access to the test as all oncologists in Alberta follow the same clinical practice guidelines, including those practicing at associate cancer centers.

One of the pathologists we interviewed was skeptical about the utility of Oncotype DX for all patients who fall in the intermediate risk category. Based on the cases that this person had observed, Oncotype DX might have only marginal added value for a very select group of patients. This individual further elaborated that with the availability of centralized lab services as is the case in Alberta, Oncotype DX may be of limited utility.

5.3.3.2 Provision of IHC4 testing in Alberta

Key informants indicate that the major barriers to the use of Ki67 and IHC4 testing in Alberta include the lack of standardization of the test and the challenges in communicating the test results to oncologists. Oncologists rarely order the Ki67 test in Alberta for breast cancer patients, due to the subjectivity in interpretation of the results. Currently in Southern Alberta, only a small minority of breast cancer patients (i.e., less than 1%) would get a Ki67 test done, which translates into approximately 20-30 tests/year for breast cancer out of a total of about 6000 Ki67 tests for various types of cancer. There appear to be differences between Edmonton and Calgary with respect to how many Ki67 tests are ordered for breast tumors. In Edmonton, approximately two-thirds of the patients are having Ki67 ordered up front.

The communication of test results to oncologists and patients, in a way that supports treatment decision-making, was described by both oncologists and pathologists as a major barrier to Ki67 testing. Ki67 test results are presented in percentage points and there is a lack of standardized

guidelines for interpretation. Key informants also mentioned that the test is not validated or standardized. At this time, pathologists in Alberta are not combining the Ki67 score into an IHC4 score for oncologists. Members of the breast cancer pathology interest group are working on how this marker Ki67 (and others) is being interpreted and scored in an attempt to standardize the test analysis and interpretation. An example of a Ki67 report is included in Appendix E. The first page of an Oncotype DX report is included in Appendix F, for comparison purposes.

IHC3 (i.e., ER, PR and HER2 status) testing is routinely done on breast tumours, with Ki67 testing only being done when requested by an oncologist. This testing is only being done in specialized labs based in Edmonton and Calgary. Specialized testing in Edmonton is done primarily through the University of Alberta and the Cross Cancer Institute. All testing in Calgary is done through Calgary Laboratory Services (i.e., both community and specialty testing). Although routine immunohistochemistry tests would be done in Red Deer and in Northern Alberta, IHC and biomarker testing done to discern treatment options and prognosis (i.e., Ki67, ER, PR or HER2's) is only done at specialty labs in Calgary and Edmonton.

5.3.3.3 Current studies underway in Alberta comparing IHC4 and Oncotype DX

Key informants described two small studies currently under development in Alberta. A Calgary study, under health research ethics review as of December 2012, will be comparing regular IHC4 and aqua system IHC4 with Oncotype DX to determine whether IHC4 can provide similar information to that provided by Oncotype DX. If this small study (n=approximately 70) shows that IHC4 done locally is comparable to Oncotype DX, then it may lend support to the

development of internal capacity for conducting and reporting IHC4 in a way that oncologists can understand and use.

The second study, underway at the Cross Cancer Institute in Edmonton, is a small feasibility pilot project being done in collaboration with Oncotype DX to assess the utility of their test. Oncologists in Calgary had an opportunity to participate in the TAILORx clinical trial which included Oncotype DX testing, whereas Edmonton oncologists have had no prior opportunity to gain any experience with it. The purpose of this pilot is to look at both physician and patient experience with Oncotype DX through a cohort of about 30 patients. This pilot began in November 2012 and should be completed in March 2013.

5.3.4 Future considerations

5.3.4.1 Potential resource requirements

If over time the challenges with the Ki67 component of the ICH4 test were overcome and it became the test of choice for clinicians there was a mix of perspectives as to how many additional resources would be required. One perspective was that two extra pathologists, one in the North and one in the South would be required, perhaps an extra support person, and potentially some more equipment (i.e., another immunestainer costing \$50,000 to \$100,000). Another perspective was that it would not cost much more money to do IHC4 in Alberta. We are already doing ER, PR and HER2, and lots of Ki67 for other cancers are already paid for as well. The issue is how much it will cost to come up with a standard interpretation of Ki67. There are mechanisms in place to ensure inter-lab concordance, and this would fit into the provincial QI program. In the end, Ki67 might cost \$100 more than the IHC3. A complete projected cost analysis would be relevant if a decision was made to increase local capacity to do more Ki67

stains. Regardless of the decision made, any recommendations for expansion would require funding. For example, the recommendation was that Oncotype DX should be funded, then a budget would be required to pay for those tests. It was noted that this budget might be challenging to determine, at least initially, as it may be challenging to determine how many tests are likely to be ordered.

5.3.4.2 Other options available to the patient population or sub-set population

Many pathologists described Oncotype DX as the “*first test out of the blocks*” in GEP for breast cancer. There is considerable research going on in this area now, so there is an expectation that there will be more options available in the near future that will provide similar information about risk of recurrence of breast cancer. The test described by a number of individuals as showing a lot of promise is the Pam50 test, which is another gene expression test that looks at the expression of 50 genes. One pathologist noted that PAM 50 is a completely different test, so it is likely more robust; it establishes biological sub-type and can begin to tailor chemotherapy treatment. Based on the research conducted, the consensus at this time seems to be that the most accurate prognostic information for determining risk of recurrence is obtained through a combination of these tests (i.e., Oncotype DX, Pam50 and ICH4); that they all have their strengths and weaknesses. Other studies and ongoing work described by the key informants are briefly described in Appendix G.

5.3.4.3 Perspectives on the future of this type of testing and implications for Alberta

This is a field where there is considerable research being done, so the number of comparators and the evidence about their effectiveness is changing quickly. This means that decisions about

the ‘best’ test to fund are going to need to be continually revisited as the evidence base evolves.

The current problems with standardization of the Ki67 test is an international phenomenon, so although there is work actively underway internationally to try and assess the reproducibility of the Ki67 test, it is an area that is still under development. There are other tests (i.e., other than Oncotype DX or Ki67) that could possibly be used in Alberta in the future. There are also studies underway looking at expanding Oncotype DX eligibility to patients who are ER- and LN+. ⁶⁴

There is recognition that the evidence base in this area is changing rapidly. Key informants noted that it is important to take into consideration the costs to patients of being treated unnecessarily; there are many short and long term side effects of chemotherapy, as well as the immediate time and energy associated with chemotherapy.

Finally, a number of key informants described the importance of taking the national and North American context into consideration when making a decision about what practice is going to be supported in Alberta. It is generally acknowledged that Oncotype DX, even with its shortcomings, is increasingly becoming the standard of care in North America. Some women do come in asking about the test, and wonder why some provinces in Canada are funding the test but Alberta is not. People realize that there is not an unlimited pot of money, but they do want equal standards across the country; otherwise it is perceived as unfair.

5.3.5 Discussion

Overall, the key informants interviewed were relieved and pleased to see that the province was tackling what they felt was an important policy question: *“Should Oncotype DX be publicly funded in Alberta?”*

The current practice in Alberta is to use classic risk of recurrence criteria to inform the decision about whether a patient is likely to benefit from adjunct chemotherapy (i.e., along with hormone therapy). There is concern, however, that using this approach results in many patients in this subgroup receiving chemotherapy who are unlikely to benefit from it. This concern, especially in light of the recent advances in genetic profiling of breast cancer patients, led to a general agreement that the status quo was not a viable option.

With respect to effectiveness and the clinical utility of Oncotype DX and Ki67/IHC4, there were varying perspectives and a marked difference in opinion between the pathologists and the oncologists. The oncologists interviewed felt that the Oncotype DX test provided valid, reliable and understandable information that they were confident in using to inform treatment decisions. They lacked trust in the results of the IHC4 test due to a lack of research done on the test and the lack of standardization. The way the tests results were communicated made them difficult to interpret, and therefore unhelpful with respect to informing treatment decision.

The pathologists felt that Oncotype DX still required more research to show how the risk of recurrence score was connected with long-term survival, with and without adjunct chemotherapy. They felt that the marketing of Oncotype DX, along with the black and white way

of presenting the results, provided a somewhat false sense of confidence. The pathologists believed that IHC4, and other tests such as the PAM50, had the potential to be superior to Oncotype DX but acknowledge that they require additional research before they will be useful in clinical practice.

Finally, there was general agreement that for this sub-group of patients, access to Oncotype DX was increasingly becoming the standard of practice in Canada and across North America. A policy decision needs to be made based on the evidence currently available, and requires consideration of this context. Any decision will require reassessment as the evidence base evolves.

5.4 Experiences and attitudes towards genetic testing in women with Breast Cancer

5.4.1 Methods

A systematic literature review was conducted on the lived experience of individuals with breast cancer who have been tested. The purpose of this review was to understand the impact of genetic testing from a patient perspective thus, this review focused solely on qualitative literature.

MEDLINE, Cochrane CENTRAL Register of Controlled Trials, EMBASE, PsycINFO, ERIC, Education Complete, the Psychological and Behavioral Collection database and CINAHL were searched from 1950-December 17th, 2012. The search strategy for this review focused on combining terms for breast cancer, genetic testing and experience. Terms such as breast neoplasm, breast cancer, mammary tumor (or tumour) and breast carcinoma were searched. This

first set of terms was combined using the Boolean operator “or.” The second set of terms focused on genetic tests, and combined words such as Oncotype DX, pam50, genetic analysis, genetic profiling and IHC using the Boolean operator “or.” The last set of terms, focusing on experience, combined words such as attitude, behaviour, belief, experience, perception, preference and satisfaction using the Boolean operator “or.” To obtain the final results, the three sets of terms were combined using the Boolean operator “and.” Details of this search can be found in Appendix F. Results were filtered to exclude non-human studies. All languages were included in this search.

Abstracts identified were screened in duplicate. Abstracts were included for full-text review if they reported original data, included adult individuals with breast cancer who had undergone genetic testing, and reported on at least one of the following four objectives: experience with testing; comprehension of results; influence testing had on treatment decision-making; and/or ethical discussions regarding genetic testing. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review. Full texts were screened by two reviewers. Studies were included if they met all of the inclusion criteria presented in Table 9 and did not meet any of the exclusion criteria presented therein. Any disagreement between reviewers was resolved through discussion and consensus. A kappa statistic for reviewer agreement was calculated.

