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Malek Hannouf, *The University of Western Ontario*

Supervisor: Dr. Gregory S. Zaric, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Epidemiology and Biostatistics

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ECONOMIC EVALUATION OF POTENTIAL APPLICATIONS OF GENE EXPRESSION PROFILING IN CLINICAL ONCOLOGY

(Integrated Article)

by

Malek Bassam Hannouf

Graduate Program in Epidemiology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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Abstract

Histopathological analysis of tumor is currently the main tool used to guide cancer management. Gene expression profiling may provide additional valuable information for both classification and prognostication of individual tumors. A number of gene expression profiling assays have been developed recently to inform therapy decisions in women with early stage breast cancer and help identify the primary tumor site in patients with metastatic cancer of unknown primary. The impact of these assays on health and economic outcomes, if introduced into general practice, has not been determined. I aimed to conduct an economic evaluation of regulatory-approved gene expression profiling assays for breast cancer and cancer of unknown primary for the purpose of determining whether these technologies represent value for money from the perspective of the Canadian health care system. I developed decision-analytic models to project the lifetime clinical and economic consequences of early stage breast cancer and metastatic cancer of unknown primary. I used Manitoba Cancer Registry and Manitoba administrative health databases to model current "real-world" Canadian clinical practices. I applied available data about gene expression profiling assays from secondary sources on these models to predict the impact of these assays on current clinical and economic outcomes. In the base case, gene expression profiling assays in early stage breast cancer and cancer of unknown primary resulted in incremental cost effectiveness ratios of less than $100,000 per quality-adjusted life-year gained. These results were most sensitive to the uncertainty associated with the accuracy of the assay, patient-physician response to gene expression profiling information and patient survival. The potential application of these gene expression profiling assays in clinical oncology appears to be cost-effective in the Canadian healthcare system. Field evaluation of these assays to establish their impact on cancer management and patient survival may have a large societal impact and should be initiated in Canada to ensure their clinical utility and cost-effectiveness. The use of Canadian provincial administrative population data in decision modeling is useful to quantify uncertainty about gene expression profiling assays and guide the use of novel funding models such as conditional funding alongside a field evaluation.

Keywords

Cost-Effectiveness, Oncology, Gene Expression Profiling, Breast Cancer, Cancer of Unknown Primary, 21-Gene Recurrence Score Assay, Tissue of Origin Test, Incremental Cost Effectiveness Ratio, Quality Adjusted Life Year.

Co-Authorship Statement

Malek Bassam Hannouf designed the studies, performed the statistical analyses and drafted the manuscripts. Bin Xie, Muriel Brackstone, Eric Winquist, Sisira Sarma, Salah Mahmud, George Rodrigues, Peter Rogan, Jeffery Hoch participated in the design of the studies and interpretation of the results. Gregory S. Zaric participated in the design of the studies, participated in statistical analyses and drafting the manuscripts.

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Chapter 1

1 Introduction

1.1 Gene expression profiling

Current goals in cancer research include the discovery of new cellular targets to exploit for new targeted treatments, new biomarkers for early cancer detection, and providing a better classification of cancers for prognostication and treatment decision [1]. Toward this end, significant research efforts have been made to understand the molecular basis of carcinogenesis and the biologic behavior of human cancers [1]. Due to the complexity of the molecular alterations in tumor cells, progress has been slow. Carcinogenesis is a multistep process in which cells accumulate altered expression of numerous genes as they progress to a more malignant phenotype [2]. Confounding this complexity, many of the so-called oncogenes and tumor suppressor genes are signaling molecules, which control the expression of a subset of downstream genes [2].

Cells respond to environmental signals by modulating the expression of genes contained within the nucleus. When genes are activated, they are transcribed to generate messenger RNA (mRNA), which is transported from the nucleus to the cytoplasm and translated into protein by the ribosomes.

Approximately 3 to 5 percent of genes are active in a particular cell, even though all cells have the same information contained in their DNA. Most of the genome is selectively repressed, a property that is managed by the regulation of gene expression, mostly in transcription (i.e. the production of messenger RNA from the DNA). Changes in gene expression in response to a cellular perturbation take place that result in the expression of hundreds of gene products and the suppression of others. This molecular heterogeneity is thought to explain, at least in part, the variability in outcome and response to therapy that characterizes tumors of different histology [1-2].

Even tumors of a specific histological type can be quite heterogeneous. In general, histopathological analysis of tumor tissue is the main tool that guides clinical management decisions and prognostic estimates [1-2]. However, tumor behavior cannot

be adequately understood through the analysis of one or a small numbers of genes, particularly for the common solid tumors.

The analysis of multiple expressed genes or proteins provides more valuable information for both classification and prognostication of individual tumors [1-2]. The development of microarray methodology, which permits the expression of thousands of genes to be tested simultaneously, represents a powerful technique to read the "molecular signature" of an individual patient's tumor [3]. This process is called gene expression profiling. Analyzing gene expression patterns among individual patients with the similar disease may disclose molecular differences. Such classification may allow better treatment selection and prognostication [2, 4].

While these discoveries increase our understanding of molecular pathogenesis, they can also suggest novel therapeutic targets, provide information about drug resistance pathways, and refine diagnostic and prognostic classifications [4]. For instance, a major problem in clinical oncology is the heterogeneous response of histologically similar tumors to treatments such as cytotoxic chemotherapy [5]. With the exception of estrogen or progesterone receptor, and human epidermal growth factor receptor 2 (HER-2) expression in breast cancer (for hormonal therapy and trastuzumab, respectively) [6], epidermal growth factor receptor (EGFR) kinase domain mutations and genomic amplification in lung cancer (in EGFR targeted inhibitors gefitinib or erlotinib) [7], and K-ras mutations in colon cancer (lack of response to EGFR-targeted antagonists) [8], there are no other single molecules that are clinically valuable predictors of response validated for any form of anticancer therapy.

Growing data suggest that prediction of response to chemotherapy or biologically targeted agents may be possible by analyzing gene expression profiles [9]. With rapid advances in the DNA microarray technologies and more sophisticated studies, microarray analysis has begun to make ways into clinical trials and practices in oncology [10-12]. Particularly, two major areas of investigation are the use of gene expression profiling assays to guide cancer therapy and cancer diagnosis.

1.1.1 Gene expression profiling to guide cancer therapy

A major area of investigation is the use of such molecular profiling to predict response to therapy [13-17]. Gene expression profiling analysis by DNA microarray is now available in patients with breast cancer to quantify the likelihood of a breast cancer recurrence in women with newly diagnosed, hormone receptor-positive early stage breast cancer [11, 18-20]. Furthermore, there is growing evidence that gene expression profiling analyses can help predict which patients are most likely to benefit from chemotherapy [11, 18-20]. To date, several gene expression-based tests have demonstrated the potential value of this approach. The 21-gene recurrence score (RS) assay (Oncotype DX, Genomic Health Inc., Redwood City, CA) [11, 18] and MammaPrint (Agendia, Irvine, CA and Amsterdam, The Netherlands) [21-22] are commercially available gene expression profiling assays that are used to inform treatment decisions based on tumour biology. However, the RS-assay is becoming widely accepted as having clinical validity and utility for this purpose [23].

The RS-assay is a RT-qPCR based signature that measures the expression of 21 genes (16 cancer related and 5 reference genes). RNA is obtained from formalin-fixed paraffin-embedded (FFPE) tissue samples. The RS-assay is recommended for patients with hormone receptor positive and human epidermal growth factor receptor 2 (HER-2) not over expressed axillary lymph node negative early stage breast cancer. The test requires assessment of estrogen receptor and HER-2 status by an alternative method [18]. The RS-assay became the most widely used clinical gene expression assay in the United States. The genes in the assay were selected from 250 candidates that were tested for association with survival in a cohort of 447 tumor samples, from the tamoxifen treated and node negative cases of the National Surgical Adjuvant and Breast Project (NSABP) B-20 clinical trial [24]. The RS-assay was validated in a large cohort of estrogen receptor positive node negative breast cancer patients treated with tamoxifen, enrolled in the NSABP B-14 study [18]. In this study, the rates of distant recurrence at 10 years were 6.8%, 14.3%, and 30.5% for the low-risk, intermediate, and high-risk groups, respectively [18]. The RS is a continuous variable, ranging from 0 to 100, and constitutes a measure of the risk of relapse within 10 years. The score is an independent prognostic factor for patients with hormone receptor positive breast cancer treated with adjuvant

tamoxifen. Patients can be classified into three categories on the basis of RS. Low risk (RS<18), intermediate (RS 18-31), and high (RS>31), which equate with 10 year relapse rates of 7%, 14%, and 30%, respectively. Women in the low risk group do not seem to benefit from adjuvant chemotherapy as shown in the NSABP-B20 analysis that randomly assigned patients to receive cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy with concurrent tamoxifen or tamoxifen alone [11]. Only a small subset of tissues was available for analysis (651 samples from 2363 randomized patients). The analysis showed that their distant metastasis free survival is higher than 90% regardless whether or not they received CMF chemotherapy. In contrast, women in the high-risk group derived benefit from adjuvant CMF chemotherapy [11]. The question remains unanswered for women who fall into the intermediate-risk group. The current ongoing Trial Assigning IndividuaLized Options for Treatment (TAILORx) [25] and Southwest Oncology Group (SWOG) S-1007 [26]) seeks to answer this question by randomly assigning patients with intermediate RS to adjuvant chemotherapy followed by anti-estrogen treatment or anti estrogen treatment alone.

MammaPrint (Agendia, Irvine, CA and Amsterdam, The Netherlands) is a microarray-based gene-expression profiling assay of RNA [21-22]. The test is comprised of 70 genes identified from an initially unselected set of all >25,000 genes within the human genome which were obtained from fresh frozen samples of tumor tissue [21]. New studies have demonstrated that the test could be done by RT-qPCR, both in fresh frozen and formalin-fixed paraffin embedded tissue, with equivalent performance [27]. The genes are associated with all hallmarks of cancer including proliferation, invasion, and angiogenesis. The genes were obtained from tissue of 78 patients with lymph node negative breast cancers, most of which were hormone receptor positive tumors and did not receive adjuvant systemic therapy [21]. This signature has been validated on numerous cohorts of node negative patients, and has demonstrated to provide independent prognostic information beyond standard clinicopathological variables such as age, histology, tumour grade and pathological stage [21, 28-29]. The test can be used in estrogen negative breast tumors.

Mammaprint is the first and so far only Food and Drug Administration (FDA)-approved gene-expression assay to be used as prognostic test for women with node-negative breast cancers [30]. The test yields two prognostic groups: low-risk and high-risk. This signature is predictive of both distant disease-free survival and overall survival when adjusted for lymph node status. Patients in the low-risk group have a distant metastasis free survival of over 90% without the addition of systemic chemotherapy [21].

Overall published evidence supports MammaPrint as a better predictor of the risk of distant recurrence than traditionally used tumour characteristics or algorithms, but its performance in therapeutically homogenous populations is not yet known with precision, and it is unclear for how many women the lowest predicted risks are low enough to forgo chemotherapy [23]. No evidence is available to permit conclusions regarding the clinical utility of MammaPrint to select women who will benefit from chemotherapy [23].

The key components of the RS-assay used for clinical care are the RS and corresponding RS category [23]. These data are based on the clinical trials from which the RS-assay method was derived and validated. Although the MammaPrint and other assays under development [30] do provide risk categories, the available evidence does not show that the results of these assays have equivalent clinical utility to the RS-assay [23]. In particular, the RS can be interpreted in the context of the NSABP B14 and B20 clinical trials [11, 18] data to estimate the probability of recurrence without treatment and of chemotherapy benefit, respectively. The equivalent data cannot be extracted from other assays. In addition, direct prospective comparisons between the RS-assay and alternatives are lacking.

Gene expression profiling assays are also being investigated as a tool to predict the likelihood of disease recurrence and guide adjuvant treatment in individuals with colon cancer [31]. Currently, five tests have been launched and shown to have prognostic value in independent patient series, although the designs and sample numbers of the validation analyses have varied [32-33]. The 12-gene assay (Oncotype Dx® Colon Cancer, Genomic Health Inc., Redwood City, CA) [34] is the only test that is available outside of research settings, although it has not yet been recommended for clinical use.

This assay is based on the use of quantitative reverse transcriptase-PCR (RT-PCR) that measures the expression level of a subset of 12 genes, which includes seven genes for relapse-free survival prognosis and five reference genes that yielded a prognostic recurrence score (RS) [35], ranging between 0 and 100. Patients are classified into three categories based on their RS: low risk (RS < 30), intermediate risk (RS 30–40), or high risk (RS > 40). Moreover, this test reveals another parameter termed, treatment score that may point on the degree of benefit from adjuvant chemotherapy [35].

The test was based on four adjuvant studies that were conducted by the "National Surgical Adjuvant Breast and Bowel Project" (NSABP) and the "Cleveland Clinic Foundation" [36]. A validation study using archival fixed paraffin-embedded tumor tissue specimens from 1,436 patients with stage II colon cancer who were randomly assigned between adjuvant chemotherapy and surgery alone (QUASAR) confirmed the clinical utility of the RS score [35]. It is essential to emphasize that the test is mostly accurate in early stages of colorectal cancer, when a 5-FU-based chemotherapy is being considered. High-risk patients, as well as, patients that are candidates for other chemotherapeutic treatments, require further investigation [37].

1.1.2 Gene expression profiling to guide cancer diagnosis

Another major area of investigation is the use of gene expression profiling for diagnosis in patients with cancer [38-40]. Specific gene expression profiles based on the tissue of origin have been identified for many tumor types. Because histogenetic information is maintained during metastatic process, gene expression pattern of a metastasis may reflect the histogenetic make-up of the primary tumour [41]. It is becoming possible to use gene expression-based analysis to assist in identification of the primary site [41]. Thus, several multigene assays have been developed for the purpose of identifying the tissue of origin in patients with cancer of unknown primary.

To date, several gene expression-based tests have demonstrated the potential value of this approach. Although these tests use different microarray platforms, classification algorthims, and sample selection criteria, the overall accuracy of the confirmation of the primary site of origin was 75% to 89% [12, 39, 42-53]. Most of the commercially available tests have shown promising results in the internal validations (i.e., using same

specimens used for a test development) and have been translated to RT-PCR or robust microarray platforms [48]. However, other well identified requirements should be taken into account when translating and validating these tests for clinical use. According to guidelines for translation of genomic classifiers and for validation of clinical molecular tests [54-56], demonstration of reproducibility and adequate external validation analysis (using specimens other than those used for a test development) are required. External validation of a test for tumour classification needs to have a statistically valid sample size, inclusion of enough specimens for each tumour class to be identified, and inclusion of indeterminate results in overall performance [54-55]. According to these guidelines we will review in the following two paragraphs the publicly available evidence for each commercially available test.

The Tissue of Origin (TOO) test is commercially available by Response Genetics (Los Angeles, CA) and clinically offered in the United States. The test is the only assay that has been reviewed and cleared by the Food and Drug Administration [57]. The TOO test compares the RNA profile (a 2000-gene profile) of a tumour FFPE specimen to established RNA profiles of 15 known tissues, representing 90% of all solid tumours. The test measures the degree of similarity between the expression patterns of the tumour and those of a panel of 15 different tissue types [58]. The tumour tissue types represented are bladder, breast, colorectal, gastric, hepatocellular, kidney, non-small cell lung, ovarian, pancreatic, prostate, thyroid carcinomas, melanoma, testicular germ cell tumour, non-Hodgkin's lymphoma, and sarcoma. The test result is presented as 15 separate similarity score (SS) (which are interpreted as probabilities), one for each tissue type on the panel. The highest SS indicates the most likely tissue of origin. Any tissue type on the panel with an SS of ≤5% is ruled out as a possible origin of tumour tissue with >99% confidence.

The test requires an FFPE biopsy block (including block of solid tissue, cell buttons from fine needle aspirates, cell buttons from malignant effusions, or core needle biopsies) containing at least 1mm^2 of tumour tissue [58]. The test can also be performed using a minimum of 3 unstained slides of at least 5μm-thickness from any of the biopsies mentioned. A minimum of 30 ng FFPE-derived RNA is sufficient to perform the test [58].

The test was developed on a gene expression microarray (PathChip) platform that showed adequate reproducibility in an interlaboratory comparison study. Thus, the platform appears suitable for clinical application. The test was validated on independent 462 FFPE specimens derived from metastatic or poorly differentiated tumor specimens of known primary cancers and showed 89.3% accuracy in identifying tumour's primary site [59]. The large number of specimens included in the external validation allowed for class representation of at least 25 specimens per tissue type, and inclusion of indeterminate results. Thus, the test appears to fulfill the criteria for successful translation outlined above [54-55] as was also judged by the FDA [60].

The first gene expression-based test for determination of the primary tumour site to be clinically available was the Cancer-TYPE ID test, developed by BioTheranostics as a laboratory-developed test (LDT). The test is an RT-PCR 92-gene assay that is reported to classify 39 different tumour types and 64 subtypes [11]. The test was evaluated with independent 119 FFPE tumour specimens and showed an overall accuracy of 86% [11]. However, the reproducibility of the test has not yet been adequately shown [48]. Another test available in the United States is the miRview mets test from Rosetta Genomics (Philadelphia, Pennsylvania), which is also offered as an LDT. The test is an RT-PCR 48-microRNA (miRNA) assay that is reported to classify 25 different tumour types [49]. The test was evaluated in 80 independent tumour specimens (12 frozen /68 FFPE) but the study authors did report the overall accuracy of the confirmation of the primary site [49]. It is not possible to determine if the assay was successfully translated to the RT-PCR platform due to lack of published data, including data regarding reproducibility of the test [48]. The CUPrint test is a 1900-gene GEM test that was developed by Agendia BV (Amesterdam, The Netherlands) and is only available outside the United states in Agendia's CLIA-certified laboratory. This test is reported to classify 11 different tissue types. Agendia did not translate the test to an RT-PCR platform but used a robust customized microarray instead [61]. In terms of external validation, the test was evaluated on an independent sample set of 84 primary and metastatic tumours representing 9 tumour types and showed an overall accuracy of 83% [45]. The CUP assay, developed by Veridex (LA Jolla, California), evaluates the expression of 10 tissue-type specific gene markers by using quantitative RT-PCR and is designed to detect

tumours from 6 specific sites: lung, breast, colon, ovary, pancreas, and prostate [12, 51]. The test is not commercially available. The small number of genes evaluated has limited the number of tissues that can be distinguished by this assay. The test was evaluated with independent 37 FFPE tumour specimens and showed an overall accuracy of 75.6%. 50% of tumours outside of the 6 targeted tissue types were incorrectly assigned to 1 of these tissue types [48].

Overall, peer-reviewed evidence has shown that the quality of the external validation studies for these tests is insufficient [48]. These validation studies have been restricted to a small number of specimens and do not have adequate representation for all tumour tissue types being evaluated. For instance, a claim has been made of 100% sensitivity for a specific tissue type, with only 1 or 2 specimens for the tissue type in the validation sample [48]. Furthermore, data regarding specificity (i.e., how often the negative result is correct) are not publically available for these tests.

Although different assays have been used, these panels appear to be accurate in 80 to 90 percent of cases of patients using tissue from metastases in patients with known primary tumors [39]. Experience in patients with adenocarcinoma of unknown primary is more limited. The accuracy of diagnosis by molecular profiling has recently been studied retrospectively in a group of 20 patients who initially had CUP but subsequently had a primary site identified clinically [38]. The primary sites identified by the molecular profiling assay (from the original metastatic tumor biopsy) matched the subsequent clinical diagnosis in 15 of 20 patients, further supporting the value of this diagnostic method [38].

Gene expression profiling is likely to be a valuable addition to the diagnosis and management of patients with CUP. However, definitive demonstration of its value in improving treatment outcome for these patients is not available. Ongoing clinical trials are evaluating the efficacy of treatment directed by RT-PCR assay results, as well as comparing the utility of the several available assays.

1.1.3 Obstacles to incorporating gene expression profiling in clinical practice

Using these gene expression profiling tests in clinical oncology poses several questions: How convincing is the data? Most companies support their claims about these tests, which cost from about $3,000 to more than $5,000 per patient, with data from retrospective analyses rather than prospective trials. Large ongoing trials for some of these tests may increase practitioners' comfort with them, but final data are years away and a funding decision may need to be made prior to having full efficacy or effectiveness data of these gene expression applications. Thus, reimbursement policies and clinical validation are still the main obstacles for personalized medicine in oncology. The impact of these innovations on health and economic outcomes, if introduced into general practice, has not yet been determined. As these tests are expensive there are important tradeoffs to consider in deciding whether to adopt these tests in a resource constrained system such as the Canadian health care system.

1.2 Cost Effectiveness Analysis

Cost effectiveness analysis (CEA) is a commonly used technique to assess the "value-for-money" of new medical technologies such as drugs, devices, policies, medical procedures. For a given level of resources available, society or decision maker wishes to maximize the total aggregate health benefit conferred [62]. International decision making bodies such as the National Institutes for Health and Clinical Excellence (NICE) in the United Kingdom (UK) [63] and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia [64] have formally incorporated CEA into their processes for reviewing new medical technologies and inform health technology adoption decisions [65]. Similarly, the Common Drug Review (CDR) in Canada [66] considers CEA when considering reimbursement of new pharmaceuticals.

CEA involves a formal comparison of the incremental costs and incremental benefits associated with incorporating a new medical technology into an existing standard of care. Costs are expressed in currency units, and benefits are expressed in common units such as life expectancy (i.e., "life years gained"). The frequent use of "life year gained" which

has been used as the chief outcome variable in CEA is considerably restrictive. CEA produces a more robust and meaningful outcome measure by combining the quality and quantity of the outcomes [67]. Therefore, Quality Adjusted Life Year (QALY) has become a common metric in CEA. QALYs are life years that have been adjusted by a value between 0 and 1 to reflect difference in quality of life for difference health conditions. Results of a CEA are usually presented in the form of a ratio called the incremental cost-effectiveness ratio (ICER) where the ICER associated with incorporating a new medical technology is given as by:

$$ICER = \frac{Cost_{New} - Cost_{Current}}{Health_{New} - Health_{Current}}$$

Because CEA involves marginal cost and benefits, the choice of which current standard of care or technology to compare can drive the calculation and the conclusion of a CEA (i.e., an appropriate definition for "Current" in the ICER equation). Therefore, CEA is very sensitive to the choice of strategies being compared. The new medical technology is then considered "cost-effective" based on a value judgment (what cost is considered a good price for an additional outcome) [68]. Several heuristics are commonly used to assist in making this value judgment including plotting the incremental cost and effectiveness in a cost-effectiveness plane [69] comparisons with other technologies in a league table [70] and comparisons with pre-specified thresholds (e.g., £30,000 / QALY gained in UK [71] or $100,000 / QALY gained in Canada [62, 72]).

1.2.1 Models and parameterization in CEA

There are two common approaches for parameterization in CEA of a new medical intervention. In the first, data for CEA are estimated directly from a single clinical trial (i.e., use of resources are collected concurrently with the clinical trial). In this case, the economic data can be viewed as experimental and are typically analyzed in the same way as the clinical data. In the second approach, decision analytic models (e.g., decision trees, Markov models, and Monte Carlo simulation models [73]) are used and data from a number of sources are synthesized [74]. The data for this type of CEA could be a mix of

experimental (e.g., efficacy data from randomized clinical trials), observational (e.g., resource-use data extracted from patient chart review or a claims database), routine statistics (e.g., data delineating the unit costs or prices of resources), local surveys (e.g., data showing how therapies effect patients' quality of life), or expert opinions (e.g., data describing the physical quantities of resources consumed by the strategies being compared). Even randomized clinical trial-based CEAs often use some data obtained from outside the clinical trial, such as the prices (or unit costs) of health care resources. It has been argued that CEAs using experimental data are the most internally valid and meet the biostatistical and epidemiological rules, in that the differences between medical interventions being compared are unlikely to be biased [74]. However, several factors may still limit the internal and external validity of experimental data and consequently the results from CEAs using these data.

Clinical trials usually include only a small fraction of the targeted general population. Thus, the experience of participants in these trials may not reflect the experience of the targeted general population [75-76]. Studies have suggested that the observed effects in these trials may not necessary reflect the effects of the treatments or technologies under investigation [77-78]. Clinical trials are usually of limited duration of follow up relative to the possible duration of impact of the alternatives. In addition, many CEA guidelines call for use of a "lifetime" horizon. This set of factors necessitates extrapolation of clinical trial data when used in cost-effectiveness analyses using models (e.g. Markov chain simulation) to assess the long-term impact of the alternative treatment options on cost and effectiveness [79]. Moreover, there are circumstances where randomization may not be possible such as studies aiming to investigate the impact of adherence to drug treatmenton clinical outcomes in real-world settings.

A modeling-based CEA offers the potential for generalization and for transferring the results to other settings. However, clinical (both experimental or observational) and economic data reported in the literature and commonly used in these analyses, may not be entirely relevant to the population in the studied geographic region and setting in which alternatives are likely to be applied in the real world [80]. Ultimately, data used in CEAs should be extracted from settings that accommodate socioeconomic variability and are likely to reflect regular clinical and economic experience of the relevant patient

population under investigation in the studied geographic region with long follow up periods [81].

Disease registries and administrative health databases can be valuable clinical and economic data sources for conducting CEAs [82]. These databases contain records of events that have occurred under everyday conditions. The main advantage of using these databases is that interventions or technologies studied in CEAs can be described under actual "real world" conditions that are relevant to the studied geographic region [81].The alternative is to use literature from clinical trials or observational studies data. These databases are often population based (i.e., minimizing selection bias), have high rates of disease ascertainment (i.e., disease prevalence and incidence), and include a large-enough population over a long-enough time period to evaluate effectiveness and costs among different age- or race-specific population subgroups [83-84].

1.2.2 Administrative health data in Canada

1.2.2.1 Provincial administrative health databases

In Canada, provincial governments are generally responsible for the funding of inpatient and outpatient hospital services and physician services (Table 1) as per the Canada Health Act [85]. In addition, some provincial governments fund other services such as non-physician professional services (e.g. chiropractic, optometry), prescription drugs (i.e., with eligibility criteria), vaccines, home care, and long-term care. Each provincial government maintains records of utilization for most of these services. The maintenance of these records forms the provincial administrative health databases (Table 1).

In addition, each province maintains a population registry where each resident is assigned a unique identifier (scrambled ID) which is often in the form of a health plan number (health insurance number). For example in Ontario, the unique identifier is the Ontario Health Insurance Plan (OHIP) number. This unique identifier is used to record each service in the provincial databases. Via the unique identifier, an analyst can link available records for drugs, physician visits, hospital discharges, and some outpatient visits to form a unique patient record. This record could include all information for all the patient's services.

Linkage is useful because it allows analysts to identify patients with specific characteristics in one database, and then gather additional information about those patients using other databases. For example, patients who received hospital-based and community-based emergency and ambulatory care can be identified in Ontario using the National Ambulatory Care Reporting System (NACRS) and then get their OHIP billing claims before and after.

1.2.2.2 National administrative health databases

The Canadian Institute for Health Information (CIHI) facilitates the development and maintenance of an integrated health information system at a national level. In particular, CIHI, in co-operation with the provincial governments, develops data standards for some databases such as inpatient care, ambulatory care, and pharmaceuticals. The provinces maintain their own data systems which may be more complete than the requirements specified by CIHI, and submit their patient or client data on hospital care and physician care to CIHI using the CIHI standards on a quarterly or annual basis.

The CIHI databases are most useful when one wants to obtain data on overall counts of services and on overall costs without identifying how many people have received these services. CIHI does have unique identifiers, but they do not have population registry data. Unique identification is not always accessible to researchers outside CIHI, whereas some provinces (Manitoba, Quebec, and Ontario in particular) have a long history of successful research collaboration with academics.

1.2.2.3 Disease registries

Disease registries are surveillance systems which maintain records of patterns of medical history, diagnostics or treatment in patients with a specific disease and follow outcomes or survival patterns over time. In Canada, patients are often identified using the same unique identifiers used in the population registry. This allows researchers to link disease registries with administrative databases to build detailed longitudinal records of their treatments and health care utilization.

There are several disease registries in Canada. However, the most well established are the cancer registries. These cover the entire population, with all provincial and territorial

registries reporting to the Canadian Cancer Registry (CCR). The overall coverage for cancer incidence data is estimated to be at least 95% [86]. Although these registries differ somewhat in their approaches and methods, their procedures for registration are fairly consistent, and comparable surveillance data from each province are reported up to the CCR level.

