Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined a recurrence score (RS), based on a 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay for the prediction of distant recurrence-free survival (DRFS) in lymph-node-negative (LN-), oestrogen-receptor-positive (ER+) patients with early-stage breast cancer (ESBC) receiving hormonal therapy with tamoxifen.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of women with LN-, ER+ ESBC who were expected to receive 5 years of hormonal therapy.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some resource use data were estimated from studies published from 1991 to 2004. The costs came from studies published between 1991 and 2005. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A Markov model was constructed to assess the expected quality-adjusted survival and costs of using the RS, compared with no test, in a hypothetical cohort of 100 women with LN-, ER+ ESBC who were expected to receive 5 years of hormonal therapy. Two main branches of the decision tree were considered. In scenario 1, patients were classified by NCCN criteria as low risk (e.g. tumour size <1 cm) and did not receive chemotherapy. In scenario 2, patients were classified by NCCN criteria as high risk (e.g. tumour size >2 cm) and were recommended to receive chemotherapy. The RS was assumed to reclassify recurrence risk independent of NCCN risk criteria. In the base-case, all patients classified as intermediate or high risk by the RS underwent chemotherapy, while all patients classified as low risk by the RS did not receive chemotherapy. The structure of the model was depicted. The time horizon of the model was lifetime. The cycle length was one year.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the probability of distant recurrence by 10 years;
- the relative risk reduction of distant recurrence with chemotherapy;
- the probability of metastatic progression after distant recurrence;
- the probabilities of minor, major, or fatal chemotherapy toxicity;
- the probability of cancer;
- the probability of risk reclassification with the RS; and
- the utility values.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature was undertaken to identify the primary studies. The clinical data came from a clinical trial, a meta-analysis of clinical trials, and other studies, the design and characteristics of which were not provided. In particular, risk classification by NCCN criteria or the RS was based on the National Surgical Adjuvant Breast Cancer Project (NSABP) B-14 that included 668 patients.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The use of a clinical trial and a meta-analysis should have ensured the validity of the primary studies. However, the robustness of the other sources was not discussed.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Seven primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The probability of distant recurrence by 10 years was 21.9% if classified as high risk by NCCN criteria and 7.8% if classified as low risk.

The relative risk reduction of distant recurrence with chemotherapy was 15% if classified as intermediate or high risk by the RS and 45% if classified as low risk.
The probability of a response to metastatic breast cancer (MBC) treatment after primary response was 38% if Her2/neu- and 54% if Her2/neu+.

The probability of metastatic progression after distant recurrence was 59.7% for response to MBC treatment if Her2/neu- and 53.7% for response to MBC treatment if Her2/neu+.

The probability of metastatic progression after distant recurrence was 98.3% for nonresponse to MBC treatment if Her2/neu- and 88.5% for nonresponse to MBC treatment if Her2/neu- (one of these results should presumably have been for Her2/neu+).

The probabilities of minor, major, or fatal chemotherapy toxicity were 60%, 5% and 0.5%, respectively.

The probability of cancer Her2/neu+ was 25%.

With respect to the probability of risk reclassification with the RS, for the 7.9% women assigned as having low risk for recurrence based on NCCN criteria, the clinical trial showed a 28% (95% confidence interval, C): 16.8 - 42.4) probability of reclassification to intermediate or high risk with the RS. For the other 92.1% women assigned as having high risk for recurrence based on NCCN criteria, the clinical trial showed a 49% (95% CI: 44.5 - 52.6) probability of reclassification to low risk based on the RS. In fact, of the 53 patients in the NSABP who would have been classified as low risk by the NCCN criteria, only 38 were classified as high risk using the RS while 15 were classified as intermediate or high risk. Of the 615 patients that would have been classified as high risk by the NCCN criteria, only 315 were also classified as high risk by the RS while 300 were classified as low risk.

The utility values were:

<table>
<thead>
<tr>
<th>Event</th>
<th>Utility Value</th>
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<tbody>
<tr>
<td>0.98 after chemotherapy, no distance recurrence;</td>
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<tr>
<td>0.84 for recurrence if respond to chemotherapy for advanced breast cancer;</td>
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<tr>
<td>0.70 for recurrence if stable;</td>
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<tr>
<td>0.49 for recurrence if progressive; and</td>
<td></td>
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<tr>
<td>0.50 associated with chemotherapy (6 months only).</td>
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</tbody>
</table>

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
The propensity to change treatment due to risk reclassification based on the RT-PCR result was 100% if classified as intermediate or high risk by the RS or if low risk by the RS.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were overall survival and the quality-adjusted life-years (QALYs). The DRFS was also reported. Overall survival and the QALYs were estimated using a modelling approach. An annual discount rate of 3% was applied. Limited information on the source of the utility values used to calculate QALYs was provided.