The four objectives outlined above were used as a lens for analyzing each study. Information relevant to the four objectives was extracted from each study. Recurrent themes and key concepts within these were identified.

Table 9: Inclusion and Exclusion Criteria for Qualitative Review

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Women or men over 18 years of age with breast cancer • Original research • Reported on one of the following from the patients perspective: <ul style="list-style-type: none"> ○ Experience with testing ○ Test or result comprehension ○ Influence testing had on treatment decision ○ Ethical discussion of genetic testing 	<ul style="list-style-type: none"> • Individuals who have never had breast cancer • Case studies, reviews, meta-analyses • Individuals who have not had genetic testing • Abstracts (with no full-text available) • Did not report on at least one of the following from the patients perspective: <ul style="list-style-type: none"> ○ Experience with testing ○ Test or result comprehension ○ Influence testing had on treatment decision ○ Ethical discussion of genetic testing • Physician accounts of genetic testing • Inclusion of participants under 18 years old • Presymptomatic genetic testing due to family history

5.4.2 Results

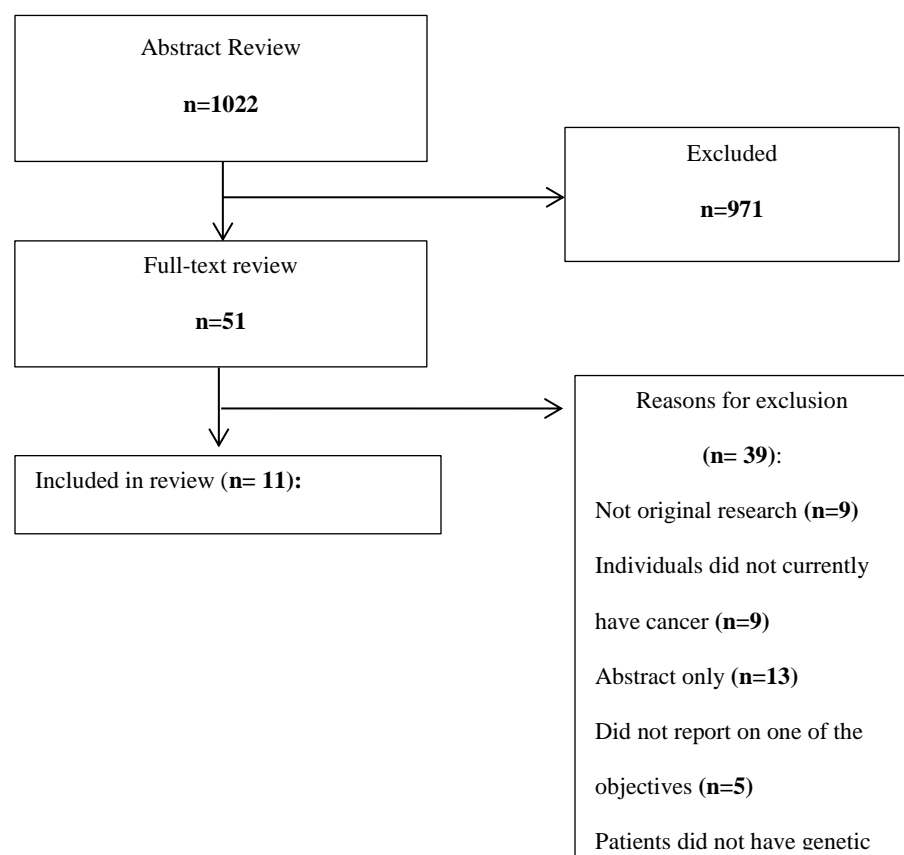
Summary of patient perspectives on genetic testing:

Patients generally report that their experience with testing is positive, and that they value having a shared decision-making role with their oncologist. However, comprehension of test results is low, thus health care practitioners must pay particular attention to ensuring patients understand the meaning and relevance of the test results they receive.

One-thousand and twenty-two abstracts were retrieved using the search strategy outlined above. Of these 971 were excluded and 51 proceeded to full-text review (Figure 7). Of the 51, 39 full-

texts were excluded (n=9 not original research, n=9 populations who did not currently have breast cancer, n=13 only available in abstract form, n=5 did not report information on any of the four objectives, n=1 patients had not undergone genetic testing). The remaining eleven studies were included. The characteristics of these included studies are outlined in Table 10. The Kappa calculated for inter-rater agreement was “good” at 0.6107 (95% CI:0.398-0.823).³⁸

Figure 7: Flow Chart of Included and Excluded Studies



5.4.2.1 General experience

Six of the included articles looked at general experience with genetic testing, such as reasons for undergoing testing and the impact of testing on anxiety and distress levels.⁶⁵⁻⁷⁰

Reasons for undergoing testing: Two studies reported reasons for undergoing GEP testing^{68;70}. Reasons identified included cost, knowledge of the test, understanding of how the test can impact treatment decisions, repercussions on health and life insurance, and a fear of false-positive results. The most commonly cited reason was to understand risk of recurrence in order to be able to make preventative surgical decisions. The associated decision-making framework was assessed for consistency in one study, and it was found that women who tested positive for the BRCA1/2 mutation were more likely to have a bilateral mastectomy.

Impact on anxiety: Four studies reported anxiety outcomes^{53;69-71}. All studies reported women who underwent genetic testing experienced additional anxiety prior to the testing. However, the majority of women would recommend testing (range from 75% to 95%) and felt satisfied with their testing experience. In addition, two studies reported that patients preferred to have a shared role in decision making and treatment discussions which were enabled by GEP testing.

5.4.2.2 Comprehension of test results

Seven of the included articles assessed the ease of comprehending the test results, and whether participants accurately understood the ramifications of the test results.^{65;68;69;72-75} Patients may overestimate their risk of having recurrent cancer. Understanding of risk may be tied to patient's health literacy, anxiety, and level of social support⁷⁴⁻⁷⁷. These findings highlight the importance of patient education and social support.

Reporting format of the test impacts patient understanding of the results, where simplicity and fewer details are preferred over complex and overly detailed reports. Complicated reporting

formats can potentially lead to misinterpretation of the test results. If the test results are only available in a format that is difficult to comprehend by an average patient, then the physician may have to provide additional patient support⁶⁵. Patients are more likely to turn to the internet (and not their health care provider) as their primary source of information. Heavy reliance on the internet can also contribute to the risk of acquiring inaccurate information⁷⁸.

5.4.2.3 Impact on treatment decisions

Only one of the included studies focused primarily on how the results of the genetic tests changed treatment decisions. Kwong et al. conducted interviews with twelve Chinese women who had undergone BRCA 1/2 testing after being diagnosed with breast cancer⁶⁶. Within the interviews, participants were asked to comment on the impact genetic testing had on their decisions, and both long- and short- term impact of their decisions. All women who received positive BRCA 1/2 results opted to have prophylactic mastectomy. They all cited anxiety of reoccurrence as the main reason for making this treatment decision.

Table 10: Characteristics of Included Studies

Author	Year of Publication	Date of Data Collection	Country	Study Design	Number of Participants	Mean age (range)	Type of Genetic Testing	Themes
Brewer (2009) ⁷²	2009	February-August 2005	United States	Interview	163	59 (36-87)	Adjuvant! Online and Oncotype DX	Comprehension of results Influence of testing on treatment
Brewer (2012) ⁶⁵	2012	May 2009-November 2010	United States	Interview or mailed questionnaire	133	59 (34-85)	Oncotype DX	Experience with genetic testing Comprehension of results
Kwong ⁶⁶	2012	August 2007-August 2010	China	Semi-structured Interview	259	47 (34-55)	BRCA1/2	Experience with genetic testing Influence of testing on treatment
Lipkus (2010) ⁷⁴	2010	NR	United States	Questionnaire	105	56	Adjuvant! Online	Comprehension of results
Lipkus (2011) ⁷³	2011	NR	United States	Mailed Questionnaire	64	59	Oncotype DX	Comprehension of results Influence of testing on treatment
Lo ⁶⁷	2010	December 2005-August 2006	United States	Questionnaire	89	55 (35-77)	Adjuvant! Online	Experience with genetic testing Influence of testing on treatment
Liu ⁷⁵	2010	NR	United States	Telephone Interview	531	NR	Adjuvant! Online	Comprehension of results
O'Neill ⁷¹	2007	2005	United States	Questionnaire	139	58	"Risk for recurrence" testing	Influence of testing on treatment
Peters ⁶⁸	2005	2002	United States	Mailed Questionnaire	31	50.1 (42-59)	BRCA1/2	Comprehension of results Experience with genetic testing
Tzeng ⁶⁹	2010	December 2008-May 2009	United States	Mailed Questionnaire	77	57.7	Oncotype DX	Experience with genetic testing Comprehension of results Influence of testing on treatment
Wevers ⁷⁰	2012	January 2004-November 2008	Netherlands	Questionnaire	26	38.4 (20-60)	BRCA1/2	Experience with genetic testing Influence of testing on treatment

NR=not reported

5.4.3 Discussion

Based on 11 studies, the experience with testing was consistently described as “positive”. The majority of patients in these studies reported that they would take the test again if they had to make the decision again, and many of the studies noted that a majority of their participants would recommend testing to others. Anxiety and distress were common drawbacks cited by those who underwent genetic recurrent risk testing. Although there are some drawbacks to the use of genetic risk recurrence tests, it was generally reported that patients thought that the benefits of testing outweighed the risks.

Comprehension was a common theme. However, the current literature is varied on whether women understand the results of testing with several studies reported that understanding was high, while others reported that understanding was low. The included studies were heterogeneous thus, the varied findings may be due to the type of genetic test, study design and/or study population. A number of studies proposed that understanding of test results may vary depending on factors such as health literacy, numeracy or the format that results are presented in. It was clear from all of the included studies that high importance is placed on ensuring that patients fully comprehend their test results and the meaning of them. It was suggested that health care practitioners should pay particular attention to whether their patients understand the test results, and provide their patients with reliable reference material for further information.