There are other disease registries in Canada that have also instituted surveillance operations and built databases of patients with specific diseases. The Canadian Organ Replacement Registry, managed by CIHI, organizes organ replacement and end stage renal failure records for all 84 organ replacement centers across the country. Starting in May 2001, the Canadian Joint Replacement Registry (CJRR), managed by CIHI and orthopedic surgeons, collects information on hip and knee joint replacements performed in Canada. The CJRR follows joint replacement patients over time to monitor their revision rates and outcomes. The Canadian Trauma Registry has accommodated the records of all Ontario accidental injuries and is currently expanding to cover all Canada. In addition, the Institute for Clinical Evaluative Sciences (ICES) has recently received Canadian Institute for Health Research (CIHR) funding to develop a Canadian stroke registry.

1.2.3 Use of administrative health data for descriptive costing studies

In Canada, analysts can use the information in health administrative databases to describe the health care utilization and direct costs that are associated with persons with specific medical conditions or who use specific drugs or services. The utility of administrative data for descriptive costing has been demonstrated in a number of analyses. For example, Krahn et al. [87] used the Ontario Cancer Registry, Discharge Abstract Database, Claims History Database of the OHIP, National Ambulatory Care Reporting System and other administrative databases in Ontario to estimate the total healthcare costs and costs attributable to prostate cancer across all stages of disease. Another analysis by Carriere et al. [88] used the Canadian Institute for Health Information's Inpatient Discharge Abstract

Database for the province of Alberta and Alberta Health Insurance Plan Registry to determine the cost per day for the treatment of community-acquired pneumonia.

1.2.3.1 Case definition

When using administrative data to estimate cost of health care utilization of disease (i.e., cost of illness) the analyst must first develop criteria to identify the patient population of interest. For instance, Blanchard et al. [89] developed such criteria for identifying diabetes cases using Manitoba administrative data. Blanchard et al. [89] defined a diabetes case as a patient record with two or more diabetes diagnoses at different visits in the physician billings data during a two-year period or one diagnosis in the hospital inpatient data. Another analysis by Simpson et al. [90] used an expanded definition with Saskatchewan administrative data to measure costs during a 10-year period for persons who had no previous diabetes records. In that definition, the dispensing of insulin or an oral antidiabetic drug was added to the list of possible indications. In case of a narrower target patient population of interest (i.e., persons with diabetes who have nephropathy) the analyst must develop a more detailed algorithm to define the disease. For example, Bernstein [91] used Manitoba administrative data and developed a case definition for inflammatory bowel disease (IBD). Bernstein [91] defined a case as IBD if the physician billing records showed at least five physician visits that were coded as IBD during any time span that was greater than two years. When cases with specific medical conditions of interest are captured by disease registries, the analyst may use data captured by these registries to identify those cases. For instance, a recent analysis by Oliveira et al. [92] used the Ontario Cancer Registry to identify patients diagnosed with the 21 most common cancer sites in Ontario. After identifying the patient population of interest, the analyst can take an incidence approach or prevalence approach for costing of illness using administrative data.

1.2.3.2 Incidence approach for costing of illness

The incidence approach allows analysts to track costs (i.e., longitudinal costing) from the time when the disease is diagnosed until a desired end point (e.g., cure, disease progression, or death). For a chronic disease, the tracking may require years of

observation. For instance, Johnston et al. [93] measured the cost of hospital, physician, and drug services for persons with diabetes, for 10 years from the time of incidence.

Analysts may find the incidence approach to be useful in determining cost of resource use that is avoided because of cases that avoided. This approach would be useful in particular to planners who want to determine the economic impact of a preventive measure. Analysts may also find the incidence approach for costing to be useful in examining the impact of disease severity at diagnosis on health care utilization and costs. For instance, Mittman et al. [94] used the Ontario Cancer Registry to identify incident cases of colorectal cancer and obtained information about colorectal cancer stage at diagnosis. Mittman et al [94] linked those cases with the Home Care Administration database and the Registered Persons Database to estimate the cost of home care services over the patient observation time by stage of colorectal cancer at diagnosis. Importantly, the incidence approach for costing has been useful in examining the impact of the phase of care on health care utilization and costs.

In the phase-based costing approach to costing, the analyst divides the patient's follow up time to discrete phases. The time frame for each phase should be defined and a hierarchy of time frames should be specified when necessary so that all phases stay mutually exclusive. In 2013, Oliveira et al. [92] used a phase-based approach to examine the costs of health care incurred before and after cancer diagnosis. Oliveira [92] used the Ontario Cancer Registry and Ontario administrative data to identify incident cases of cancer. Patient's observation time was divided into two discrete periods: the pre-diagnosis phase and initial care phase. The pre-diagnosis phase was defined as the 3 months before diagnosis. The initial care phase included the date of diagnosis and the subsequent 12 months. Recently, Mittmann el al. [94] used a phase-based costing approach to costing home care services for incident cases with colorectal cancer in Ontario. Mittman et al. [94] divided the time horizon following diagnosis into three discrete care phases: initial, continuing, and terminal. The initial care phase was defined as the first 6 months following the diagnosis of colorectal cancer. The terminal care phase was defined as the 6 months before death and applied to patients who died during follow-up period. The continuing care phase was defined as the time between the initial and terminal phases.

The following hierarchy of time frames was used: terminal care> initial care> continuing care, such that all phases were mutually exclusive.

1.2.3.3 Prevalence approach for costing of illness

The prevalence approach focuses on the costs of all cases with the disease during a fixed period (e.g., a year). Using this approach, the analyst will include all cases with the diagnosis, even if the incidence of the disease occurred in a prior year. Jacobs et al. [95] used the prevalence approach to calculate the direct medical care costs of diabetes using administrative databases from Manitoba. Jacobs et al. [95] studied the net (i.e., attributable costs) by subtracting the costs per person with diabetes from the per-person costs of the non-diabetic population. Simpson et al. [90] used the same approach to estimate direct medical care cost of diabetes using administrative databases from Saskatchewan. However, Simpson et al. [90] used diagnostic codes to identify services that were related to the diagnoses of diabetes.

1.2.4 Use of administrative health data in CEA

Despite the potential advantages from disease registries and administrative health data in CEAs, the use of these data to conduct CEAs in Canada is relatively uncommon. In one of the first economic evaluations using Canadian administrative data, Brown MG [96] studied the cost-effectiveness of New Brunswick's Extra-Mural Hospital (EMH) home health care program using population-based administrative data on physician services utilization to examine whether home care services act indirectly as substitutes for physician services. Brown MG suggested that the introduction and expansion of New Brunswick's EMH home health care program have unanticipated substitution effects, which reduce health system costs by reducing the rate of growth of per-capita utilization of physician services.

In another analysis, Najafzadeh et al [97] studied the cost-effectiveness of herpes zoster (HZ) vaccine versus status quo (no HZ vaccine) from the perspective of the Canadian healthcare payer. They estimated health resource utilization using administrative data retrieved from the British Colombia from 1994 to 2003. They reported an ICER of 41,709 per QALY gained for a cohort of elderly subjects aged ≥ 60 years and concluded that HZ vaccination of adults, specially for individuals aged 60-70 years, seems to be a

cost-effective intervention and might be considered by Canadian decision makers. Recently, Sander et al [98] reported an economic evaluation of Ontario's universal influenza immunization program (UIIP) compared to a targeted influenza immunization program (TIIP) using Ontario health administrative data. They estimated an ICER of 10,797 per QALY gained and concluded that the UIIP compared TIIP is an economically attractive intervention.

1.2.5 Decision Analytic Models and Cost Effectiveness Analysis in Oncology

Decision analytic models have been used extensively to evaluate health technologies related to oncology. Examples include cost effectiveness analyses of preventive strategies for women with BRCA1 or BRCA2 mutations [99]; HER testing and trastuzumab treatment for breast cancer [100]; the cost effectiveness of various strategies for screening for colorectal cancer [101-104]; the cost effectiveness of different treatment options for prostate cancer [105-106]; and cost effectiveness analyses of specific drugs [107-110]. This represents a portion of work in the area. Searches of common medical databases for terms related to cost effectiveness analysis and oncology yield thousands of results.

Chapter 2

2 Objectives and research framework

I aimed to conduct an economic evaluation of potential application of major gene expression profiling assays in breast cancer and cancer of unknown primary for the purpose of determining whether these applications represent value for money from the perspective of the Canadian health care system. The research proceeded with the following steps:

- Develop decision-analytic models. These models include decision trees with several Markov models as the terminal nodes in the trees. Markov models are used to simulate cancer progression correspondent with certain disease severity or different types of cancer.
- Fit models parameters using three main sources of information: Manitoba Cancer Registry, Manitoba health administrative databases, and use of secondary sources and the existing literature to estimate some additional models parameters of interest, such as quality of life for various health states and sensitivity and specificity of molecular profiling assays.
- Set the models to perform cost effectiveness analyses of different molecular profiling assays. The cost-effectiveness analyses are conducted according to recommendations by the Canadian Agency for Drugs and Technologies in Health [111]. Results are presented in the form of ICER which provides a measure of average cost per additional unit of health benefit. Outcomes for health effects are measured in QALYs (i.e., life-years weighted by utility estimates to produce QALYs). Cost outcomes are measured as the mean cost per patient.
- Conduct one-, two- and three-way deterministic sensitivity analyses on parameters of interests to characterize uncertainty in the output measures and determine the minimum conditions in terms of cost and accuracy for which these molecular profiling assays would be cost effective. This helps to provide insights about the potential economic attractiveness of assays that are still in various stages of development and regulatory approval.

- Conduct probabilistic sensitivity analysis using Monte Carlo simulation to understand the robustness of the results. Each iteration consists of a random draw from an appropriate distribution for all model inputs to produce a distribution of model outputs.
- Conduct value-of-information analysis [112] as part of the sensitivity analysis to determine the expected monetary value of perfect information about these molecular profiling assays in the Canadian setting. In particular, baseline decision models are set up to express molecular profiling assay related parameters (i.e., sensitivity and specificity of the assay) as probability distributions (i.e., reflecting uncertainty of that assay in the Canadian setting) on the basis of available validation analyses and the entire model is set up as a probabilistic model. Using simulation techniques (i.e., making random draws of the probabilistic model), the level of uncertainty in the model is assessed. Using a willingness to pay threshold [69], the opportunity cost associated with the choice of a molecular profiling assay as the optimal strategy is calculated and presented as a total of expected value of perfect information (EVPI) about a given assay per patient. Using the size of patient population, the EVPI about a gene expression profiling assay is calculated for the entire target population that could potentially benefit from more research on the predictive value of that assay in the Canadian setting. The EVPI provides decision makers with valuable information about the use of novel funding models such as conditional funding alongside a field evaluation [113].

Chapter 3

3 Cost-effectiveness of a 21-gene recurrence score assay versus Canadian clinical practice in women with early-stage estrogen- or progesterone-receptor-positive, axillary lymph-node negative breast cancer

3.1 Abstract

A 21-gene recurrence score (RS) assay may inform adjuvant systematic treatment decisions in women with early stage breast cancer. I sought to investigate the cost effectiveness of using the RS-assay versus current clinical practice (CCP) in women with early-stage estrogen- or progesterone-receptor-positive, axillary lymph-node negative breast cancer (ER+/ PR+ LN- ESBC)from the perspective of the Canadian public healthcare system. I developed a Markov model to project the lifetime clinical and economic consequences of ESBC. I evaluated adjuvant therapy separately in post- and pre-menopausal women with ER+/ PR+ LN- ESBC. I assumed that the RS-assay would reclassify pre- and post-menopausal women among risk levels (low, intermediate and high) and guide adjuvant systematic treatment decisions. The model was parameterized using 7 year follow up data from the Manitoba Cancer Registry, cost data from Manitoba administrative databases, and secondary sources. Costs are presented in 2010 CAD. Future costs and benefits were discounted at 5%.The RS-assay compared to CCP generated cost-savings in pre-menopausal women and had an ICER of $60,000 per QALY gained in post-menopausal women. The cost effectiveness was most sensitive to the proportion of women classified as intermediate risk by the RS-assay who receive adjuvant chemotherapy and the risk of relapse in the RS-assay model. The RS-assay is likely to be cost effective in the Canadian healthcare system and should be considered for adoption in women with ER+/ PR+ LN- ESBC. However, ongoing assessment and validation of the assay in real-world clinical practice is warranted.

3.2 Introduction

In 2011, an estimated 23,200 women in Canada will be diagnosed with breast cancer [114]. Approximately half of them will be diagnosed with early-stage estrogen- or progesterone-receptor-positive, axillary lymph-node negative breast cancer (ER+/ PR+ LN- ESBC) [115]. Standard care for these patients usually includes local therapy (surgery with or without radiation) followed by adjuvant systematic therapy such as endocrine therapy alone (tamoxifen or aromatase inhibitors) or chemotherapy followed by endocrine therapy [116]. Canadian guidelines specify that a patient's risk of recurrence can be classified as low, intermediate or high and that adjuvant chemotherapy may be added when the benefits of treatment outweigh toxicities of therapy [117]. However, evaluating the risks and benefits of chemotherapy based on the Canadian guidelines is difficult because the histopathologic measures that inform the guidelines are not accurate predictors of risk or benefits of chemotherapy [18, 117-120]. A validated software program Adjuvant!Online (AOL) has been developed that projects outcomes at 10 years to assist oncologists in adjuvant decision-making process. However, AOL is also based on histopathologic measures.

The 21-gene recurrence score assay (Oncotype DX) produces a "tumor signature" reflecting tumor biology and risk of relapse [11, 18]. An algorithm produces a continuous variable known as the "recurrence score" (RS) reflecting prognosis, which ranges from 1 (lower risk) to 100 (higher risk), based on the expressions of the 21 genes isolated from tumor samples. Women with a score of less than 18 have a low risk of recurrence and typically have good outcomes from endocrine therapy alone, whereas those with a score of 31 or more have a high risk of recurrence and gain the largest expected benefit from the addition of chemotherapy to endocrine therapy. Women with a score between 18 and 30 have an intermediate risk and do not appear to have a large benefit from chemotherapy but the uncertainty in the estimate cannot exclude a clinically important benefit [11, 25].

The prognostic and predictive value of the RS-assay in women with ER+/PR+ LN- ESBCwas evaluated in retrospective analyses of the National Surgical Adjuvant Breast and Bowel Project (NSABP) chemotherapy-tamoxifen trials (B-14 and B-20) [11, 18,

121] in the United States. It was shown that among ER+/PR+ LN- ESBC patients, approximately, 51% had a low RS, 22% an intermediate RS, and 27% a high RS [11, 18, 121]. The assay was found to be more accurate than histological measures alone in predicting the likelihood of breast cancer recurrence (both loco-regional [121] and distant recurrence [11, 18]) and patient survival within 10 years of initial diagnosis [11], as well as benefit from adjuvant chemotherapy [11, 121]. Additionally, clinical significance of the RS-assay has been reported in the Asian population [81].

In 2007 the RS-assay was recommended in the National Comprehensive Cancer Network and American Society for Clinical Oncology guidelines as "evidence-based" to guide the use of adjuvant chemotherapy in all women with ER+/ PR+ LN- ESBC [122-123]. Public coverage of the 21-gene assay is limited and inconsistent across Canada. However, the use of the test with reimbursement mechanisms is likely increasing. It is available in Ontario through "out-of-country health services" which requires a request from an oncologist and pre-approval [124-125]. In 2010 the Ontario Health Technology Advisory Committee (OHTAC) recommended that the assay be made available "within the context of a field evaluation" [126]. It is also available in a limited fashion in British Columbia and Quebec [125]. The test is not widely used and in 2010 less than 1000 patients received the test across Canada [125] but few field evaluations to establish its impact on Canadian practice are ongoing in British Columbia and Ontario.

According to the Annual Report Card of the Cancer Advocacy Coalition of Canada, the RS-assay will cost $CAD 4,000 per patient including all Canadian system expenses [124]. Previous cost-effectiveness analyses of the RS-assay in women with ER+/ PR+ LN- ESBC in the US [127-128], Japan [129-130], Israel [131] and Canada [132-134] suggested that it is likely to be cost saving or cost effective in this patient group. However, findings from studies in Israel [131] and Japan [19-20] cannot be extrapolated to the Canadian context because of possible variations in clinical practice and different approaches to pricing and reimbursement. Additionally, analyses from the US [127-128] and Canada [132-134] did not use all relevant data and suffer from other limitations as indicated elsewhere [135].

Generation of recommendations for Canadian clinical practice guidelines regarding the use of RS-assay requires a comprehensive health economic evaluation of the assay in the Canadian setting. The purpose of this study was to conduct a cost-effectiveness analysis of the RS-assay versus current clinical practice (CCP) regarding adjuvant chemotherapy treatment in women with ER+/ PR+ LN- ESBC from the perspective of the Canadian healthcare system.

3.3 Methods

3.3.1 Overview of Model-Structure

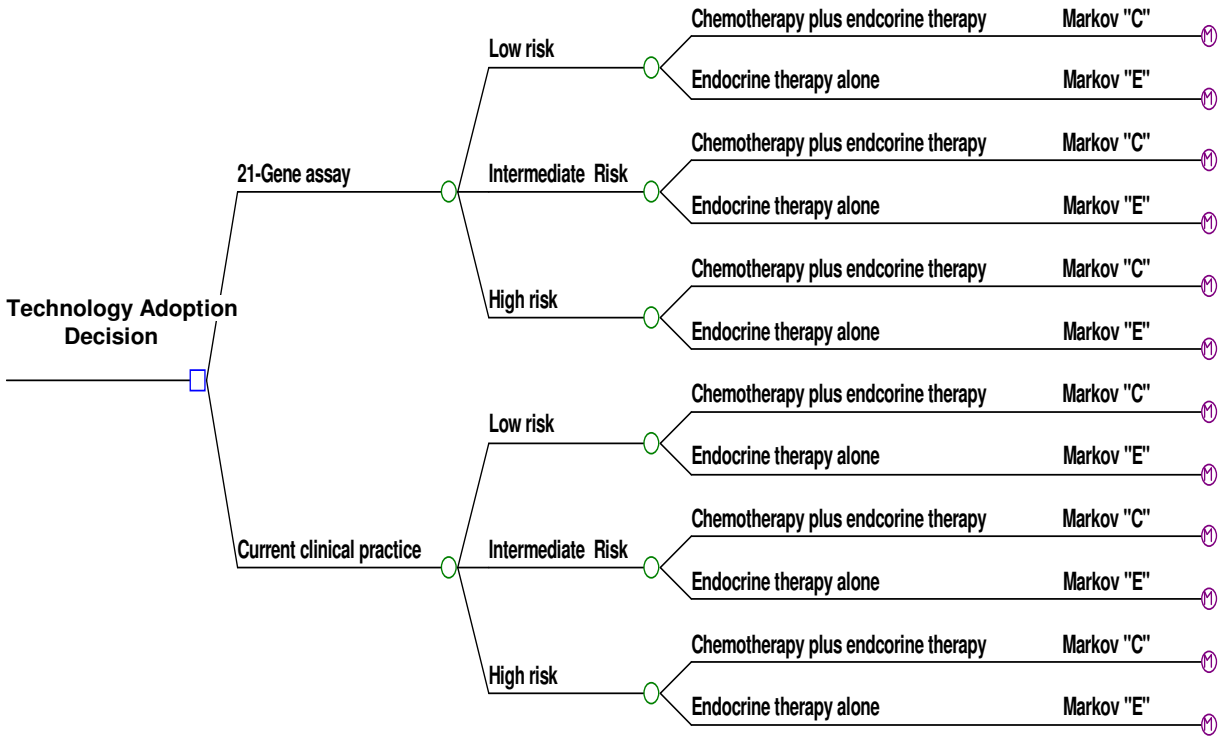
I developed a decision analytic model (Figure 1) to project the lifetime clinical and economic consequences of ER+/ PR+ LN- ESBC under two different treatment strategies. The model begins with a decision to use the RS-assay or to continue with CCP (Figure 1a). I assumed that each strategy (RS or CCP) classifies patients to three risk levels (low, intermediate and high) and corresponding treatment regimens (endocrine therapy plus chemotherapy or endocrine therapy alone). Patients receiving endocrine therapy alone entered model "E" (Figure 1b) and those receiving chemotherapy plus endocrine therapy entered model "C" (Figure 1c).

Model "E" simulated monthly transitions among the following four distinct health states: (1) remission; (2) loco-regional recurrence (LR); (3) distant recurrence (DR); (4) death. Model "C" simulated monthly transitions among the following five distinct health states: (1) remission with no chemotherapy-related serious adverse effects (CSAE); (2) remission with CSAE; (3) LR; (4) DR; (5) death.

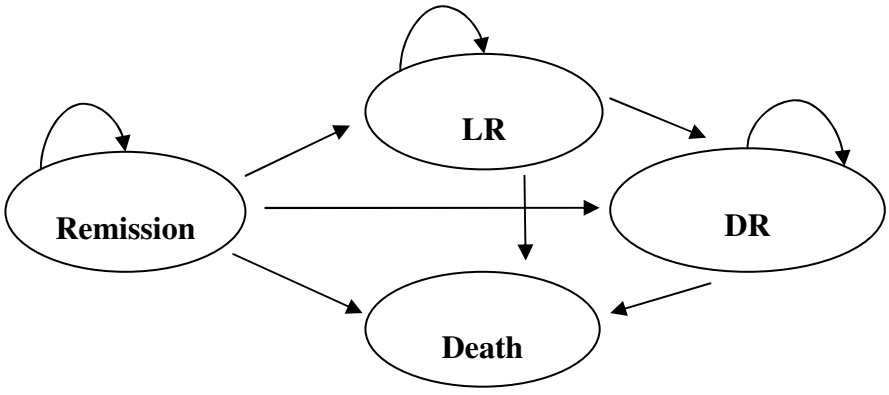
I used a lifetime horizon and half cycle correction [136]. Future costs and benefits were discounted at 5% annually following Canadian guidelines [72]. Data collection and analysis involving Manitoba administrative databases (including the Manitoba Cancer Registry, the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network) were approved by the University of Manitoba Health Research Ethics Board.

Figure 1. Decision model for early stage breast cancer.

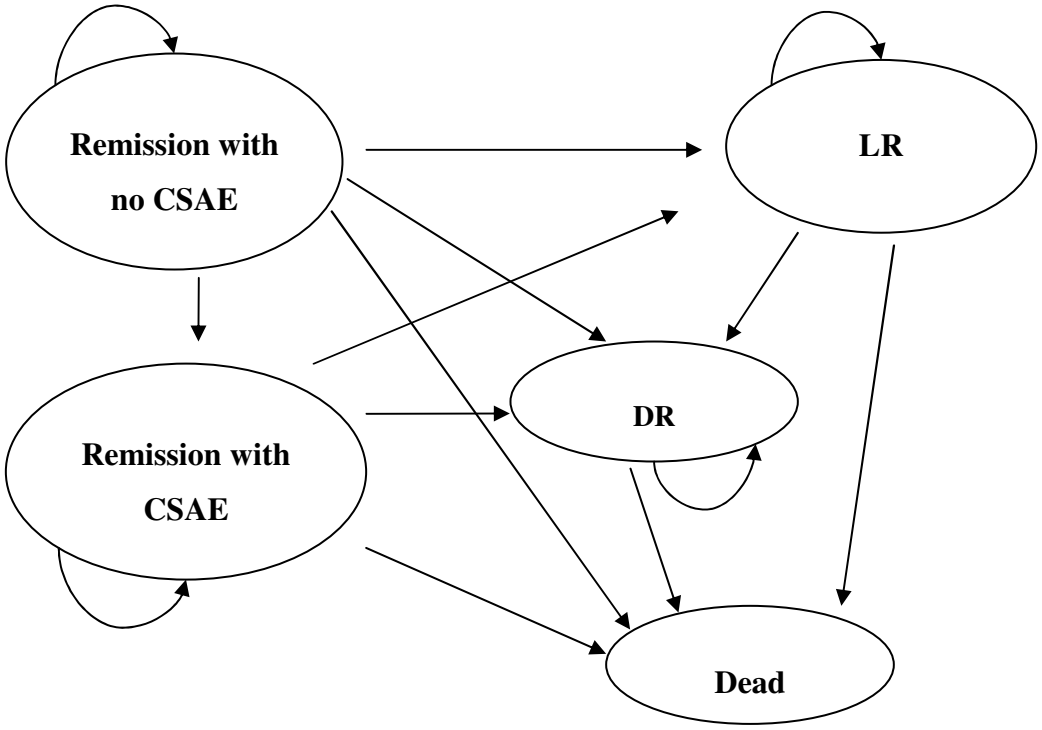
a RS-assay versus Canadian clinical practice±.



b Schematic representation of the Markov model structure "E"*‡.



c Schematic representation of the Markov model structure "C"†‡.



± The risk classification criteria in the Canadian clinical practice arm was based on the Canadian clinical practice guidelines for adjuvant systemic therapy for women with node-negative breast cancer [117].
* Patients entering Markov model "E" start the model and remain in the remission state unless they relapse (LR, DR or Dead).
† Patients entering Markov model "C" start the model in the remission state with no CSAE. Within the first cycle patients may develop CSAE. These patients will make a transition to the remission state with CSAE. During the first cycle, patients also may transition to DR, LR and Dead states. After the first cycle, patients may remain in the two remission states unless they relapse in to LR, DR or Dead.
‡ In both Markov models, patients who developed LR, remain in the LR state or make transition to DR or Dead states. Patients who developed DR remain in the DR state or make transition to the Dead state. The cycle length was 1 month.
LR, loco-regional recurrence; DR, distant recurrence; CSAE, chemotherapy-related serious adverse effects.

3.3.2 Risk distribution and transition probabilities

The Manitoba Cancer Registry is a provincial database that contains records for more than 99.5% of all cancer patients in Manitoba [137]. Information on breast cancer staging, based on the American Joint Commission on Cancer (version 5), has been collected for breast cancers diagnosed since January 1995 [138]. I used the Registry to identify a study cohort consisting of all pre-menopausal (defined as age <50 years) and post-menopausal (age ≥50 years) women living in Manitoba diagnosed with ER+/ PR+ LN- ESBC (stage I/II) during the period from January 1, 2000 to December 31, 2002.Although data on human epidermal growth factor receptor 2 (HER-2) status were not collected by the registry during this time frame, the majority of these women are likely HER-2 negative since women with HER-2 positive are only found in approximately 10% to 15% of endocrine positive breast cancers such as those in our study population [139-143]. I used data from women diagnosed during this period so that a long follow up period would be available. Seven-year follow-up information from the time of diagnosis was available for each patient. This included breast cancer recurrence (LR and DR) and treatments (surgery, radiation therapy, endocrine therapy and chemotherapy). I linked the study cohort identified using the Registry with administrative data held by Manitoba Health and Healthy Living including the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network. To protect confidentiality, the linkage in this study was performed, via scrambled health number, using anonymatized versions of these databases.

To verify that the proportion of women who received adjuvant chemotherapy in our study cohort would reflect more recent clinical practice regarding adjuvant chemotherapy administration, I examined a second cohort, consisting of all women diagnosed between January 1, 2003 and December 31, 2005. I did not find the proportion receiving adjuvant chemotherapy to differ between the two time periods (chi-square test, level of significance of 0.05) and thus used the earlier time period with longer follow-up data to parameterize the model.

For the CCP model I estimated the risk distribution and proportion receiving chemotherapy within each risk level (Table 1). According to the Canadian clinical practice guidelines, risk can be specified on the basis of tumor size, histological or nuclear grade, and lymphatic and vascular invasion [117]. The Manitoba Cancer Registry collects this information with the exception of lymphatic and vascular invasion. Given the significant correlation between tumor size and lymphatic and vascular invasion[144], I classified pre- and post-menopausal women for this analysis as belonging to three risk levels (low, intermediate and high risk) on the basis of tumor size and histological or nuclear grade only. I defined current clinical practice according to the observed administration of adjuvant therapy in the ER+/ PR+ LN- ESBC cohort during the study period. I conducted survival analyses using Kaplan-Meier estimates for pre- and post-menopausal women separately, stratified by use of adjuvant chemotherapy, using 7 years of follow up data from the Manitoba Cancer Registry, and used this information to estimate all transition probabilities in the CCP Markov models.

For the RS-assay model, I derived the risk distribution and monthly transition probabilities from remission to LR, DR and Death over 10 years within each risk level from retrospective analyses of the NSABP chemotherapy-tamoxifen trials (B-14 and B-20) (Table 1) [11, 121]. Investigators from the B-14 and B-20 studies provided Kaplan Meier curves for LR, DR and death events stratified by risk level. To account for menopausal status, I adjusted all transition probabilities derived from these summary statistics based on corresponding risk ratios (for LR, DR and death) comparing pre- to post-menopausal women derived from our studied ESBC cohort. The risk ratios were weighted using the menopausal status balance reported in the B-14 and B-20 trials [11, 121].

