

Cost–utility analysis of 21-gene assay for node-positive early breast cancer

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ABSTRACT

Background For women with lymph node (LN)–positive, estrogen receptor–positive, and HER2 (human epidermal growth factor receptor 2)–negative breast cancer (BCa), current guidelines recommend treatment with both hormonal therapy and chemotherapy. The 21-gene Recurrence Score (RS) assay might be helpful in selecting patients with BCa who can be spared chemotherapy when they have 1–3 positive LNs and a lower risk of recurrence. In the present study, we performed a cost–utility analysis comparing use of the 21-gene RS assay with current practice from the perspective of a Canadian health care payer.

Methods A Markov model was developed to determine costs and quality-adjusted life-years (QALYs) over a patient's lifetime. Patient outcomes in both study groups were examined based on published clinical trials. Costs were derived primarily from published Canadian sources. Costs and outcomes were discounted at 1.5% annually, and costs are reported in 2016 Canadian dollars. A probabilistic analysis was used, and the model parameters were varied in a sensitivity analysis.

Results The results indicate that use of the 21-gene RS assay was less costly (\$432 less) and more effective (0.22 QALYs) than current practice. The probabilistic analysis revealed that 70% of the 10,000 simulated incremental cost-effectiveness ratios were in the southeast quadrant. The results were sensitive to the probability of a low RS and to the probability of receiving chemotherapy in the low-risk RS category and in current practice.

Conclusions Use of the 21-gene RS assay could be a cost-effective strategy for Ontario patients with estrogen receptor–positive, HER2-negative early BCa and 1–3 positive LNs.

Key Words Cost-effectiveness, breast cancer, 21-gene assay, chemotherapy

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INTRODUCTION

Breast cancer (BCa) is the most common cancer and the 2nd leading cause of death from cancer among Canadian women¹. For women with lymph node (LN)–positive, estrogen receptor (ER)–positive BCa, current guidelines recommend treatment with both hormonal therapy and chemotherapy^{2,3}. In ER-positive disease, the addition of adjuvant chemotherapy to tamoxifen reduces the risk of BCa recurrence by approximately 30% and the risk of BCa mortality by approximately 20%.

The 21-gene Recurrence Score (RS) assay is a genomic test used in determining the likelihood of chemotherapy

benefit after surgical treatment for early-stage BCa⁴. Patients are defined as having a high (RS ≥ 31), intermediate (RS = 18–30), or low (RS < 18) risk of distant recurrence. The 21-gene RS assay might be helpful in selecting patients with a lower risk of recurrence, for whom chemotherapy could be omitted. It is routinely used to guide adjuvant treatment decisions in patients with node-negative BCa.

The clinical utility of the RS assay has also been demonstrated in studies involving LN-positive patients^{4–7}. A growing body of evidence is showing that the RS assay can lead to tailored treatment by sparing patients with 1–3 positive LNs and a low RS unnecessary chemotherapy that could be associated with an increased risk of toxicity

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and a reduction in health-related quality of life⁸. In addition, tailored treatment might save the health care system unnecessary drug and administration costs, and the costs associated with complications⁹.

Studies have shown that the 21-gene RS assay might be a cost-effective option for patients with LN-negative, ER-positive BCa^{10–13}. A few studies^{9,14–16} have also examined the cost-effectiveness of the 21-gene RS assay in patients with LN-positive, ER-positive BCa and have shown that it might be a cost-effective option.

Currently in Ontario, the most populous province in Canada, the assay is reimbursed by the publicly funded health care system only for LN-negative and micrometastatic LN-positive early-stage BCa. In the present study, we performed a cost-utility analysis of the 21-gene RS assay compared with current practice (no RS assay) for patients with LN-positive (1–3 positive LNs), ER-positive, and HER2 (human epidermal growth factor receptor 2)-negative early BCa from the perspective of the Ontario Ministry of Health and Long-Term Care.

METHODS

Model Structure

Using the TreeAge Pro 2014 software application (TreeAge Software, Williamstown, MA, U.S.A.), a Markov model with yearly cycle lengths (Figure 1) was developed to compare the 21-gene RS assay with current practice in terms of lifetime clinical consequences [quality-adjusted life-years (QALYs)] and economic consequences (cost). The model simulated a cohort of patients 60 years of age diagnosed with LN-positive (1–3 positive LNs), ER-positive, HER2-negative early BCa. The starting age of 60 years was chosen because that is the median age of patients with BCa in Canada (clinical expert opinion, 2018).