Little information was available on the influence of genetic testing on decision-making. One of the key messages that came from the included studies is that patients consistently prefer to have either a shared or an active decision-making role with their oncologist. Very few participants in the included studies preferred to have a passive role in treatment decision-making.

6 ECONOMIC (E) AND FISCAL CONSIDERATIONS

6.1 Research Objectives

- To determine the cost-effectiveness of Oncotype DX and other relevant comparators (e.g. IHC4) as decision support tools for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer
- To determine the budget impact of Oncotype DX as a decision support tool for adjuvant chemotherapy treatment decisions in women with early stage invasive breast cancer

6.2 Methods

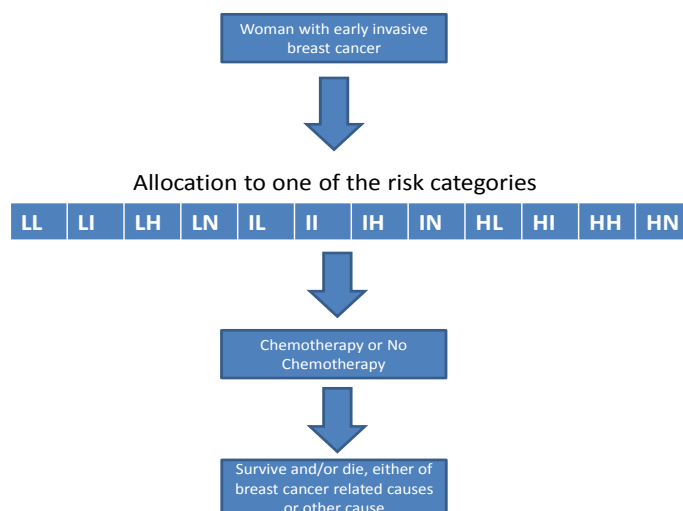
In an effort to limit duplication and leverage other high-quality economic evaluations examining the use of Oncotype DX, a review of other HTAs and economic models was completed. Based on this review, a decision was made to update and adapt the analysis conducted by the Ontario Health Technology Assessment Committee (OHTAC)⁷⁹ to the Alberta context. Whenever possible, Alberta specific estimates of costs were used. Other parameters such as risk/probability estimates, as well as the utility estimates remained the same. The objective of the economic analysis was to evaluate the cost-effectiveness of the Oncotype DX, when used in conjunction with Adjuvant! Online.

Given the lack of data for LN+ patients, the model considers only LN- patients. The patient population was a hypothetical cohort of 50-year-old women diagnosed with LN-, ER+ and/or PR+, HER2/neu negative early breast cancer, who are candidates for adjuvant chemotherapy.

The cohort was followed over a lifetime. Costs were measured in 2012 Canadian dollars, and a discount rate of 5% was applied to costs and outcomes.

6.2.1 Structure of economic model

The simplified schematic of the economic model is presented in Figure 8. Patients were first stratified by Adjuvant! Online risk group. Each Adjuvant! Online risk group may be provided with Oncotype DX; if provided, the respective Adjuvant! Online risk group was further stratified by Oncotype DX risk group. This resulted in patients being assigned to one of 12 risk categories. All patients were assumed to undertake adjuvant tamoxifen treatment for 5 years, with some patients also provided with adjuvant chemotherapy. Higher risk patients were assumed to receive more complex chemotherapy regimens. All chemotherapy patients risked toxicity requiring hospital treatment. Patients are at risk of developing a distant recurrence over their lifetime. All patients eventually died, either due to breast cancer or for other reasons.



Adjuvant Online and Oncotype DX risk categories, respectively:
 LL = low-low, LI = low-intermediate, LH = low-high, LN = Low-none
 IL = intermediate-low, II = intermediate-intermediate, IH = intermediate-high, IN = intermediate-none,
 HL = high-low, HI = high-intermediate, HH = high-high, HN = high-none

Figure 8: Model schematic

6.2.2 Model Parameters

Table 11 shows the clinical model parameters that were used for assessing the cost-effectiveness of providing Oncotype DX. Table 12 and Table 13 present the cost and utility parameters used.

Distributions were assigned to parameters according to best practices in economic evaluations⁸⁰. Probabilities and proportions were assigned beta distributions (in the case of events with two outcomes) or dirichlet distributions (in the case of events with three or more outcomes). The parameters of the distribution were informed by the frequency of each outcome observed in the published literature. The costs associated with treatment of chemotherapy toxicity were assigned lognormal distributions since the cost data were highly skewed and positive. Utility weights were assigned beta distributions to constrain the possible values between 0 and 1, with the exception of the utility weight for the ‘dead’ state which was fixed at 0. Where no measure of uncertainty was available, a fixed value was used.

Table 11: Clinical model parameters

Parameter	Oncotype DX Low Risk	Oncotype DX Intermediate Risk	Oncotype DX High Risk	Not Provided	Total
Proportion of patients assigned to each risk category^{A(81)}					
Adjuvant! Online low risk	32.34%	12.57%	8.08%	--	52.99%
Adjuvant! Online intermediate risk	8.53%	3.59%	6.59%	--	18.71%
Adjuvant! Online high risk	9.73%	6.14%	12.43%	--	28.29%
Proportion of patients in each risk category provided adjuvant chemotherapy^{B(57)}					
Adjuvant! Online low risk	9.79%	17.62%	63.44%	46.05%	--
Adjuvant! Online intermediate risk	13.73%	36.56%	98.61%	55.06%	--
Adjuvant! Online high risk	13.72%	36.65%	99.73%	57.57%	--
Risk of 10 year distant recurrence without chemotherapy^{B(81,49)}					
Adjuvant! Online low risk	2.61%	5.78%	24.78%	6.75%	--
Adjuvant! Online intermediate risk	4.24%	13.40%	45.71%	20.60%	--
Adjuvant! Online high risk	4.24%	13.40%	45.71%	24.12%	--
Risk of 10 year distant recurrence with chemotherapy^{B(81,49,82-86)}					
Adjuvant! Online low risk	3.81%	4.46%	6.48%	4.93%	--
Adjuvant! Online intermediate risk	4.64%	6.23%	7.37%	6.07%	--
Adjuvant! Online high risk	5.79%	8.18%	8.91%	7.68%	--
					VALUE
Risk of mortality due to toxicity^{B(87)}					0.35%
Median life expectancy following distant recurrence (months)^{C(88)}					21.0
Risk of mortality due from other causes^{D(89)}					Life Table
Risk of hospital visit due to toxicity^{B(90)}					17.04%
Cause of hospital visits due to toxicity^{A(90)}					
Neutropenia/fever/infections					53.56%
Injuries & trauma					11.48%
Malignant neoplasm					10.89%
Pain & pain management					7.51%
Nausea/vomiting/dehydration					6.02%
Gastrointestinal tract					5.64%
Chest pain					4.89%

A=Dirichlet Distribution, B=Beta Distribution, C=Normal Distribution, D=Fixed Distribution

Table 12: Cost model parameters

Parameter	Costs (2012 Canadian Dollars)
Cost of 21-gene assay (per patient) ^{A(91;92)}	\$4124.48 ^D
Chemotherapy costs applicable to all regimens (per cycle) ^{A(93)}	
Laboratory tests	\$62.06
Human resources	\$147.52
CMF specific costs (per cycle) ^{A(94, Expert opinion*)}	
Cyclophosphamide 600mg/m ²	\$5.52
Methotrexate 40mg/m ²	\$10.00
5-fluorouracil 600mg/m ²	\$1.50
TC specific costs (per cycle) ^{A(94, Expert opinion*)}	
Docetaxel 75mg/m ²	\$236.50
Cyclophosphamide 600mg/m ²	\$5.52
FEC-D specific costs (per cycle) ^{A(94, Expert opinion*)}	
5-fluorouracil 500mg/m ²	\$1.25
Epirubicin 100mg/m ²	\$35.00
Cyclophosphamide 500mg/m ²	\$4.60
Docetaxel 100mg/m ² = 173mg	\$315.00
G-CSF prophylaxis (per day) ^{A(94, Expert opinion*)}	
Filgrastim 300mcg	\$186.81
Hormone therapy (per day) ^{A(94, Expert opinion*)}	
Tamoxifen 20mg	\$0.35
Ongoing care for recurrence-free patients (per month) ^{A(95)}	
1 st Year	\$55.24
2 nd Year	\$49.89
3 rd Year	\$44.54
4 th Year	\$39.19
5 th Year and beyond	\$33.83
Cost of treating distant recurrence ^{B(95)}	
Initial cost of treatment (one time)	\$8,356.23
Ongoing care (per month)	\$717.57
End of life care (last 3 months) ^{B(95)}	\$22,040.96
Treatment of non-fatal chemotherapy toxicity ^{C(96)}	
Neutropenia/fever/infections	\$6,827.45
Injuries & trauma	\$8,730.53
Malignant neoplasm	\$6,754.79
Pain & pain management	\$4,352.07
Nausea/vomiting/dehydration	\$4,142.12
Gastrointestinal tract	\$6,773.66
Chest pain	\$3,022.78
Treatment of fatal toxicity ^{C(96)}	\$33,807.98

A=Fixed Distribution, B=Modeled Distribution, C=Lognormal Distribution

D=21-gene assay cost of USD\$4175.00 (2012) at 0.9879 US/Canadian dollar exchange rate (30 April 2012)

*=Expert opinion was sought for Alberta-specific chemotherapy costs

Table 13: Utility model parameters

Parameter	Utility weights
First year following diagnosis (while on hormone therapy) ^{A(97)}	0.744
First year following diagnosis (while on chemotherapy) ^{A(97)}	0.620
Second and following years prior to distant recurrence ^{A(97)}	0.779
Following distant recurrence ^{A(97)}	0.685
Dead ^{B(97)}	0

6.3 Results

Summary of economic evaluation: Oncotype DX testing for all patients compared to not offering Oncotype DX to any patients had a cost per quality-adjusted life year (QALY) gained of \$3789. Depending on uptake of Oncotype DX testing among the eligible Alberta patient population, publicly funding Oncotype DX would cost between \$367,000 and \$3.66 million annually.