There is still uncertainty as to whether chemotherapy is necessary for women with intermediate risk. Reported usage in this group varies, including estimates of 56% [145], 50% [146], 47% [147], 38% [148], 33% [131], and 26% [149]. In the base case I assumed that 50% of women in the intermediate risk group would receive adjuvant chemotherapy.

There is no data suggesting that outcomes after first relapse are affected by the primary adjuvant therapy received [150]. Thus, I assumed that transition probabilities following first relapse in the RS-assay model would be the same as those in the CCP model.

To extrapolate beyond the follow-up period of the ESBC cohort and the clinical trials used for this study, I assumed that the observed average monthly transition probabilities from remission to LR, DR and Death during the last observed year of follow-up would be constant over the extrapolated lifetime. I used female age-adjusted life tables for Manitoba to adjust the probabilities from remission to death in order to account for the incremental mortality risk over the extrapolated time [151].

Table 1. Parameter estimates and sources.

Variables	Pre-menopausal Women		Post-menopausal Women		Duration	Distribution used in PSA†	Source
	Base case value	Range tested in sensitivity analyses	Base case value	Range tested in sensitivity analyses			
Risk classification by CCP (%)							
High risk	21.1	15.8 – 32.6	22.3	18 – 27		Dirichlet	MCR
Chemotherapy-treated women	100	85.1 – 100	53.8	43 – 64.4		Beta	MCR and PC
Intermediate risk	72.6	62.9 – 80.6	52.3	47 – 57.5		Dirichlet	MCR
Chemotherapy-treated women	65.2	53.4 – 75.4	14.2	9.9 – 20		Beta	MCR and PC
Low risk	6.3	0 – 10	25.4	21.2 – 30.2		Dirichlet	MCR
Chemotherapy-treated women	16.7	10 – 20	3.4	0 – 10		Beta	MCR and PC
Overall chemotherapy-treated women by CCP (%)	69	60 – 83	19	13 – 27.7			MCR and PC
Risk classification by RS-assay (%)							
High risk	27.7	22.9– 33.1	23.1	18.7 – 28.3		Dirichlet	[11]
Chemotherapy-treated women	100	90 – 100	100	90 – 100		Beta	[11]
Intermediate risk	19.5	15.4 – 24.4	21.5	17.1 – 26.5		Dirichlet	[11]
Chemotherapy-treated women	50	0 – 100	50	0 – 100		Beta	[131, 148-149, 152]
Low risk	52.6	46.9 – 58.3	55.4	49.7 – 61		Dirichlet	[11]
Chemotherapy-treated women	0	0 – 10	0	0 – 10		Beta	[11]
Overall chemotherapy-treated women by RS-assay (%)	37.5	30 – 47.8	33.8	27 – 44.3			[11, 131, 148-149, 152]
Chemotherapy-related serious adverse effects (%)	2.5	0 – 10.6	4	0 – 12.3		Beta	MCR and HA
Health-State Utilities‡							
Remission state							
Remission on chemotherapy regimen with minor or no toxicity	0.85	-20%	0.783	-20%	6 months	Beta	[153-155]
Remission on chemotherapy regimen with	0.623	-20%	0.577	-20%	6 months	Beta	[153-155]

major toxicity							
Remission after chemotherapy regimen	0.872	-20%	0.808	-20%	Life	Beta	[155-156]
Remission on hormonal therapy	0.881	-10% – +10%	0.816	-10% – +10%	60 months	Beta	[153-155]
Remission after hormonal therapy	0.89	-10% – +10%	0.824	-10% – +10%	Life	Beta	[153-155]
Loco-regional recurrence, under treatment	0.623	-10% – +10%	0.577	-10% – +10%	12 month	Beta	[150, 153-155]
Loco-regional recurrence, after treatment	0.757	-10% – +10%	0.700	-10% – +10%	Life time	Beta	[150, 153-155]
Distant recurrence	0.445	-10% – +10%	0.412	-10% – +10%	Life time	Beta	[150, 153-155]
Death state	0		0				
Cost associated with remission (per month), $							
First year after diagnosis with ESBC							
Cost of surgery[a]	3390	3000 – 3780	3642	3384 – 3900	One time	LogNormal	PC. HA and CL
Cost of radiation therapy[b]	3410	2737 – 4252	3027	2430 – 3776	One time	LogNormal	PC and CL
Cost of endocrine therapy[c]							
Tamoxifen	12.4	11.6 – 13.2	12.4	11.6 – 13.2	12 months	LogNormal	DPIN
Aromatase inhibitors			156	120 – 193	12 months	LogNormal	DPIN
Aromatase +tamoxifen			72	62 – 81	12 months	LogNormal	DPIN
Cost of chemotherapy[d]							
Nursing, overhead and administration costs	317.6		317.6		During chemotherapy	LogNormal	CL
Related physician costs	23.4	21.5 – 25.2	23.4	21.5 – 25.2	During chemotherapy	LogNormal	PC
Chemotherapy regimen options							
CMF	478		823		5 months	LogNormal	MCR
AC	806		1918		3 months	LogNormal	MCR
FAC	924		1270		5 months	LogNormal	MCR
TAC	2455		2800		5 months	LogNormal	MCR
Weighted average cost of chemotherapy regimens[e]					5 months	LogNormal	MCR
First three months on chemotherapy	1142		1099		3months	LogNormal	MCR
Next	419		432		2months	LogNormal	MCR
Cost of CSAE[f]	1263	978 – 1581	1,750	1376-2168	During chemotherapy	LogNormal	PC, HA and CL

Surveillance[g]							
Low risk	79	47 – 111	74	62 – 85	12 months	LogNormal	PC
Intermediate risk	93	76 – 108	66	60 – 68	12 months	LogNormal	PC
High risk	106	78 – 133	77	69 – 82	12 months	LogNormal	PC
After first year of diagnosis with ESBC							
Cost of endocrine therapy[c]							
Tamoxifen	12.4	11.6 – 13.2	12.4	11.6 – 13.2	48 months	LogNormal	DPIN
Aromatase inhibitors			156	120 – 193	48 months	LogNormal	DPIN
Aromatase +tamoxifen			72	62 – 81	48 months	LogNormal	DPIN
Surveillance[g]							
Low risk	39	18 – 59	33	30 – 54	Life time	LogNormal	PC
Intermediate risk	35	32– 40	45	38 – 53	Life time	LogNormal	PC
High risk	102	65 – 126	39	32 – 45	Life time	LogNormal	PC
Cost associated with LR (per month), $							
First year after LR							
Cost of Surgery[a]	3522	889 – 7280	2806	1068 – 3111	One time	LogNormal	PC, HA and CL
Cost of Radiation therapy[b]	1098	878 – 1371	2120	1695 – 2651	One time	LogNormal	PC, HA and CL
Cost of endocrine therapy[c]							
Tamoxifen	12.4	11.6 – 13.2	12.4	11.6 – 13.2	12 months	LogNormal	DPIN
Aromatase Inhibitors			156	120 – 193	12 months	LogNormal	DPIN
Sequential aromatase → tamoxifen			72	62 – 81	12 months	LogNormal	DPIN
Cost Chemotherapy[d]	278	181 – 619	311	200 – 688	5 months	LogNormal	PC and CL
Surveillance during first year[g]	118	48 – 189	123	64 – 179	12 months	LogNormal	PC
After first year of LR							
Cost of endocrine therapy[c]							
Tamoxifen	12.4	11.6 – 13.2	12.4	11.6 – 13.2	48 months	LogNormal	DPIN
Aromatase Inhibitors			156	120 – 193	48 months	LogNormal	DPIN
Sequential aromatase → tamoxifen			72	62 – 81	48 months	LogNormal	DPIN
Surveillance after first year of LR[g]	98	33 – 162	78	18 – 139	Life time	LogNormal	PC

Cost associated with DR (per month), $							
First year after DR							
Hospitalization cost	841	138 – 253	1569	185– 3177	12 months	LogNormal	HA and CL
Physicians cost	247	64 – 431	353	205 – 501	12 months	LogNormal	PC
Drugs cost	19	5 – 34	83	29 – 134	12 months	LogNormal	DPIN
After first year of DR							
Hospitalization cost	1293	146 – 3014	783	72 – 1618	Life time	LogNormal	HA and CL
Physicians cost	204	86 – 322	183	62 – 337	Life time	LogNormal	PC
Drugs cost	52	5 – 121	100	33 – 167	Life time	LogNormal	DPIN

† Beta distribution was used for other probability parameter estimates not included in this table.

‡ The baseline utility for post-menopausal women aged 50 to 80 was 0.824 and for premenopausal women aged 20 to 49 was 0.89[155]. I derived utilities for each state by multiplying these baseline utility values by utility estimates for women with breast cancer [150, 153, 156-157], consistent with methodology as described by Fryback [154].

[a] Cost of breast cancer surgery: I used the Hospital Discharge Database and the Physician Claims Database to estimate the mean cost of hospitalization due to any breast cancer surgery (including one day hospitalization and using the ICD-9-CM procedure codes for a hospital abstract) within one year after diagnosis with ESBC and LR by menopausal status.

[b] Cost of radiation therapy: Cost of radiation therapy included cost of radiation therapy–related physician claims in addition to administrative cost. I used the Physician Claims Database to estimate the mean cost of radiation therapy–related physician claims (using the tarrif code for a medical claim) within one year after diagnosis with ESBC and LR by menopausal status. Administrative costs were derived from the cost list for Manitoba health services.

[c] Cost of endocrine therapy: I used the Drug Program Information Network to estimate the mean cost of tamoxifen and aromatase inhibitors by menopausal status (using the drug identification number for a drug claim) within the time periods, between diagnosis with ESBC and before any relapse, and diagnosis with LR and before any relapse.

[d] Cost of chemotherapy: Nursing, overhead and administration costs were derived from the cost list for Manitoba health Services. I used the Physician Claims Database to estimate the mean cost of chemotherapy–related physician claims costs (using the tariff code for a medical claim) within one year after diagnosis with ESBC and LR by menopausal status. Chemotherapy regimens costs were estimated based on the market prices as of May 2010.

[e] Weighted average cost of adjuvant chemotherapy regimens: I calculated the average cost of adjuvant chemotherapy regimens weighted to the observed proportion use of anthracyclines and taxanes by menopausal status. Weighted average cost of adjuvant chemotherapy regimens = proportion of women received non-anthracycline containing adjuvant chemotherapy × cost of CMF + proportion of women received anthracycline containing adjuvant chemotherapy (no added taxanes) × cost of AC + proportion of women received anthracyclines and taxanes containing adjuvant chemotherapy × cost of TAC.

[f] Cost of CSAE: I used the Hospital Discharge Database and the Physician Claims Database to estimate the mean cost associated with hospitalizations due to any of the eight diagnoses which were considered CSAE among women who develop CSAE. I stratified the analysis by menopausal status.

[g] Cost of surveillance: I defined the cost of breast cancer surveillance as the incremental cost of health care utilization (medical claims)after diagnosis with ESBC versus the time before diagnosis. I used the Physician Claims Database to collect medical claims for both post- and pre-menopausal women, within 3 years before and 7 years after diagnosis with ESBC. I estimated the mean cost of medical claims by menopausal status within 3 years before diagnosis in order to reflect the usual cost of health care utilization. I calculated the incremental mean cost of health care utilization by menopausal status during the period from diagnosis with ESBC and before any relapse (excluding cost of claims related to surgery, radiation therapy, chemotherapy and CSAE) stratified by the time following diagnoses (first year versus later). Similarly, I calculated the incremental mean cost of health care utilization by menopausal status after LR.

PSA= probabilistic sensitivity analysis; MCR= Manitoba Cancer Registry: PC= physician claims; HA= hospital abstracts; CL= cost list for Manitoba health services; DPIN=Drug Program Information Network records; ESBC= early stage breast cancer; LR, loco-regional recurrence; DR= distant recurrence; CMF= 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil; AC= 4 cycles of doxorubicin, cyclophosphamide; FAC=6 cycles of fluorouracil, doxorubicin, cyclophosphamide; TAC=6 cycles of docetaxel, doxorubicin, cyclophosphamide; CCP= current clinical practice.

Table 2. Proportion of patient population receiving adjuvant chemotherapy by diagnosis time period and menopausal status.

Diagnosis time period	**No. of women diagnosed with ER+ or PR+ LN- ESBC**		**No. of women received adjuvant chemotherapy (%)**			
	Pre-menopausal women	Post-menopausal women	Pre-menopausal women	2000-2002 vs. 2003-2005 ρ value†	Post-menopausal women	2000-2002 vs. 2003-2005 ρ value†
2000–2002	109	389	74 (69)	.88	73 (18.8)	.7
2003–2005	106	506	71 (67)		90 (17.7)	

† Chi-square test.

3.3.3 Adjuvant Chemotherapy Regimens

In Canada, from 2000-2002, two adjuvant chemotherapy regimens were recommended for women with ER+/ PR+ LN- ESBC: (1) 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or (2) anthracycline-containing chemotherapy regimen such as 4 cycles of doxorubicin (Adriamycin), cyclophosphamide (AC) or 6 cycles of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) [117]. Four cycles of AC has been used preferentially as a component of chemotherapy regimens for the adjuvant treatment of ESBC [158]. Recently, chemotherapy regimens containing taxanes, such as 6 cycles of docetaxel, doxorubicin, cyclophosphamide (TAC), have been recommended for the LN- ESBC population [159].

The majority of adjuvant chemotherapy-treated women in our study cohort received anthracycline-containing adjuvant chemotherapy regimens (Table 2). Information on specific chemotherapy agents (e.g. CMF, AC, FAC, and TAC) was not available. I assumed patients who received non-anthracycline-containing adjuvant chemotherapy regimens received 6 cycles of CMF; that patients who received anthracycline-containing adjuvant chemotherapy regimens with no added taxanes received four cycles of AC; and that patients who received anthracycline and taxane-containing adjuvant chemotherapy regimens received 6 cycles of TAC. Thus, in the base case analysis, I used the weighted average cost of CMF, AC and TAC.

Anthracycline-containing regimens may have a survival advantage compared to CMF regimens [160]. However, other studies showed anthracycline-containing regimens to have equivalent clinical outcomes compared to CMF regimens, particularly in women with favourable prognostic features (LN-, ER+/PR+) such as our study cohort [117, 161-162]. Thus, in sensitivity analysis I considered each of the CMF, AC, FAC and TAC regimens separately as the standard adjuvant chemotherapy regimen for women with ER+/ PR+ LN- ESBC.

3.3.4 Adjuvant chemotherapy-related Serious Adverse Effects (CSAE)

I defined CSAE as hospitalization for any of the following eight diagnoses (as defined by their ICD-9-CM diagnosis and procedure codes)occurring within one year of diagnosis with ESBC: 1) abnormal electrolytes or dehydration; 2) constitutional symptoms and nonspecific symptoms associated with therapy; 3) nausea, emesis, and diarrhea; 4) infection and fever; 5) malnutrition; 6) anemia and red cell transfusion; 7) neutropenia or thrombocytopenia; 8) deep venous thrombosis or pulmonary embolus[163-164]. These diagnoses were selected based on their association with chemotherapy in previous clinical trials[116]. I estimated the incremental rate of occurrence of CSAEs from the frequency of occurrence of these ICD-9 codes in hospital abstracts of adjuvant chemotherapy recipients versus non-recipients, stratified by menopausal status and adjusting for comorbidity indices using the method developed by Charlson et al excluding cancer diagnoses[165].

3.3.5 Costs

Treatment costs, including surgery, radiation therapy, chemotherapy, endocrine therapy, surveillance, and CSAE, are all publicly funded in Manitoba and are thus recorded in the administrative databases. For each patient in the studied cohort I gathered all treatment costs for the first 7 years following diagnosis with primary breast cancer (Table 1). I used this to estimate the cost per unit time in each Markov state.

3.3.6 Utilities

The baseline utility for post-menopausal women aged 50 to 80was 0.824 and for premenopausal women aged 20 to 49 was 0.89, based on representative values for the U.S. population [155]. I derived utilities for each health state by multiplying these baseline utility values by utility estimates for women with early-stage breast cancer [150, 153-154, 156-157] (Table 1). I performed sensitivity analysis on the utility values after

chemotherapy to account for potential long term side effects of primary adjuvant chemotherapy [166].

3.4 Results

Patient, tumor, treatment and event characteristics of the study cohort are summarized in Table 2. There were 109 pre-menopausal and 389 post-menopausal women diagnosed with ER+/ PR+ LN- ESBC in Manitoba from January 1, 2000 to December 31, 2002. The median age was 44 years (range 29-49 years) in pre-menopausal women and 62 years (range 50-88) in post-menopausal women. All pre- and post-menopausal women received surgery (mastectomy or breast-conserving surgery) for their primary breast cancer. Adjuvant therapy including radiation therapy, endocrine therapy (tamoxifen or aromatase inhibitors) and chemotherapy were administered in 63%, 81% and 69% of pre-menopausal women, respectively, and in 52%, 79% and 19% of post-menopausal women, respectively.

In pre-menopausal women, the RS-assay led to an increase of 0.05 QALY per person and decrease in cost of $50 per person resulting in a cost saving compared to CCP. In post-menopausal women, the RS-assay led to an increase of 0.062 QALY per person and an increase in cost of $3,700 per person, resulting in an incremental cost effectiveness ratio (ICER) of $ 60,000 per QALY gained compared to CCP.

Table 3. Characteristics of 489 patients diagnosed during the time period of 2000 to 2002 with ER+ or PR+ 1-3 LN+ ESBC stratified by menopausal status and risk of recurrence using Canadian clinical practice guidelines.

Characteristic	Pre-menopausal women (n=109)				Post-menopausal women (n=389)				ρ value†
	Low risk* (n=11)	**Intermediate risk* (n=78)**	**High risk* (n=20)**	**Overall (n=109)**	**Low risk* (n=115)**	**Intermediate risk* (n=196)**	**High risk* (n=78)**	**Overall (n=389)**	
Age (years)									
Mean (range)	41.8 (30 – 49)	43.6 (29 – 49)	42.7 (33-49)	43 (29-49)	63.4 (50 -85)	64 (50 – 88)	61.8 (50 -86)	63 (50-88)	
<40	3 (27.3)	17 (21.8)	4 (20)	24 (22)	—	—	—	—	
40 – 49	8 (72.7)	61 (78.2)	16 (80)	85 (78)	—	—	—	—	
50 – 64	—	—	—	—	64 (55.7)	111 (56.6)	53 (68)	228 (58.6)	
≥65	—	—	—	—	51 (44.3)	85 (43.4)	25 (32)	161 (41.4)	
Primary tumor size – no. of women (%)									
<2 cm	11 (100)	51 (65.4)	7 (35)	69 (63.3)	115 (100)	117 (59.7)	17 (21.8)	260 (66.8)	.78
2-5 cm	0	27 (34.6)	11 (55)	38 (34.9)	0	79 (40.3)	55 (70.5)	123 (31.7)	
>5 cm	0	0	2 (10)	2 (1.8)	0	0	6 (7.7)	6 (1.5)	
Receptor status – no. of women (%)									
ER+ and PR-	0	11 (14.1)	7 (35)	18 (16.6)	25 (21.7)	54 (27.5)	30 (38.5)	109 (28)	.016
ER- and PR+	0	4 (5.2)	3 (15)	7 (6.4)	1 (0.9)	4 (2.1)	6 (7.7)	11 (2.8)	
ER+ and PR+	11 (100)	63 (80.7)	10 (50)	84 (77)	89 (77.4)	138 (70.4)	42 (53.8)	269 (69.2)	
Tumor grade – no. of women (%)									
1	6 (54.5)	14 (18)	1 (5)	21 (19.3)	89 (77.4)	17 (8.7)	1(1.3)	107 (27.5)	.37
2	0	50 (64.1)	5 (25)	55 (50.5)	0	160 (81.6)	21 (26.9)	181 (46.5)	
3	0	5 (6.4)	14 (70)	19 (17.4)	0	6 (3)	53 (68)	59 (15.2)	
Unknown	5 (45.5)	9 (11.5)	0	14 (12.8)	26 (22.6)	13 (6.7)	3 (3.8)	42 (10.8)	
Stage									
I	11 (100)	55 (70.5)	7 (35)	73 (67)	115 (100)	145 (74)	21 (26.9)	281 (72.2)	.56
IIA	0	23 (29.5)	11 (55)	34 (31.2)	0	51 (26)	51 (65.4)	102 (26.2)	
IIB	0	0	2 (10)	2 (1.8)	0	0	6 (7.7)	6 (1.6)	
With Breast-surgery‡ – no. of women (%)	11 (100)	78 (100)	20 (100)	109 (100)	115 (100)	196 (100)	78 (100)	389(100)	
Breast-conserving surgery	8 (72.7)	51 (65.4)	9 (45)	68 (62.4)	65 (56.5)	113 (57.7)	29 (37.2)	207 (53.4)	.08
Mastectomy	3 (27.3)	27 (34.6)	11 (55)	41 (37.6)	50 (43.5)	83 (42.3)	49 (62.8)	182 (46.6)	

With Radiotherapy‡ – no. of women (%)	7 (63.6)	51 (65.4)	11 (55)	69 (63.3)	62 (54)	109 (55.6)	30 (38.5)	201 (51.7)	.03
With Endocrine therapy‡ – no. of women (%)	5 (45.4)	65 (83.3)	18 (90)	88 (81)	91 (79.1)	165 (84.1)	53 (67.9)	309 (79.4)	.76
Tamoxifen	5 (100)	49 (75.4)	13 (72)	67 (76.1)	61 (67)	104 (63)	31 (58.5)	196 (63.4)	.02
Aromatase inhibitors + tamoxifen	0	13 (20)	4 (22)	17 (19.3)	25 (27.5)	48 (29)	18 (34)	91 (29.5)	
Aromatase inhibitors	0	1 (1.5)	0	1 (1.2)	5 (5.5)	10 (6)	3 (5.7)	18 (5.8)	
Unknown type	0	2 (3)	1 (5.5)	3 (3.4)	0	3 (2)	1 (1.8)	4 (1.3)	
With adjuvant Chemotherapy‡ – no. of women (%)	3 (27.3)	51 (65.4)	20 (100)	74 (69)	3 (2.6)	28 (14.3)	42 (53.8)	73 (18.8)	< .0001
No anthracyclines	0	17 (33.3)	5 (25)	22 (35.6)	1	9 (32.1)	16 (38.1)	26 (29.7)	.88
Anthracyclines, no taxanes	3 (100)	29 (56.9)	12 (60)	44 (54.8)	1	16 (57.1)	23 (54.8)	40 (59.5)	
Anthracyclines and taxanes	0	2 (3.9)	2 (10)	4 (4.1)	0	0	3 (7.1)	3 (5.4)	
Unknown type	0	3 (5.9)	1 (5)	4 (5.5)	1	3 (10.8)	0	4 (5.4)	
Loco-regional recurrence event – no. of women (%)	0	4 (5.1)	2 (10)	7 (6.4)	1 (.86)	2 (1)	10 (12.8)	13 (3.3)	.14
Distant recurrence event – no. of women (%)	0	3 (3.8)	3 (15)	6 (5.5)	2 (1.7)	10 (5.1)	14 (17.9)	26 (6.7)	.65
Deaths – no. of women (%)	0	3 (3.8)	3 (15)	6 (5.5)	10 (8.6)	31 (15.8)	22 (28.2)	63 (16.2)	.004
Charlson co-morbidity score mean (SE, range)¶	0	0.10	0.05	0.08 (0.03, 0–2)	0.11	0.20	0.19	0.18 (0.03, 0–6)	.028
Charlson co-morbidity score – no. of women (%)¶									
0	11 (100)	71 (91)	19 (95)	101(92.6)	104 (90.4)	171 (87.3)	69 (88.4)	344 (88.4)	.86
1	0	6 (7.7)	1 (5)	7 (6.4)	9 (7.8)	18 (9.2)	6 (7.7)	33 (8.4)	
2	0	1 (1.3)	0	1 (1)	2 (1.8)	3 (1.5)	1 (1.3)	6 (1.5)	
3	0	0	0	0	0	2 (1)	1 (1.3)	3 (.8)	
4	0	0	0	0	0	0	1 (1.3)	1 (.3)	
5	0	0	0	0	0	1 (.5)	0	1 (.3)	
6	0	0	0	0	0	1 (.5)	0	1 (.3)	

*Categorization of a patient's risk for recurrence as low, intermediate, or high was according to the Canadian clinical practice guidelines [117]. Low risk: Post-menopausal women with primary tumor size < 2cm and tumor grade = 1; pre-menopausal women with primary tumor size < 1cim and tumor grade =1. High risk: All women with tumor size >3cm, or women with tumor size ≥ 1cm and ≤ 3cm with tumor grade = 3. Intermediate risk: Post-menopausal women with tumor size < 2cm and tumor grade > 1, or tumor size ≥ 2cm and < 3cm and tumor grade = 1 or 2; premenopausal women with tumor size < 1cm and tumor grade >, or tumor size ≥ 1cm and < 3cm and tumor grade=1 or 2. Given the significant correlation between tumor size, lymphatic and vascular invasion [144], and tumor grade[167], lymphatic and vascular invasion was not used in categorizing patients' risk because the Manitoba cancer registry does not collect this information and 52 patients 'risk for recurrence was categorized on the basis of tumor size only because their tumors size < 3cm with undetermined tumors grade.

†The p-value was calculated for overall pre- vs. overall post-menopausal women. Fisher's exact and chi-square tests were used for binary and categorical variables respectively. Distributions of continuous variables were summarized by their means and standard errors and compared using t-tests.

‡Women were defined as having received any of these treatments for their primary breast cancer if the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code or the Canadian Classification of Health Interventions (CCI) procedure code of any of these treatments was found before any recurrence, second primary cancer or death within one year of diagnosis with ESBC.

¶ Co-morbid diagnoses were considered present if they were found during one year before and 6 months after the diagnosis with primary breast cancer.

3.5 Sensitivity Analysis

In the base case I compared the RS assay versus CCP when weighted average cost of CMF, AC and TAC was used. I considered each of CMF, AC, FAC and TAC regimens separately as the standard adjuvant chemotherapy regimen for women with ER+/ PR+ LN- ESBC in sensitivity analysis. In premenopausal women, the RS-assay stayed cost saving with each of CMF, AC, FAC and TAC regimens. In post-menopausal women, the RS-assay had an ICER of $59,800 per QALY gained with CMF, $58,200 per QALY gained with AC, $65,000 per QALY gained with FAC and $83,100 per QALY gained with TAC. The utility during chemotherapy and the rates and costs of CSAE did not substantially influence the results with any regimen.

I performed threshold analyses on the proportion of chemotherapy-treated women classified as being in the intermediate risk group by the RS-assay, on the risk of relapse in the RS-assay model and other parameters found to influence our base case analyses (Tables 4 and 5). Among pre-menopausal women, the RS-assay generated negative incremental cost and effect (the RS-assay led to decrease in cost and effect) and when fewer than 43% of women in the RS-assay intermediate risk group received adjuvant chemotherapy. Among postmenopausal women, the RS-assay was dominated by CCP when fewer than 31% of women in the RS-assay intermediate risk group received adjuvant chemotherapy. When the absolute risk of relapse in the RS-assay model increased by approximately 2% in either pre- or post-menopausal women, the RS-assay would be dominated by CCP or associated with negative incremental cost and effect.

I also performed a probabilistic sensitivity analysis (Figure 2) comparing the RS-assay versus CCP. I simultaneously varied all parameters (probabilities, utilities and costs) using appropriate distributions (Table 1). In pre-menopausal women, using a willingneess to pay threshold of $100,000 per QALY gained, I found that the RS-assay was the prefered strategy in 54% of simulations (Figure 2 a and b). In post-menopausal women, I found that the RS-assay was the prefered strategy in 62% of simulations (Figures 2 c and d).

Table 4. Summary of important one-and two way sensitivity analyses[a].

Variable (range tested)		Interpretation of the incremental impact of the RS-assay compared to CCP					
		Negative cost and effect	Cost saving	ICER in the range 0 to 20,000 $/QALY gained	ICER in the range 20,000 to 100,000 $/QALY gained	ICER in the range >100,000 $/QALY gained	Dominated
Chemotherapy treated women in intermediate risk group by the RS-assay (0% to 100%)		0% to 42%	43% to 63%	64% to 100%			
Change in absolute risk of relapse[b] in the RS-assay model (-10% to +10%)		> +1.8%	≤ +1.8%				
Change in utility of recurrence[c] (-10% to +10%)	Lower limit cost of recurrence[c]			≤ +2.2%	+2.3% to +3.4%	+3.5% to +4%	≥ +4%
	Baseline cost of recurrence[c]	> +3%	≤ +3%				
	Upper limit cost of recurrence[c]	> +3%	≤ +3%				
Change in utility following adjuvant chemotherapy (-10% to +10%)		> +1%	≤ +1%				

CMF= 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil; AC= 4 cycles of doxorubicin, cyclophosphamide; CCP= current clinical practice.