Patients in the 21-gene RS assay strategy were stratified into 3 categories: low risk (RS < 18), intermediate risk (RS = 18–30), and high risk (RS ≥ 31) of recurrence. Patients in the high-risk category started in one of three chemotherapy health states: chemotherapy with no toxicities; chemotherapy with febrile neutropenia; or chemotherapy with nausea and vomiting. Patients in the chemotherapy health states could move to these health states: disease free

without recurrence, distant recurrence, or death. Patients who received chemotherapy could also go on to develop congestive heart failure (CHF) or leukemia 1–7 years after treatment. Of patients in the intermediate-risk category, 52% received adjuvant chemotherapy and started in one of the three chemotherapy health states (Table 1)⁷. Those who did not receive chemotherapy (48%) started in the disease-free health state. All patients in the low-risk category did not receive adjuvant chemotherapy and started in the disease-free health state, where they received tamoxifen for 5 years, followed by aromatase inhibitors for another 5 years. From the disease-free without recurrence health state, patients could remain in that health state, develop distant recurrence, or die. In the distant recurrence health state, patients stayed in that health state until death. All patients in the model eventually died from BCa or background mortality. A lifetime horizon was taken, and future costs and benefits were discounted at 1.5% annually based on guidelines from the Canadian Agency for Drugs and Technologies in Health²⁸.

Clinical Input Data

The proportion of patients assigned to each risk category based on the 21-gene RS assay was obtained from a prospective study that evaluated the effect of the assay on treatment decisions for women with LN-positive early BCa in Ontario (Table 1)⁷. A phase III randomized controlled trial (swog-8814) found that the RS was a prognostic factor for disease-free survival in patients with LN-positive, ER-positive BCa²⁵. Because recurrence-free survival was not available in swog-8814, we used its reported disease-free survival, which consisted of time to death, recurrence, or new primary cancer. We made an assumption that a large proportion of events were related to recurrence rather than to death or a new primary cancer. To calculate the annual probability of distant recurrence, we fitted a Weibull distribution to Kaplan–Meier curves for each RS category in the tamoxifen-only group (that is, no chemotherapy) and calculated an annual probability of recurrence²⁹. To obtain the risk of distant recurrence with chemotherapy for each risk group, we applied the hazard ratios from swog-8814 (Table 1)²⁵. For patients in the current-practice strategy, we estimated the weighted average risk of recurrence with and without adjuvant chemotherapy in the 3 RS categories.

Once patients developed distant recurrence, it was assumed that the transitional probability for BCa death was the same for all patients regardless of RS classification. Based on clinician input, we also assumed that all patients would die after year 20 in that health state (clinical expert opinion, 2018). We accounted for background mortality using Canadian life tables from Statistics Canada²⁷.

Chemotherapy Assignment and Toxicities

For patients in the 21-gene RS assay strategy, the proportion receiving chemotherapy was obtained from the post-RS-test treatment recommendations of oncologists in an Ontario study⁷. Patients in all RS categories were given hormonal treatment with tamoxifen for 5 years, followed by an aromatase inhibitor (letrozole) for another 5 years. Patients who received adjuvant chemotherapy started tamoxifen after chemotherapy completion.

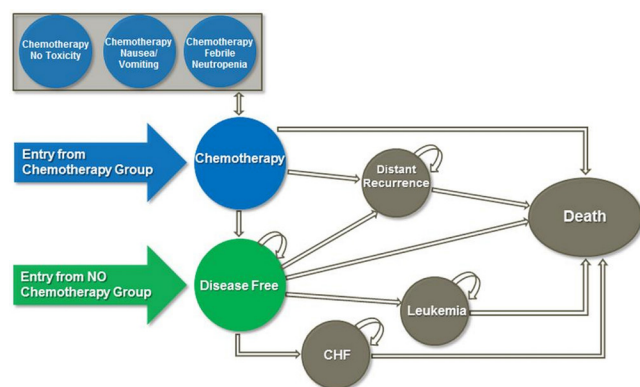


FIGURE 1 Markov model used for the analysis. CHF = congestive heart failure.