6.3.1 Results of Alberta-specific Cost-effectiveness Analysis based on Ontario Health

Technology Advisory Committee economic model

The results of the economic evaluation are presented in Figure 9 and

Table 14. Oncotype DX testing for *all* patients had a cost per QALY gained of \$3789. The strategy to provide Oncotype DX only for patients with a AOL low risk of recurrence, combined with low, intermediate or high risk defined using Oncotype DX was less effective and more costly as compared to other strategies; a dominated option. Compared to the strategy of not offering Oncotype DX to any patients, the cost per QALY gained of offering Oncotype DX to the intermediate risk group alone was \$764/QALY, followed by \$1476/QALY for high risk only and \$13116/QALY for low risk only.

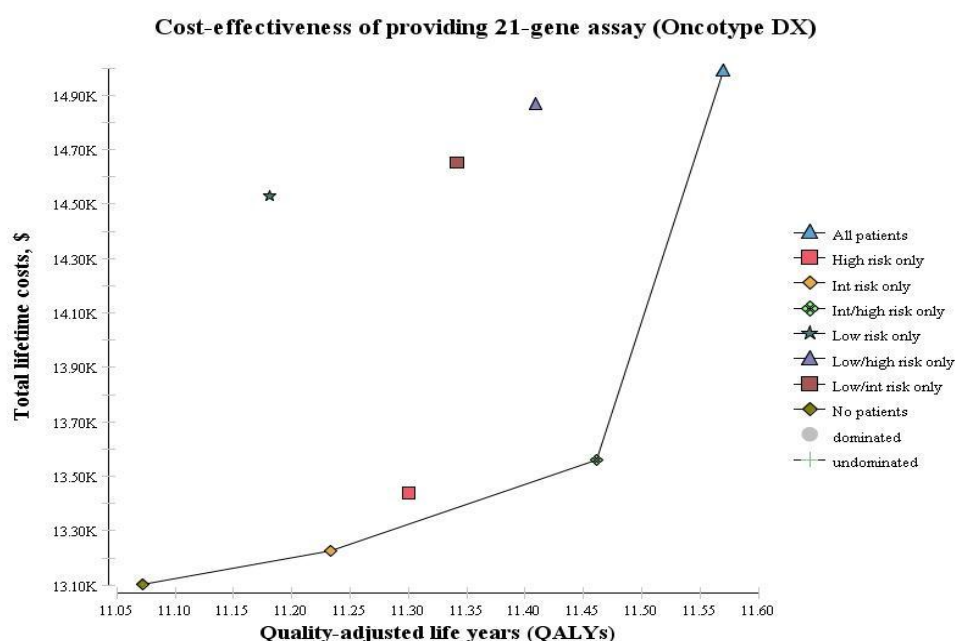


Figure 9: Cost-effectiveness of Oncotype DX in Alberta context

Table 14: Outcomes, costs, effectiveness, and cost-effectiveness of providing Oncotype DX to a population of 1000 patients

Adjuvant! Online risk groups provided with 21-gene assay	Outcomes					Costs						Effectiveness		Cost-effectiveness of 21-gene assay			
	<i>Provided 21-gene assay</i>	<i>Provided adjuvant chemo</i>	<i>Toxicity from chemo</i>	<i>10 year distant rec.</i>	<i>10 year death</i>	<i>Providing 21-gene assay</i>	<i>Providing adjuvant chemo</i>	<i>Incurred prior to dist. rec.</i>	<i>Incurred following dist. rec.</i>	<i>Incurred during last 3</i>	<i>Total lifetime costs</i>	<i>Life years</i>	<i>QALYs</i>	<i>ICER ref to no patients being tested</i>	<i>Prob. CE (\$20k)</i>	<i>Prob. CE (\$50k)</i>	<i>Prob. CE (\$100k)</i>
None	0	510	87	90	74	\$0.00m	\$1.54m	\$6.27m	\$2.64m	\$2.58m	\$13.10m	14,311	11,072	N/A	0.06%	0.00%	0.00%
High only	283	507	86	72	59	\$1.23m	\$1.52m	\$6.40m	\$2.17m	\$2.12m	\$13.44m	14,580	11,300	\$1,476	0.96%	0.19%	0.08%
Intermediate only	187	497	84	79	65	\$0.81m	\$1.49m	\$6.35m	\$2.35m	\$2.30m	\$13.23m	14,475	11,233	\$764	0.22%	0.07%	0.05%
Intermediate & High	470	493	84	61	50	\$2.04m	\$1.47m	\$6.48m	\$1.89m	\$1.84m	\$13.56m	14,745	11,461	\$1,182	51.09%	18.60%	10.60%
Low only	530	371	63	85	70	\$2.30m	\$1.26m	\$6.37m	\$2.47m	\$2.41m	\$14.53m	14,407	11,181	\$13,116	0.03%	0.00%	0.00%
Low & High	813	368	62	67	55	\$3.52m	\$1.23m	\$6.49m	\$2.00m	\$1.96m	\$14.87m	14,677	11,409	\$5,234	0.68%	0.41%	0.30%
Low & Intermediate	717	358	61	74	62	\$3.11m	\$1.21m	\$6.45m	\$2.18m	\$2.13m	\$14.65m	14,571	11,342	\$5,749	0.14%	0.11%	0.11%
All	1000	354	60	57	46	\$4.33m	\$1.18m	\$6.58m	\$1.72m	\$1.68m	\$14.99m	14,841	11,570	\$3,789	46.74%	80.60%	88.90%

Results of probabilistic sensitivity analysis (based on 10,000 iterations) show that at a willingness-to-pay threshold of \$20,000, there is a 47% probability that testing all the patients would be cost-effective (Figure 10) and a 51% probability that providing testing for the intermediate/high risk group only would be cost-effective. At the commonly accepted WTP threshold of \$50,000, there is an 80% probability that testing all patients would be cost-effective. If the WTP threshold were to be \$100,000 then the strategy of testing all patients would be cost-effective 89% of the times.

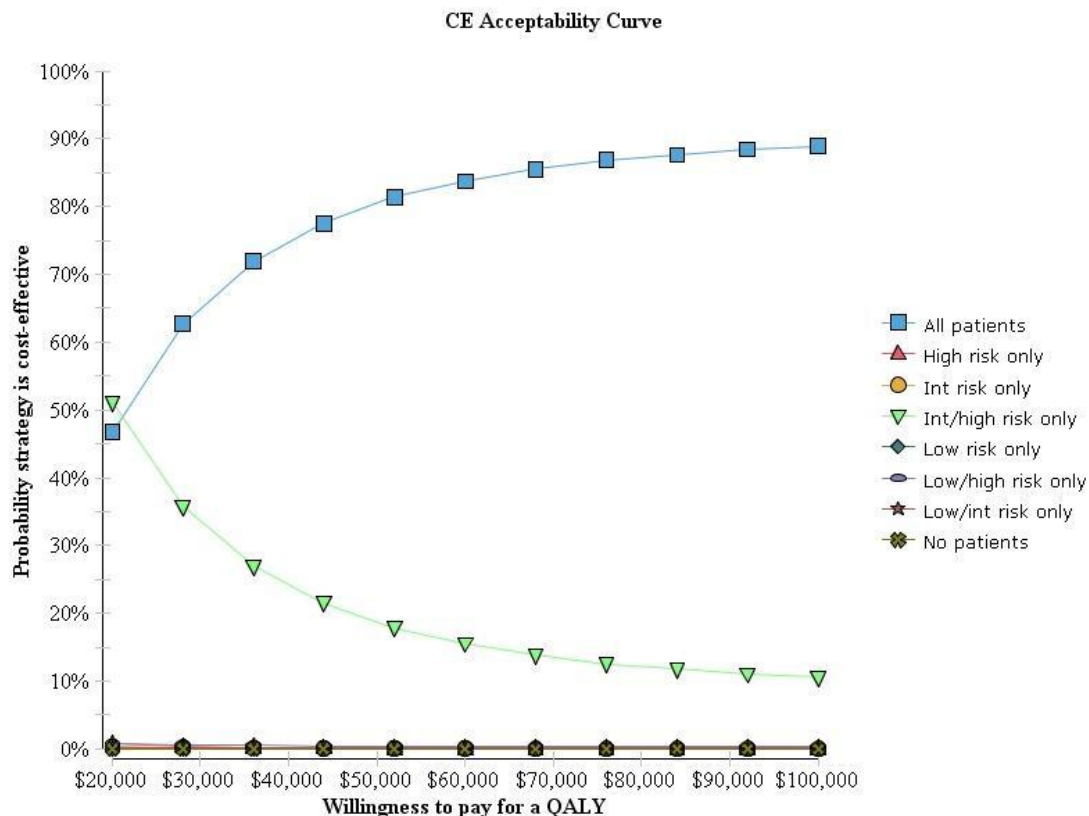


Figure 10: Probability that each strategy for the provision of the Oncotype DX across Adjuvant! Online risk groups are cost-effective, conditional upon willingness to pay threshold. Strategies not represented have less than 1% probability of being cost-effective.