[a]Values in the table show how the incremental impact of the RS-assay compared to CCP changes, over 6 significant ranges, depending on the values of certain key parameters. For example, if between 43-63% of women identified as intermediate risk by the RS-assay were to receive chemotherapy, then the RS-assay would be cost saving relative to CCP; if this proportion is 64% or greater, then the RS-assay has an ICER between 0 and $20,000 / QALY gained.

[b]Relapse includes loco-regional recurrence, distant recurrence and death due to any cause.

[c]Recurrence includes loco-regional and distant recurrences.

Table 5. Summary of important one-and two way sensitivity analyses[a].

Variable (range tested)		Interpretation of the incremental impact of the RS-assay compared to CCP					
		Negative cost and effect	Cost savings	ICER in the range 0 to 20,000 $/QALY gained	ICER in the range 20,000 to 100,000 $/QALY gained	ICER in the range > 100,000 $/QALY gained	Dominated
Chemotherapy treated women in intermediate risk group by the RS-assay (0% to 100%)				86% to 100%	42% to 85%	32% to 41%	0% to 31%
Change in absolute risk of relapse[b] in the RS-assay model (-10% to +10%)				< -3%	-3 % to +0.9%	+1% to +2%	> +2%
Change in utility of recurrence[c] (-10% to +10%)	Lower limit cost of recurrence[c]				< +9%	≥ +9%	
	Baseline cost of recurrence[c]				-10% to +10%		
	Upper limit cost of recurrence[c]				-10% to +10%		
Change in utility following adjuvant chemotherapy (-10% to +10%)				> 4.5%	-0.8% to +4.5%	-2.4% to -0.9%	≤ -2.5%

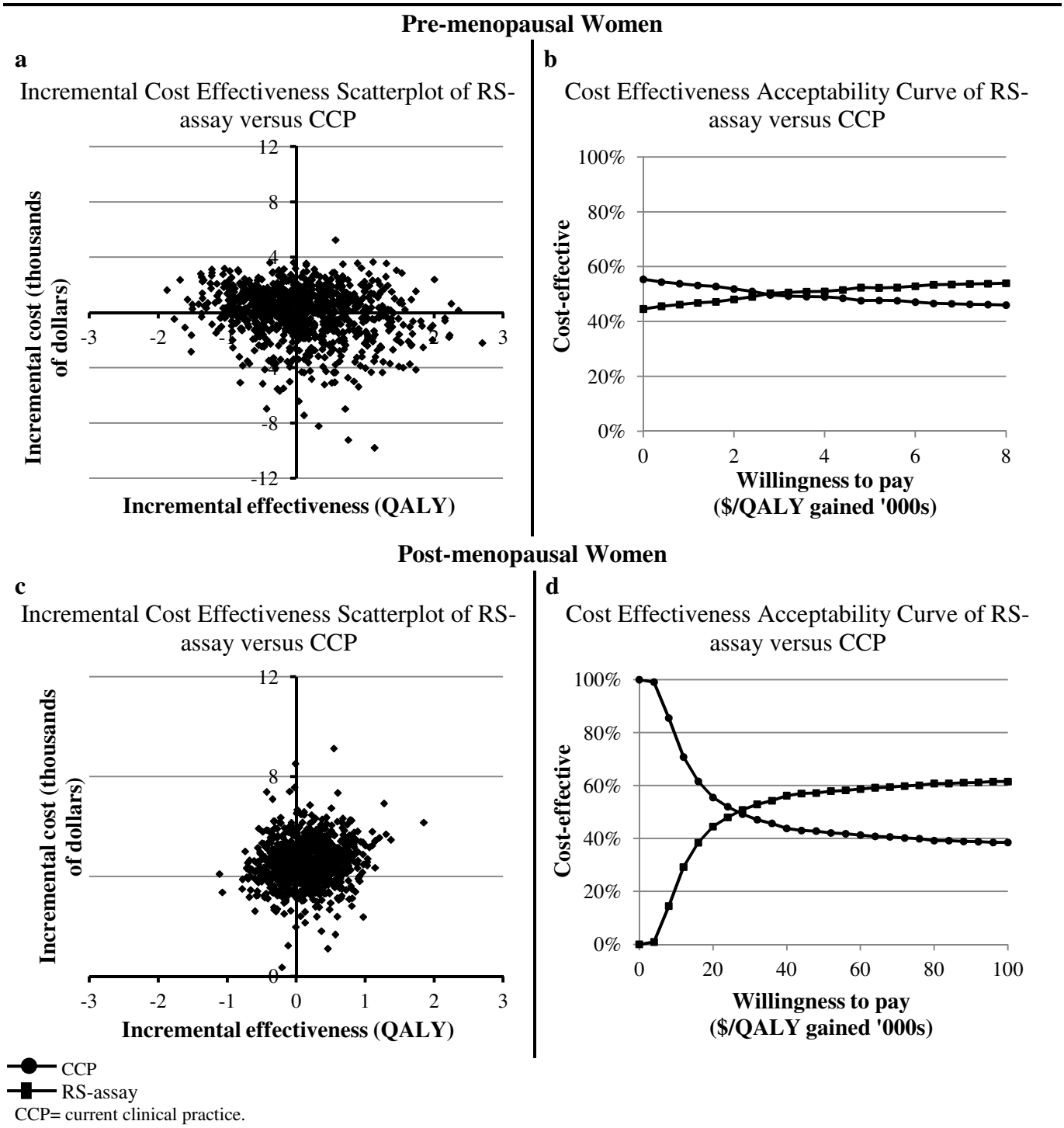
CMF= 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil; AC= 4 cycles of doxorubicin, cyclophosphamide; CCP= current clinical practice.

[a] Values in the table show how the incremental impact of the RS-assay compared to CCP changes, over 6 significant ranges, depending on the values of certain key parameters. For example, if between 43-63% of women identified as intermediate risk by the RS-assay were to receive chemotherapy, then the RS-assay would be cost saving relative to CCP; if this proportion is 64% or greater, then the RS-assay has an ICER between 0 and $20,000 / QALY gained.

[b] Relapse includes loco-regional recurrence, distant recurrence and death due to any cause.

[c] Recurrence includes loco-regional and distant recurrences.

Figure 2. Incremental cost-effectiveness scatterplot and acceptability curve of RS-assay-guided therapy versus CCP-guided therapy for pre- and post-menopausal women. Sampling distributions and summary estimates of cost, efficacy, and variance were based on 1000 replicates.



CCP= current clinical practice.

3.6 Discussion

I developed a decision-analytic model to evaluate the cost effectiveness of the RS-assay versus CCP in ER+/ PR+ LN- ESBC. In the base case I estimated that the RS-assay generated cost savings in pre-menopausal women and has an ICER of $60,000 per QALY gained in post-menopausal women.

In Canada, an ICER threshold of $100,000 per QALY gained has been suggested as representing "weak evidence for adoption and appropriate utilization" [62, 72], although there is no evidence that any Canadian decision-making body has formally implemented this threshold [168]. The ICERs of the RS-assay in post-menopausal women were within ranges of a number of cancer treatments that have recently been approved in Canada. For instance, sorafenib has an estimated ICER of $75,821 per life year gained for the treatment of hepatocellular carcinoma and has been approved for funding in Ontario through the Exceptional Access Program [169]. Sunitinib has been funded in all Canadian provinces for first-line treatment of metastatic renal-cell carcinoma with an ICER of $144,000 per QALY gained [170].

Previous cost-effectiveness analyses of the RS-assay in ER+/ PR+ LN- ESBC population have several limitations and may not be applicable in the Canadian context. One study [127] did not incorporate results from NSABP B20 [11], which established the relationship between the RS-assay and the benefit from using chemotherapy. Another two studies [128-129] included results from NSABP B20 [128]; however, the treatment strategies that they compared (tamoxifen alone for everyone and tamoxifen and chemotherapy for everyone) do not reflect observed clinical practice in Canada (Table 2). Other studies from Israel [131] and Japan [130] did not incorporate all early stage breast cancer complications such as local or regional recurrence. Three recent studies [132-134] were conducted from the Canadian health care payer's perspective; however, the first analysis [132] did not address all the limitations mentioned above, and modeling the current experience of ER+/ PR+ LN- ESBC population with regard to survival in the three analyses [132-134] was not based on Canadian data and real world clinical practice. In all studies there was no differentiation in adjuvant chemotherapy practice between pre-

and post-menopausal women as recommended by Canadian guidelines [117], whereas I observed differences in clinical practice for these two groups (Table 2).

Adjuvant chemotherapy is a widely recommended treatment in ER+/ PR+ LN- ESBC [124]. Thus, some have suggested that large cost savings can be expected by avoiding chemotherapy treatment in 25% to 35% of patients based on the results of the RS-assay [124]. Our analysis suggests that cost savings may be possible in pre-menopausal women, due the wide use of chemotherapy in this group, but would likely not occur with post-menopausal women with ER+/ PR+ LN- ESBC. According to our analysis, the RS-assay results may increase chemotherapy treatment in aproximetly15% of post-menopausal women with ER+/ PR+ LN- ESBC and would generate favorable QALYs gained and increase costs over CCP in this patient population. This scenario is likely due to both the ability of the RS-assay to better distinguish patients who likely benefit from chemotherapy compared to CCP and the possibility that many of post-menopausal women in CCP are reluctant to undergo chemotherapy and would be persuaded of its importance because of the test results [171].

In sensitivity analysis I addressed the economic impact of uncertainty in clinical guidelines for intermediate-range RS-assay values(18-30) [172]. Our analysis demonstrated that the ability of the RS-assay to guide treatment decisions in the intermediate risk group likely would be important in determining whether the RS-assay will be a cost-effective use of resources. If fewer than 43% of pre-menopausal and 31% of post-menopausal women identified as intermediate risk by the RS-assay received adjuvant chemotherapy, then the RS-assay had negative health effects compared to CCP. An ongoing prospective clinical trial will further assess the predictive value of the assay in women in the intermediate risk group and will be helpful in verifying our results [25]. However, findings from this trial will not be available for 5 to 10 years whereas an adoption decision will need to be made prior to having the results of this trial.

Our analysis has several limitations. First, there are limits to what can be ascertained through administrative data. Although the Manitoba Cancer Registry is a highly accurate source of information about breast cancer [137], errors in coding can result in incorrect or

unrecorded procedures. However, wherever possible I cross validated across databases. For instance, information on breast cancer treatments including surgery, radiation therapy, endocrine therapy and chemotherapy can be found in both the Manitoba Cancer Registry and the administrative databases held by Manitoba Health and Healthy Living. Second, validation data for the 21-gene assay was based on retrospective analyses of the NSABP chemotherapy-tamoxifen trials (B-14 and B-20) conducted in the United States [11, 121]. Thus, survival outcomes by the RS-assay may not reflect the experience of the ER+/PR+ LN- ESBC identified in Manitoba due to possible differences in patient and tumor characteristics and treatments. Results from future prospective analyses of the assay in real-world clinical practice and in Canadian settings can be used to update our model and verify our results. Third, there is still uncertainty as to whether chemotherapy is necessary for women who fall in the intermediate risk group by the RS-assay [25]. Fourth, newer third generation anthracycline-taxane regimens have different costs and slightly better efficacy so analysis with such data would be more applicable to the current practice landscape. In addition, our analysis did not account for growing data on long term side effects of primary adjuvant chemotherapy such as cardiomyopathy, neuropathy, and leukemia [166]. Finally, although several studies have found that clinical practice patterns and therapies employed in the selected time periods in Manitoba reflect practice in other jurisdictions in Canada [173-175], differences in clinical practice for women with ER+/PR+ LN- ESBC and its associated costs across Canadian provinces may still exist.

3.7 Conclusion

I compared the RS-assay versus current clinical practice in ER+/ PR+ LN- ESBC for both pre- and post-menopausal women. I found that it is likely to be cost-saving for pre-menopausal women and to have an ICER that is within ranges of a number of cancer treatments recently approved for funding in Canada for post-menopausal women. Validation of the assay in real-world clinical practice is warranted to verify the retrospective analyses of this assay in clinical trials and ensure its cost-effectiveness for routine use in this population.

Chapter 4

4 Cost-effectiveness of a 21-gene recurrence score assay versus Canadian clinical practice in post-menopausal women with early-stage estrogen or progesterone-receptor-positive, axillary lymph-node positive breast cancer

4.1 Abstract

A 21-gene recurrence score (RS) assay provides a method of guiding treatment decisions in women with early-stage breast cancer (ESBC). I investigated the cost-effectiveness of using the RS-assay versus current clinical practice (CCP) in post-menopausal women with estrogen- or progesterone-receptor-positive (ER+ or PR+), one to three positive axillary lymph-node (1-3 LN+), ESBC from the perspective of the Canadian public healthcare system. I developed a decision analytic model to project the lifetime clinical and economic consequences of ESBC. I assumed that the RS-assay would classify patients among risk levels (low, intermediate and high) and corresponding adjuvant treatment regimens. The model was parameterized using 7 year follow up data from the Manitoba Cancer Registry, cost data from Manitoba Health administrative databases and secondary sources. Costs are presented in 2012 Canadian dollars, and future costs and benefits were discounted at 5%. In the base case, the RS-assay compared to CCP led to an increase of 0.08 QALY and an increase in cost of $36.2 CAD per person, resulting in an incremental cost effectiveness ratio (ICER) of $464/QALY gained. The ICER was most sensitive to the proportion of women classified to intermediate risk by the RS-assay who received adjuvant chemotherapy, and absolute risk of relapse among patients receiving RS-assay. The RS-assay is likely to be cost effective in the Canadian healthcare system. Field evaluations of the assay in this patient population will help reduce

uncertainty in clinical guidelines for intermediate-range RS-assay values and specific disease outcomes by RS-assay which are important drivers of ICER.

4.2 Introduction

Postmenopausal women with early stage estrogen or progesterone-receptor-positive, axillary lymph-node positive breast cancer (ER+ or PR+ LN+ ESBC) are routinely treated with chemotherapy in addition to endocrine therapy [176]. Recent data in Canada and other jurisdictions have shown that these women, particularly those with favorable histopathologic features (one to three positive axillary lymph nodes (1-3 LN+)), do not benefit equally from chemotherapy [22, 177]. Further analyses have suggested that some of these women may not gain benefit from adding chemotherapy to endocrine therapy [177], [20]. These findings have highlighted the need for accurate prognostic tools to identify women with ER+ or PR+ 1-3 LN+ ESBC who could be spared chemotherapy.

A 21-gene recurrence score assay (Oncotype DX) has been developed that provides a "tumor signature" reflecting tumor biology and risk of relapse [11, 18-20]. This assay uses a proprietary algorithm to combine tumor expressions of 21 genes into a single score called the recurrence score (RS) which ranges from 1 to 100 [18]. Women with a low RS (< 18) may need adjuvant endocrine therapy only, while those with a high RS (≥ 31) may require the addition of chemotherapy to endocrine therapy [11, 19]. Women with an intermediate risk (18 – 30) do not appear to obtain a large benefit from chemotherapy. However, the uncertainty in the estimate cannot exclude a clinically important benefit [11, 20, 25].

The prognostic value of the assay has been well documented for women with early-stage estrogen or progesterone-receptor-positive, axillary lymph-node negative breast cancer (ER+ or PR+ LN- ESBC) [11, 18-19]. There is increasing evidence that the recently developed RS-assay can also identify women with ER+ or PR+ LN+ breast cancer considered for adjuvant chemotherapy who will not benefit from this treatment [20, 120, 178-179]. The most comprehensive analysis of the RS-assay in women with ER+ or PR+ LN+ breast cancer was provided by a retrospective analysis of the phase III Southwest

Oncology Group (SWOG)-8814, INT-0100 trial. The RS-assay was found to predict disease free survival and overall survival in tamoxifen-treated post-menopausal women with LN+, providing the first evidence of prognostic utility of the assay in a LN+ population receiving tamoxifen alone. In this study, it was shown that a low recurrence score by the assay may define a group of post-menopausal women with LN+ who do not appear to benefit from adjuvant chemotherapy [20]. A retrospective analysis of the "Arimidex, Tamoxifen, Alone or in Combination" trial (ATAC) validated the prognostic ability of the RS-assay in post-menopausal women with LN+ breast cancer treated with endocrine therapy (anastrozole or tamoxifen). Specifically, the study defined a group of ER+, 1-3 LN+ breast cancer patients with a low recurrence score who had less than 10 % risk of distant recurrences [179]. Consistent results by both retrospective analyses [20, 179] provided "Level I" data according to the revised Levels of Evidence (LOE) scale proposed by Simon el al [180] to determine the clinical utility of a tumor marker. Other studies have also shown similar prognostic utility of the RS-assay in LN+ disease setting [120, 178].

There are several economic evaluations suggesting that the RS-assay might be cost effective in the ER+ or PR+ LN- ESBC population in Canada [132-134, 181], and other countries [127-131]. However, findings in the LN- disease setting cannot be extrapolated to LN+ disease setting due to differences in both clinical and economic outcomes. Three economic analyses have examined the cost effectiveness of the RS-assay in both LN-and LN+ settings [130, 133-134, 182]. These analyses suggested that the assay is cost-effective for LN+ women in Canada[133], USA [182], and Japan [130]. However, none of these analyses focused on the low risk subset of LN+ disease setting (1-3 LN+) for whom the RS-assay is likely to be used in real world clinical practice, and suffered from other limitations as indicated elsewhere [181]. Additionally, findings from studies in USA and Japan cannot be extrapolated to the Canadian context because of possible variations in clinical practice and different approaches to pricing and reimbursement.

I sought to investigate the cost effectiveness of the RS-assay compared to current clinical practice (CCP) of adjuvant chemotherapy in women with ER+ or PR+ 1-3 LN+ ESBC from the perspective of the Canadian healthcare system.

4.3 Methods

4.3.1 Overview of Model-Structure

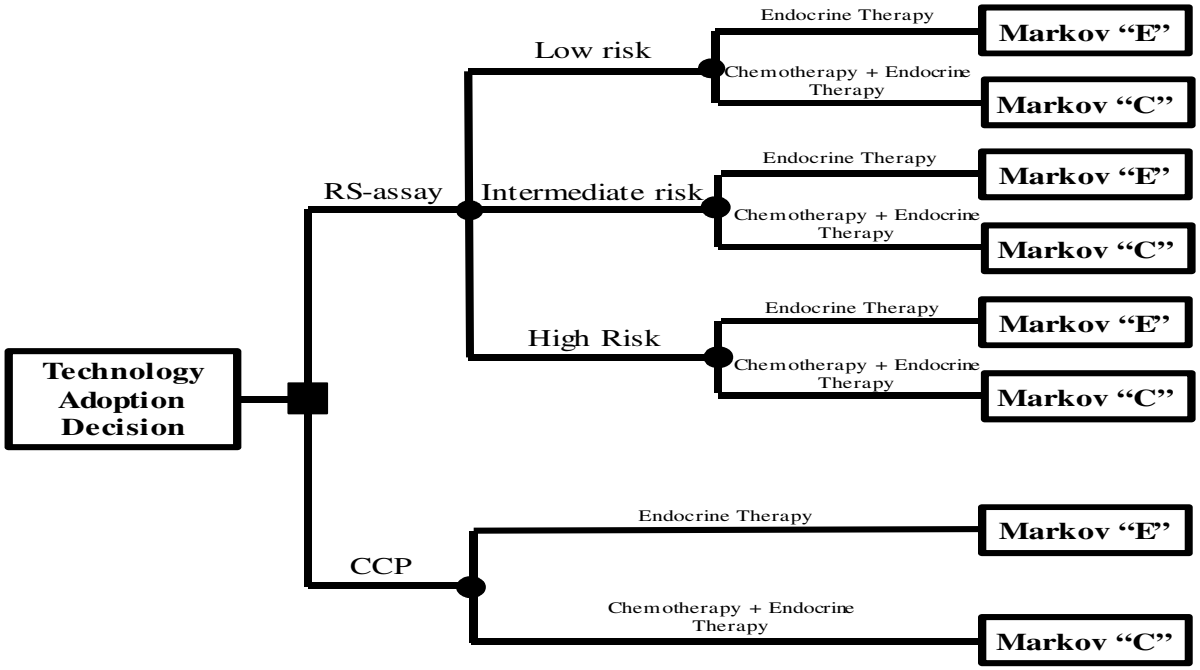
I developed a decision analytic model (Figure 3) to estimate the life time health and economic consequences of different adjuvant treatment-guiding strategies for postmenopausal women diagnosed with ER+ or PR+ 1-3 LN+ ESBC. The decision node (Figure 3 a) of this model is a decision whether to use the RS-assay or the CCP strategy. For the RS-assay-based strategy, a patient's risk classification (low, intermediate and high) was determined and followed by treatments decision (endocrine therapy plus chemotherapy versus endocrine therapy alone) according to the RS-assay. For the CCP based-strategy, all women are considered high risk and candidates for adjuvant chemotherapy [176]. CCP classifies patients to different treatment regimens after taking into consideration potential comorbidities. In either strategy, patients treated with endocrine therapy alone followed Markov model "E" (Figure 3b) and those treated with chemotherapy plus endocrine followed Markov model "C" (Figure 3c). Model "C" differs from model "E" in that it has an additional health state to account for possible chemotherapy-related serious adverse effects (CSAE) during chemotherapy.

Model "E" simulated monthly transitions among the following five distinct health states: (1) remission; (2) loco-regional recurrence (LR); (3) distant recurrence (DR); (4) second primary breast cancer (SPBC); (5) death. Model "C" simulated monthly transitions among the following six distinct health states: (1) remission with no CSAE; (2) remission with CSAE; (3) LR; (4) DR; (5) SPBC; (6) death.

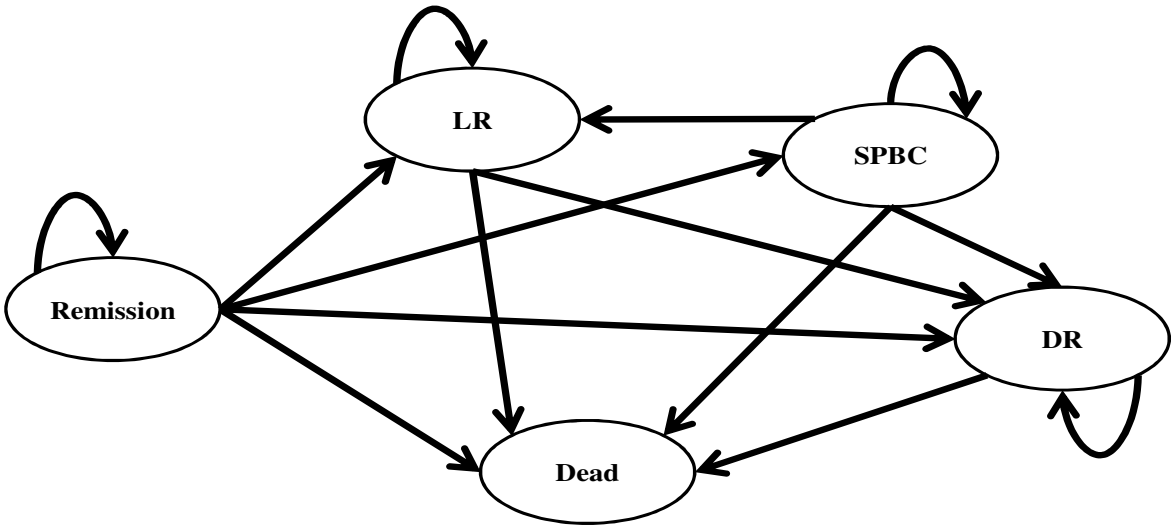
The analysis was conducted from the Canadian health care payer's perspective. I used TreeAge Software to produce and evaluate the decision analytic model, using a half cycle correction [136]. A discount rate of 5% per annum was applied to costs and quality adjusted life years (QALYs) following recommendations by the Canadian Agency for Drugs and Technologies in Health [111]. Parameter values are summarized in Table 1. Collection and analysis of registry and administrative data used for this study was approved by the University of Manitoba's Health Research Ethics Board.

Figure 3. Decision model for early stage breast cancer.

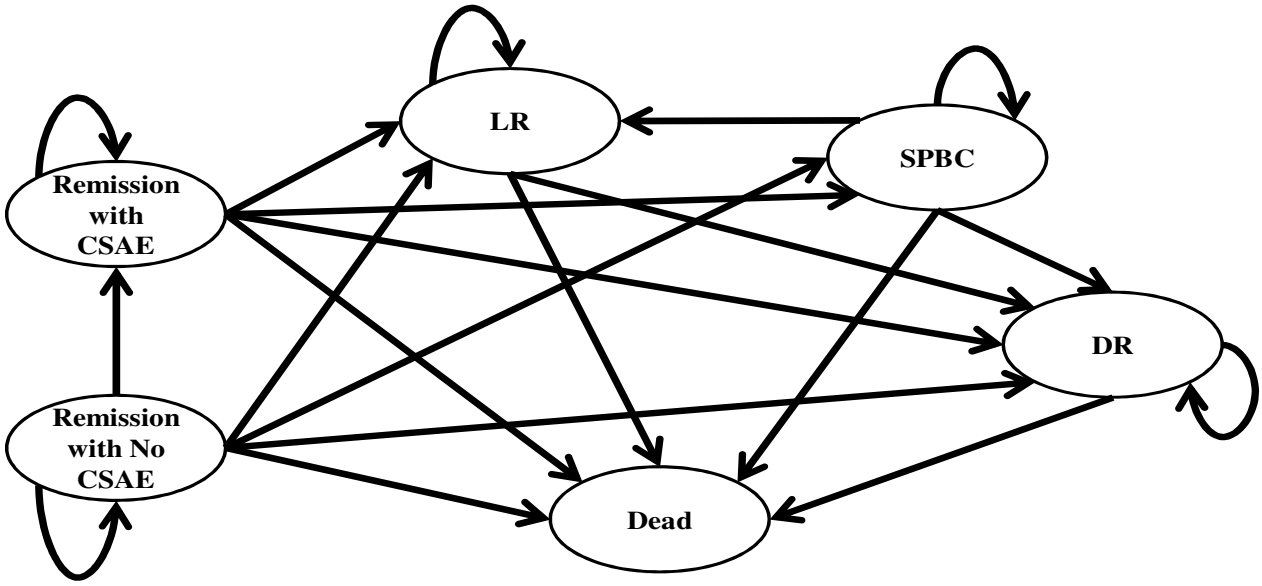
a RS-assay versus CCP-guided therapy.



b Schematic representation of the Markov model structure "E".



c Schematic representation of the Markov model structure "C".



Patients entering Markov model "E" start the model and remain in the remission state unless they relapse (LR, DR, SPBC or Death). Patients entering Markov model "C" start the model in the remission state with no CSAE. Within the first cycle patients may develop CSAE. These patients will make a transition to the remission state with CSAE. During the first cycle, patients also may transition to DR, LR, SPBC and Dead states. After the first cycle, patients may remain in the two remission states unless they relapse in to LR, DR, SPBC or Dead. In both Markov models, patients who developed LR, remain in the LR state or make transition to DR or Dead states. Patients who developed DR remain in the DR state or make transition to Dead state. Patients who developed SPBC remain in the SPBC state or make transition to LR, DR or Dead states. The cycle length was 1 month. Abbreviations: CCP= Canadian clinical practice; LR= loco-regional recurrence; DR= distant recurrence; SPBC= second primary breast cancer; CSAE= chemotherapy-related serious adverse effects; RS= recurrence score.

4.3.2 Identification of a Study Cohort

The Manitoba Cancer Registry (MCR) and Manitoba administrative databases held by Manitoba Health, including the Hospital Discharge Database, Physician Claims Database and the Drug Program Information Network (DPIN), served as the main data source for this analysis. I used the MCR to identify all post-menopausal women (defined as age ≥50 years) diagnosed with ER+ or PR+ 1-3 LN+ ESBC (stage II/III) during the period January 1, 2000 – December 31, 2002. Seven-year follow-up information from the time of diagnosis was available for each patient. This included breast cancer complications (LR, DR and SPBC) and treatments (surgery, radiation therapy, endocrine therapy and chemotherapy). I linked the study population identified using the MCR with administrative data held by Manitoba Health including the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network. Identification of our study cohort from MCR and linking with Manitoba administrative databases are described in detail elsewhere [177].

4.3.3 Risk Distribution and Transition Probabilities

For the CCP model, women were classified as belonging to two treatment groups based on observed adjuvant chemotherapy administration status (Table 6). I conducted survival analyses within each group, using 7 years of follow up data from the Manitoba Cancer Registry and Kaplan-Meier estimates, and used this information to estimate all transition probabilities in the CCP Markov models.