TABLE I Annual transition probabilities

Parameter	Probability value		Distribution	Source
	Base case	Sensitivity analyses ^a		
Proportion of patients assigned to each risk category				
Low-risk RS (<18)	0.57	0.39–0.63	Dirichlet	Torres <i>et al.</i> , 2018 ⁷
Intermediate-risk RS (18–30)	0.34	0.28–0.37	Dirichlet	
High-risk RS (≥31)	0.09	0.08–0.32	Dirichlet	
CTx assignment for RS strategy				
High-risk RS (≥31)				
CTx	1.0	0.60–1.0	Fixed	Torres <i>et al.</i> , 2018 ⁷
FEC-D	0.70	0.63–0.77	Fixed	Clinical expert opinion, 2018
dd AC-T	0.30	0.27–0.33	Fixed	
Intermediate-risk RS (18–30)				
CTx	0.52	0.47–0.55	Fixed	Torres <i>et al.</i> , 2018 ⁷
TC	1.0	0.90–1.0	Fixed	Clinical expert opinion, 2018
CTx assignment for the current-practice strategy				
CTx	0.79	0.64–0.87	Fixed	Torres <i>et al.</i> 2018 ⁷ , Hannouf <i>et al.</i> , 2014 ¹⁶
FEC-D	0.44	0.40–0.48	Fixed	Torres <i>et al.</i> , 2018 ⁷
TC	0.45	0.40–0.50	Fixed	
ddAC-T	0.11	0.10–0.12	Fixed	
CTx toxicities				
FEC-D				
Febrile neutropenia	0.09	0.04–0.19	Beta	Younis <i>et al.</i> , 2012 ¹⁷
Nausea or vomiting	0.11	0.10–0.12	Beta	Roche <i>et al.</i> , 2006 ¹⁸
Death from toxicity	0.01	0.005–0.036	Beta	Younis <i>et al.</i> , 2012 ¹⁷
Congestive heart failure	0.005	0.0045–0.0055	Beta	Goldhar <i>et al.</i> , 2016 ¹⁹
Leukemia	0.0008	0.0007–0.0009	Beta	Torres <i>et al.</i> , 2015 ²⁰
TC				
Febrile neutropenia	0.07	0.046–0.099	Beta	Younis <i>et al.</i> , 2012 ¹⁷
Nausea or vomiting	0.02	0.018–0.022	Beta	Jones <i>et al.</i> , 2009 ²¹
Death from toxicity	0.01	0.005–0.036	Beta	Younis <i>et al.</i> , 2012 ¹⁷
ddAC-T				
Febrile neutropenia	0.02	0.018–0.022	Beta	Torres <i>et al.</i> , 2015 ²⁰
Nausea or vomiting	0.05	0.045–0.05	Beta	Citron <i>et al.</i> , 2003 ²²
Death from toxicity	0.001	0.0009–0.01	Beta	Torres <i>et al.</i> , 2015 ²⁰
Congestive heart failure	0.005	0.0045–0.0055	Beta	Goldhar <i>et al.</i> , 2016 ¹⁹
Leukemia	0.003	0.0027–0.0033	Beta	Torres <i>et al.</i> , 2015 ²⁰
Probability of death from ...				
Congestive heart failure				
Year 1	0.13		Fixed	Frazier <i>et al.</i> , 2007 ²³
Year 2	0.22		Fixed	
Year 3 onward	0.31		Fixed	

TABLE I Continued

Parameter	Probability value		Distribution	Source
	Base case	Sensitivity analyses ^a		
Probability of death from ... Continued				
Leukemia				
Year 1	0.73		Fixed	Hulegardh <i>et al.</i> , 2015 ²⁴
Year 2	0.84		Fixed	
Year 3 onward	0.90		Fixed	
Annual probability of recurrence for those not treated with CTx (tamoxifen alone)				
Low-risk RS (<18)	0.0312	0.0281–0.0343	Fixed	Estimated from Albain <i>et al.</i> , 2010 ²⁵
Intermediate-risk RS (18–30)	0.0656	0.0590–0.0722	Fixed	
High-risk RS (≥31)	0.0949	0.0854–0.1044	Fixed	
HR for recurrence with the use of CTx				
Low-risk RS (<18)	1.00		Fixed	Clinical experts
Intermediate-risk RS (18–30)	0.72		Fixed	Albain <i>et al.</i> , 2010 ²⁵
High-risk RS (≥31)	0.59		Fixed	
Annual probability of recurrence for those treated with CTx				
Low-risk RS (<18)	0.0312	0.0281–0.0343	Fixed	Calculated based on HR for recurrence with the use of CTx
Intermediate-risk RS (18–30)	0.0477	0.0437–0.0525	Fixed	
High-risk RS (≥31)	0.0571	0.0514–0.0628	Fixed	
Annual probability of recurrence for those in the current-practice strategy				
Without CTx	0.0486	0.0437–0.0535	Fixed	Clinical expert opinion, 2018, weighted average
With CTx	0.0391	0.0352–0.0430	Fixed	
Death from distant recurrence				
Years 1–20	0.17	0.15–0.19	Fixed	Mouridsen <i>et al.</i> 2003 ²⁶
Year 20 onward	1		Fixed	Clinical expert opinion, 2018
Background mortality				
Life tables			Fixed	Statistics Canada, 2011 ²⁷

^a Ranges used in the sensitivity analyses were, for the most part, ±10% of the base case. Where available, additional literature was used for the sensitivity analysis ranges. As a result, some values have wide ranges.