6.3.2 Budget Impact Analysis from Alberta perspective

According to recent estimates, 1950 new cases of breast cancer are diagnosed in Alberta each year⁹. Of these, approximately 878 may be eligible for Oncotype DX testing based on their clinico-pathological features such as lymph-node and hormone receptor status⁷⁹. The Budget Impact Analysis (Table 15) shows different scenarios where uptake of the test is ranging from 10% to 100%. For each scenario, there is an estimate of upfront testing costs, as well as chemotherapy treatment costs. Patients eligible for testing are a mix of low, intermediate and high risk profiles (roughly 53% are low risk, 19% intermediate and 28% are high risk). If uptake is less than 100%, then the patients who were not tested will incur chemotherapy costs using the ‘no uptake’ estimates for treatment costs. Chemotherapy costs avoided are calculated in comparison to the “no uptake” scenario and they go down as uptake goes down

The assumptions that were used in the economic model apply to the Budget Impact Analysis. However, only chemotherapy costs are included in this analysis. There may be other long term cost benefits that are beyond the scope of the calculations represented here

Table 15: Budget Impact Analysis from Alberta Perspective

	No uptake	100% uptake	50% uptake	25% uptake	10% uptake
Number of eligible patients	878	878	439	220	88
Oncotype DX costs	0	3,665,650	1,832,825	918,500	367,400
Chemotherapy costs	\$1,355,696.02	\$1,209,213.92	\$1,282,454.97	\$1,319,764.11	\$1,341,323.25
Chemotherapy costs avoided	Comparator	-\$146,482.09	-\$73,241.05	-\$35,931.91	-\$14,372.76

6.4 Discussion

Oncotype DX testing for *all* patients had a cost per QALY gained of \$3789. Compared to the strategy of not offering Oncotype DX to any patients, the cost per QALY gained of offering Oncotype DX to the intermediate risk group alone was \$764/QALY, followed by \$1476/QALY for high risk only and \$13116/QALY for low risk only. Results of the economic model remained robust after the probabilistic sensitivity analysis.

In the Alberta context, the cost per QALY gained with Oncotype DX is less than in other contexts. A 2011 report from the National Institute for Clinical and Health Excellence (NICE) reported an incremental cost for treatment guided using Oncotype DX of £26,940 pounds per QALY gained compared to current practice³⁷, OTHAC reported a cost per QALY of \$23,983 when offered to all patients⁹⁸ and a 2010 analysis reported a cost per QALY of \$63,064 in a Canadian setting⁹⁹. The difference in the cost per QALY in Alberta is due to the relatively low costs of chemotherapy in Alberta which covers less expensive chemotherapy agents in compared to Ontario and the UK.

The model has several limitations. The model assumes that Oncotype DX is correctly assigns patients into their risk category. However, there are limited low quality ad-hoc retrospective analyses assessing the ability of Oncotype DX to correctly identify patients who will benefit from chemotherapy. In addition, allocation of patients to various risk categories was based on a mix of retrospective as well as unpublished data; the possibility of local recurrence was ignored; and long term side effects of chemotherapy were not considered. Further, the data used for estimating the impact of Oncotype DX on clinical decision making was based on a non-Canadian study which may not fully reflect the attitudes or preferences of Canadian oncologists.

Results of the Budget Impact Analysis show that Oncotype DX provision to the eligible patient population in Alberta will result in direct expenses of approximately \$1 million, \$1.8 million and \$3.6 million per year for 25%, 50% and 100% adoption respectively. Costs of chemotherapy avoided are not substantial enough to significantly offset the upfront cost of Oncotype DX.

7 CONCLUSIONS OF THE STE ANALYSIS

7.1 Conclusions

Based on 2 ad hoc retrospective analyses of RCTs in each of LN+ and LN- population, the survival difference between those treated with chemotherapy and those treated with hormones is greater in those with a high risk Oncotype DX score than those with a low risk Oncotype DX score. These studies represent limited, low quality evidence supporting the clinical utility of Oncotype DX to predict benefit from chemotherapy. In addition, this study design has a high risk of bias; 1) the studies are not powered to detect differences among risk subgroups as the subgroup analysis is not part of the original design, 2) ad-hoc analyses are likely to identify

spurious relationships due to chance alone, 3) the treatment received and outcome of the women is known and may influence the Oncotype DX risk score classification and finally 4) the generalizability of the population is compromised as the ad-hoc analyses utilized a subset of the original RCT population.

Based on 10 observational studies of low to medium quality, Oncotype DX results lead to a change in adjuvant chemotherapy decision in 32% (95% CI : 24%-40%) of cases. There was a high degree of heterogeneity among the studies thus the pooled results must be interpreted with caution. However, all studies reported a change in practice supporting the pooling of results and conclusion that Oncotype DX does result in a clinical change.

Oncologists and pathologists in Alberta have mixed opinions which reflect skepticism about the analytic utility of Oncotype DX, especially for patients in the intermediate risk group, as well as a lack of consensus about the communication and usability of the results obtained from IHC4 testing. From a patient perspective, genetic testing may present complex information which may be hard to understand. Therefore, care providers must continue to play an active role in explaining the implications of test results and treatment options.

The cost per QALY associated with Oncotype DX compared with Adjuvant! Online for all patients is \$3789/QALY. The cost per QALY gained in Alberta varies from other jurisdictions due to the costs of chemotherapy covered within the public healthcare plan. Depending on uptake of Oncotype DX testing among the eligible Alberta patient population, publicly funding Oncotype DX would cost between \$367,000 and \$3.66 million annually.

7.2 Gaps in current knowledge

Gene Expression Profiling, including Oncotype DX and its comparators, are still evolving technologies that can help guide decision making in adjuvant treatment of early stage invasive breast cancer. The rapid evolution of research in this field calls for frequent updates to policy decisions so that they reflect the most comprehensive clinical evidence. Currently, there is a lack of prospective data assessing the clinical utility of Oncotype DX for predicting benefit from chemotherapy. A current trial (TAILORx trial) may provide data to more accurately determine patient outcomes within various Oncotype DX risk profiles. The trial is due to complete primary outcomes in April 2014. The results will contribute to the current knowledge gap in the clinical utility of Oncotype DX and support the development of more precise economic evaluations.

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APPENDIX A: Search strategy for clinical effectiveness

Search Strategies

Note: where possible variant spellings and suffixes were accommodated in all search strategies using truncation [*] and wildcard [?] functions.

MEDLINE search strategy

[Also used for the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, EED and the HTA database]

Breast Cancer Gene Tests MEDLINE July 13 2012

1. exp breast neoplasms/
2. exp mammary neoplasms/
3. exp "neoplasms, ductal, lobular and medullary"/
4. exp breast/
5. exp neoplasms/
6. 4 and 5
7. (breast* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).tw.
8. (mammar* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).tw.
9. 1 or 2 or 3 or 6 or 7 or 8
10. (MammaPrint or 70-gene or gene70 or gene?seventy or seventy?gene or amsterdam profile or Oncotype or Oncotype DX or Oncotype DX or 21-gene or gene21 or gene?twentyone or twentyone?gene or GHI Recurrence score or GHI-RS or 92-gene or gene92 or gene?ninetytwo or ninetytwo?gene or (RT-PCR adj 5 21)).tw.

11. (oncotype or Oncotype DX or nuvoselect or rotterdam signature or metastasis score or two gene ratio or 2 gene ratio or h*i* test or h*i* ratio or mammaprint or 21 gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio or 76 panel or breast cancer gene expression ratio or HOXB13?IL17BR or bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast cancer index).tw.
12. ((expression profil* or prognos* profil* or predict* profil* or mRNA expression or real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-PCR or qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or predict* signature or prognos* signature or expression signature or gene signature or prognos* expression or predict* expression or gene classifier or molecular signature) adj5 test*).tw.
13. exp Genetic Testing/
14. Gene Expression Profiling/
15. 13 and 14
16. 10 or 11 or 12 or 15
17. 9 and 16
18. (Radox or Blueprint or 80-gene or gene80 or gene?eighty or eighty?gene or PAM50 or 50-gene or gene50 or gene?fifty or fifty?gene or breast bioclassifier or Breast Cancer Index or Breast cancer gene expression ratio or 2-gene or Two-gene-index or 2-gene-index or Two?gene or gene?two or H?I or H:I or 5-gene or gene5 or gene?five or five?gene or 7-gene or seven-gene or gene7 or gene?seven or Theros or Biotheranostics or Theros breast cancer index or HOXB13* or homeobox?13* or interleukin?17B* or IL17BR or mammostrat or five-biomarker-assay or IHC4 or NPI+ or Nottingham prognostic index plus or Nottingham prognostic index +).tw.
19. 9 and 18

20. 17 or 19

21. limit 20 to yr="2011 -Current"

22. limit 21 to animals

23. limit 21 to (animals and humans)

24. 22 not 23

25. 21 not 24

EMBASE search strategy

Breast Cancer Gene Tests EMBASE July 13 2012

1. exp breast tumor/

2. exp breast/

3. exp neoplasm/

4. 2 and 3

5. (breast* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).tw.

6. (mammar* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).tw.

7. 1 or 4 or 5 or 6

8. (MammaPrint or 70-gene or gene70 or gene?seventy or seventy?gene or amsterdam profile or Oncotype or Oncotype DX or Oncotype DX or 21-gene or gene21 or gene?twentyone or twentyone?gene or GHI Recurrence score or GHI-RS or 92-gene or gene92 or gene?ninetytwo or ninetytwo?gene or (RT-PCR adj 5 21)).tw.

9. (oncotype or Oncotype DX or nuvoselect or rotterdam signature or metastasis score or two gene ratio or 2 gene ratio or h*i* ratio or h*i* test or h*i* ratio or mammaprint or 21 gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio or 76 panel or breast cancer gene expression ratio or HOXB13/IL17BR or bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast cancer index).tw.
10. ((expression profil* or prognos* profil* or predict* profil* or mRNA expression or real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-PCR or qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or predict* signature or prognos* signature or expression signature or gene signature or prognos* expression or predict* expression or gene classifier or molecular signature) adj5 test*).tw.
11. exp genetic screening/
12. exp gene expression profiling/
13. 11 and 12
14. 8 or 9 or 10 or 13
15. 7 and 14
16. (Radox or Blueprint or 80-gene or gene80 or gene?eighty or eighty?gene or PAM50 or 50-gene or gene50 or gene?fifty or fifty?gene or breast bioclassifier or Breast Cancer Index or Breast cancer gene expression ratio or 2-gene or Two-gene-index or 2-gene-index or Two?gene or gene?two or H?I or H:I or 5-gene or gene5 or gene?five or five?gene or 7-gene or seven-gene or gene7 or gene?seven or Theros or Biotheranostics or Theros breast cancer index or HOXB13* or homeobox?13* or interleukin?17B* or IL17BR or mammostrat or five-biomarker-assay or IHC4 or NPI+ or Nottingham prognostic index plus or Nottingham prognostic index +).tw.
17. 7 and 16

18. 15 or 17

19. limit 18 to yr="2011 -Current"

