Cost-utility of the 21-gene recurrence score assay in node-negative and node-positive breast cancer

Nathan W. D. Lamond · Chris Skedgel · Daniel Rayson · Lynn Lethbridge · Tallal Younis

Abstract The 21-gene recurrence score (Oncotype DX®: RS) appears to augment clinico-pathologic prognostication and is predictive of adjuvant chemotherapy benefit in node-negative (N−) and node-positive (N+), endocrine-sensitive breast cancer. RS is a costly assay that is associated with good ‘value for money’ in N− disease, while economic evaluations in N+ disease based on most recent data have not been conducted. We examined the cost-utility (CU) of a RS-guided adjuvant strategy, compared to current practice without RS in N− and N+, endocrine-sensitive breast cancer from a Canadian health care system perspective. A generic state-transition model was developed to compute cumulative costs and quality-adjusted life years (QALYs) over a 25-year horizon. Patient outcomes with and without chemotherapy in RS-untested cohorts and in those with low, intermediate and high RS were examined based on the reported prognostic and predictive impact of RS in N− and N+ disease. Chemotherapy utilization (current vs. RS-guided), unit costs and utilities were derived from a Nova Scotia Canadian population-based cohort, local unit costs and the literature. Costs and outcomes were discounted at 3% annually, and costs were reported in 2011 Canadian dollars ($). Probabilistic and one-way sensitivity analyses were conducted for key model parameters. Compared to a non-RS-guided strategy, RS-guided adjuvant therapy was associated with $2,585 and $864 incremental costs, 0.27 and 0.06 QALY gains, and resultant CUs of $9,591 and $14,844 per QALY gained for N− and N+ disease, respectively. CU estimates were robust to key model parameters, and were most sensitive to chemo utilization proportions. RS-guided adjuvant therapy appears to be a cost-effective strategy in both N− and N+, endocrine-sensitive breast cancer with resultant CU ratios well below commonly quoted thresholds.

Keywords Breast cancer · 21-RS assay · Cost-utility analysis · Economic evaluation · Adjuvant chemotherapy

Introduction

Approximately 50% of breast cancer patients present with early stage, endocrine-sensitive disease and preferentially benefit from adjuvant endocrine therapy [1]. Current consensus guidelines based on standard clinico-pathologic characteristics, however, recommend adjuvant chemotherapy plus endocrine therapy for the majority of these patients despite an uncertain and/or small benefit from chemotherapy [2, 3]. A significant proportion of these patients are likely over treated with chemotherapy, which is associated with significant cost and toxicities [4, 5]. Optimizing patient selection for chemotherapy, through the use of novel prognostic and predictive tools, may therefore reduce the cumulative clinical burden and cost of breast cancer management [4–6].
The 21-gene recurrence score (RS; Oncotype DX®, Genomic Health, Inc. Redwood City, California) is a gene-expression profile currently approved for node-negative (N−), endocrine-sensitive breast cancer [3, 7]. RS results have been shown to correlate with breast cancer recurrence risk and mortality independent of other clinico-pathologic characteristics [8–10], and predict adjuvant chemotherapy benefits in N− and more recently N+ breast cancer [9, 10]. RS testing also leads to significant changes in adjuvant treatment decisions and up to a 30% reduction in chemotherapy utilization [11, 12]. These clinical and economic benefits must be considered in the context of RS cost, $4,175 US dollars—USD (Genomic Health, Inc. Redwood City, California). Indeed, a number of economic evaluations have found the RS assay to be associated with ‘good value for money’ in N− breast cancer while evaluations based on the most recent prognostic/predictive data for node-positive (N+) disease are still awaited [13–19].

We performed a cost-utility (CU) analysis of the incremental cost per quality-adjusted life year (QALY) gained associated with RS-guided adjuvant treatment (RS test strategy) compared to current practice without RS testing (No RS Test strategy) in N− and N+, endocrine-sensitive breast cancer.