RS = Recurrence Score (Oncotype DX: Genomic Health, Redwood City, CA, U.S.A.); CTx = chemotherapy; FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide, followed by docetaxel; dd AC-T = dose-dense doxorubicin–cyclophosphamide, followed by paclitaxel; TC = docetaxel–cyclophosphamide.

Based on clinical opinion, 70% of those in the high-risk RS category received 6 cycles of FEC-D: 3 cycles of 5-fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m², followed by 3 cycles of docetaxel 100 mg/m² (clinical expert opinion, 2018). The remaining 30% received 8 cycles of ddac-T: 4 cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m², followed by 4 cycles of paclitaxel 175 mg/m². For patients assigned to the intermediate-risk RS category, 52% received chemotherapy. All patients in that category who received chemotherapy were treated with 4 cycles of TC chemotherapy (docetaxel 75 mg/m² and cyclophosphamide

600 mg/m²). All patients treated with adjuvant chemotherapy received 300 µg of filgrastim daily (clinical expert opinion, 2018). As well, patients in all chemotherapy health states received zoledronic acid every 6 months for 3 years. For patients in the current-practice strategy, the proportion receiving chemotherapy and the type of chemotherapy regimen assigned were obtained from the pre-RS-test treatment recommendations of oncologists in an Ontario study (Table 1)⁷.

Four different types of chemotherapy toxicities were considered: febrile neutropenia, nausea and vomiting, CHF, and leukemia. Febrile neutropenia and nausea and

vomiting could occur during treatment. The probability of febrile neutropenia while receiving FEC-D or TC and granulocyte colony-stimulating factor was obtained from a meta-analysis¹⁷. The probability of febrile neutropenia while on ddAC-T was obtained from an Ontario study²⁰. The probability of a patient experiencing nausea and vomiting was obtained from the respective clinical trials for each of the treatments^{18,21,22}.

Congestive heart failure and leukemia are chemotherapy toxicities that can occur after treatment. Patients treated with FEC-D and ddAC-T are at risk for those toxicities because of their anthracycline content. The proportions of patients experiencing leukemia, by treatment type, and experiencing CHF were obtained from two studies that used Ontario population data²⁰. The proportion of patients experiencing CHF was obtained from a study examining the risk of heart failure associated with adjuvant trastuzumab in patients with BCa¹⁹. The probability of experiencing CHF that we used was the same for both FEC-D and ddAC-T. The risk of death from CHF for years 1–3 was obtained from a study that provided the Kaplan–Meier probabilities of survival for women with non-ischemic stroke over 4 years²³. Afterward, a constant probability of death was assumed. The probability of death associated with leukemia from years 1–3 was taken from a study that examined patients with treatment-related secondary acute myeloid leukemia in Sweden²⁴. After year 3, a constant probability of death was assumed.

Utilities

The utility values (Table II) associated with the various health states³⁰ and the chemotherapy toxicities came from various published sources and were derived using a variety of methods^{17,31,32,37}.

Costs

Costs were obtained from various sources (Table II). To obtain a total cost for filgrastim for each chemotherapy regimen, we assumed that 50% of patients would receive filgrastim type 1 and the other 50% would receive filgrastim type 2 (Sunnybrook Health Sciences Centre database, 2017).

Each chemotherapy regimen was associated with a different quality-based procedure band for systemic therapy, which included the cost of nursing and pharmacy time (Sunnybrook Health Sciences Centre database, 2017). We also included the costs of a physician consultation (fee code A445), medical-specific assessment (fee code A444), and partial assessment (fee code A448) for each chemotherapy regimen³⁵. Lastly, we included the cost of a peripherally inserted central catheter and technologist for each chemotherapy regimen (\$376) (Sunnybrook Health Sciences Centre database, 2017).

The costs of ongoing care for the patients who were disease-free (that is, recurrence-free) and the costs of treating distant recurrence were obtained from a Canadian study that estimated the health care costs associated with the lifetime management of women diagnosed with BCa³³. The cost averaged for all stages of BCa was used. Costs for treating distant recurrence might be underestimated given that costs have increased with the introduction of

cyclin-dependent kinase 4/6 inhibitors in the treatment of those patients.

The costs associated with chemotherapy toxicities were obtained from a variety of published sources (Table II)³⁶. We assumed that a patient could experience, at most, 1 episode of febrile neutropenia during chemotherapy (clinical expert opinion, 2018) and that nausea and vomiting happen after each chemotherapy cycle and last for 1 week. The costs of nausea and vomiting therefore differed with the chemotherapy regimen (clinical expert opinion, 2018). The costs associated with leukemia came from a Canadian study that examined the cost of cancer by phase of care. The analysis included the direct health care costs for the initial phase of cancer (that is, the first year after the cancer diagnosis) for patients who survived beyond year 1³⁹. Lastly, the costs associated with CHF were obtained from a cost-effectiveness study³⁸. All costs were inflated to 2016 Canadian dollars using the Consumer Price Index for health care services in Ontario⁴⁰.