20. limit 19 to animals

21. limit 19 to (human and animals)

22. 20 not 21

23. 19 not 22

WOS search strategy

[also used for BIOSIS]

1. Topic=((((breast* and (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))))) OR

Title=((((breast* and (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))))

DocType=All document types; Language=All languages;

2. Topic=((((mammar* and (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))))) OR Title=((((mammar* and (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))))

3. #2 OR #1

4. Title=(((Randex or Blueprint or 80-gene or gene80 or geneeighty or gene eighty or eightygene or eighty gene or PAM50 or 50-gene or gene50 or genefifty or gene fifty or fiftygene or fifty gene or breast bioclassifier or Breast Cancer Index or Breast cancer gene expression ratio

or 2-gene or Two-gene-index or 2-gene-index or Twogene or Two gene or genetwo or gene two
or HI or 5-gene or gene5 or genefive or gene five or fivegene five gene or 7-gene or seven-gene
or gene7 or geneseven or gene seven or Theros or Biotheranostics or Theros breast cancer index
or HOXB13* or homeobox13* or homeobox 13 or interleukin17B* or interleukin 17B or
IL17BR or mammostrat or five-biomarker-assay or IHC4 or NPI or Nottingham prognostic index
plus or Nottingham prognostic index))))

5. Title=(((oncotype or Oncotype DX or nuvoselect or rotterdam signature or metastasis score or
two gene ratio or 2 gene ratio or hi ratio or h i ratio or hi test or h i test or mammaprint or 21
gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio
or 76 panel or breast cancer gene expression ratio or HOXB13IL17BR or HOXB13 IL17BR or
bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast
cancer index))))

6. Title((((expression profil* or prognos* profil* or predict* profil* or mRNA expression or
real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-
PCR or qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or
predict* signature or prognos* signature or expression signature or gene signature or prognos*
expression or predict* expression or gene classifier or molecular signature) and test*))))

7. Title=(((MammaPrint or 70-gene or gene70 or geneseventy or gene seventy or seventygene or
seventy gene or amsterdam profile or Oncotype or Oncotype DX or Oncotype DX or 21-gene or
gene21 or genetwentyone or gene twentyone or twentyonegene or twentyone gene or GHI
Recurrence score or GHI-RS or 92-gene or gene92 or geneninetytwo or gene ninetytwo or
ninetytwogene or ninetytwo gene or (RT-PCR and 21))))

8. #7 OR #6 OR #5 OR #4

9. #8 AND #3

10. Topic=((MammaPrint or Oncotype* or IHC4 or Randox or PAM50 or Breast Cancer Index or Mammostrat or NPI plus)) AND Title=((MammaPrint or Oncotype* or IHC4 or Randox or PAM50 or Breast Cancer Index or Mammostrat or NPI plus))

11. #10 AND #3

12. #11 OR #9

[DocType=All document types; Language=All languages, for all searches]

CINAHL search strategy

1. (MH "Breast Neoplasms+") OR (MH "Carcinoma, Ductal, Breast") OR (MH "Neoplasms, Ductal, Lobular, and Medullary+") [39874]

2. (MH "Breast+") AND (MH "Neoplasms+") [1412]

3. TI ((breast* and (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) OR AB ((breast* and (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) [30231]

4. TI ((mammar* and (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) OR AB ((mammar* and (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) [570]

5. S1 or S2 or S3 or S4 [44767]

6. TI ((MammaPrint or 70-gene or gene70 or geneseventy or gene seventy or seventy gene or seventygene or amsterdam profile or Oncotype or Oncotype DX or Oncotype DX or 21-gene or gene21 or genetwentyone or gene twentyone or twentyonegene or twentyone gene or GHI Recurrence score or GHI-RS or 92-gene or gene92 or geneninetytwo or gene ninetytwo or ninetytwogene or ninetytwo gene or (RT-PCR and 21))) OR AB ((MammaPrint or 70-gene or gene70 or geneseventy or gene seventy or seventy gene or seventygene or amsterdam profile or Oncotype or Oncotype DX or Oncotype DX or 21-gene or gene21 or genetwentyone or gene twentyone or twentyonegene or twentyone gene or GHI Recurrence score or GHI-RS or 92-gene or gene92 or geneninetytwo or gene ninetytwo or ninetytwogene or ninetytwo gene or (RT-PCR and 21))) [320]

7. TI ((oncotype or Oncotype DX or nuvoselect or rotterdam signature or metastasis score or two gene ratio or 2 gene ratio or hi ratio or h i ratio or hi test or h i test or mammaprint or 21 gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio or 76 panel or breast cancer gene expression ratio or HOXB13IL17BR or HOXB13 IL17BR or bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast cancer index)) OR AB ((oncotype or Oncotype DX or nuvoselect or rotterdam signature or metastasis score or two gene ratio or 2 gene ratio or hi ratio or h i ratio or hi test or h i test or mammaprint or 21 gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio or 76 panel or breast cancer gene expression ratio or HOXB13IL17BR or HOXB13 IL17BR or bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast cancer index)) [2543]

8. TI (((expression profil* or prognos* profil* or predict* profil* or mRNA expression or real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-PCR or

qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or predict* signature or prognos* signature or expression signature or gene signature or prognos* expression or predict* expression or gene classifier or molecular signature) and test*)) OR AB (((expression profil* or prognos* profil* or predict* profil* or mRNA expression or real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-PCR or qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or predict* signature or prognos* signature or expression signature or gene signature or prognos* expression or predict* expression or gene classifier or molecular signature) and test*)) [3126]

9. (MH "Genetic Screening") AND (MH "Gene Expression Profiling") [9]

10. TI ((Randox or Blueprint or 80-gene or gene80 or geneeighty or gene eighty or eightygene or eighty gene or PAM50 or 50-gene or gene50 or genefifty or gene fifty or fiftygene or fifty gene or breast bioclassifier or Breast Cancer Index or Breast cancer gene expression ratio or 2-gene or Two-gene-index or 2-gene-index or Twogene or Two gene or genetwo or gene two or HI or H I or H:I or 5-gene or gene5 or genefive or gene five or fivegene or five gene or 7-gene or seven-gene or gene7 or geneseven or gene seven or Theros or Biotheranostics of Theros breast cancer index or HOXB13* or homeobox13* or homeobox 13* or interleukin17B* or interleukin 17B* or IL17BR or mammostrat or five-biomarker-assay or IHC4 or NPI+ or Nottingham prognostic index plus or Nottinham prognostic index +)) OR AB ((Randox or Blueprint or 80-gene or gene80 or geneeighty or gene eighty or eightygene or eighty gene or PAM50 or 50-gene or gene50 or genefifty or gene fifty or fiftygene or fifty gene or breast bioclassifier or Breast Cancer Index or Breast cancer gene expression ratio or 2-gene or Two-gene-index or 2-gene-index or Twogene or Two gene or genetwo or gene two or HI or H I or H:I or 5-gene or gene5 or genefive or gene five or fivegene or five gene or 7-gene or seven-gene or gene7 or geneseven or

gene seven or Theros or Biotheranostics of Theros breast cancer index or HOXB13* or

homeobox13* or homeobox 13* or interleukin17B* or interleukin 17B* or IL17BR or

mammostrat or five-biomarker-assay or IHC4 or NPI+ or Nottingham prognostic index plus or

Nottinham prognostic index +)) [9752]

11. S6 or S7 or S8 or S9 or S10 [13475]

12. S5 and S11 [276] limit by year only [Jan 2011-Aug 2012 publication date]

APPENDIX B: Data Abstraction form

Author	Year	Study Type	Country	Number of participants	Intervention (ODX or IHC4)	Control (AOL or CPF)	Quality Assessment Results	AOL or CPF recommendation for CT	AOL or CPF recommendation for No CT	ODX recommendation for CT	ODX recommendation for No CT	Overall total movement (CT to No CT or No CT to CT)	Movement from CT to No CT	Movement from No CT to CT	Net movement from CT to No CT	Distant recurrence ODX/IHC4	Distant recurrence AOL or CPF	Overall survival ODX/IHC4	Overall survival AOL or CPF	10 year death ODX or IHC4	10 year death AOL or CPF	MD/PT confidence ODX or IHC4	MD/PT confidence AOL or CPF

APPENDIX C: Newcastle Ottawa scale for study quality

[NB: * indicates for which answers studies receive a star]

Q1. Representatives of the exposed cohort

- a) truly representative of the average CLBP (describe) in the community *
- b) somewhat representative of the average CLBP in the community *
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

Q2. Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort *
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

Q3. Ascertainment of exposure

- a) a. secure record (e.g. surgical records) *
- b) structured interview *
- c) written self-report
- d) no description

Q4. Demonstration that outcome of interest was not present at start of study

- e) YES *
- f) NO

Q5. Comparability of cohorts on the basis of the design or analysis (2 possible stars)

- a) study controls for level of pain (select the most important factor) *
- b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Q6. Assessment of outcome

- a) independent blind assessment *
- b) record linkage *
- c) self-report
- d) no description

Q7. Was follow-up long enough for outcomes to occur?

- a) YES (select an adequate follow up period for outcome of interest) *
- b) NO

Q8. Adequacy of follow-up of cohorts

- a) complete follow up - all subjects accounted for *
- b) subjects lost to follow up unlikely to introduce bias - small number lost < __ (select an adequate %) follow up, or description provided of those lost) *
- c) follow up rate \geq __% (select an adequate %) and no description of those lost
- d) no statement

APPENDIX D: Key informant interview guide

Pathologist Interview Questions

Introduction

HTA project background

Policy Question

The primary policy question to be answered in this review is:

Should Oncotype DX be publicly funded in Alberta?

Research Questions

- To determine the burden of illness, patterns of care and capacity in Alberta as it relates to Oncotype DX and other relevant comparators (e.g. IHC4) in terms of informing treatment decisions in breast cancer patients.
- To determine the safety and effectiveness/efficacy of Oncotype DX for breast cancer screening.
- To determine the cost-effectiveness of Oncotype DX and other relevant comparators (e.g. IHC4) for breast cancer screening.
- To determine the budget impact of Oncotype DX for breast cancer screening.