Methods

Decision analysis

The cumulative costs and QALY associated with ‘RS Test’ compared with ‘No RS Test’ strategies were examined within a decision analysis framework (Fig. 1) that incorporated (i) upfront costs of the RS test ($3,991 Canadian dollars—CAD), (ii) proportion of low-, intermediate- and high-risk RSs, (iii) proportion of patients treated with chemotherapy (Chemo) and (iv) downstream costs and QALYs associated with Chemo vs. No Chemo in each scenario derived from a Markov model (Fig. 2). The key parameters in the CU analysis are shown in Table 1 [8–12, Breast Cancer Res Treat 123

![Fig. 1 Decision analysis framework. The decision analysis framework incorporates RS assay costs to compute the overall incremental costs and QALYs associated with ‘RS Test’ vs. ‘No RS Test’ strategies. RS testing identifies low, intermediate and high RS groups. Costs and QALYs are derived from a Markov model of ‘Chemotherapy’ vs. ‘No Chemo’ in various scenarios according to relevant chemotherapy utilization proportions. CA cancer, QALY quality-adjusted life year, RS recurrence score, Chemo chemotherapy](image-url)
The distribution among low-, intermediate- and high-risk RS groups in the primary analysis was provided by Genomic Health, Inc. based on all RS assay results performed in Canada and was varied in the sensitivity analysis to a weighted average distribution derived from all relevant published studies. In the No RS strategy, Chemo chemotherapy-induced nausea and vomiting, FN febrile neutropenia, AML/MDS acute myeloid leukaemia/myelodysplastic syndrome, CHF congestive heart failure.

Table 1 Key parameters

<table>
<thead>
<tr>
<th>Key parameters</th>
<th>N−</th>
<th>N+</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Year relapse risk without chemo</td>
<td>17%</td>
<td>31%</td>
<td>[27]</td>
</tr>
<tr>
<td>Baseline chemo use</td>
<td>26%</td>
<td>70%</td>
<td>[20]</td>
</tr>
<tr>
<td>Baseline chemo benefit (RR&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>0.51</td>
<td>0.78</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>RS&lt;sup&gt;b&lt;/sup&gt; risk stratification (L/I/H&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>56%/34%/10%</td>
<td>56%/34%/10%</td>
<td>Genomic Health, Inc. &lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>RS prognostication</td>
<td>NSABP B20 cohort</td>
<td>SWOG 8814 cohort</td>
<td>[8–10]</td>
</tr>
<tr>
<td>Post-RS chemo use (L/I/H)</td>
<td>7%/26%/92%</td>
<td>7%/70%/92%</td>
<td>[11, 12, 21–26]</td>
</tr>
<tr>
<td>Post-RS chemo benefit&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NSABP B20 cohort</td>
<td>SWOG 8814 cohort</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>Median age</td>
<td>50-Year old</td>
<td>50-Year old</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative-risk based on event rates from NSABP B20 and SWOG 8814

<sup>b</sup> Recurrence score

<sup>c</sup> Low-/intermediate-/high-risk

<sup>d</sup> According to RS risk stratum and including no chemotherapy benefit in low RS

<sup>e</sup> These correspond to 30 and 60% rates without tamoxifen in N− and N+ disease, respectively

<sup>f</sup> Personal communication based on all Canadian RS assay use to date

Fig. 2 Markov model schema. Health states incorporated in the model are shown in circles, and possible transitions among health states are depicted by arrows. All patients enter the model in a ‘disease-free’ state and move to other health states according to transition probabilities. Patients in ‘disease-free’ state could develop ‘local relapse’ or ‘distant relapse’. Patients undergoing ‘chemotherapy’ could experience adverse events during (i.e. CINV or FN) or after (i.e. AML/MDS or CHF) treatment. ‘Death’ could occur with or without relapse or due to chemotherapy adverse events. CINV chemotherapy-induced nausea and vomiting, FN febrile neutropenia, AML/MDS acute myeloid leukaemia/myelodysplastic syndrome, CHF congestive heart failure.
utilization proportions were derived from a recent population-based study in Nova Scotia, Canada [20]. In the RS strategy, Chemo utilization was RS dependent and was derived from the literature [11, 12, 21–26]. Chemo utilization in the intermediate-risk stratum was assumed to be similar to the No RS strategy given the current uncertainty regarding the predictive value of the RS assay in the intermediate RS group [9, 10]. Separate analyses were conducted for N− and N+ breast cancer as well as mixed nodal status with 40% N+ disease [20].