Analysis

We estimated an incremental cost-effectiveness ratio (ICER) representing the incremental cost for 1 QALY gained with use of the 21-gene RS assay instead of current practice. We also estimated an incremental cost per life-year gained. For the base case, a probabilistic analysis was conducted to assess the uncertainty of all parameters. We used a Dirichlet distribution for multinomial data, gamma distributions for costs, and beta distributions for probabilities and utilities. All parameters were randomly sampled from their assigned distributions and 10,000 simulations were performed. We estimated the likelihood of each strategy being more favourable across a range of willingness-to-pay thresholds using cost-effectiveness acceptability curves. The results were also summarized on a cost-effectiveness plane. A deterministic 1-way sensitivity analysis was conducted on all key model parameters (such as the probability of recurrence with chemotherapy and the RS stratification).

Validation

The model structure and outcomes were evaluated. For each RS category, we obtained the proportion of deaths attributable to CHF, leukemia, distant recurrence, short-term toxicity, and background mortality. Those estimates were shown to clinician experts to determine whether they were in line with clinical practice (supplementary Tables I and II).

RESULTS

The results indicated that the 21-gene RS strategy dominated current practice. The 21-gene RS strategy was less costly (\$432 less) and more effective (0.22 QALYs) than current practice over a lifetime horizon (Table III). In addition, 0.17 life-years were gained with the 21-gene RS assay strategy.

The probabilistic analysis revealed that 70% of the 10,000 simulated ICERs were located in the southeast quadrant, meaning that the 21-gene RS assay strategy was less costly and more effective than current practice (Figure 2). If 1 QALY gained was valued at \$50,000, then 95% of the simulated ICERs were considered cost-effective (Figure 3).

TABLE II Utilities and annual cost estimates for tests, medications, and health states

Parameter	Estimated value		Distribution	Source
	Base case	Sensitivity analyses		
Utilities				
Year 1 after Dx, hormone therapy	0.74	0.67–0.81	Beta	Lidgren <i>et al.</i> , 2007 ³⁰
Year 1 after Dx, CTx	0.62	0.56–0.68	Beta	
Year 2 onward, either treatment	0.78	0.74–0.81	Beta	
Distant recurrence	0.69	0.62–0.73	Beta	
Congestive heart failure	0.53	0.48–0.58	Beta	Kirsch <i>et al.</i> , 2000 ³¹
Leukemia	0.26	0.23–0.29	Fixed	Barr <i>et al.</i> , 1996 ³²
Febrile neutropenia	0.62	0.56–0.68	Fixed	Clinical expert opinion, 2018
Nausea or vomiting	0.62	0.56–0.68	Fixed	
21-Gene RS assay (\$)	5,177	4,659-5,695	Fixed	Genomic Health Ltd. ^a
Ongoing care for disease-free patients (\$)				
Years 1 and 2	1,538	1,384–1,692	Gamma	Will <i>et al.</i> , 2000 ³³
Years 3 and 4	1,138	1,024–1,252	Gamma	
Year 5 onward	924	832–1,016	Gamma	
Treating distant recurrence (\$)				
Initial cost (one-time cost)	10,314	9,283–11,345	Gamma	Will <i>et al.</i> , 2000 ³³
Ongoing care	8,703	7,833–9,573		Will <i>et al.</i> , 2000 ³³
End of life care (last 12 months of life)	19,894	17,905–21,883	Gamma	de Oliveria <i>et al.</i> , 2016 ³⁴
Cost of tamoxifen (20 mg daily)	176	158–194	Fixed	Sunnybrook Health Sciences Centre database, 2017
Cost of letrozole (2.5 mg daily)	575	518–633	Fixed	
Cost of zoledronic acid (intravenous)	21	19–23	Fixed	
Cost of CTx (\$ per regimen)			Fixed	
FEC-D (6 cycles)				
5-Fluouracil (500 mg/m ²)	6.47			
Epirubicin (100 mg/m ²)	109			
Cyclophosphamide (500 mg/m ²)	176			
Docetaxel (100 mg/m ²)	275			
FEC-D total	566	509–523		
Filgrastim type 1	6,484			
Filgrastim type 2	7,770			
Filgrastim total for FEC-D ^b	7,127	6,414–7,840		
TC (4 cycles)				
Docetaxel (75 mg/m ²)	275			
Cyclophosphamide (600 mg/m ²)	281			
TC total	556	500–612		Sunnybrook Health Sciences Centre database, 2017
Filgrastim type 1	4,935			
Filgrastim type 2	5,914			
Filgrastim total for TC ^b	5,425	4,883–5,968		
ddAC-T (8 cycles)				
Doxorubicin (60 mg/m ²)	72			
Cyclophosphamide (600 mg/m ²)	281			
Paclitaxel (175 mg/m ²)	143			
ddAC-T total	496	446–546		
Filgrastim type 1	9,870			
Filgrastim type 2	11,829			
Filgrastim total for dd AC-T ^b	10,850	9,765–11,935		