- Thank you again for agreeing to participate in this interview.
- As you may be aware an important part of this project is getting input from health professionals practicing in Alberta. This is essential to increase our understanding of the current practice in Alberta with respect to genomic testing (i.e., Oncotype DX and its comparators) for this subgroup of people with breast cancer.
- Everything we talk about will be confidential, in that your name won't be attached to anything you tell me.
- I am wondering whether it would be okay for me to audiotape our conversation, just so that I can get down everything you have to say.
- Before we get started, do you have any questions about the project or this interview.

A. Patient sub-group

Approximately how much of the testing you're involved with would fit into the category of 'genomic testing' (i.e., IHC4, other) for this patient sub-group: diagnosed with early-stage, estrogen-receptor positive, and lymph-node-negative invasive breast cancer in the past year?

Approximately how many of these kinds of tests would you have done in the past year? Could you break it down by test-type, if you're involved with more than one kind of test?

What % is this of your work overall?

B. Genomic testing

Could you describe each of the following tests?

21 gene assay (Oncotype DX)

Immunohistochemistry 4 (IHC4)

Adjuvant! Online

Other

The literature shows the use of other variants of the immunohistochemistry tests. If we were to select a valid comparator for Oncotype DX in terms of its ability to provide probabilities around risk of cancer recurrence, will it be the entire 4-protein panel or a subset only?

Please describe the kind of information that these tests provide (i.e., risk scores, other).

What is the difference between Oncotype DX and its comparators with respect to the information they provide?

Based on your experience, what would you say are the strengths and weaknesses of each of these tests?

How confident are you in the information obtained from each of these tests? [Probe around: sensitivity and specificity]

How does the Oncotype DX risk score differ from the risk scores provided by IHC4 and other tests)?

C. Communication of test results

How do you communicate these test results to oncologists?

How easy do you think these test results are for oncologists to interpret?

Do you talk with oncologists about these test results? If yes, what kinds of questions do they have?

D. Barriers to doing genomic testing

Are there barriers to doing this kind of testing?

Is this kind of testing complex?

Does it require special skills and/or training?

Does it take extra resources (e.g., time)?

Logistic issues – in-house testing vs. outsourcing

Is there capacity in the system to do this testing?

Probe around: Oncotype DX; IHC4; other

E. Closing and next steps

Is there anything else you think I should know that we haven't talked about yet?

Oncotype DX EAG Oncologists Interview Questions

Introduction

- Thank you again for agreeing to participate in this interview.

Policy Question

The primary policy question to be answered in this review is:

- Should Oncotype DX be publicly funded in Alberta?

Research Questions

- To determine the burden of illness, patterns of care and capacity in Alberta as it relates to Oncotype DX and other relevant comparators (e.g. IHC4) in terms of informing treatment decisions in breast cancer patients.
- To determine the safety and effectiveness/efficacy of Oncotype DX for breast cancer screening.
- To determine the cost-effectiveness of Oncotype DX and other relevant comparators (e.g. IHC4) for breast cancer screening.
- To determine the budget impact of Oncotype DX for breast cancer screening.

- As you may be aware an important part of this project is getting input from health professionals practicing in Alberta. This is essential to increase our understanding of the current practice in Alberta with respect to the use of these diagnostic tools (i.e., Oncotype DX and its comparators), and where the use of these tools fits into the overall care pathway for this subgroup of people with breast cancer.
- Everything we talk about will be confidential, in that your name won't be attached to anything you tell me.
- I am wondering whether it would be okay for me to audiotape our conversation, just so that I can get down everything you have to say.
- Before we get started, do you have any questions about the project or this interview.

A. Patient sub-group

Approximately how many of your patients would fit into this patient sub-group: diagnosed with early-stage, estrogen-receptor positive, and lymph-node-negative invasive breast cancer in the past year?

- Approximately what % of all your breast cancer patients fit into this sub-group?

B. Care pathway

Could you step me through a typical care pathway for this sub-group of patients with breast cancer? *[Note to self: refer to NICE care pathway]*

- What is the current treatment that this sub-group of patients would receive (e.g., % receiving hormone therapy; % receiving both hormone & chemo therapy)? (i.e., current standard of practice)
- What is the typical decision-making process you go through with these patients?
- Where does testing such as: IHC4 and Oncotype DX fit into this pathway? What about Adjuvant! Online?

C. Genomic testing

Could you describe for me the process you go through in deciding which of these tests (i.e., Oncotype DX or ICH4 or others) to order?

- How do you make the decision about which kinds of tests to order?
- How do engage your patients in making decisions about what kinds of tests would be useful to help inform their treatment decisions?

Do you use Adjuvant! Online? If yes, how you use the risk-score information obtained from AO in conjunction with the risk-score you obtain from the other tests you order? [refer back to tests they talked about above]

What are the pros and cons of each of these tests and tools?

How confident are you in the risk-scores obtained from each of these?

Please describe the information you obtain through these tests, and how you use this information to inform your treatment recommendations?

- Which test(s) do you use to help decide which patients are more likely to benefit from adding chemotherapy to their hormonal treatments?
- Since you started using this testing, how has it influenced your treatment recommendations?
- How do you engage your patients in this decision-making process?
 - How do you share the risk results information with them?
 - How easy is it to explain these kinds of test results to patients?

D. Clinical Practice Guidelines

Are there provincial CPG's for treating breast cancer patients? If yes:

- Do you follow them?
- Do they include the use of genomic testing?

If no, are there other CPG's out there that you use?

- Do they include the use of genomic testing?

E. Barriers to Providing Optimal Care

Are there barriers to providing optimal patient care? [Note to self: go through the care pathway]

- To the genomic testing
- To the treatment
 - Hormone therapy
 - Chemotherapy
 - Other

Probe around:

- SES
- Patient distance from healthcare services

- Ethnicity
- Age
- Gender
- Other

F. Administrative data

What ICD-9 code(s) do you use for this patient group?

What SOMB code(s) do you use for each of the tests you order?

- IHC4
- Oncotype DX
- Other

G. Closing and next steps

Is there anything else you think I should know that we haven't talked about yet?

Next steps:

Want to get input from medical oncologists across AB who would treat this sub-group of women, including ordering these kinds of tests.

- Do you know approximately how many such oncologists there are and where they would practice?
- Do you know how we might get an accurate list that includes contact information?
- In your opinion, what's the best way to obtain input from this group of oncologists (e.g., online survey, paper survey, phone interview, other)?

APPENDIX E: Sample IHC4 report



CROSS CANCER INSTITUTE
 Department of Laboratory Medicine
 11560 University Avenue
 Edmonton, Alberta T6J 1Z2
 Phone: 780-432-8454 Fax: 780-432-8455

Patient Name:	[REDACTED]	Loc/Rm #:	WMC
PHN, #:	[REDACTED]	Phys:	HUGH, DR. JUDITH C *WMC
DOB:	[REDACTED]		DEPT OF ANATOMICAL PATHOLOGY,
Chart #:	[REDACTED]	Sex: F	5B4 WALTER MACKENZIE CENTRE,
			EDMONTON AB T6G2B7
Pt. Home Phone #:	[REDACTED]		
Health Record No.:	0		
Prov./ Postal Code:	AB		
	NA		

CCI - Biomarker Report

* Amended - Report Replaces all Previous Reports *

Accession #:	HR12-[REDACTED]	Specimen Type:	Left Breast Wire-Localized Partial Mastectomy
Collected:	6/12/2012		
Received:	6/21/2012		
Reported:	9/4/2012		

Amended Report

Specimen History:

UAH Path: U12-[REDACTED] Invasive lobular carcinoma, alveolar variant grade 2/3.

BIOMARKER IMMUNOHISTOCHEMISTRY RESULTS:

ADDITIONAL BIOMARKER RESULTS

MIB-1 (KI 67) PROLIFERATION INDEX: 3 (THREE)%

Result is based upon the pathologist's visual estimation of the percentage MIB-1 immunoreactivity within tumor cell nuclei. Additional computer image analysis was employed as an adjunctive aid to enhance reproducible quantitation. Three microscopic field images (20x objective) were acquired (files available) to illustrate active regions of tumor cell proliferation for quantitation using ImageJ / IMMUNORATIO, and this data was visually validated and integrated by the pathologist. NOTE: This Ki-67 evaluation is not yet formally standardized and controlled as a quantitative Class II biomarker in our laboratory, as discussed.

ESTROGEN RECEPTOR (SP1): ER POSITIVE (3+ STRONG)

PROGESTERONE RECEPTOR (PgR636): PR POSITIVE (3+ MODERATE)

HER-2/neu PROTEIN (polyclonal): HER-2 EQUIVOCAL (2+)

CISH RESULTS:

FINAL HER 2 IN SITU HYBRIDIZATION INTERPRETATION: NEGATIVE
No HER-2/neu gene amplification

HER-2/neu CHROMOGENIC IN SITU HYBRIDIZATION (CISH)
HER-2neu gene (SPot-Light Her2probe)

Patient Name: [REDACTED]
PHN: [REDACTED]

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Printed: 11/16/2012 7:15:00 AM

APPENDIX F: Oncotype DX sample report

The Oncotype DX[®] assay provides an individualized Recurrence Score[®] result

NODE-NEGATIVE, ER+ PATIENTS: Prognosis

Genomic Health | **oncotype DX[®]**
Breast Cancer Assay

Genomic Health, Inc.
301 Peninsula Drive
Redwood City, CA 94063 USA
Toll Free Tel: 866-ONCOTYPE (866-662-6897)
Worldwide Tel: +1 650-599-2080
www.oncotypedx.com

Page 1 of 3

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
Date of Birth: 01-Jan-1950
Medical Record/Patient #: 556677771
Date of Surgery: 25-Sep-2008
Specimen Type/ID: Breast/SURG-0001

Requisition: R00003G
Specimen Received: 05-May-2009
Date Reported: 15-May-2009
Client: Community Medical Center
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Recipient: Dr. Sally M Jones

BREAST CANCER ASSAY DESCRIPTION

Oncotype DX Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score[®] is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

**Breast Cancer
Recurrence Score = 12**

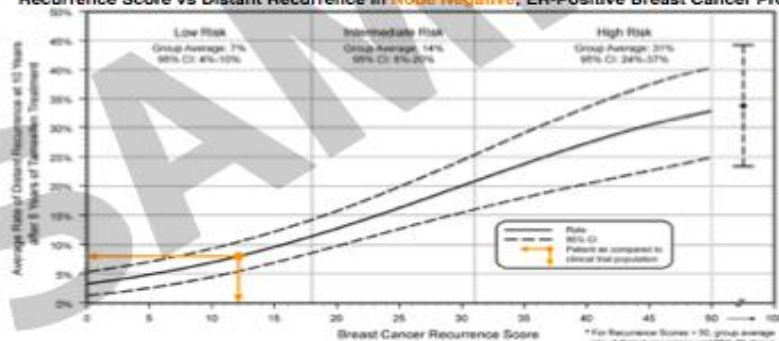
The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, **Node Negative**, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 12 had an Average Rate of Distant Recurrence of **8% (95% CI: 5%-10%)**.