For the RS-assay model, I used retrospective analysis of the phase III SWOG-8814, INT-0100 trial to calculate the risk distribution and monthly transition probabilities to LR, DR, SPBC and Death over 10 years within each risk level (Table 6) [20]. I obtained Kaplan Meier (KM) survival curves for DFS and death events stratified by risk level from SWOG investigators. These survival curves were restricted to women with 1-3 LN+ for the purpose of our patient population of interest. DFS was defined as survival free from recurrence (LR or DR), SPBC, and death from any cause. I estimated the distribution of DFS events across LR, DR, SPBC and death categories based on a corresponding

distribution of DFS events across these categories derived from our studied ER+/ PR+ 1-3 LN+ ESBC cohort.

Ongoing research is yet to clarify what the best adjuvant treatment approach is for women with intermediate-range RS-assay values. For LN+ patients, the only available data were provided recently by a survey of physician practice showing an overall reduction in recommendation for chemotherapy in LN+ patients following the RS-assay [183]. However, the study did not provide the actual usage of chemotherapy in intermediate risk women with LN+ disease. In the base case I assumed that 50% of women in the intermediate risk group would receive adjuvant chemotherapy as suggested elsewhere [181]. I varied this assumption in sensitivity analysis.

Outcomes after first relapse (LR, DR, SPBC and Death) may not be affected by the primary adjuvant therapy received [150]. Thus, only the probabilities of first relapse differed between the CCP and RS-assay based strategy. I assumed the observed average monthly transition probability from remission to first relapse during the last observed year of follow up in the studied population and the SWOG-8814, INT-0100 trial to be constant over the extrapolated time period. I used the age-adjusted female-specific life tables for Manitoba to adjust the probabilities from remission to death in order to account for the incremental mortality risk over the extrapolated time [151].

Table 6. Base case parameter estimates and sources.

Variables	Base case value	Duration	Range tested in sensitivity analyses€	Distribution used in PSA†	Data Source
Risk classification when using CCP (%)					
High risk	100				
Risk classification when using RS- assay (%)					
High risk	32.2		27.6 – 37.1	Dirichlet	[20]
Intermediate risk	28.1		23.7 – 32.9	Dirichlet	[20]
Low risk	39.8		34.9 – 44.9	Dirichlet	[20]
Chemotherapy administration by risk group (%)					
CCP – High risk	64		56.3 – 70.1	Beta	MCR and PC
RS-Assay – High risk	100		90 – 100	Beta	[20]
RS-Assay – Medium Risk	50		0 – 100	Beta	[131, 148-149, 152]
RS-Assay – Low Risk	0		0 – 10	Beta	[20]
CSAE (%)	6		0 – 14.6	Beta	MCR and HA
Health-State Utilities‡					
Remission state					
Remission on chemotherapy regimen with minor or no toxicity[β]	0.783	6 months	-20%	Beta	[153-155]
Remission on chemotherapy regimen with major toxicity[β]	0.577	6 months	-20%	Beta	[153-155]
Remission after chemotherapy regimen	0.808	Lifetime	-20%	Beta	[155-156]
Remission on hormonal therapy	0.816	60 months	-10% – +10%	Beta	[153-155]
Remission after hormonal therapy	0.824	Lifetime	-10% – +10%	Beta	[153-155]
LR/SPBC, under treatment	0.577	12 month	-10% – +10%	Beta	[150, 153-155, 184]
LR/SPBC, after treatment	0.700	Lifetime	-10% – +10%	Beta	[150, 153-155, 184]
Distant recurrence	0.412	Lifetime	-10% – +10%	Beta	[150, 153-155]
Death state	0				
Cost associated with remission (per month), $					
First year after diagnosis with ESBC					
Cost of surgery[a]	3529	One time	3187 – 3871	LogNormal	PC, HA and CL
Cost of radiation therapy[b]	3276	One time	2628 – 4086	LogNormal	PC and CL
Cost of endocrine therapy[c]					
Tamoxifen	12.4	12 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	12 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	12 months	62 – 81	LogNormal	DPIN
Cost of chemotherapy[d]					
Nursing, overhead and administration costs	317.62	During chemotherapy		LogNormal	CL
Related physician costs	27	During chemotherapy	24 – 30	LogNormal	PC
Chemotherapy regimen options					
CMF	823	5 months		LogNormal	MCR
CA	1151	3 months		LogNormal	MCR
TAC	2800	5 months		LogNormal	MCR
Weighted average cost of chemotherapy regimens[e]					
First three months on chemotherapy	1099	3months		LogNormal	MCR
Next	432	2months		LogNormal	MCR
Cost of CSAE[f]	1,750	During chemotherapy	1376 – 2168	LogNormal	PC, HA and CL
Surveillance[g]					
Endocrine alone treated-patient	56	12 months	54 – 62	LogNormal	PC
Chemo + endocrine treated-patient	99	12 months	96 – 103	LogNormal	PC

After first year of diagnosis with ESBC					
Cost of endocrine therapy[c]					
Tamoxifen	12.4	48 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	48 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	48 months	62 – 81	LogNormal	DPIN
Surveillance[f]					
Endocrine alone treated-patient	34	Lifetime	30– 39	LogNormal	PC
Chemo + endocrine treated-patient	44	Lifetime	39 – 51	LogNormal	PC
Cost associated with LR (per month), $					
First year after LR					
Surgery[a]	1768	One time	1092 –3313	LogNormal	PC, HA and CL
Radiation therapy[b]	1725	One time	1353 – 2181	LogNormal	PC, HA and CL
Cost of endocrine therapy[c]					
Tamoxifen	12.4	12 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	12 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	12 months	62 – 81	LogNormal	DPIN
Chemotherapy[d]	438	5 months	278 – 970	LogNormal	PC and CL
Surveillance during first year[g]	110	12 months	41 – 261	LogNormal	PC
After first year of LR					
Cost of endocrine therapy[c]					
Tamoxifen	12.4	48 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	48 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	48 months	62 – 81	LogNormal	DPIN
Surveillance after first year of LR[g]	40	Lifetime	30 – 87	LogNormal	PC
Cost associated with SPBC (per month), $					
First year after SP					
Surgery[a]	1494	One time	923 – 2800	LogNormal	PC, HA and CL
Radiation therapy[b]	1092	One time	286 – 510	LogNormal	PC, HA and CL
Endocrine therapy (options)[c]					
Tamoxifen	12.4	12 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	12 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	12 months	62 – 81	LogNormal	DPIN
Chemotherapy[d]	553	5 months	353 – 1235	LogNormal	PC and CL
Surveillance during first year[g]	124	12 months	60 – 278	LogNormal	PC
After first year of SPBC					
Cost of endocrine therapy[c]					
Tamoxifen	12.4	48 months	11.6 – 13.2	LogNormal	DPIN
Aromatase Inhibitors	156	48 months	120 – 193	LogNormal	DPIN
Sequential aromatase→ tamoxifen	72	48 months	62 – 81	LogNormal	DPIN
Surveillance after first year from SPBC[g]	55	Lifetime	35 – 95	LogNormal	PC
Cost associated with DR (per month), $					
First year after DR					
Hospitalizations cost	2993	12 months	216 – 6273	LogNormal	HA and CL
Physicians cost	314	12 months	166 – 462	LogNormal	PC
Drugs cost	85	12 months	37 – 113	LogNormal	DPIN
After first year of DR					
Hospitalizations cost	840	Lifetime	309 – 1361	LogNormal	HA and CL
Physicians cost	257	Lifetime	153 – 362	LogNormal	PC
Drugs cost	56	Lifetime	6 – 108	LogNormal	DPIN

€ Ranges used in sensitivity analyses were based on the same data sources as baseline values. Ranges used in sensitivity analyses of parameters estimated from the Manitoba Cancer Registry and administrative databases in Manitoba were based on observed confidence intervals. Ranges used in sensitivity analysis of parameters estimated from the retrospective analysis of the phase III SWOG-8814, INT-0100 trial were based on confidence intervals reported in this study. Ranges used in sensitivity analysis of utility estimates were based on arbitrary ranges reported in utility sources.

† Beta distribution was used for other probability parameter estimates not included in this table.

‡ Utility estimates were based on visual analog scales (VAS). The baseline utility for post-menopausal women aged 50 to 80 was 0.824, based on representative values for the US population [155]. I derived utilities for each state by multiplying this baseline utility value by utility estimates for patients with breast cancer [150, 153, 156, 184] in the US, consistent with methodology as described by Fryback [154].

β I used a disutility of 10% for a patient receiving chemotherapy with minor toxicity, a disutility of 30% for a patient receiving chemotherapy with major toxicity, and a disutility of 0% for patients receiving chemotherapy with no toxicity [153]. The disutility for major toxicity was applied to women experienced a major toxicity in our study population (i.e., 6% of our study population). A disutility average of 5% (i.e., average of 10% and

0% disutility estimates with minor toxicity and no toxicity respectively) was applied to all other women with minor or no toxicity.

a Cost of breast cancer surgery: I used the Hospital Discharge Database and the Physician Claims Database to estimate the mean cost of hospitalization due to any breast cancer surgery (including one day hospitalization and using the ICD-9-Cprocedure codes for a hospital abstract) within one year after diagnosis with ESBC, LR and SPBC.

b Cost of radiation therapy: Cost of radiation therapy included cost of radiation therapy–related physician claims in addition to administrative cost. I used the Physician Claims Database to estimate the mean cost of radiation therapy–related physician claims (using the tariff code for a medical claim) within one year after diagnosis with ESBC, LR and SPBC. Administrative costs were derived from the cost list for Manitoba health services.

c Cost of endocrine therapy: I used the Drug Program Information Network (DPIN) to estimate the mean cost of tamoxifen and aromatase inhibitors (using the drug identification number (DIN) for a drug claim) within the time periods, between diagnosis with ESBC and before any relapse, diagnosis with LR and before any relapse, and diagnosis with SPBC and before any relapse.

d Cost of chemotherapy: Nursing, overhead and administration costs were derived from the cost list for Manitoba health Services. I used the Physician Claims Database to estimate the mean cost of chemotherapy–related physician claims costs (using thetariff code for a medical claim) within one year after diagnosis with ESBC, LR and SPBC. Chemotherapy regimens costs were estimated based on the market prices as of May 2012.

e Weighted average cost of adjuvant chemotherapy regimens: I calculated the average cost of adjuvant chemotherapy regimens weighted to the observed proportion use of anthracyclines and taxane reported somewhere else [177]. Weighted average cost of adjuvant chemotherapy regimens = proportion of women received non-anthracyclines containing adjuvant chemotherapy × cost of CMF + proportion of women received anthracyclines containing adjuvant chemotherapy (no added taxanes) × cost of AC + proportion of women received anthracyclines and taxanes containing adjuvant chemotherapy × cost of TAC.

f Cost of CSAE: I used the Hospital Discharge Database and the Physician Claims Database to estimate the mean cost associate with hospitalizations due to any of the eight diagnoses which were considered CSAE among women who developed CSAE.

g Cost of surveillance: I defined the cost of breast cancer surveillance as the incremental cost of health care utilization (medical claims) after diagnosis with ESBC versus the time before diagnosis. I used the Physician Claims Database to collect medical claims for all women studied, within 3 years before and 7 years after diagnosis wit ESBC. I estimated the mean cost of medical claims within 3 years before diagnosis in order to reflect the usual cost of health care utilization. I calculated the incremental mean cost of health care utilization during the period from diagnosis with ESBC and before any relapse (excluding cost of claims related to surgery, radiation therapy, chemotherapy, CSAE) stratified by the time from diagnoses (first year versus after). Similarly, I calculated the incremental mean cost of health care utilization after LR and SPBC.

PSA= probabilistic sensitivity analysis; MCR= Manitoba Cancer Registry: PC= physician claims; HA= Hospital abstracts; CL= cost list for Manitoba health services; DPIN=Drug Program Information Network records; ESBC= early stage breast cancer; LR, loco-regional recurrence; DR= distant recurrence; SPBC=second primary breast cancer; CMF= 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil; AC= 4 cycles of doxorubicin, cyclophosphamide; FAC= 6 cycles of fluorouracil, doxorubicin, cyclophosphamide; TAC= 6 cycles of docetaxel, doxorubicin, cyclophosphamide; CCP= current clinical practice; CSAE= chemotherapy-related serious adverse effects; RS= recurrence score.

4.3.4 Adjuvant Chemotherapy Regimens and Adjuvant chemotherapy-related Serious Adverse Effects

Data on specific chemotherapy agents are not collected by the MCR and Manitoba administrative databases. I was able to ascertain a non-anthracycline-, anthracycline- or taxane-containing chemotherapy regimen by linking with the Physician Claims Database and identifying the specific tariff index for services relating to those agents as described elsewhere [177]. I considered patients who received non-anthracycline-containing adjuvant chemotherapy regimens received 6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil (CMF); that patients who received anthracycline-containing adjuvant chemotherapy regimens with no added taxanes received four cycles of doxorubicin (Adriamycin), cyclophosphamide (AC); and that patients who received anthracycline and taxane-containing adjuvant chemotherapy regimens received 6 cycles of docetaxel, doxorubicin, cyclophosphamide (TAC). In Canada, these three adjuvant chemotherapy regimens were available for women with ER+ or PR+ 1-3 LN+ ESBC during the time period of 2000-2003 [176-177]". In the base case analysis I used the weighted average cost of CMF, AC and TAC. In sensitivity analysis I considered each of these regimens separately as the standard adjuvant chemotherapy regimen for postmenopausal women with ER+ or PR+ 1-3 LN+ ESBC. I linked the study population with the Hospital Discharge Database in order to estimate the rate of adjuvant chemotherapy-related serious adverse effects (CSAE) using the method developed by Charlson et al. excluding cancer diagnoses [165] as described in detail elsewhere [181].

4.3.5 Cost and Utility Values

According to the Annual Report Card of the Cancer Advocacy Coalition of Canada, the RS-assay will cost $4,000 CAD per patient including all Canadian system expenses [124]. I estimated all relevant treatment costs for ESBC including the cost of surgery, radiation therapy, chemotherapy, and endocrine therapy, and the cost of CSAE management and surveillance over 7 years following diagnosis. All these treatments are publically funded in Manitoba and recorded in Manitoba health databases. I used these

cost estimates to derive the cost per unit time in each Markov state (Table 6). All costs are expressed in 2012 CAD using the bank of Canada inflation calculator [185].

I assumed a baseline utility of 0.824 for postmenopausal women in order to account for background morbidity [155]. I multiplied the baseline utility by utility estimates for women with breast cancer [150, 153-154, 156, 184] to calculate utilities across health states (Table 6). I examined the impact of potential long term side effects of adjuvant chemotherapy on health related-quality of life [166] by performing sensitivity analysis on utility values following adjuvant chemotherapy.

4.3.6 Analysis

The cost-effectiveness analysis was conducted according to recommendations by the Canadian Agency for Drugs and Technologies in Health [111]. Results are presented in the form of cost-effectiveness ratio (ICER) which provides a measure of average cost per additional unit of health benefit. Outcomes for health effects are measured in QALYs (i.e., life-years weighted by utility estimates to produce QALYs). Cost outcomes were measured as the mean cost per patient. To characterize uncertainty in the output measures, I conducted one and two-way deterministic sensitivity analyses on parameters of interests. In addition, I conducted probabilistic sensitivity analysis using Monte Carlo simulation with 1000 iterations. Each iteration consisted of a random draw from an appropriate distribution for all model inputs to produce a distribution of model outputs.

I conducted value-of-information analysis [112] to determine the expected monetary value of perfect information about the RS-assay in the Canadian setting. In particular, I set up our baseline model to express RS-assay related parameters (i.e., risk classification by RS-assay, adjuvant chemotherapy assignment following RS-assay and probabilities of first relapse following RS-assay) as probability distributions (i.e., reflecting uncertainty of the RS-impact in the Canadian setting) on the basis of retrospective analysis of the phase III SWOG-8814, INT-0100 trial [20] and the entire model is set up as a probabilistic model. Using simulation techniques (i.e., making random draws of the probabilistic model), the level of uncertainty in the model is assessed. Using a willingness to pay threshold of $100,000 per QALY gained [69], the opportunity cost

associated with the choice of RS-assay as the optimal strategy for guiding adjuvant therapy is calculated and presented as a total of expected value of perfect information (EVPI) about the RS-assay per patient. Using the size of ER+ or PR+ 1-3 LN+ ESBC population, one can calculate the EVPI about the RS-assay for the entire target population that could potentially benefit from more research on the predictive value of the RS-assay in the Canadian setting. In particular, the EVPI may provide decision makers with valuable information about the use of novel funding models such as conditional funding alongside a field evaluation [113].

4.4 Results

Patient, tumor, treatment and event characteristics of the study cohort are reported elsewhere [177]. There were 161 post-menopausal women diagnosed with ER+ or PR+ 1-3 LN+ ESBC during the period from January 1, 2000 to December 31, 2002 in Manitoba. The median patient age was 61 years (range 50–89 years). The majority of women (95%) received surgery (mastectomy or lumpectomy) for their primary breast cancer. Radiation therapy, endocrine therapy (tamoxifen or aromatase inhibitors) and chemotherapy were administered in 60%, 89% and 64% of women respectively. The RS-assay led to an increase of 0.08 QALY per person and an increase in cost of $36.2 CAD per person, resulting in an incremental cost effectiveness ratio (ICER) of $464 per QALY gained (Table 7).

Table 7. Baseline outcomes†.

Strategy	Effectiveness	Incremental Effectiveness	Cost	Incremental Cost	ICER
CCP	15.73 QALY	0.08 QALY	$49093.0	$36.2	$464 per QALY gained
RS-assay	15.81 QALY		$49129.2		

† Due to rounding, numbers may not balance

CCP= current clinical practice; RS=recurrence score; ICER= incremental cost effectiveness ratio; QALY= quality adjusted life year.

4.5 Sensitivity Analyses

In the base case I compared the RS assay versus CCP when the weighted average cost of CMF, AC and TAC was used. I considered each of CMF, AC, and TAC regimens separately as the standard adjuvant chemotherapy regimen for women with ER+ or PR+ 1-3 LN+ ESBC in sensitivity analysis. The RS-assay had an ICER of $4,150 per QALY gained with CMF, $152 per QALY gained with AC, and was cost saving with TAC. The utility during chemotherapy and the rates and costs of CSAE did not substantially influence our baseline results (Table 8).

I performed threshold analyses on the proportion of chemotherapy-treated women in the intermediate risk group by the RS-assay, risk of relapse in the RS-assay model, and several other parameters (Table 8). The RS-assay generated negative cost and effect (the RS-assay led to decrease in cost and effect) when fewer than 36% of women in the RS-assay intermediate risk group received adjuvant chemotherapy. If the absolute risk of relapse in the RS-assay model increased by approximately 2.6% then RS-assay would be dominated by CCP.

I performed a probabilistic sensitivity analysis (Figure 4a) comparing the RS-assay versus CCP. I simultaneously varied all parameters (probabilities, utilities and costs) using appropriate distributions (Table 6). Using a willingness to pay threshold of $100,000 per QALY gained, I found that the RS-assay was the preferred strategy in 72% of simulations (Figure 4b).

I also performed a value-of-information analysis in which I estimated the expected value of removing all statistical uncertainty of the RS-assay related parameters [112]. This type of analysis is necessary to estimate, in monetary values, the societal impact of future research that can evaluate the RS-assay in real life Canadian clinical practice. Using a willingness to pay threshold of $100,000 per QALY gained, the opportunity cost associated with the choice of RS-assay as the optimal strategy for guiding adjuvant therapy resulted in a total of EVPI of $4,200 per post-menopausal woman with ER+ or PR+ 1-3 LN+ ESBC. Subsequently, I estimated the expected value for the entire ER+ or

PR+ 1-3 LN+ ESBC population that could potentially benefit from more research on the predictive value of the RS-assay in the Canadian setting. In Manitoba, there were approximately 80 women diagnosed with ER+ or PR+ 1-3 LN+ ESBC. Based on the size of Manitoba relative to the rest of Canada, I anticipate a total of approximately 2216 postmenopausal women diagnosed with ER+ or PR+ 1-3 LN+ ESBC who would be eligible for the 21 gene assay in Canada. The resulting population EVPI was more than $9.3 CAD million per year.

Table 8. Summary of important one-and two way sensitivity analyses[a].

Variable (range tested)		Interpretation of the incremental impact of the RS-assay compared to CCP					
		Negative cost and effect	Cost savings	ICER in the range 0 to < 20,000 $/QALY gained	ICER in the range ≥ 20,000 to ≤100,000 $/QALY gained	ICER in the range > 100,000 $/QALY gained	Dominated
Chemotherapy treated women in intermediate risk group by the RS-assay (0% to 100%)		0% to 36%	37% to 47%	48% to 100%			
Change in absolute risk of relapse[b] in the RS-assay model(-10% to +10%)				<+2.2%	≥ +2.2% to ≤ 2.3%	> +2.3% to ≤+2.6%	> +2.6%
Change in utility of recurrence[c] and SPBR (-10% to +10%)	Lower limit cost of recurrence[c] and SPBR			≤ -6%	> -6%		
	Baseline cost of recurrence[c] and SPBR			-10% to +10%			
	Upper limit cost of recurrence[c] and SPBR		-10% to+10%				
Change in utility during adjuvant chemotherapy (-20% to 0%)				-20% to 0%			
Change in utility following adjuvant chemotherapy (-10% to +10%)				≤ +1.5%	+1.6% to <+2 %	≥+2% to ≤+2.2%	> +2.2%
Chemotherapy-related serious adverse effects (0% to 14.6%)				(0% to 14.6%)			
Cost of chemotherapy-related serious adverse effects ($1376 to $2168)				($1376 to $2168)			

CCP= current clinical practice; SPBR= second primary breast cancer; RS=recurrence score;

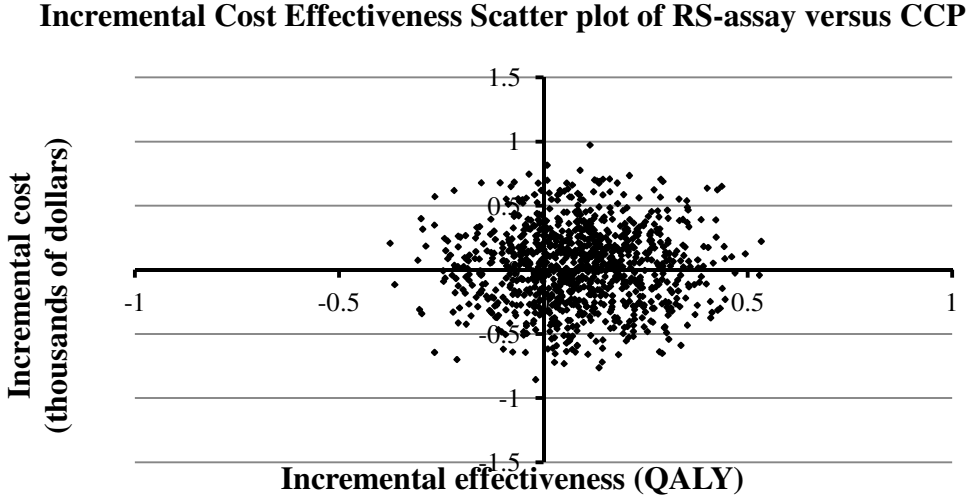
[a]Valuesin the table show how the incremental impact of the RS-assay compared to CCP changes, over 6 significant ranges, depending on the values of certain key parameters. For example, if between 37%-47% of women identified as intermediate risk by the RS-assay were to receive chemotherapy, then the RS-assay would be cost saving relative to CCP; if this proportion is 48% or greater, then the RS-assay has an ICER between 0 and $20,000 / QALY gained.

[b]Relapse includes loco-regional recurrence, distant recurrence, SPBR and death due to any cause.

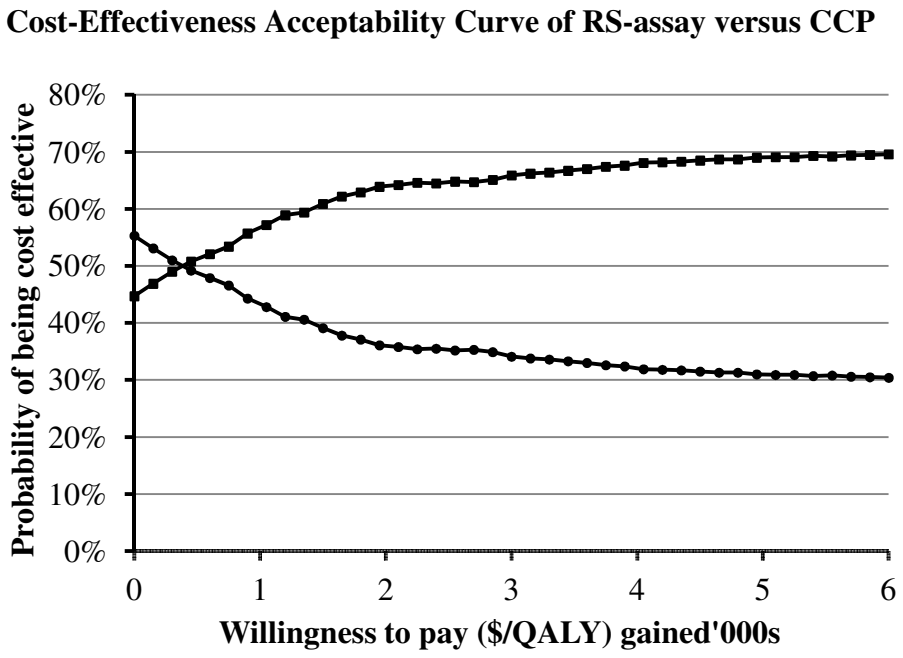
[c]Recurrence includes loco-regional and distant recurrences.

Figure 4. Incremental cost-effectiveness scatterplot and acceptability curve of recurrence score (RS)-assay versus CCP-guided therapy. Sampling distributions and summary estimates of cost, efficacy, and variance were based on 1000 replicates.

a



b



CCP= current clinical practice.

4.6 Discussion

I developed a decision-analytic model to evaluate the cost effectiveness of the RS-assay versus CCP in post-menopausal women with ER+ or PR+ 1-3 LN+ ESBC. In the base case, I estimated that the RS-assay has an ICER of $464 per QALY gained. Our ICER estimate is significantly lower than $20,000 per QALY gained, a level which has been suggested in Canada to define "strong evidence in support of adoption" [69] and below levels of recently adopted cancer treatments (e.g., [169-170]).

Previous cost-effectiveness analyses of the RS-assay in LN+ disease population have several limitations and may not be applicable in the Canadian context. Two studies did not incorporate results from the retrospective analysis of the phase III SWOG-8814, INT-0100 trial [20], which established the relationship between the RS-assay and the benefit from using chemotherapy in the LN+ disease setting. One of these analyses [130] was based on data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 trial for LN- disease [11] with relevant adjustments for baseline relapse risk and reported a favourable ICER of$5,685 USD per QALY gained in a subset analysis involving LN+ disease. The second analysis [182] found the RS-assay to be cost saving in LN+ disease setting due to predicted reductions of chemotherapy utilization after RS testing, but did not employ specific disease outcomes according to RS risk groups. One recent study has incorporated specific disease outcomes from the retrospective analysis of SWOG 8814trial. However, modeling the current experience of LN+ disease (i.e., without the RS-assay) with regard to survival in this study was not based on Canadian data and did not reflect real world clinical practice, and the model did not incorporate all breast cancer complications such as second primary breast cancer [132-133]. More importantly, the study did not focus on the low risk subset of LN+ disease setting (1-3 LN+) for whom the RS-assay is likely to be used in real life clinical practice and instead considered women with all levels of nodal involvement to be eligible for the RS-assay. There is no robust Canadian or international data yet to suggest that women with extensive nodal involvement (i.e., $\geq$ 4LN+) would not benefit from a treatment strategy

including chemotherapy [186]. Thus, the RS-assay may have no clinical utility for these women.

Our finding is consistent with earlier analyses of the RS-assay in the LN- disease setting. The ICER of the RS-assay in post-menopausal women with ER+ or PR+ 1-3 LN+ ESBC was within ICER ranges of the assay in women with LN- disease in Canada. For instance, in a recent analysis the RS-assay compared to CCP in LN- patient population generates cost-savings in pre-menopausal women and has an ICER of $60,000 per QALY gained in post-menopausal women (2012) [181]. Other ICER estimates for LN- disease in Canada are at $9,591 (2012) [133] and $63,064 (2010) [132] per QALY gained.