TABLE II Continued

Parameter	Estimated value		Distribution	Source
	Base case	Sensitivity analyses		
Cost of care associated with CTx			Fixed	
FEC-D				
Nursing and pharmacy time	1,587			
Physician visits	463			
PICC line	376			
FEC-D total	2,426	2,184–2,669		
TC				Sunnybrook Health Sciences Centre database, 2017 and Ontario Schedule of Benefits, Physician Services ³⁵
Nursing and pharmacy time	1,587			
Physician visits	340			
PICC line	376			
TC total	2,303	2,073–2,534		
ddAC-T				
Nursing and pharmacy time	2,517			
Physician visits	449			
PICC line	376			
ddAC-T total	3,342	3,008–3,676		
Costs of CTx toxicities				
Febrile neutropenia	7,905	7,115–8,696	Gamma	Lathia <i>et al.</i> , 2010 ³⁶
Nausea or vomiting			Fixed	Lachaine <i>et al.</i> , 2005 ³⁷
FEC-D	3,378	3,040–3,716		
ddAC-T	4,981	4,483–5,479		
TC	2,492	2,243–2,741		
Congestive heart failure	20,719	18,647–22,791	Gamma	Younis <i>et al.</i> , 2011 ³⁸
Leukemia	34,530	31,077–37,983	Gamma	De Oliveria <i>et al.</i> , 2013 ³⁹

^a In 2017.^b Filgrastim type 1, 0.50; filgrastim type 2, 0.50.

Dx = diagnosis; RS = Recurrence Score (Oncotype DX: Genomic Health, Redwood City, CA, U.S.A.); CTx = chemotherapy; FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide, followed by docetaxel; TC = docetaxel–cyclophosphamide; dd AC-T = doxorubicin–cyclophosphamide, followed by paclitaxel; PICC = peripherally inserted central catheter.

The tornado diagram in supplementary Figure 1 shows the main variables that influenced the results. All other sensitivity analyses (within the specified ranges) did not affect the results. If the probability of receiving chemotherapy in the low-risk RS category increased to 50% from 0%, then the ICER was approximately \$21,299 per QALY gained (the 21-gene RS assay strategy was more costly and more effective). If the probability of being in the low-risk RS category decreased to 0.39 from 0.57, the 21-gene RS assay strategy was dominated by current practice. Lastly, if the probability of receiving chemotherapy in the current practice arm decreased to 0.64 from 0.79, the ICER was \$2,159 per QALY gained.

DISCUSSION

We found that the 21-gene RS assay strategy could be a cost-effective option for Ontario patients with LN-positive (1–3 LNs), ER-positive, HER2-negative early BCa. Many cost-effectiveness studies have been conducted for LN-negative

patients^{10,11,13,14,16,41}. A number of studies found that the 21-gene RS assay is primarily a cost-effective option (that is, the ICER falls below the willingness-to-pay threshold)^{11,13,14,41}; a few found that the 21-gene RS assay is not cost-effective for the LN-negative population^{10,16}.