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in **Node Negative, ER-Positive Breast Cancer Prognosis**



Node Negative

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

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GH004 Rev021

APPENDIX G: Ongoing studies

Study or resource	Description
BC (under Stephen Chia) did a local study on the impact of Oncotype DX on decision-making	This study conducted in B.C. asked oncologists to assess whether patients would go for chemo, then presented Oncotype DX recurrence scores, and there then was a shift in 30% shift away from chemo (i.e., without the Oncotype DX testing, 1/3 patients would be going for chemo unnecessarily). This was presented in 2011-2012, but is not published yet.
Taylor X trial	This is a clinical trial that Calgary patients were involved in where everyone gets tamoxifen, and patients between 18 and 31 Oncotype DX risk scores (i.e., the intermediate risk recurrence group), are randomized to either hormones vs. hormones plus chemo. It will take years to get results, but believes that the results will show that chemo offered to benefit to this group of patients OR at the very least a razor-thin benefit. [Note that one of the pathologist also spoke about the importance of this trial]
An international Ki67 reproducibility study	Nielsen TO, Polley M-YC, Leung SCY, Mastropasqua MG, Zabaglo LA, Bartlett JMS, Viale G, McShane LM, Hayes DF, Dowsett M, on behalf of the International Ki67 in Breast Cancer Working Group of the BIG-NABCG collaboration. University of British Columbia, Vancouver, BC, Canada; National Cancer Institute, Bethesda, MD; European Institute of Oncology, Milan, Italy; The Institute of Cancer Research, London, United Kingdom; Ontario Institute for Cancer Research, Toronto, ON, Canada; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Royal Marsden Hospital, London, United Kingdom; Breast International Group-North American Breast Cancer Group Collaboration http://www.sabcs.org/ProgramSchedule/Day3.asp
Clinical utility study of the impact of Oncotype DX	A prospective clinical utility study of the impact of the 21-gene recurrence score assay (Oncotype DX) in estrogen receptor positive (ER+) node negative (pN0) breast cancer in academic Canadian centers. – ASCO http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail

	view&confID=114&abstractID=97457
Prospective comparison study	<p>Prospective comparison of recurrence score and independent central pathology assessment of prognostic tools in early breast cancer (BC): Focus on HER2, ER, PR, Ki-67 results from the phase III WSG-Plan B trial.</p> <p>http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=100237</p>
Welcome Trust UK group working on comparing Oncotype DX with Pam50 test	<p>They have compared Oncotype DX, Pam50 and ICH4; and IHC4 was superior (may not be reproducible, however). Subsequent publications from the same group, that showed oncotype dx was slightly better than the Pam50. [N.B.: s/he sent along some published studies comparing Pam50 with an IHC panel; with Pam50 assessed as being a slightly more accurate prognostic. [See Prat et al (2012)]</p>
IHC5 research being done out of Memorial Sloan Kettering in New York	<p>What they are obtaining through this is a something that is close to the Oncotype DX score. Memorial isn't releasing algorithm yet, however. You need experience doing it, setting it up, correlating it with recurrence scores in your lab. We're just not there yet in AB. As soon as you bring in a new test it takes time to validate it. Won't trust it until he's seen correlation with Oncotype DX recurrence scores locally.</p>

APPENDIX H: Search strategy for qualitative review

MEDLINE (OVID)

Cochrane CENTRAL Register (OVID)

1. exp Breast Neoplasms/
2. ((breast* or mammary) adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
3. 1 or 2
4. limit 3 to animals
5. limit 3 to (animals and humans)
6. 4 not 5
7. 3 not 6
8. Genetic Testing/
9. Gene Expression Profiling/
10. ((gene* or genom*) adj3 (analysis or profile* or profiling or test*)).tw.
11. (oncotype dx or pam50 or pam-50 or protein expression).tw.
12. exp Immunohistochemistry/
13. immunohistochemistry.tw.
14. (IHC or IHC4 or radox assay or mammaprint or blueprint or breast cancer index or mammostrat or NPI plus).tw.
15. Adjuvant! Online.tw.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. attitude/ or attitude to death/ or attitude to health/ or health knowledge, attitudes, practice/
18. behavior/ or health behavior/ or illness behavior/ or information seeking behavior/ or risk reduction behavior/
19. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experience* or interest or interests or perceived or perception* or preference* or satisfaction or understand*).tw.
20. 17 or 18 or 19
21. 7 and 16 and 20
22. Recurrence/
23. Neoplasm Recurrence, Local/
24. (reappear* or re-appear* or recur* or reoccur* or re-occur* or repeat* or return*).tw.
25. 22 or 23 or 24
26. 21 and 25

EMBASE (OVID)

1. exp breast cancer/
2. ((breast* or mammary) adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
3. 1 or 2
4. limit 3 to animal studies
5. limit 3 to (human and animal studies)
6. 4 not 5
7. 3 not 6
8. genetic screening/
9. gene expression profiling/

10. ((gene* or genom*) adj3 (analysis or profile* or profiling or test*)).tw.
11. (oncotype dx or pam50 or pam-50 or protein expression).tw.
12. immunohistochemistry/
13. immunohistochemistry.tw.
14. (IHC or IHC4 or randox assay or mammaprint or blueprint or breast cancer index or mammostrat or NPI plus).tw.
15. Adjuvant! Online*.tw.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 7 and 16
18. attitude to health/ or attitude/ or attitude to illness/ or patient attitude/ or exp attitude to death/
19. health behavior/ or health belief/ or health belief model/
20. behavior/
21. psychological aspect/
22. risk reduction/
23. information seeking/
24. personal experience/
25. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experience* or interest or interests or perceived or perception* or preference* or satisfaction or understand*).tw.
26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 17 and 26
28. cancer recurrence/
29. tumor recurrence/
30. recurrent disease/
31. (reappear* or re-appear* or recur* or relaps* or reoccur* or re-occur* or repeat* or return*).tw.
32. 28 or 29 or 30 or 31
33. 27 and 32

PsycINFO (OVID)

1. exp Breast Neoplasms/
2. ((breast* or mammary) adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
3. 1 or 2
4. limit 3 to animal
5. limit 3 to (animal and human)
6. 4 not 5
7. 3 not 6
8. gene expression/
9. genetic testing/
10. ((gene* or genom*) adj3 (analysis or profile* or profiling or test*)).tw.
11. (oncotype dx or pam50 or pam-50 or protein expression).tw.
12. Immunocytochemistry/
13. immunohistochemistry.tw.
14. (IHC or IHC4 or randox assay or mammaprint or blueprint or breast cancer index or mammostrat or NPI plus).tw.

15. Adjuvant! Online*.tw.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 7 and 16
18. attitudes/ or health attitudes/ or psychologist attitudes/
19. behavior/ or health behavior/ or illness behavior/
20. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experience* or interest or interests or perceived or perception* or preference* or satisfaction or understand*).tw.
21. 18 or 19 or 20
22. 17 and 21
23. "Relapse (Disorders)"/
24. (reappear* or re-appear* or recur* or relaps* or reoccur* or re-occur* or repeat* or return*).tw.
25. 23 or 24
26. 22 and 25

CINAHL (EBSCO)

1. (MH "Breast Neoplasms)
2. ((breast* or mammary) N3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
3. 1 or 2
4. (MH "Genetic Screening") OR (MH "Gene Expression Profiling") OR (MH "Immunohistochemistry")
5. ((gene* or genom*) N3 (analysis or profile* or profiling or test*))
6. (oncotype dx or pam50 or pam-50 or protein expression or immunohistochemistry)
7. (IHC or IHC4 or radox assay or mammaprint or blueprint or breast cancer index or mammostrat or NPI plus or Adjuvant! Online)
8. 4 or 5 or 6 or 7
9. 3 and 8
10. (MH "Attitude") OR (MH "Behavior") OR (MH "Attitude to Illness") OR (MH "Attitude to Health") OR MH "Health Knowledge") OR (MH "Decision Making, Patient")
11. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experience* or interest or interests or perceived or perception* or preference* or satisfaction or understand*)
12. 10 or 11
13. 9 and 12
14. (MH "Recurrence") OR (MH "Neoplasm Recurrence, Local")
15. (reappear* or re-appear* or recur* or reoccur* or re-occur* or repeat* or return*).tw.
16. 14 or 15
17. 13 and 16

ERIC (EBSCO)

Education Complete (EBSCO)

Psychological and Behavioral Collection (EBSCO)

1. (breast* or mammary) N3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
2. (reappear* or re-appear* or recur* or reoccur* or re-occur* or repeat* or return*)

3. 1 and 2
4. (gene* or genom*) N3 (analysis or profile* or profiling or test*)
5. (oncotype dx or pam50 or pam-50 or protein expression)
6. immunohistochemistry
7. (IHC or IHC4 or randox assay or mammaprint or blueprint or breast cancer index or mammostrat or NPI plus)
8. (Adjuvant! Online)
9. 4 or 5 or 6 or 7 or 8
10. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experience* or interest or interests or perceived or perception* or preference* or satisfaction or understand*)
11. 3 and 9 and 10