As of January 2013, the test is not publically funded for women with 1-3 LN+ disease in any Canadian province and these women are not currently eligible for inclusion in ongoing field evaluations of the RS-assay [186]. However, unlike the use of the RS-assay in LN+ disease, the use of the assay in LN- disease with reimbursement mechanisms is increasing across Canada. It became available for women with LN- disease in several provinces in a limited fashion or within context of a field evaluation [124-126]. Our value of information analysis in ER+ or PR+ 1-3 LN+ ESBC setting demonstrated that future research that can characterize the role of the RS-assay in real world Canadian practice may have a large societal impact, when willingness to pay levels of recently accepted cancer treatments are considered. Taken together with recent Canadian findings [177] on adjuvant chemotherapy efficacy in this particular patient population, this suggest that future field evaluations of the assay to establish its impact on Canadian practice should include postmenopausal women with 1-3 LN+ disease in addition to women with LN- disease.

The results of the retrospective analysis of SWOG 8814trial [20]are the first and only findings that indicate the prognostic utility of the RS-assay in LN+ disease population receiving tamoxifen alone. Our model was sensitive to the disease specific outcomes by the RS-assay derived from this analysis particularly for women included with 1-3 LN+ disease. Additionally, our analysis demonstrated that the ability of the RS-assay to guide treatment decisions in the intermediate risk group will likely be important in determining

whether the RS-assay will be a cost-effective use of resources. An ongoing prospective randomized trial (SWOG S-1007) [26] will determine the effect of chemotherapy in patients with 1-3 LN+ disease who do not have high RS by RS-assay. This trial will provide new evidence regarding the clinical utility of the RS-assay in this particular disease setting and further assess the predictive value of the assay in women falling in the intermediate risk group. However, findings from this trial will not be available for 5 years whereas an adoption decision will need to be made prior to having the results of this trial.

I used the Manitoba Cancer Registry and Manitoba Health administrative databases to model current real-world Canadian clinical practice. This approach may increase model complexity but it has the advantage of providing us with longitudinal patient, clinical and treatment data on a large number of patients and for a long follow up time (7 years). This allows us to estimate significant clinical outcomes (e.g., local recurrence, regional recurrence, second primary, chemotherapy-related serious adverse effects) that are otherwise hard to model using secondary data sources. This approach to decision modeling and cost-effectiveness analyses have been considered helpful in identifying data needs and quantifying uncertainty about a new medical intervention in the "real world" Canadian setting [187]. A more thorough discussion of the use of registry and administrative data to conduct cost-effectiveness analyses in the Canadian setting has been discussed elsewhere [188].

This study has limitations. First, the clinical utility of the RS- assay in women with 1-3 LN+ disease was based on retrospective analysis of the phase III SWOG-8814, INT-0100 trial conducted in the United States [20]. Thus, disease outcomes by the RS-assay may not necessarily reflect the experience of the ER+/PR+ 1-3 LN+ ESBC identified in Manitoba due to potential differences in patient and tumor characteristics and treatments. In regard to this shortcoming, reports from prospective analyses of the assay in real-world Canadian clinical practice are awaited to update our model and verify our results. Second, clinical guidelines are still awaited for women with intermediate-range RS-assay values [26]. Third, outcomes and costs of therapies given in the 2000-2002 population do not necessary reflect the possible benefits and costs of other newer types of adjuvant therapies (e.g., third generation anthracycline-taxane regimens) or dosing schedules used

in current practice so analysis with such data would be more applicable to the current practice landscape. Finally, although clinical practice patterns employed in the selected time period in Manitoba have shown to reflect practices in other jurisdictions in Canada [88, 174-175], management of women with ER+/PR+ 1-3 LN+ ESBC and its associated costs may be still different.

4.7 Conclusion

The RS-assay compared to CCP is likely to be cost-effective in postmenopausal women with ER+ or PR+ 1-3 LN+ ESBC. Current use of the assay with public reimbursement mechanisms should be extended to include cases with 1-3 LN+ disease in addition to LN- cases. Field evaluations of the assay to establish its impact on CCP in women with ER+/PR+1-3 LN+ ESBC should be initiated to ensure its clinical utility and cost-effectiveness in this patient population.

Chapter 5

5 Cost-effectiveness of using a microarray-based gene expression test to aid in identifying primary tumor versus Canadian clinical practice in patients with cancer of unknown primary

5.1 Abstract

A microarray-based gene expression test called the tissue of origin (TOO) test provides a method to predict the likely primary tumor site in cancer of unknown primary (CUP) by testing the biopsy specimen of the metastatic tumor. I sought to investigate the cost-effectiveness of using the TOO test to help identify primary tumor versus current clinical practice (CCP) in patients with CUP from the perspective of the Canadian public healthcare system. I developed a decision analytic model to project the lifetime clinical and economic consequences of CUP. I assumed that CUP patients present with occult primary tumor sites. Within each occult primary tumor setting, the TOO test may either lead to tumor specimen classification or indeterminate results. I assumed that TOO tumor classification would be interpreted after careful clinicopathologic and radiologic assessment and this may lead to correctly or incorrectly diagnose primary tumor or primary tumor stays undiagnosed, and correspondently guide patient management. The model was parameterized using 2 year follow up data from the Manitoba Cancer Registry, cost data from Manitoba Health administrative databases and secondary sources. Costs are presented in 2013 Canadian dollars (CAD), and future costs and benefits were discounted at 5%. In the base case, the TOO-based strategy compared to CCP led to an increase of 0.28 life year (LY) and 0.24 quality-adjusted life year (QALY) and an increase in cost of $10,807 CAD per person, resulting in an incremental cost effectiveness ratio (ICER) of $37,774 per LY gained and $44,151 per QALY gained. The

ICER was most sensitive to the accuracy of the TOO test, diagnostic results following TOO tumor classification and patient survival response following correct primary diagnosis. The TOO test is likely to be cost effective in the Canadian healthcare system and should be considered for adoption in patients with CUP. However, field evaluations of the test to establish its impact on Canadian management of CUP and resulting survival outcomes are warranted for further investigation.

5.2 Introduction

The Canadian Cancer Society estimates that approximately 186,400 new cases of cancer will occur in Canada in 2013 [189]. Of these new cases, up to 4% are of metastatic cancer types not readily classified in the course of the initial diagnostic work up which includes careful exanimation of clinical history, full physical examination (including head and neck, breast, pelvic and rectal examination) and chest radiograph [190]. International and Canadian clinical guidelines recommend a further diagnostic work-up for these metastatic patients including blood and biochemistry survey, urinalysis, fecal occult blood test, imaging procedures, cytogenetic studies, electron microscopy and immunohistochemical (IHC) analysis [190]. Additional evaluation and endoscopies are recommended to be sign-or symptom-guided [190]. In the past decade, improvements in the number and accuracy of IHC stains have enabled to make highly accurate tissue-of-origin diagnosis in many of these metastatic patients. However, the current success rate of the diagnostic work-up, even after exhaustive clinical and pathologic investigation, varies from 20% to 25% [39, 41]. Consequently, over 3% of all incident cancer cases are metastatic cancer of unknown primary origin (CUP) recorded annually in tumor registries across Canada, accounting for approximately 5000-7000 cases of CUP annually. The majority of these CUP cases were proven by autopsy series to have small clinically undetectable (i.e., occult) primary tumor sites [191].

In the absence of a specific tumor diagnosis, there has been no consensus of defined treatment guidelines. Several broad-spectrum empiric chemotherapeutic regimens (not specific for the nature of cancer) based on combination regimens of platinum or taxane have generally been used [192-193]. However, patients have a poor prognosis with a

median survival of 8-12 months from diagnosis and 1-year survival probabilities ranging from 15% to 35% [41].

The ability to identify a primary tumor site has been and continues to be the most important goal in the clinical management of any patient with metastatic cancer. When tumor origins are known, patient outcomes and even survival may improve [194-195]. This is because oncologists have better information on which to base treatment strategies and can allow patients to benefit from the increasing availability of specific and more effective therapy regimens, which may include specific chemotherapy or therapy designed to target biologic characteristics of specific malignancies.

Prediction of the likely primary tumor site by testing the biopsy specimen of the metastatic tumor is improving through the use of gene expression profiling techniques [196-197]. To date, several gene expression-based tests have demonstrated the potential value of this approach in identifying the primary site. However, only one test called “the Tissue of Origin (TOO)” test is clinically viable option and fulfill criteria for successful translation [54-55] according to publically available evidence [48, 59]. The TOO test (Response Genetics, Inc., Los Angeles, CA) is a microarray-based gene expression test for identifying a tumor’s primary site using formalin-fixed paraffin-embedded (FFPE) specimens. The test compares the RNA profile of a tumor FFPE specimen to established RNA profiles of 15 known tissues. The test measures the degree of similarity between the expression patterns of the tumor and those of a panel of 15 different tissue types. The TOO test result is presented as 15 separate similarity scores (SS) (which are interpreted as probabilities), one for each tissue type on the panel. The highest SS indicates the most likely tissue of origin. An SS of 30 or less indicates indeterminate results. When a specimen is found to include less than 60% of tumor content and more than 20% necrosis the TOO test results are considered indeterminate regardless of SS.

The test was validated on independent 462 formalin-fixed paraffin-embedded (FFPE) specimens derived from metastatic or poorly differentiated tumor specimens of known primary cancers and showed 89.3% accuracy in identifying tumor’s primary site [59]. The analysis included at least 25 specimens per tissue type and considered indeterminate results. In 2012, the test was reviewed and cleared by the Food and Drug Administration and has been clinically offered in the United States [60]. The TOO test results are

intended for use in the context of the patient's clinicopathologic and radiologic history by a qualified oncologist and pathologist [198-200]. For instance, initial or additional clinical history, IHC analyses, and computed tomography (CT) scan images should be correlated and consistent with TOO tumor classification when suggesting a potential primary tumor site.

The impact of the test on health and economic outcomes, if introduced into general clinical practice for CUP patients, has not been determined. The TOO test has official list price of $4,400 CAD per patient. As of January 2014, the test is not publically funded in any Canadian province and clinical management of CUP patients has not been influenced by TOO testing. Developing recommendations for Canadian clinical practice regarding the use of TOO test in CUP requires a comprehensive health economic evaluation of this approach in the Canadian setting [69]. I sought to evaluate the cost-effectiveness of using the TOO test to help diagnose the primary tumor and guide treatment decisions compared to current clinical practice (CCP) in patients diagnosed with CUP from the perspective of the Canadian health care system.

5.3 Methods

5.3.1 Model Overview

I developed a decision analytic model (Figure 5) to estimate the lifetime clinical and economic consequences of different clinical management strategies for patients diagnosed with CUP. The model begins with a decision to use the TOO test or to continue with CCP (Figure 5a). In the CCP-based strategy (Figure 5b), I classified CUP patients according to their occult primary tumor sites. Within each occult primary tumor site, I assumed that patients are treated according to existing clinical guidelines when primary tumor site stays undiagnosed. In the TOO-based strategy (Figure 5c), I classified CUP patients according to their occult primary tumor sites. Within each occult primary tumor site I assumed that the TOO test results would either classify the tumor specimen to one of the 15 tissue types included in the test panel or lead to indeterminate results (i.e., when SS is ≤ 30, encounter unique specimens harboring less than 60% tumor content, or actual tissue of origin for a given tumor specimen is not covered by the 15

tissue types included in the test panel) (Figure 5c). When TOO test results classify the tumor specimen, these results would either be correct or incorrect. I assumed that TOO tumor classification would be interpreted after careful clinicopathologic and radiologic assessment (CRA). When clinicopathologic correlation can be established with TOO test results (i.e., correct or incorrect), I assumed that TOO tumor classification would be considered and may lead to correct or incorrect cancer diagnosis and guide treatment decisions (Figure 5c). When clinicopathologic correlation cannot be established with the TOO test results (i.e., correct or incorrect), I assumed that TOO tumor classification would not be considered and primary tumor may stay undiagnosed (Figure 5c).

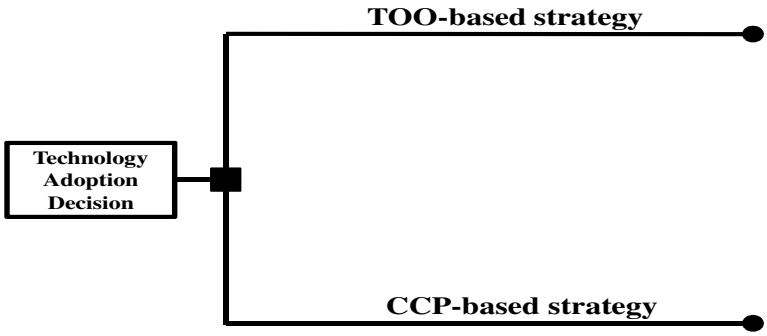
CUP patients whose primary tumor stays undiagnosed in both strategies or those who have their primary tumor incorrectly diagnosed in the TOO-based strategy entered model "A" (Figure 5d). CUP patients who have their primary tumor correctly diagnosed in the TOO-based strategy entered model "B" (Figure 5e). Model "A" differs from model "B" in that it has an additional health state to account for possible detection of an eventual primary tumor later during the course of the disease (latent primary).

Model "A" simulated monthly transitions among the following five distinct health states: (1) Initial diagnosis of metastasis (IDM); (2) diagnosis of latent primary (LP); (3) diagnosis of second primary (SP); (4) palliative care (PC); (5) death. Model "B" simulated monthly transitions among the following four distinct health states: (1) IDM; (2) SP; (3) PC; (4) death.

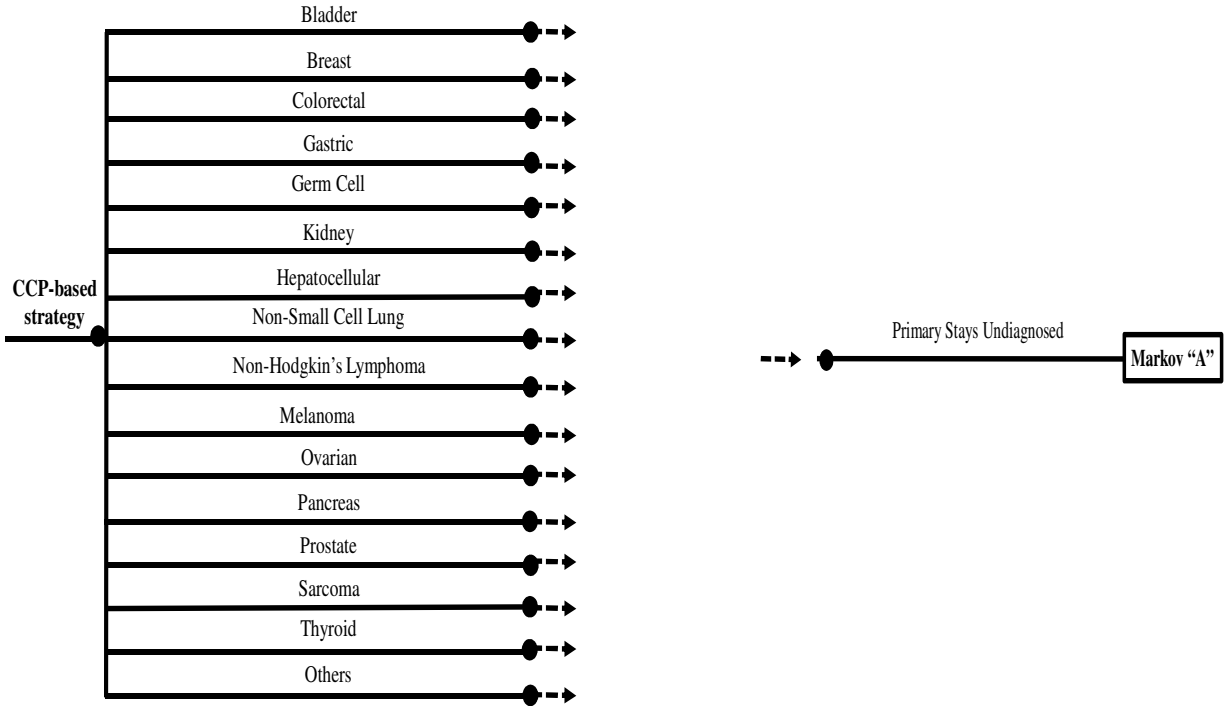
The analysis was conducted from the Canadian health care payer's perspective. I applied a discount rate of 5% per annum to costs, life years (LY) and quality adjusted life years (QALYs) following recommendations by the Canadian agency for Drugs and Technologies in Health [111]. I used a lifetime horizon and half cycle correction [136]. I used TreeAge Software to populate and evaluate the decision analytic model [136]. Data collection and analysis using Manitoba administrative databases (including the Manitoba Cancer Registry, the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network) were approved by the University of Manitoba Health Research Ethics Board and Western University Health Research Ethics Board.

Figure 5. Decision model for CUP.

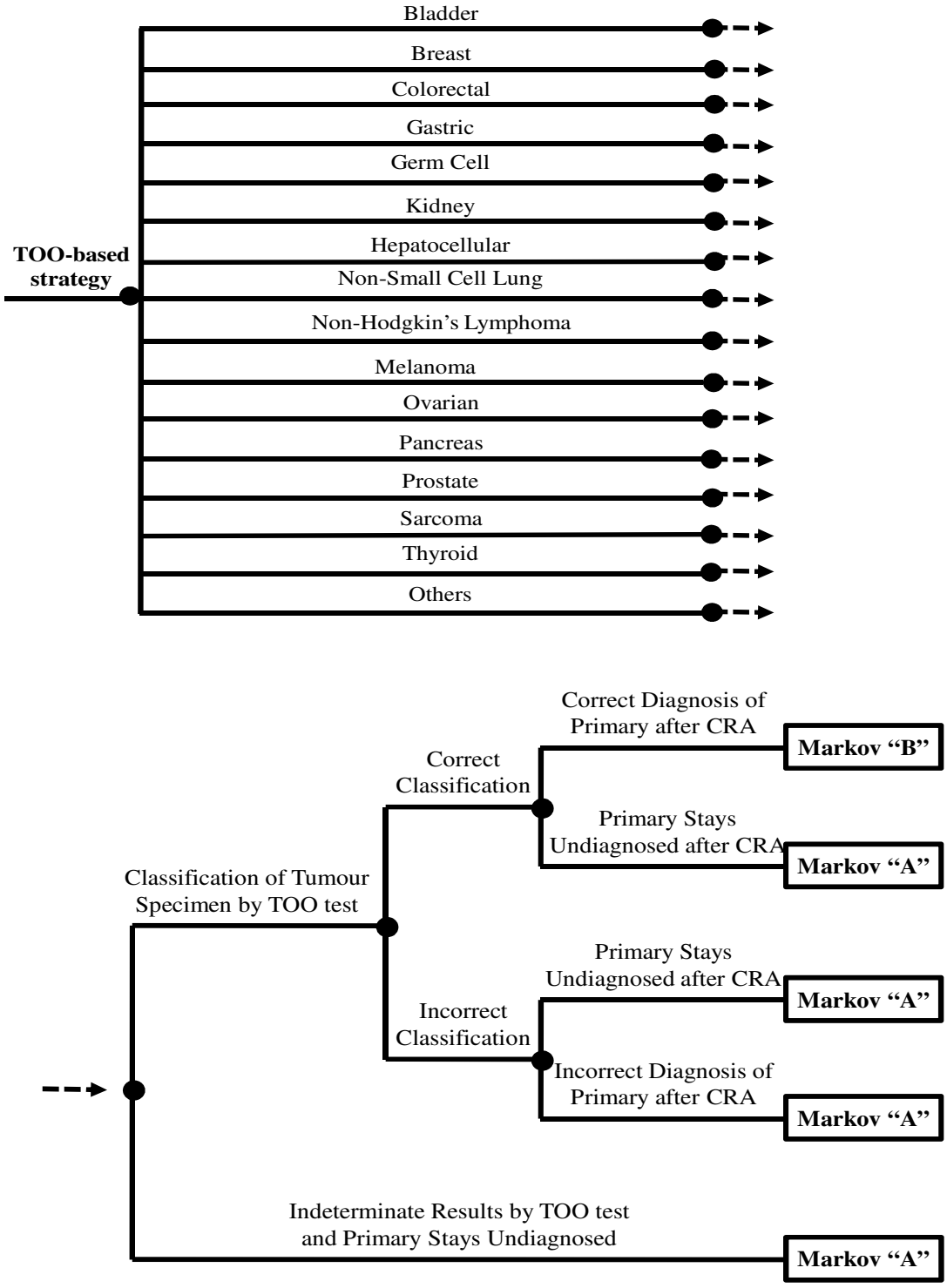
a TOO testversus CCP-guided clinical management.



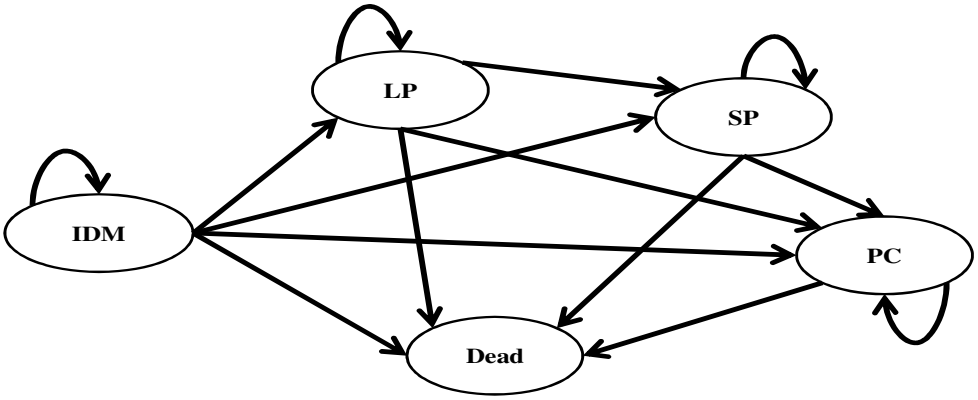
b CCP-guided clinical management.



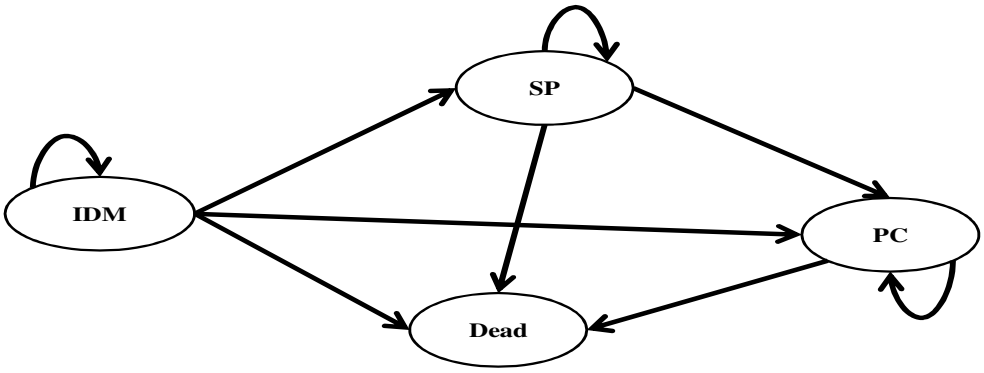
c TOO-guided clinical management.



d Schematic representation of the Markov model structure "A".



e Schematic representation of the Markov model structure "B".



■ Decision node ● Chance node → Transition

Patients entering Markov model "A" start the model and remain in the IDM state unless they develop LP or SP, start PC, or die. Patients who developed LP remain in the LP state or make transition to SP, PC, or Dead states. Patients entering Markov model "B" start the model and remain in the IDM state unless they develop SP, start PC, or die. In both Markov models, patients who developed SP, remain in the SP state or make transition to PC or Dead states. Patients who started PC remain in the PC state or make transition to Dead state. The cycle length was 1 month. Abbreviations: CCP= Canadian clinical practice; TOO= Tissue of Origin; CRA= clinicopathologic and radiologic assessment; IDM= initial diagnosis of metastasis; LP= diagnosis of latent primary; SP= diagnosis of second primary; PC= palliative care.

5.3.2 Identification of a Study Cohort

The MCR is a provincial database that contains the records for more than 99.5% of all cases of cancer in Manitoba and is a comprehensive cancer registry [137]. Information on cancer staging, based on the American Joint Commission on Cancer (Version 5), has been routinely collected for all cancer sites since January 1995 [138]. The MCR also collects information on demographics, clinical tumor characteristics, disease progression, SP cancer, death, and cancer treatments. I used the MCR to identify a study cohort consisting of all metastatic cancer patients (defined as diagnosed initially with stage IV or diagnosed with distant metastasis within 4 months of initial diagnosis) during the period from January 1, 2002 to December 31, 2011. I limited the study cohort to those who are Manitoba residents, 18 to 90 years old and with no history of malignancy at initial diagnosis. Since the end of the accrual period is 2011, a minimum of two-year follow-up information from the time of initial diagnosis was available for each patient. This included diagnosis of SP, cancer treatments (e.g., surgical procedures, therapeutic radiology procedures, endocrine therapy, chemotherapy, biological therapy, and palliative care) and death. I linked all patients with administrative data held by Manitoba Health including the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network. To protect confidentiality, the linkage was performed with a scrambled health number using anonymatized versions of these databases.
For each patient in our study cohort, I used the MCR to establish the initial diagnosis status of primary tumor site. I used initial tumor specific-files (i.e., historical data) available on cancer patients in the registry and search for codes representing the anatomical sites (i.e., using the International Classification of Diseases for Oncology (ICD-O) topography diagnosis codes). I linked all patients with their tumor specific-updated files available in the MCR (i.e., linkage performed via both tumor ID and scrambled health number). I then identified those who have their initial primary anatomical site status changed to different site at least 6 months after their initial diagnosis. This 6 month window is considered necessary and reasonable to ensure that the diagnoses of the later primary anatomical sites were not the results of extension in the initial diagnostic work up [10]. I considered these patients to have a LP tumor site subsequently detected during their life or at autopsy.

I stratified our study cohort to three patient groups; (1) metastatic patients diagnosed initially with CUP: defined as those who were initially diagnosed with CUP (i.e., using the ICD-O topography diagnosis code c80.9) and either had their LP detected or undetected later during their life or at autopsy; (2) metastatic patients diagnosed initially with their true primary site: defined as those who were initially diagnosed with known primary and had no change detected with their primary diagnosis later during their life or at autopsy); (3) metastatic patients diagnosed initially with their incorrect primary site: defined as those who were initially diagnosed with a given known primary and had a LP detected later during their life or at autopsy). For each patient group, I ascertained PC from both the MCR and by linking with the Physician Claims Database and using the specific tariff index of PC as provided by physicians.

5.3.3 Distributions and Transition Probabilities

I defined CCP for CUP according to the observed administration of treatments and survival outcomes in metastatic patients diagnosed initially with CUP (i.e., patient group "1"). I conducted survival analyses using Kaplan-Meier estimates using 2 years of follow up data from the MCR, and used this information to estimate all transition probabilities in the CCP Markov model "A".

For the TOO model I estimated the distribution of occult primary tumor sites among CUP patients (Table 9) based on the observed distribution of LPs among the subset of patients initially diagnosed with CUP who had their LP tumor site subsequently detected during their life or at autopsy. For each occult primary tumor site in the TOO model, I extracted the distribution of patients across TOO test results (i.e., classification of tumor specimen (correct and incorrect) or indeterminate results) and across diagnostic results after CRA (correct diagnosis of primary, incorrect diagnosis of primary, and undiagnosed primary) from a recent validation analysis [59] and clinical verification of the TOO test performance [198] (Table 9).

I assumed that CUP patients whose primary is correctly diagnosed would have survival outcomes similar to those of observed metastatic patients diagnosed initially with their true primary site [191]. Thus, I conducted survival analyses using Kaplan-Meier estimates for metastatic patients diagnosed initially with their true primary site (i.e.,

patient group “2”). I stratified this analysis by primary tumor site, using 2 years of follow up data from the MCR, and used this information to estimate all transition probabilities in the TOO Markov models following the chance nodes when the primary is correctly diagnosed. I assumed that CUP patients whose primary stays undiagnosed or is incorrectly diagnosed would have survival outcomes similar to those of observed metastatic patients diagnosed initially with CUP(i.e., patient group “1”) [191].
To extrapolate transition probabilities for lifetime, I assumed the observed average monthly transition probabilities during the last observed year of follow up in the studied population to be constant over the extrapolated time period. However, projected survival beyond 2 years was low in our metastatic patient population.

Table 9. Base case probabilities and sources.