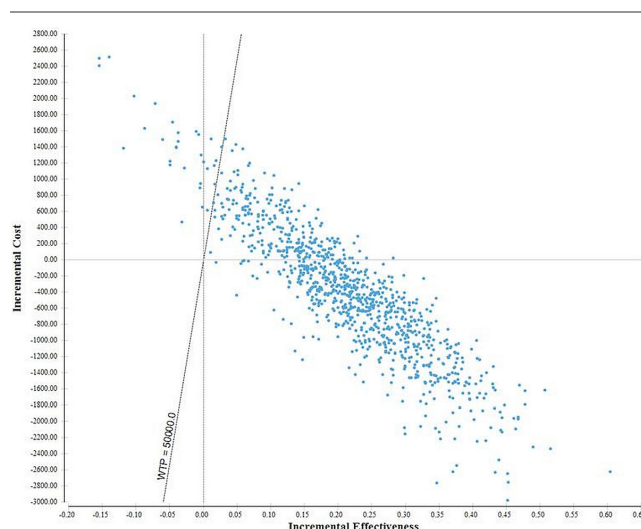
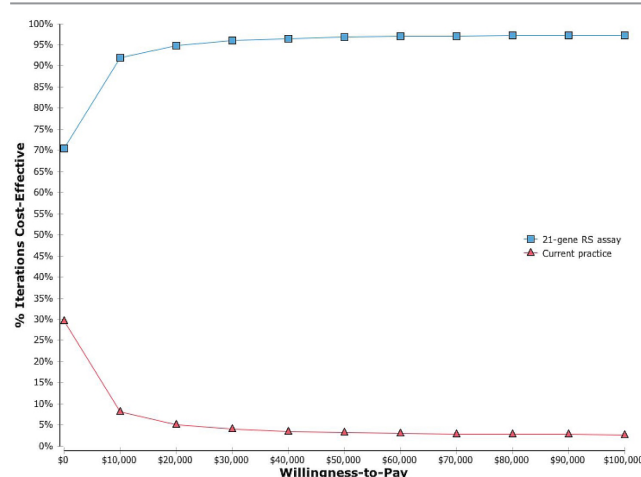
Studies involving patients with LN-positive BCa have been conducted in various countries, and most have determined that the 21-gene RS assay strategy might be a cost-effective option. To our knowledge, our Canadian cost-utility analysis is the only one focused on 1–3 LN-positive, ER-positive, HER2-negative BCa. Of two cost-utility studies conducted in Canada^{14,16}, the first¹⁴ examined the costs and effects of the 21-gene RS assay from the perspective of the Canadian health care payer over a 25-year time horizon. The population consisted of patients 50 years of age with LN-positive, endocrine-sensitive BCa. The number of LNs was not specified. The results indicated that the 21-gene RS assay cost \$864 more and led to 0.06 QALYs gained (ICER: \$14,844 per QALY gained). All 1-way sensitivity analyses were

TABLE III Expected costs, quality-adjusted life-years (QALYs), life-years, and incremental cost effectiveness ratios (ICERs)

Variable	Practice type	
	Current	With 21-gene assay
<i>Discounted</i>		
Total expected cost (\$)	54,502	54,070
Incremental cost (\$)		−432
Total expected QALYs	12.11	12.33
Incremental QALYs		0.22
Total expected life-years	16.02	16.20
Incremental life-years		0.18
ICER		Dominant
<i>Undiscounted</i>		
Total expected cost (\$)	62,875	62,355
Incremental cost (\$)		−520
Total expected QALYs	14.33	14.60
Incremental QALYs		0.27
Total expected life-years	18.93	19.17
Incremental life-years		0.24
ICER		Dominant

within the \$50,000-per-QALY willingness-to-pay threshold (ICER: \$6,199–\$14,297). That study took into consideration drug costs associated with 2 chemotherapy regimens (FEC-100 and FEC-D). The cost per regimen was higher in the present study because the costs of the treatment regimen, the care associated with chemotherapy, and granulocyte colony-stimulating factors were included. The present study was therefore more comprehensive in its costing approach. Also, the other cost-utility study assumed that, after RS stratification, chemotherapy use would be 7%, 70%, and 92% for the low-risk, intermediate-risk, and high-risk RS categories respectively. In contrast, our study assumed that no patients in the low-risk RS category would receive adjuvant chemotherapy and that 100% of patients in the high-risk RS category would.

The second Canadian cost-utility study¹⁶ examined the costs and effects of using the 21-gene RS assay strategy over the lifetime of a patient diagnosed with early-stage ER-positive or progesterone receptor-positive, axillary LN-positive (1–3 LNs) BCa. It found that in postmenopausal women, the 21-gene RS assay strategy cost \$36.20 more and led to 0.08 QALYs gained (ICER: \$464 per QALY gained). The sensitivity analysis revealed that, if fewer than 36% of the women in the intermediate-risk RS group received adjuvant chemotherapy, then the 21-gene RS assay led to a negative cost and effect. Their model differs from ours in that they also modelled local recurrence, a second primary BCa, and remission with or without chemotherapy-associated serious adverse events. For the chemotherapy-associated adverse events, they considered 8 different diagnoses that resulted in hospitalizations. The types of serious adverse

**FIGURE 2** Cost-effectiveness plane, with 10,000 simulated incremental cost-effectiveness ratios from probabilistic analysis. WTP = willingness to pay.**FIGURE 3** Cost-effectiveness acceptability curve. RS = Recurrence Score (Oncotype Dx: Genomic Health, Redwood City, CA, U.S.A.).

events considered were not reported in the publication. The treatment regimens that the authors considered also differed slightly from ours. The costs of their chemotherapy regimens were lower than the costs of ours. (They might not have included the costs associated with nursing and pharmacy time, a peripherally inserted central catheter, physician visits, and granulocyte colony-stimulating factor). Our study adds to the literature given that we used—and made explicit—detailed costs of the chemotherapy regimens.