Markov model

The Markov model incorporated ten distinct health states (Fig. 2) to compute the cumulative costs and QALYs based on hypothetical cohorts of 1,000 women with early stage, endocrine-sensitive breast cancer undergoing adjuvant Chemo or No Chemo. All patients entered the model in a ‘disease-free’ state and could move to other health states according to event rates derived from the literature [8–10, 27–39]. Each health state was assigned a utility value and cost (Table 2) [30, 31, 40–50]. The costs and health consequences, including utilities, of being in each health state were aggregated over a defined number of monthly cycles reflecting the 25-year horizon examined. Costs and outcomes were discounted at 3% annually. The model was developed in Excel (Microsoft Corporation, Redmond, WA, USA).

Event rates

Event rates were derived from the literature [8–10, 27–39]. The prognostic and predictive impacts of RS testing in N− and N+ disease were computed from the event rates observed in the relevant RS analyses of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 and Southwest Oncology Group (SWOG) 8814 studies, respectively [9, 10].

Breast cancer relapses without chemotherapy were based on the nodal status in the no RS strategy [27] as well as the reported prognostic impact of the RS test in the RS strategy [8–10]. Relapses post-chemotherapy was computed from event rates in NSABP B20 and SWOG 8814 [9, 10]. Disease-free (DFS) and overall survival (OS) were derived from breast cancer relapse risk combined with the general mortality (death without recurrence) for women with a median age of 50 [28], as per our previous study [30, 35–37].

<table>
<thead>
<tr>
<th>Health state</th>
<th>Cost ($)</th>
<th>Utility</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free</td>
<td>42/month [30, 31, 40]</td>
<td>0.90 [41, 42]</td>
<td>Life</td>
</tr>
<tr>
<td>On chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC-100</td>
<td>6,189/patient° [30, 31]</td>
<td>0.74 [41–43]</td>
<td></td>
</tr>
<tr>
<td>FEC-D</td>
<td>6,515/patient° [30, 31]</td>
<td>0.74 [41–43]</td>
<td></td>
</tr>
<tr>
<td>Local relapse</td>
<td>11,535/event [30, 31, 40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First relapse</td>
<td>0.70 [41, 42]</td>
<td></td>
<td>4 Months [30, 31]</td>
</tr>
<tr>
<td>Second relapse</td>
<td>0.50 [41, 42]</td>
<td></td>
<td>4 Months [30, 31]</td>
</tr>
<tr>
<td>Treated relapse</td>
<td>0.90 [41, 42]</td>
<td></td>
<td>Life [30, 31]</td>
</tr>
<tr>
<td>Distant relapse</td>
<td>35,230/event [30, 31, 40]</td>
<td>0.60 [41, 42]</td>
<td>21 Months [40]</td>
</tr>
<tr>
<td>Early adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINV b</td>
<td>61/event [31, 44]</td>
<td>0.85 [44]</td>
<td>18 Weeks [30, 31]</td>
</tr>
<tr>
<td>FN c</td>
<td>14,802/event [31, 40, 45]</td>
<td>0.47 [45]</td>
<td>3 weeks [30, 31]</td>
</tr>
<tr>
<td>Late adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML/MDS e</td>
<td>66,015/event [31, 47]</td>
<td>0.26 [49]</td>
<td>9 Months [32]</td>
</tr>
<tr>
<td>CHF f</td>
<td>19,008/event [31, 48]</td>
<td>0.64 [50]</td>
<td>12 Months [33, 34]</td>
</tr>
<tr>
<td>Death</td>
<td>–</td>
<td>0.00 [41, 42]</td>
<td>–</td>
</tr>
</tbody>
</table>

° Developing during the 16 weeks of chemotherapy

Chemotherapy-induced nausea and vomiting

Febrile neutropenia

Developing any time for 7 years after chemotherapy

Acute myeloid leukaemia and/or myelodysplastic syndrome

Congestive heart failure

Include drug acquisition costs, supportive medication, adjunct testing and medical resource utilization

Springer
Chemo-associated adverse events were based on FEC-100 (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² q 3 weekly for 6 cycles) and FEC-D (FEC-100 q 3 weekly for 3 cycles followed by docetaxel 100 mg/m² q 3 weekly for 3 cycles) regimens commonly employed in Canada for N− and N+ disease, respectively (Online Resource Table 1) [38, 39].