Variables	Base case Value	Duration	Range tested in sensitivity analyses	Distribution used in PSA†	Data Source
Distribution of occult primary tumor sites among CUP patients (%)					MCR
Bladder	0			Dirichlet	
Breast	1.5			Dirichlet	
Colorectal	8.9			Dirichlet	
Gastric	3.8			Dirichlet	
Testicular germ cell	0.5			Dirichlet	
Kidney	3.5			Dirichlet	
Hepatocellular	1			Dirichlet	
Non-small cell lung	27			Dirichlet	
Non-Hodgkin's lymphoma	5.3			Dirichlet	
Melanoma	4.56			Dirichlet	
Ovarian	9.6			Dirichlet	
Pancreas	8.9			Dirichlet	
Prostate	1.5			Dirichlet	
Sarcoma	1.27			Dirichlet	
Thyroid	0.76			Dirichlet	
Others	21.91			Dirichlet	
Distribution of patients according to classification provided by the TOO within each occult primary tumor site (%)					[59]
Bladder					
Classification of tumor specimen	93		90 – 100		[198]
Incorrect classification	79.3		60.3 – 92		[59]
Correct classification	20.7		8 – 39.7	Beta	[59]
Indeterminate results	7		0 – 10	Beta	[198]
Breast					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	96.5		87.9 – 99.6		[59]
Incorrect classification	3.5		0.4 – 12.1	Beta	[59]
Indeterminate results	7		0 – 10	Beta	[198]
Colorectal					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	91.7		77.5 – 98.2		[59]
Incorrect classification	8.3		1.8 – 22.5	Beta	[59]
Indeterminate results	0		0 –10	Beta	[198]
Gastric					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	72		50.6 – 87.9		[59]
Incorrect classification	28		12.1 – 49.4	Beta	[59]
Indeterminate results	7		0 –10	Beta	[198]
Hepatocellular					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	96		79.6 – 99.9		[59]
Incorrect classification	4		0.1 – 20.4	Beta	[59]
Indeterminate results	7		0 –10	Beta	[198]
Germ cell					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	84		63.9 – 95.5		[59]
Incorrect classification	16		4.5 – 36.1	Beta	[59]
Indeterminate results	7		0 –10	Beta	[198]
Kidney					
Classification of tumor specimen	93		90 – 100		[198]
Correct classification	89.3		71.8 – 97.7		[59]
Incorrect classification	10.7		0.3 – 28.2	Beta	[59]

Indeterminate results	7	0 –10	Beta	[198]
Melanoma				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	84	63.9 – 95.5		[59]
Incorrect classification	16	0.5 – 36.1	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Non-Hodgkin's lymphoma				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	89.7	72.6 – 97.8		[59]
Incorrect classification	10.3	2.2 – 27.4	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Non-small cell lung				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	85.2	66.3 – 95.8		[59]
Incorrect classification	14.8	4.2 – 33.7	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Ovarian				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	88.9	75.9 – 96.3		[59]
Incorrect classification	11.1	3.7 – 24.1	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Pancreas				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	85.7	67.3 – 96		[59]
Incorrect classification	14.3	4 – 32.7	Beta	[59]
Indeterminate results	7	0 – 10	Beta	[198]
Prostate				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	96	79.6 – 99.9		[59]
Incorrect classification	4	0.1 – 20.4	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Sarcoma				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	88.9	70.8 – 97.6		[59]
Incorrect classification	11.1	2.4 – 29.2	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Thyroid				
Classification of tumor specimen	93	90 – 100		[198]
Correct classification	90.3	74.2 – 98		[59]
Incorrect classification	9.7	2 – 25.8	Beta	[59]
Indeterminate results	7	0 –10	Beta	[198]
Others				
Classification of tumor specimen	67			[198]
Correct classification	0			[59]
Incorrect classification	100			[59]
Indeterminate results	33	0–50	Beta	[198]
Distribution of patients across diagnostic results after CRA within each occult primary tumor site (%)				
Correct classification				
Correct diagnosis of primary	100	90 – 100	Beta	[198]
Undiagnosed primary	0	0 – 10		[198]
Incorrect classification				
Undiagnosed primary	100	90 – 100	Beta	[198]
Incorrect diagnosis	0	0 – 10		[198]

† Beta distribution was used for other probability parameter estimates not included in this table.
PSA= probabilistic sensitivity analysis; MCR= Manitoba Cancer Registry; CUP= Cancer of unknown primary; CRA= Clinicopathologic and radiologic assessment.

5.3.4 Costs

The cost of the TOO test, after all Canadian health system expenses are added, is estimated at $4,400 CAD per patient. The management costs of metastatic cancer including treatment costs (e.g., surgical procedures, radiation therapy, chemotherapy, endocrine therapy, biological therapy, etc.), costs of follow up, costs of managing treatment side effects, and cost of palliative care are all publicly funded in Manitoba and recorded in the administrative databases held by Manitoba Health.

I used the Hospital Discharge Database to estimate the costs of inpatients and one day procedure stays for our study cohort during their disease course following the initial diagnosis. I used the Resource Intensity Weights [201-202] recorded for inpatient stays and Day Procedure Group Weights [201-202] recorded for day procedure stays to reflect the resources consumed during hospital contacts. I converted these weights into dollars using a multiplier known as the Cost Per Weighted Case [201-202]. I used the Physician Claims Database to estimate the cost of medical claims made by physicians (and other health care providers) for insured services provided to our patient cohort during their disease course following the initial diagnosis. In addition, I used the Drug Program Information Network to estimate the cost of prescription claims made by our study cohort during their disease course following the initial diagnosis.

I used the costs of hospital stays, medical claims and prescription claims for our study cohort to estimate the cost per unit time in each Markov state (Table 10). I used the costs collected for metastatic patients diagnosed initially with CUP (i.e., patient group “1”) to estimate the cost per unit time in each state of Markov model following the chance nodes when the primary stays undiagnosed in both the CCP and TOO-based strategy. I used the costs collected for metastatic patients diagnosed initially with their true primary site (i.e., patient group “2” stratified by primary tumor site) to estimate the cost per unit time in each state of TOO Markov models following the chance nodes when the primary is correctly diagnosed. To account for costs associated with incorrect primary diagnosis in the TOO-based strategy, I used the costs collected for metastatic patients diagnosed initially with their incorrect primary site (i.e., patient group “3” stratified by primary

tumor site) to estimate the cost per unit time in each “IDM” state of TOO Markov models following the chance nodes when the primary is incorrectly diagnosed. I estimated cost per unit time in other states of TOO Markov models following the chance nodes when the primary is incorrectly diagnosed by using costs collected for metastatic patients diagnosed initially with CUP (i.e., patient group “1” stratified by primary tumor site). All costs are expressed in 2013 CAD.

Table 10. Base case cost estimates and sources.

Variables	Base case value	Duration	Distribution used in PSA†	Data Source
Cost associated with IDM (per month), $				
Breast				
First year after IDM				
Costs of inpatients and one day procedure stays	983	12 months	Normal	HA
Physicians and other health care providers cost	257	12 months	Normal	PC
Cost of prescription claims	73	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	490	Lifetime	Normal	HA
Physicians and other health care providers cost	131	Lifetime	Normal	PC
Cost of prescription claims	89	Lifetime	Normal	DPIN
Colorectal				
First year after IDM				
Costs of inpatients and one day procedure stays	1273	12 months	Normal	HA
Physicians and other health care providers cost	533	12 months	Normal	PC
Cost of prescription claims	73	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	730	Lifetime	Normal	HA
Physicians and other health care providers cost	284	Lifetime	Normal	PC
Cost of prescription claims	89	Lifetime	Normal	DPIN
Gastric				
First year after IDM				
Costs of inpatients and one day procedure stays	1425	12 months	Normal	HA
Physicians and other health care providers cost	398	12 months	Normal	PC
Cost of prescription claims	46	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1372	Lifetime	Normal	HA
Physicians and other health care providers cost	271	Lifetime	Normal	PC
Cost of prescription claims	72	Lifetime	Normal	DPIN
Hepatocellular				
First year after IDM				
Costs of inpatients and one day procedure stays	943	12 months	Normal	HA
Physicians and other health care providers cost	185	12 months	Normal	PC
Cost of prescription claims	42	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	737	Lifetime	Normal	HA
Physicians and other health care providers cost	19	Lifetime	Normal	PC
Cost of prescription claims	27	Lifetime	Normal	DPIN
Kidney				
First year after IDM				
Costs of inpatients and one day procedure stays	1353	12 months	Normal	HA
Physicians and other health care providers cost	373	12 months	Normal	PC
Cost of prescription claims	78	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1019	Lifetime	Normal	HA
Physicians and other health care providers cost	224	Lifetime	Normal	PC
Cost of prescription claims	93	Lifetime	Normal	DPIN
Melanoma				
First year after IDM				
Costs of inpatients and one day procedure stays	508	12 months	Normal	HA
Physicians and other health care providers cost	290	12 months	Normal	PC
Cost of prescription claims	78	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	748	Lifetime	Normal	HA
Physicians and other health care providers cost	164	Lifetime	Normal	PC

Cost of prescription claims	85	Lifetime	Normal	DPIN
Non-Hodgkin's lymphoma				
First year after IDM				
Costs of inpatients and one day procedure stays	1620	12 months	Normal	HA
Physicians and other health care providers cost	346	12 months	Normal	PC
Cost of prescription claims	123	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1414	Lifetime	Normal	HA
Physicians and other health care providers cost	183	Lifetime	Normal	PC
Cost of prescription claims	77	Lifetime	Normal	DPIN
Non-small lung				
First year after IDM				
Costs of inpatients and one day procedure stays	885	12 months	Normal	HA
Physicians and other health care providers cost	241	12 months	Normal	PC
Cost of prescription claims	33	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	773	Lifetime	Normal	HA
Physicians and other health care providers cost	164	Lifetime	Normal	PC
Cost of prescription claims	83	Lifetime	Normal	DPIN
Ovarian				
First year after IDM				
Costs of inpatients and one day procedure stays	2618	12 months	Normal	HA
Physicians and other health care providers cost	392	12 months	Normal	PC
Cost of prescription claims	69	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1144	Lifetime	Normal	HA
Physicians and other health care providers cost	187	Lifetime	Normal	PC
Cost of prescription claims	58	Lifetime	Normal	DPIN
Pancreas				
First year after IDM				
Costs of inpatients and one day procedure stays	1164	12 months	Normal	HA
Physicians and other health care providers cost	294	12 months	Normal	PC
Cost of prescription claims	36	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1345	Lifetime	Normal	HA
Physicians and other health care providers cost	241	Lifetime	Normal	PC
Cost of prescription claims	171	Lifetime	Normal	DPIN
Prostate				
First year after IDM				
Costs of inpatients and one day procedure stays	961	12 months	Normal	HA
Physicians and other health care providers cost	243	12 months	Normal	PC
Cost of prescription claims	60	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	771	Lifetime	Normal	HA
Physicians and other health care providers cost	119	Lifetime	Normal	PC
Cost of prescription claims	64	Lifetime	Normal	DPIN
Sarcoma				
First year after IDM				
Costs of inpatients and one day procedure stays	1451	12 months	Normal	HA
Physicians and other health care providers cost	552	12 months	Normal	PC
Cost of prescription claims	127	12 months	Normal	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	470	Lifetime	Normal	HA
Physicians and other health care providers cost	119	Lifetime	Normal	PC
Cost of prescription claims	176	Lifetime	Normal	DPIN
Germ cell				
First year after IDM				
Costs of inpatients and one day procedure stays	1109	12 months	Normal	HA
Physicians and other health care providers cost	606	12 months	Normal	PC
Cost of prescription claims	129	12 months	Normal	DPIN

After first year of IDM					
Costs of inpatients and one day procedure stays	903	Lifetime	Normal	HA
Physicians and other health care providers cost	139	Lifetime	Normal	PC
Cost of prescription claims	26	Lifetime	Normal	DPIN
Thyroid					
First year after IDM					
Costs of inpatients and one day procedure stays	854	12 months	Normal	HA
Physicians and other health care providers cost	417	12 months	Normal	PC
Cost of prescription claims	39	12 months	Normal	DPIN
After first year of IDM					
Costs of inpatients and one day procedure stays	484	Lifetime	Normal	HA
Physicians and other health care providers cost	89	Lifetime	Normal	PC
Cost of prescription claims	45	Lifetime	Normal	DPIN
CUP					
First year after IDM					
Costs of inpatients and one day procedure stays	1145	12 months	Normal	HA
Physicians and other health care providers cost	210	12 months	Normal	PC
Cost of prescription claims	51	12 months	Normal	DPIN
After first year of IDM					
Costs of inpatients and one day procedure stays	541	Lifetime	Normal	HA
Physicians and other health care providers cost	90	Lifetime	Normal	PC
Cost of prescription claims	100	Lifetime	Normal	DPIN
Cost associated with latent primary (per month), $					
Patients initially diagnosed with CUP					
First year after latent primary					
Costs of inpatients and one day procedure stays	970	12 months	Normal	HA
Physicians and other health care providers cost	191	12 months	Normal	PC
Cost of prescription claims	88	12 months	Normal	DPIN
After first year of latent primary					
Costs of inpatients and one day procedure stays	1724	Lifetime	Normal	HA
Physicians and other health care providers cost	150	Lifetime	Normal	PC
Cost of prescription claims	88	Lifetime	Normal	DPIN
Cost associated with palliative care (per month), $					
Breast					
Costs of inpatients and one day procedure stays	1214	Lifetime	Normal	HA
Physicians and other health care providers cost	236	Lifetime	Normal	PC
Cost of prescription claims	98	Lifetime	Normal	DPIN
Colorectal					
Costs of inpatients and one day procedure stays	1226	Lifetime	Normal	HA
Physicians and other health care providers cost	204	Lifetime	Normal	PC
Cost of prescription claims	77	Lifetime	Normal	DPIN
Gastric					
Costs of inpatients and one day procedure stays	790	Lifetime	Normal	HA
Physicians and other health care providers cost	149	Lifetime	Normal	PC
Cost of prescription claims	56	Lifetime	Normal	DPIN
Germ cell					
Costs of inpatients and one day procedure stays	594	Lifetime	Normal	HA
Physicians and other health care providers cost	10	Lifetime	Normal	PC
Cost of prescription claims	0	Lifetime	Normal	DPIN
Kidney					
Costs of inpatients and one day procedure stays	1277	Lifetime	Normal	HA
Physicians and other health care providers cost	259	Lifetime	Normal	PC
Cost of prescription claims	184	Lifetime	Normal	DPIN
Hepatocellular					
Costs of inpatients and one day procedure stays	544	Lifetime	Normal	HA
Physicians and other health care providers cost	142	Lifetime	Normal	PC
Cost of prescription claims	27	Lifetime	Normal	DPIN
Non-small lung					
Costs of inpatients and one day procedure stays	1116	Lifetime	Normal	HA
Physicians and other health care providers cost	175	Lifetime	Normal	PC

Cost of prescription claims	67	Lifetime	Normal	DPIN
Non-Hodgkin's lymphoma				
Costs of inpatients and one day procedure stays	1012	Lifetime	Normal	HA
Physicians and other health care providers cost	242	Lifetime	Normal	PC
Cost of prescription claims	268	Lifetime	Normal	DPIN
Melanoma				
Costs of inpatients and one day procedure stays	853	Lifetime	Normal	HA
Physicians and other health care providers cost	241	Lifetime	Normal	PC
Cost of prescription claims	94	Lifetime	Normal	DPIN
Ovarian				
Costs of inpatients and one day procedure stays	1182	Lifetime	Normal	HA
Physicians and other health care providers cost	158	Lifetime	Normal	PC
Cost of prescription claims	71	Lifetime	Normal	DPIN
Pancreas				
Costs of inpatients and one day procedure stays	819	Lifetime	Normal	HA
Physicians and other health care providers cost	144	Lifetime	Normal	PC
Cost of prescription claims	55	Lifetime	Normal	DPIN
Prostate				
Costs of inpatients and one day procedure stays	1358	Lifetime	Normal	HA
Physicians and other health care providers cost	200	Lifetime	Normal	PC
Cost of prescription claims	88	Lifetime	Normal	DPIN
Sarcoma				
Costs of inpatients and one day procedure stays	1215	Lifetime	Normal	HA
Physicians and other health care providers cost	197	Lifetime	Normal	PC
Cost of prescription claims	112	Lifetime	Normal	DPIN
Thyroid				
Costs of inpatients and one day procedure stays	463	Lifetime	Normal	HA
Physicians and other health care providers cost	102	Lifetime	Normal	PC
Cost of prescription claims	49	Lifetime	Normal	DPIN
CUP				
Costs of inpatients and one day procedure stays	1233	Lifetime	Normal	HA
Physicians and other health care providers cost	184	Lifetime	Normal	PC
Cost of prescription claims	83	Lifetime	Normal	DPIN
Cost associated with second primary (per month), $				
Breast				
Costs of inpatients and one day procedure stays	527	Lifetime	Normal	HA
Physicians and other health care providers cost	265	Lifetime	Normal	PC
Cost of prescription claims	42	Lifetime	Normal	DPIN
Colerectal				
Costs of inpatients and one day procedure stays	1283	Lifetime	Normal	HA
Physicians and other health care providers cost	511	Lifetime	Normal	PC
Cost of prescription claims	128	Lifetime	Normal	DPIN
Gastric				
Costs of inpatients and one day procedure stays	464	Lifetime	Normal	HA
Physicians and other health care providers cost	102	Lifetime	Normal	PC
Cost of prescription claims	11	Lifetime	Normal	DPIN
Germ cell				
Costs of inpatients and one day procedure stays	711	Lifetime	Normal	HA
Physicians and other health care providers cost	1217	Lifetime	Normal	PC
Cost of prescription claims	27	Lifetime	Normal	DPIN
Kidney				
Costs of inpatients and one day procedure stays	2518	Lifetime	Normal	HA
Physicians and other health care providers cost	285	Lifetime	Normal	PC
Cost of prescription claims	164	Lifetime	Normal	DPIN
Non-small lung				
Costs of inpatients and one day procedure stays	1147	Lifetime	Normal	HA
Physicians and other health care providers cost	317	Lifetime	Normal	PC
Cost of prescription claims	62	Lifetime	Normal	DPIN
Non-Hodgkin's lymphoma				
Costs of inpatients and one day procedure stays	876	Lifetime	Normal	HA

	Physicians and other health care providers cost	343	Lifetime	Normal	PC
	Cost of prescription claims	138	Lifetime	Normal	DPIN
Melanoma					
	Costs of inpatients and one day procedure stays	1022	Lifetime	Normal	HA
	Physicians and other health care providers cost	437	Lifetime	Normal	PC
	Cost of prescription claims	166	Lifetime	Normal	DPIN
Ovarian					
	Costs of inpatients and one day procedure stays	600	Lifetime	Normal	HA
	Physicians and other health care providers cost	202	Lifetime	Normal	PC
	Cost of prescription claims	29	Lifetime	Normal	DPIN
Prostate					
	Costs of inpatients and one day procedure stays	1573	Lifetime	Normal	HA
	Physicians and other health care providers cost	254	Lifetime	Normal	PC
	Cost of prescription claims	83	Lifetime	Normal	DPIN
Sarcoma					
	Costs of inpatients and one day procedure stays	1246	Lifetime	Normal	HA
	Physicians and other health care providers cost	517	Lifetime	Normal	PC
	Cost of prescription claims	256	Lifetime	Normal	DPIN
Thyroid					
	Costs of inpatients and one day procedure stays	219	Lifetime	Normal	HA
	Physicians and other health care providers cost	142	Lifetime	Normal	PC
	Cost of prescription claims	48	Lifetime	Normal	DPIN
CUP					
	Costs of inpatients and one day procedure stays	910	Lifetime	Normal	HA
	Physicians and other health care providers cost	307	Lifetime	Normal	PC
	Cost of prescription claims	34	Lifetime	Normal	DPIN

Patients initially diagnosed with metastatic hepatocellular and pancreatic cancer did not have a second primary over the study follow up period and thus costs associated with second primary are not included for hepatocellular and pancreas.
PSA= probabilistic sensitivity analysis; MCR= Manitoba Cancer Registry: PC= physician claims; HA= Hospital abstracts; DPIN= Drug Program Information Network records; CUP= Cancer of unknown primary; IDM= Initial diagnosis of metastasis.

5.3.5 Utilities

I undertook a systematic review of both primary research studies and economic models to determine utilities for each health state in the Markov models (Table 11). I derived different utility estimates for metastatic patients diagnosed initially with different known primary sites. I assumed that CUP patients whose primary is correctly diagnosed may have quality of life outcomes similar to those of metastatic patients diagnosed initially with known primary site.

One recent study has focused on health related quality of life (HRQoL) among CUP patients [203]. CUP patients were found to experience 13% more impaired HRQoL compared with metastatic patients of known primary. In this study, I estimated the weighted average utility of metastatic patients of known primary (i.e., weighted average was based on the observed distribution of latent primary tumor sites in our CUP cohort (Table 1)) at 0.64 (Table 11). When primary tumor site stays undiagnosed I estimated the baseline utility at 0.56 after applying 13% reduction on the weighted average utility of metastatic patients of known primary. When patients have the latent primary tumor site subsequently detected during their life, I assumed that patients would experience quality of life similar to those of metastatic patients diagnosed initially with corresponding known primary site. I performed sensitivity analysis on the utility values to account for uncertainty.

Table 11. Utility values and sources.

Health states	Utility[β]	Duration	Range tested in sensitivity analyses	Distribution used in PSA	Data Source
Initial diagnosis of metastasis					
Breast	0.715	LT	-20% – +20%	Beta	[60]
Colorectal	0.730	LT	-20% – +20%	Beta	[204]
Gastric	0.729	LT	-20% – +20%	Beta	[205]
Hepatocellular	0.650	LT	-20% – +20%	Beta	[206]
Kidney	0.760	LT	-20% – +20%	Beta	[207]
Melanoma	0.580	LT	-20% – +20%	Beta	[208]
Non-Hodgkin's lymphoma	0.805	LT	-20% – +20%	Beta	[209]
Non-small Lung	0.530	LT	-20% – +20%	Beta	[210]
Ovarian	0.740	LT	-20% – +20%	Beta	[211]
Pancreas	0.600	LT	-20% – +20%	Beta	[212]
Prostate	0.740	LT	-20% – +20%	Beta	[213]
Sarcoma	0.690	LT	-20% – +20%	Beta	[214]
Testicular germ cell	0.776	LT	-20% – +20%	Beta	[215-216]
Thyroid	0.780	LT	-20% – +20%	Beta	[216-217]
Other primary tumor sites					
Buccal cavity and pharynx	0.670				[218]
Esophagus	0.670				[218]
Small intestine	0.730				[204]
Gallbladder	0.650				[206]
Non-hepatocellular	0.650				[206]
Other digestive system	0.730				[204]
Other female genital system	0.740				[211]
Other male genital system	0.740				[213]
Small cell lung	0.530				[210]
Other lung	0.530				[210]
Ureter	0.760				[207]
Other urinary system	0.760				[207]
Multiple myeloma	0.805				[209]
Other endocrine	0.800				[216-217]
Weighted average utility of other primary tumor sites^	0.649	LT	-20% – +20%	Beta	
Weighted average utility of metastatic patients of known primary^	0.645	LT	-20% – +20%	Beta	
CUP*	0.560	LT	-20% – +20%	Beta	[203]
Diagnosis of latent primary					
Patient diagnosed with a given latent primary	Corresponding utility of patient initially diagnosed with metastasis of that primary tumor	LT	-20% – +20%	Beta	
Second primary tumor	7% reduction of corresponding utility of a given primary tumor site	LT	-20% – +20%	Beta	[219]
Palliative care	0.4	LT	-20% – +20%	Beta	[220]
Death	0				

β All utility estimates were based on EuroQOL five dimensions questionnaire (EQ-5D).
^ Weighted average was based on the observed distribution of latent primary tumor sites in our CUP cohort.
* Utility with CUP was derived after applying 13% reduction on the weighted average utility of latent primary tumor sites in CUP.
CUP= cancer of unknown primary; LT= lifetime.

5.4 Results

5.4.1 Base-case scenario

There were 1,214 metastatic patients initially diagnosed in Manitoba from January 1, 2002 to December 31, 2011 with CUP and 405 (33%) of those patients had their latent primary tumor site subsequently detected during their life or at autopsy. During the same time period, there were 11,731 patients initially diagnosed with metastatic of known primary in Manitoba and 2417 (20%) of those patients had their initial primary tumor incorrectly identified and their true latent primary tumor detected later during life or at autopsy. Patient, tumor, treatment and event characteristics of the study cohort are summarized elsewhere [221].

Our model predicted 1.13 LY, 0.63 QALY and $17,802 CAD for CUP whereas when primary tumor is properly identified our model outcomes ranged from 0.74 LY, 0.45 QALY, and $14,278 with hepatocellular to 4.35 LY, 3.37 QALY, $69,400 CAD with testicular germ cell. A detailed summary for all Markov model outcomes is depicted in Table 4. The TOO-based strategy led to an increase of 0.28 LY and 0.24 QALY per person and an increase in cost of $10,807 CAD per person, resulting in an incremental cost effectiveness ratio (ICER) of $37,774 per LY gained and $44,151per QALY gained compared to CCP. Baseline outcomes are summarized in Table 12.

Table 12. Baseline Markov model outcomes.

Primary Tumor site	Effectiveness		Cost
	LY	QALY	
Breast	1.79	1.08	$30,874
Colorectal	2.00	1.40	$38,978
Gastric	1.09	0.73	$26,985
Hepatocellular	0.74	0.45	$14,278
Kidney	1.51	1.02	$34,157
Melanoma	2.30	1.29	$33,056
Non-Hodgkin's lymphoma	3.05	2.41	$68,662
Non-small Lung	1.08	0.53	$20,165
Ovarian	1.86	1.31	$50,000
Pancreas	0.75	0.43	$18,157
Prostate	2.62	1.78	$40,942
Sarcoma	1.88	1.22	$36,015
Testicular germ cell	4.35	3.37	$69,400
Thyroid	3.77	2.97	$40,200
Unknown primary	**1.13**	**0.63**	**$17,802**

LY= life year; QALY= quality adjusted life year.

Table 13. Baseline study outcomes†.

Strategy	Effectiveness		Incremental Effectiveness		Cost	Incremental Cost	ICER	
	LY	QALY	LY	QALY			Per LY gained	Per QALY gained
CCP	1.13	0.63	0.28	0.24	$17,802	$10,807	$37,774	$44,151
TOO test	1.42	0.87			$28,609			

† Due to rounding, numbers may not balance

CCP= current clinical practice; TOO test= Tissue of Origin test; ICER= incremental cost effectiveness ratio; LY= life year; QALY= quality adjusted life year.