Three studies conducted in the United States and the United Kingdom also considered the patient population considered in the present work^{9,15,42}. Chandler *et al.*⁴² found that, compared with current clinical practice and taking a health care payer perspective, the 21-gene RS assay strategy resulted in an ICER of \$188,125 per QALY gained. The results were most sensitive to test accuracy and utilities. With perfect test accuracy, the cost-effectiveness ratio was \$28,947 per

QALY. If the utilities took into consideration the effect on the patient of decreased worry by receiving information about recurrence risk, the ICER was \$58,431 per QALY. Vanderlaan *et al.*¹⁵ examined the cost-effectiveness of the 21-gene RS assay strategy from a health care payer perspective over a 30-year time horizon. That study separated patients in the 21-gene RS assay arm into low-risk and high-risk RS categories. The results indicated that the intervention was less costly than current practice (\$384 less) and more effective (0.127 QALYs gained). The intervention dominated current practice. The sensitivity analysis revealed that if the proportion of tested patients who received chemotherapy after assay testing decreased to 42% from 54%, then the intervention resulted in even more cost savings. One study from the United Kingdom examined the same patient population from the perspective of the health care payer over a lifetime horizon⁹. That study stratified patients into low-risk and high-risk RS categories. The results revealed a mean incremental cost of £860 and incremental effectiveness of 0.16 QALYs gained (ICER: £5,529). The results were sensitive to the price of the 21-gene RS assay, the model time horizon, the relative risk of CHF, quality of life while on chemotherapy, and RS cut-offs for low-risk and high-risk. It is difficult to compare our overall results with the results from that study, given that its RS stratification omitted the intermediate-risk RS category.

Strengths and Limitations

The major strength of our study is that most of the data were obtained from published Canadian sources and reflect current practice. That approach makes our model applicable to the Ontario setting and potentially helpful for guiding practice in the province. As well, our model takes into consideration current treatment regimens within the Canadian setting. We addressed most of the modelling concerns reported in a systematic review of cost-effectiveness analyses of the 21-gene RS assay⁴³. Specifically, we considered both the short-term and long-term toxicities associated with chemotherapy; we selected a diagnosis age of 60 years, because that is the average age of patients presenting with BCa; and we assumed that that patients in the low-risk RS group had the same risk of distant recurrence whether they were treated with adjuvant chemotherapy or not.

Our study has a number of limitations to highlight. First, because of a lack of published data, it did not consider local recurrence. Having that information might make the 21-gene RS assay strategy look even more economically attractive. Second, the cost of the disease-free health state might have been underestimated given that the costs were obtained from a study that reported costs for women diagnosed with BCa in 1995³³. Third, our model did not include the cost of antiemetic drugs to treat nausea and vomiting. Adding the cost of those drugs would make the 21-gene assay strategy more economically attractive. Fourth, a number of assumptions were made that might have influenced the findings. For example, the risks of recurrence for patients in the low-risk RS category receiving and not receiving chemotherapy were assumed to be the same. In addition, the risk of recurrence became zero after 20 years, and the risks of CHF and leukemia occurred only during years 1–7 after chemotherapy. Nevertheless, those

assumptions were made based on existing literature and were confirmed by clinicians to be clinically appropriate. Lastly, because our model was Ontario-specific, the generalizability of the findings might be limited to settings with a similar context.

It is important to note that, although BCa recurrence with chemotherapy was not shown in the 1-way sensitivity analysis to have a significant effect on the results (within the clinically plausible ranges), the results could change in favour of current practice depending on the method used for estimation of recurrence. The recurrence rates used in our study were obtained for each RS risk category and for LN-positive women²⁵. A study by Pan *et al.*⁴⁴ of BCa recurrence in women with ER-positive BCa and 1–3 positive LNs reported that the annual rate of distant recurrence was 2.2% in year 1 and 1.8% in year 20. We could not directly compare their estimates with the estimates from Albain *et al.*²⁵, because Pan *et al.* did not separate their estimates by RS risk category.

CONCLUSIONS

The 21-gene RS assay was found to be an economically attractive option compared with no 21-gene RS assay in women with LN-positive (1–3 LNs), ER-positive, HER2-negative BCa in Ontario, given certain model assumptions. Those findings might be of considerable interest to policy-makers and health care providers in their decision-making process for personalized medicine for BCa patients in similar settings.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: funding for this study was received by Genomic Health Ltd. However, the research was conducted independently of Genomic Health Ltd. AE received funding from Genomic Health Ltd. for a decision study in which she was the principal investigator. ST received funding from Genomic Health Ltd. for a decision study in which she was a co-investigator and also fellowship support from Genomic Health Ltd. MT received funding from Genomic Health Ltd. for a decision study in which she was a co-investigator. IT received fees as an advisory board member for Teva Pharmaceuticals. LM, KWC, HS, and WI have no conflicts of interest to disclose.

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