Costs and utilities

The upfront costs of chemo were derived from local unit costs at the Queen Elizabeth II Health Sciences Centre, in Halifax, Nova Scotia, Canada [30], while the downstream costs of follow up, treatment of recurrent disease and adverse events were derived from the literature (Table 2) [30, 31, 40, 45, 47, 48]. The analysis took a third-party direct payer perspective. Costs were adjusted to 2011 Canadian dollars ($) using the Consumer Price Index (health care component) [51]. Utility weights (Table 2) were derived from a published database [37, 41].

Sensitivity analysis

The robustness of the CU results was tested in a probabilistic sensitivity analysis, which allowed all input parameters to vary simultaneously (Online Resource Table 1). The impact of several key parameters (Table 1), as well as a 25% reduction in RS assay costs, was examined in a series of one-way sensitivity analyses (Fig. 4). Key parameters were varied according to alternate reported data in the literature or assumptions regarding reasonable ranges of uncertainty around point-estimates. As an example, the baseline chemo efficacies were varied to those expected with second and third generation Chemo regimens for N− and N+ disease, respectively. RS risk stratification was varied to a weighted average distribution derived from all relevant published studies [8–12, 21–26]. Other non-key assumptions in the model (Online Resource Table 2) were also varied in sensitivity analyses [35–37, 39].

Results

RS testing was associated with incremental costs and QALY gains relative to a No RS Test strategy in both N− and N+ disease (Table 3). For the former, RS was associated with an incremental cost of $2,585 (95% CI 2,084–3,019) and 0.27 (95% CI 0.22–0.32) QALY gains with a resultant CU of $9,591 (95% CI 7,401–12,289) per QALY gained (Online Resource Fig. 1). For the latter, RS was associated with an incremental cost of $864 (95% CI 83–1,457) and 0.06 (95% CI 0.04–0.08) QALY gains with a resultant CU of $14,844 (95% CI 3,616–25,646) per QALY gained (Online Resource Fig. 1). In the mixed nodal-disease cohort, RS was associated with an incremental cost of $1,852 (95% CI 1,319–2,276) and 0.18 (95% CI 0.15–0.21) QALY gains with a CU of $10,316 (95% CI 7,279–13,667) per QALY gained.

A cost-effectiveness acceptability curve (Fig. 3) generated through probabilistic sensitivity analysis suggests that there was virtually a 100% probability of RS testing being a cost-effective strategy relative to no RS testing at a $50,000 per QALY threshold [52, 53]. As well, the CU results from all one-way sensitivity analyses (Fig. 4) for both N− ($6,199–14,297 per QALY gained) and N+ ($6,934–24,448 per QALY gained) disease were within the $50,000 per QALY threshold. CU results for the latter group, however, were more sensitive to changes in key parameters compared with the former. A 25% reduction in RS cost improved the CUs to $5,924 per QALY gained and cost saving for N− and N+ disease, respectively.

Discussion

Economic evaluations have become a pivotal component in the comprehensive assessment of novel medical treatments and/or interventions [54–56]. This CU evaluation suggests that RS-guided adjuvant treatment is a cost-effective strategy for N− and N+ breast cancer. The resultant CU

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Δ Costs $</th>
<th>Δ QALY</th>
<th>Cost per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>N−</td>
<td>2,585 (2,084–3,019)</td>
<td>0.27 (0.22–0.32)</td>
<td>9,591 (7,401–12,289)</td>
</tr>
<tr>
<td>N+</td>
<td>864 (83–1,457)</td>
<td>0.06 (0.04–0.08)</td>
<td>14,844 (3,616–25,646)</td>
</tr>
<tr>
<td>Combined</td>
<td>1,852 (1,319–2,276)</td>
<td>0.18 (0.15–0.21)</td>
<td>10,316 (7,279–13,667)</td>
</tr>
</tbody>
</table>

QALY quality-adjusted life year

a Results based on cohort with 60 and 40% N− and N+ disease, respectively
b Incremental
c Canadian dollars
d 95% Confidence intervals based on probability sensitivity analysis are shown in parentheses

Table 3 CU results
estimates of $9,591 and $14,844 per QALY gained, respectively, are well below the commonly reported North American threshold of $50,000–100,000 per QALY, and fall within the ‘highly cost-effective’ category as designated by the WHO [52, 53, 57].