5.4.2 Sensitivity Analysis

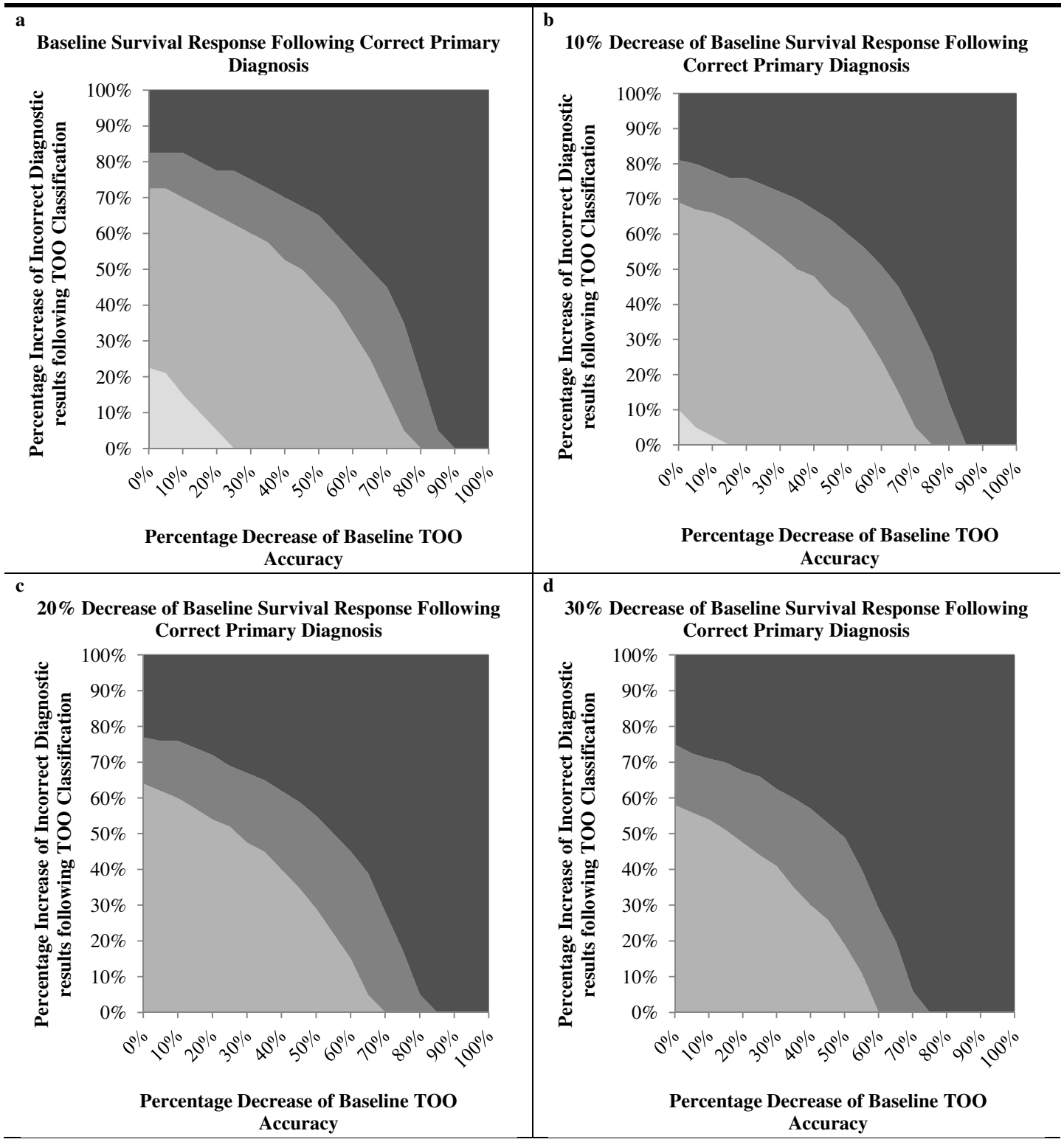
In three-way sensitivity analysis I tested three groups of parameters: (1) Parameters related to sensitivity of the TOO test across occult primary sites (i.e., correct or incorrect classification of tumor specimen); (2) Parameters related to incorrect diagnostic results following TOO specimen classification (i.e., when primary stays undiagnosed following correct TOO classification of tumor specimen or when primary is incorrectly diagnosed following incorrect TOO classification of tumor specimen); (3) Parameters related to survival response following correct primary diagnosis (i.e., the transition probabilities from IDM to PC, SP, or dead states in the TOO Markov models following the chance nodes when the primary is correctly diagnosed). The TOO-based strategy generated an ICER greater than $100,000 per QALY gained when the sensitivity of the TOO test decreased by 50%, incorrect diagnostic results following TOO specimen classification increased by 20% and survival response following correct primary diagnosis decreased by 30% (Figure 6). Cost of the test and indeterminate TOO results across occult primary sites did not substantially influence our baseline outcomes (Figure 7).

I performed a probabilistic sensitivity analysis (Figure 8a) comparing the TOO versus CCP-based strategy. I simultaneously varied all parameters (probabilities, utilities and costs) using appropriate distributions (Table 1, 2 and 3). Using a willingness to pay threshold of $50,000 and $100,000 per QALY gained, I found that the TOO-based strategy was the preferred strategy in 78.2% and 99.6% of simulations respectively (Figure 8b).

I also performed a value-of-information analysis [112] to determine the expected monetary value of perfect information about the impact of TOO test. This analysis is necessary to estimate the societal impact of future research that can evaluate the TOO test in real life Canadian clinical practice [112]. In particular, I set up our baseline model to express all parameters related to the accuracy of the TOO test, diagnostic results following TOO specimen classification, and survival response following correct primary diagnosis as probability distributions (Table 9) and the entire model is set up as a probabilistic model. I assessed the level of uncertainty in the model using simulation techniques (i.e., making 1000 random draws of the probabilistic model). Using our baseline ICER value of $44,151 per QALY gained as our willingness to pay, the

opportunity cost associated with the choice of TOO-based strategy for guiding management of CUP resulted in a total of expected value of perfect information (EVPI) of $1,265.81 per patient diagnosed with CUP. Subsequently, I estimated the expected value for the entire CUP population that could potentially benefit from more research on the predictive value of the TOO test and its impact in the Canadian setting. In Manitoba, there were 105 patients diagnosed with CUP in 2011. Based on the size of Manitoba relative to the rest of Canada, I anticipate a total of approximately 2,923 patients annually diagnosed with CUP who would be eligible for the TOO test in Canada. The resulting population EVPI was 3.7million per year.

Figure 6. Sensitivity of the ICER to TOO accuracy[1], incorrect diagnostic results[2]following TOO classification and survival response[3]following correct primary diagnosis.



ICER ≤ $50,000 per QALY gained | $50,000 < ICER ≤ $100,000 per QALY
$100,000 < ICER ≤ $150,000 per QALY | ICER > $150,000 per QALY

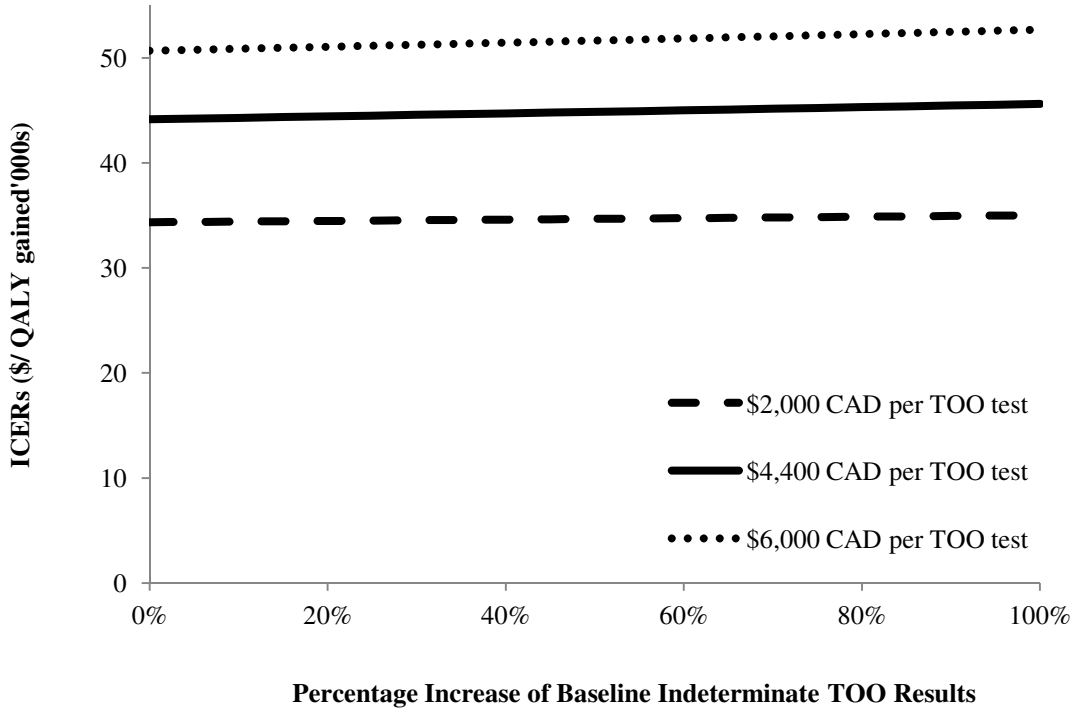
[1]TOO test agreement with reference cancer diagnosis.

[2]Incorrect diagnostic result was defined as when primary stays undiagnosed following correct TOO classification of tumor specimen or when primary is incorrectly diagnosed following incorrect TOO classification of tumor specimen.

[3] Survival response following correct primary diagnosis was defined as the transition probabilities from IDM to PC, SP, or dead states in the TOO Markov models following the chance nodes when the primary is correctly diagnosed. Survival response following correct diagnosis of hepatocellular, pancreas or non-small lung primary site was not included in sensitivity analyses as these potential primary sites were found to have worse QALYs compared to overall CUP group (Table 4).

TOO test= Tissue of Origin test; ICER= incremental cost effectiveness ratio; QALY= quality adjusted life year; CUP= cancer of unknown primary.

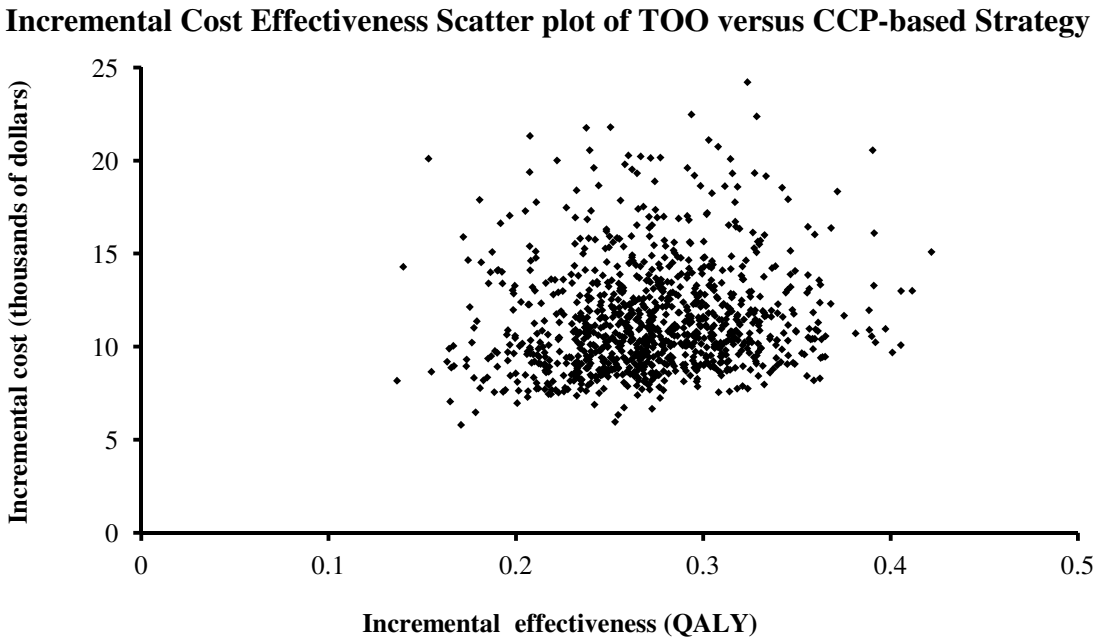
Figure 7. Sensitivity of the ICER to cost of the TOO test and indeterminate TOO results.



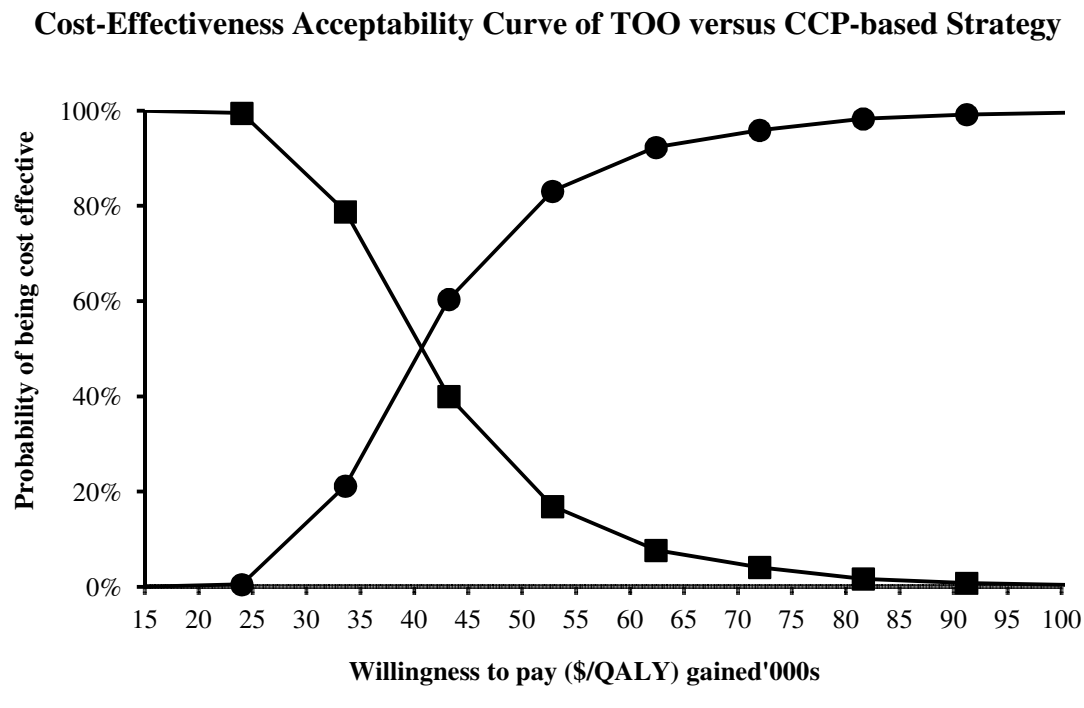
TOO test= Tissue of Origin test; ICER= incremental cost effectiveness ratio; QALY= quality adjusted life year.

Figure 8. Incremental cost-effectiveness scatter plot and acceptability curve of TOO versus CCP-based strategy. Sampling distributions and summary estimates of cost, efficacy, and variance were based on 1000 replicates.

a



b



TOO test= Tissue of Origin test; CCP= current clinical practice.

5.5 Discussion

I developed a decision-analytic model to evaluate the cost effectiveness of using the TOO test to help diagnose primary tumors versus CCP in patients with CUP for whom no anatomical primary tumor site was found after diagnostic work up undertaken according to real life clinical practice in Manitoba. In the base case I found that the TOO-based strategy has an ICER of $37,774 per LY gained and $44,151 per QALY gained.

In Canada, an ICER of $20,000 to $100,000 per QALY gained has been suggested as representing "moderate evidence for adoption and appropriate utilization" [62, 72], although there is no evidence that any Canadian decision-making body has formally implemented these thresholds [168]. The ICER of the TOO-based strategy in patients with CUP were within ranges of the microarray-based 21-gene expression test for breast cancer that has recently been partly adopted in clinical practice in Canada [124-126]. The 21-gene assay for guiding adjuvant chemotherapy in early stage breast cancer has an estimated ICER of up to $63,064 per QALY gained [132]. It became available in several provinces in a limited fashion or within context of a field evaluation for hormone positive and lymph node negative disease [124-126].

A recent cost-effectiveness analysis of the TOO test was reported among patients with metastatic and poorly differentiated cancer of uncertain primaries (i.e. difficult-to-diagnose primary) for whom the majority had primary tumor site diagnoses reported by their physicians prior to TOO testing. The test was found to have an ICER of $46,858 per QALY gained from a US third-party payer perspective. These results in uncertain cancers cannot be extrapolated to the CUP setting since with CUP, despite extensive clinical and pathological diagnostic evaluation, patients are left without a primary tumor site diagnosis and as a result management and clinical outcomes are different. In our study I examined the cost-effectiveness of incorporating TOO testing in patients diagnosed with CUP for who all had no anatomically defined primary tumor site after the diagnostic work up that was undertaken according to real life clinical practice in Manitoba.

Our sensitivity analysis (Figure 6a) demonstrated that the accuracy of the TOO test in

classifying tumor specimens and diagnostic results following TOO tumor classification are important drivers of the ICER. Both factors further impacted the ICER when addingthe possibility that CUP patients may not respond as well as their counterparts with metastatic of known primary cancers when occult primary is identified and treated with current site-specific therapy (i.e. survival response following correct primary diagnosis). For instance, when these three factors were negatively modified by approximately 35% (Figure 6d) the ICER became well above ranges of a number of cancer treatments recently approved for funding in Canada [169-170] and TOO-based strategy may no longer deemed a cost effective use of resources.

Validation of the TOO test accuracy and clinical verification of resulting diagnostic decisions in real-life CUP population remains a challenge since, by definition, the primary tumor site is not found except rarely in the clinical course or commonly at autopsy [10, 222]. Analyses of the TOO tests [59, 198] used in our study were conducted in the United States in patients with known primary cancers. Genetic profiles of occult cancers giving rise to CUP may differ from known primary cancers [222]. A more direct study to evaluate the reliability of TOO test and its impact on diagnostic decision making in CUP patients would be the correlation with an eventual primary tumor detected later during the course of the disease (latent primary) or at autopsy. Such research approach would be useful in the Canadian setting to address concerns over potential incorrect TOO classification and resulting diagnostic decisions and to update our model and verify our results.

Our value of information analysis demonstrated that future research that can characterize the TOO test accuracy and resulting diagnoses and survival outcomes in CUP-real world Canadian practice may have a large societal impact, when willingness to pay levels of recently accepted cancer treatments are considered. Taken together with the lack of future randomized trials of TOO testing in CUP population worldwide, this suggests that field evaluations of the test to establish its impact on Canadian management of CUP and resulting survival outcomes should be a priority.

Controversies have recently been raised on whether validation analyses of gene

expression profiling assays may have been subject to tumor-biopsy specimen sampling bias due to potential intratumoral heterogeneity [223]. Although analysts have run the TOO test on duplicate samples from 44 cases (both clinical and research cases) and found no differences in test outcome, I still remain uncertain as to whether these concordant results may apply on the overall heterogeneous CUP population. Thus, future studies of TOO testing in CUP population should further explore any potential impact of intratumoral heterogeneity on its results using multiple tumor-biopsy samples.

Our analysis has limitations. First, there are limits to what can be ascertained through administrative data. Even though the Manitoba Cancer Registry is a highly accurate source of information about all cancer sites [137], errors in coding can result in incorrect or unrecorded procedures. However, wherever possible I cross validated across databases. For instance, information on palliative care can be found in both the Manitoba Cancer Registry and the administrative databases held by Manitoba Health. Second, outcomes and costs of therapies given in the 2002-2011 population do not necessary reflect the possible benefits and costs of newer types of therapies or dosing schedules used in current practice so analysis with such data would be more applicable to the current practice landscape. Finally, although clinical practice patterns employed in the selected time period in Manitoba have shown to reflect practices in other jurisdictions in Canada [88, 174-175], management of patients with CUP and its associated costs could be different.

5.6 Conclusion

I compared the use of TOO test to aide in primary tumor diagnosis versus CCP in patients diagnosed with CUP. I found that the TOO-based strategy appears to provide good value for money in this patient population. However, field evaluations of the test to establish its accuracy and impact on diagnostic decisions and survival in the CUP setting should be initiated in Canada to ensure its clinical utility and cost-effectiveness.

Chapter 6

6 General discussion

6.1 Implications and recommendations

Creating evidence-based review of gene expression profiling technologies in clinical oncology is becoming the primary challenge with the limited evidence base available [224]. In particular, randomized controlled clinical trials and other high-quality evidence is generally lacking for these technologies [225]. Moreover, Canadian data on patient and clinician behavior based on these gene expression profiling results and the outcomes of treatment decisions (i.e., effectiveness) may not be available [224]. I used Manitoba administrative health databases and Manitoba Cancer Registry to parameterize decision analytic models and predict the role of such emerging gene expression profiling technologies in real world Canadian clinical oncology practice. This approach may have increased model complexity but it has the advantage of providing us with longitudinal patient, clinical and treatment data on a large number of patients and for a long follow up time. This allowed us to estimate significant clinical outcomes (e.g. local recurrence, regional recurrence, second primary, chemotherapy-related serious adverse effects, and latent primary) that are otherwise hard to model using secondary data sources. This thesis highlights the usefulness of the Canadian provincial administrative health databases and disease registries as a source of information to inform health care decision making and policy development. In Canada, administrative health and disease registry data have been used for research purposes for decades. It was the establishment of the Manitoba Center for Health Policy and Evaluation and the subsequent development of their population health information system, POPULIS, which brought this data source into the spotlight. Similar developments in other Canadian provinces since that time now offer health researchers access to provincial administrative health data that can be linked across services [82]. A more thorough discussion of the use of registry and administrative data to conduct cost-effectiveness analyses in the Canadian setting has been discussed elsewhere [188].

It should be noted that emerging gene expression profiling technologies may not yet be incorporated into the Canadian clinical practice and thus data about these technologies may not be available from provincial administrative health databases or disease registries in Canada. However, I have shown that analysts can still predict the role of these technologies in real-world clinical practice when these databases are used to model current real-world Canadian clinical practices (the current practice without these technologies). Analysts can then apply available data about these technologies, which might be derived from non-Canadian settings, on observed current clinical practice models to examine how these data may alter the observed current clinical and economic outcomes. Such decision modeling and cost-effectiveness analyses are helpful in identifying data needs and quantifying uncertainty about these technologies in the real world Canadian setting. For instance, value of information analysis (VOI) [112] can be performed on these decision analytic models to inform policy options such as conditionally funded field evaluation (CFFE) (i.e., coverage with evidence development) [113].

Canadian provincial decision makers (e.g., the Ontario Health Technology Advisory Committee (OHTAC)) are currently facing promising gene expression profiling (e.g., 21-gene assay) that may improve patient safety and likely pose low risk of harm, but have significant uncertainty associated with their clinical value [87, 226]. In such cases, Canadian decision makers can recommend promising gene expression profiling technologies for a conditionally funded field evaluations (CFFE) to be undertaken to reduce uncertainty, and this could take the form of studies on quality, safety, efficacy, effectiveness, and cost-effectiveness [113]. For instance, following a recommendation by OHTAC, in Ontario the 21-gene assay became available for women with early stage lymph node negative breast cancer within the context of field evaluation in December 2010 [227]. Organizations that provide the analysis to support provincial decision making bodies (e.g. The Programs for Assessment of Technology in Health (PATH) Research Institute) often use VOI analyses to determine the expected value of perfect information (EVPI) about the technology. Comparing the EVPI with the cost of conducting a CFFE can determine if it is worthwhile before actually conducting the evaluation [113]. If the CFFE is determined not to be worthwhile (i.e., the cost of research is greater than the

VOI gained from the research), this information is fed back to high level decision makers and CFFE would not be considered [113]. On the other hand, if it is determined that the CFFE is worthwhile, information on uncertainty from the economic model is further used to refine CFFE study design. Hence, our VOI analyses in this thesis are likely relevant to Canadian provincial decision makers who must make difficult decisions.

A close observation on the pharmaceutical industry may demonstrate that Canadian decision makers will increasingly face this scenario with gene expression profiling and other personalized medicine technologies in the near future and therefore use of health administrative health data in decision analytic analyses should be a priority. The use of administrative databases to model existing clinical practices would be the best approach that analysts can take to predict the role of these technologies when compared with existing clinical practices in real-world settings and to support health technology assessment.

In addition, a current paradigm shift in pharmaceutical industry strongly suggests the need to build an evidence base for clinical practice and policies in Canada using provincial administrative health databases and disease registries. In this era, it becomes reasonable to forgo randomized phase III clinical trials for drugs and medical technologies that demonstrate substantial activity in early-phase clinical trials, particularly for diseases with high unmet medical need [228]. In Canada, pharmaceutical companies can get accelerated drug approval from the Therapeutic Product Directorate (TPD) of Health Canada through the Notice of Compliance (NOC) policy which requires less onerous evidentiary requirements and the review process itself is also significantly accelerated [229]. In turn this will allow promising new drugs and technologies to potentially be made widely available to patients sooner by avoiding the delays and cost that seem inherent in completing phase III randomized clinical trials [228-230]. However, forgoing randomized phase III clinical trials leads to less-definitive data regarding the safety and efficacy of the new drug or technology [228]. Thus, conducting post-marketing studies to confirm clinical benefit becomes necessary. The Health Products and Food Branch (HPFB) in Canada has, by virtue of the Food & Drugs Act and regulations, nominal jurisdiction to ensure a manufacturer's compliance through post-

market surveillance [229]. When this occurs, drugs and medical technologies might be released into the marketplace and their availability might deter patient participation in post-marketing studies. Many pharmaceutical companies have failed or faced difficulties in completing randomized or non-randomized confirmatory post-marketing studies due to poor patient accrual [228, 231]. Decision analytic modeling techniques might then be used to assess indirect evidence. In this regard, provincial health administrative databases and disease registries in Canada may provide a great opportunity to assess the clinical effectiveness of such drugs in real world Canadian clinical practice. It should be noted that the development of specific billing codes for new drugs and emerging medical technologies should be a priority in this era [232]. Such an effort will allow provincial health administrative databases and disease registries to capture the use of these drugs or technologies in the Canadian clinical practice [233]. In addition, analysts will be able to conduct their decision modeling and cost-effectiveness analyses to assess effectiveness and inform recommendations for appropriate clinical decision making. Such an effort will contribute to building a high quality evidence base for examining these drugs and technologies in real-world Canadian clinical practice. As well, efforts to maintain and develop health administrative data standards across provinces, specifically to monitor new drugs and emerging technologies through coding development would be helpful for cross-regional comparisons. Provincial and territorial health ministries and disease registries which hold and maintain administrative and registry data should share and allow use of these data to academics and pharmaceutical industry. For instance, allowing pharmaceutical companies to access Canadian health administrative databases and disease registries will be helpful in conducting confirmatory post-marketing studies on their drugs or medical technologies which might be a unique and effective tool for these companies to assess the clinical and cost effectiveness of their products in real-world settings [228, 230-231].

Given the promising role of health administrative data in this era, the process of accessing and linking provincial health administrative databases and registries in Canada should be accelerated and improved across all Canadian provinces. At the same time, it is essential to ensure there is adequate privacy and security protection for personal health information when data sets are linked. For instance, in Ontario, a collaborative agreement

between the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario (CCO) has lead to the initiation of the Ontario Cancer Data Linkage Project ('cd-link'). This was an initiative of the Ontario Institute for Cancer Research and Cancer Care Ontario Health Services Research Program to establish a data release program whereby administrative datasets relevant to cancer health services research such as the Ontario Cancer Registry and Ontario Health Insurance Plan claims are linked, de-identified and, with the protections of a comprehensive Data Use Agreement, provided directly to researchers. Such a provincial initiative is helping to speed research that contributes to the effectiveness, quality, equity and efficiency of health care and health services in Ontario. Similar initiatives in other Canadian provinces should be developed to offer health researchers and other stakeholders' access to provincial health administrative and registry data that can be efficiently linked across services.

Currently, the emphasis in virtually all analyses evaluating gene expression profiling technologies in clinical oncology is on the establishment of the value of each of these profiling predictors over standard clinical predictors. However, as gene expression profiling technologies mature and proliferate, an important question will be how they compare to each other when these technologies target the same patient population, and whether there is value in their combination or sequencing. In the therapeutic domain, this has been called "comparative effectiveness" research. Such research has traditionally been difficult to fund by government or by industry, because it may not hold out as much therapeutic promise as new discoveries and industry understandably is not anxious to fund head-to-head comparisons with competitive products. In the diagnostic domain, such research is necessary to compare the effectiveness of combining different available diagnostic technologies. For instance, Gould et al. developed a decision analytic model to identify the most effective approaches to diagnose and manage solitary pulmonary nodules [234]. Gould et al. compared 40 clinically plausible combinations of 5 available diagnostic interventions, including computed tomography, positron emission tomography with the glucose analogue 18-fluorodeoxyglucose (FDG-PET), transthoracic needle biopsy, surgery, and watchful waiting [234]. This same dynamic could easily take hold in the gene expression profiling arena with a proliferation of licensed gene expression assays without any clear notion of what new ones are contributing over previous assays.

Thus, future decision analyses of new gene expression profiling technologies in clinical oncology should study their incremental clinical and economic value over pre-existing gene expression profiling and clinicopathologic methods. For instance, our breast cancer decision analytic model can be expanded to project the lifetime clinical and economic consequences of early stage breast cancer under many different treatment strategies. Such a model may begin with a decision to use the MammaPrint, the RS-assay, the RS-assay following by the MammaPrint, Adjuvant!Online (AOL) following by the RS-assay, AOL following by the MammaPrint or to continue with CCP.

6.2 Conclusion

The potential applications of certain gene expression profiling assays in clinical oncology appear to be clinically promising and economically attractive in the Canadian healthcare system. However, uncertainty about these gene expression profiling assays in real world Canadian setting remains the primary challenge for adoption. Novel funding models such as conditional funding alongside a field evaluation of these assays to establish their impact on cancer management and patient survival may have a large societal impact and should be initiated in Canada to ensure their clinical utility and cost-effectiveness.

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Curriculum Vitae

Name: Malek Bassam Hannouf

Post-secondary Education and Degrees:
Philadelphia University
Amman, Jordan
2002-2006 B.Sc.

The University of Western Ontario
London, Ontario, Canada
2008-2014Ph.D.

Honours and Awards:
CIHR Strategic Training Program in Cancer Research and Technology Transfer (CaRTT) Doctoral Fellowship
2010-2014

American Association for Cancer Research (AACR) Scholarship Award
2010

Graduate Thesis Research Award, Western University
2010

Schulich Graduate Scholarship, Western University
2008-2013

Related Work Experience
Teaching Assistant
The University of Western Ontario
2009-2013

Publications:

1. Louie AV, Rodrigues G, Hannouf MB, Zaric GS, Palma DA, Cao JQ, Yaremko BP, Malthaner R, Mocanu JD. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. Int J RadiatOncolBiolPhys 2011;81:964-73.
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