Our CU result for N− disease is consistent with other published reports that revealed favourable CU estimates in various jurisdictions [13–19]. The highest reported CU estimate ($63,064 CAD per QALY gained) was from another Canadian evaluation of RS-guided adjuvant chemotherapy compared with an ‘Adjuvant!’ online-guided strategy [17]. This evaluation is limited by its assumptions, which include an uniform chemotherapy efficacy for the intermediate and high RS groups relative to the RS-untested cohort as well as a 2% increase in chemotherapy use post-RS testing. The former effectively undermines the clinical benefit of the RS in identifying those patients who derive greater benefits from chemotherapy, while the latter is contrary to the observed reduced chemotherapy use post-RS testing [11]. Another more
recent CU analysis, based on a prospective assessment of actual chemotherapy utilization in clinical practice, reported a 28% absolute reduction in chemotherapy use and a CU of $10,770 USD per QALY gained [18].

The role of RS in N+ breast cancer continues to evolve. The retrospective RS analysis of the SWOG 8814 cohort is the first clinical study to specifically underscore the prognostic and predictive characteristics of the RS assay in the N+ population [10]. To the best of our knowledge, our economic evaluation provides the first CU estimate for RS testing in N+ disease based on these recently reported outcomes [10]. Two other studies also reported on the CU of the RS assay in N+ disease although neither incorporated specific disease outcomes from the SWOG 8814 analysis. A previous CU analysis, based on data from the NSABP B20 trial for N– disease with relevant adjustments for baseline relapse risk, reported a favourable CU of $5,685 USD per QALY gained in a subset analysis involving N+ disease [19]. As well, another study supported by Genomic Health, Inc., found RS to be cost saving due to predicted reductions of chemotherapy utilization after RS testing, but did not employ specific disease outcomes according to RS risk groups [58].

Our study has limitations. First, and as in all economic analyses, the CU results may not be generalizable to all health care jurisdictions due to differences in costs and/or practices. Our results from a Canadian health care system perspective, however, are in line with economic evaluations conducted elsewhere for N– disease [13–19]. Second, all economic evaluations, including ours, primarily rely on chemotherapy efficacy data from studies employing older chemotherapy regimens [9, 10]. We derived chemotherapy costs and adverse effects from the more current chemotherapy regimens commonly employed in Canada, and also examined the impact of varying relative chemotherapy benefits. Other CU analyses, however, should also be conducted based on commonly utilized regimens in relevant jurisdictions. Finally, RS performance was primarily based on the retrospective analyses from the two relevant clinical trials [8–10], while chemotherapy utilization in various scenarios was derived from a single population-based cohort in Nova Scotia [20], the literature [11, 12, 18, 21–26] and a number of assumptions. Our CU results were, however, robust to reasonable ranges of uncertainties tested.

In summary, RS testing strategy is associated with higher costs and QALY gains compared to no RS testing, with CU estimates within currently accepted CU thresholds. From an economic perspective therefore, RS testing to guide adjuvant treatment decisions appears to be a favourable economic strategy with ‘good value for money’ in endocrine-sensitive, N– and N+ breast cancers. Future economic evaluations of RS, however, should continue to integrate evolving data from relevant clinical trials, including TAILORx [59].

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Conflict of interest The authors have no conflict of interest to declare. The CU study was not supported by pharmaceutical companies or Genomic Health, Inc.

References


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This text appears to be a collection of references, likely from a scientific or medical publication. It contains citations of various research studies, each with a specific focus on different aspects of breast cancer treatment and its economic implications. The references span a range of years, from 2003 to 2012, indicating a body of work that has evolved over time in the field.