**Direct costs**
The authors stated that the cost analysis was performed from a societal perspective, although only the direct medical costs were included in the analysis. The health services included in the economic evaluation were assay, chemotherapy, cancer surveillance and end-of-life care. Chemotherapy included the costs associated with infusion, patient time, use of colony-stimulating factors to prevent myelosuppressive complications, and the treatment of chemotherapy-related side
effects. Resource use appears to have been mainly derived from published studies and guidelines. The cost of the assay was based on the manufacturer's price, while the cost of chemotherapy came from Red Book prices. Other costs came from published sources. The unit costs were not presented separately from the quantities of resources used. Discounting was relevant, owing to the long timeframe of the model, and an annual rate of 3% was applied. The price year was 2004.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Several univariate and multivariate sensitivity analyses were performed to examine the robustness of the estimated costs and benefits to variations in the base-case model inputs. For example, the propensity to change chemotherapy decision based on the RS, the relative risk reduction of chemotherapy plus tamoxifen versus tamoxifen alone, the cost of chemotherapy, and the proportion of patients defined by NCCN criteria as low risk. The inclusion of the cost of patient travel and lost work productivity was also investigated. A probabilistic analysis (Monte Carlo) was also undertaken to determine the effect of uncertainty in all variables on the cost-utility ratio for the cohort.

**Estimated benefits used in the economic analysis**
Using the NCCN criteria, performing chemotherapy in patients at low risk resulted in higher overall survival (0.37), but lower QALYs (-0.04) per patient. Performing chemotherapy in patients at high risk resulted in higher overall survival (1.53) and QALYs (0.65) per patient. This result confirmed the usefulness of chemotherapy only in patients classified as high risk by the NCCN criteria.

Reclassifying patients who were NCCN-defined as low risk to intermediate or high risk by the RS was projected to increase overall survival (1.86) and quality-adjusted survival (0.81). Reclassifying NCCN-defined high-risk patients as low risk by the RS was projected to increase the QALYs per patient (0.15).

In the comparison between RS test and no test in all patients (in a hypothetical cohort of 100 patients), the estimated DRFS was 2,836 patient-years with no test and 2,831 patient-years with the test (difference -4.85). Overall survival was 2,976 patient-years with no test and 2,972 patient-years with the test (difference -4.21). The estimated QALYs were 1,814 with no test and 1,822 with the test (difference 8.60).

**Cost results**
In a hypothetical cohort of 100 women, the total costs were $4,320,377 with no test and $4,117,549 with the test (difference -202,828). The lower were mainly due to a reduction in the cost of adjuvant chemotherapy, given that the RS reclassified as low risk about 50% of patients classified as high risk by the NCCN criteria. Thus, the extra cost of the assay was more than offset by the reduction of other costs.

**Synthesis of costs and benefits**
The authors stated that incremental cost-effectiveness and cost-utility ratios would have been calculated to combine the costs and benefits of the test strategy in comparison with no test. However, in the base-case, no ratios were calculated because the test strategy was dominant (i.e. it was more effective and less expensive than the no test strategy).
The sensitivity analysis showed the robustness of the base-case results. The use of the RS was almost always more effective and cost-saving. However, there were two exceptions. First, the propensity to not use chemotherapy if the RS reclassified patients from high to low risk and, second, the proportion of patients tested with the RS who were low risk according to NCCN criteria. In particular, if only 50% of high-to-low reclassified patients were to forego chemotherapy, then the test would be cost increasing and the cost per QALY gained would be $17,234. Testing only NCCN-defined high-risk patients had a minimal effect on the QALYs, but resulted in larger cost-savings. Testing only NCCN-defined low-risk patients had a larger benefit in QALYs and was cost increasing, with a cost per QALY of $31,529.

The authors stated that the inclusion of the cost of patient travel and lost work productivity, equal to $17 per infusion, made RS testing more cost-saving.

In the probabilistic analyses, more than two-thirds of simulations showed the RS to improve QALYs and save costs. The upper 95th percentile of the cost-utility ratio equaled $16,874.

**Authors' conclusions**
The analysis had three primary findings. First, reclassifying patients who were National Comprehensive Cancer Network (NCCN)-defined as low risk to intermediate/high risk by the recurrence score (RS) was projected to increase overall survival, quality-adjusted survival and costs. Second, reclassifying NCCN-defined high-risk patients as low risk by the RS was cost-saving. Third, in a population of 100 patients with characteristics similar to those of the NSABP B-14 participants, more than 90% of whom were NCCN-defined as high risk, using the 21-gene reverse transcriptase-polymerase chain reaction (RTPCR) assay was expected to improve quality-adjusted survival and save costs.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear. The recently developed test was appropriately compared with current guidelines. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a synthesis of published studies. However, only limited details on the design and characteristics of the primary studies were reported. In particular, some data were derived from a clinical trial and from a meta-analysis of published clinical trials. No information on the sources of the utility values or other model inputs was reported. Thus, it was not possible to assess the validity of the primary studies. Some assumptions were also made to derive clinical data that were not available from the literature. The issue of uncertainty was extensively addressed in the sensitivity analysis and the most relevant clinical parameters were varied.

**Validity of estimate of measure of benefit**
The benefit measures used in the analysis were appropriate as they capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). In addition, QALYs and overall survival are easily compared with the benefits of other health care interventions. Discounting was applied, as recommended by US guidelines. Very limited information on the source of the utility weights was provided.

**Validity of estimate of costs**
The cost analysis was restricted to direct medical costs, despite the fact that the authors stated that a societal perspective was adopted. The impact of indirect costs, such as productivity losses, was investigated in the sensitivity analysis. The inclusion of non-medical costs would have been interesting. The costs were presented as macro-categories and a detailed breakdown of the items was not reported, which limits the possibility of replicating the cost analysis in other settings. The source of the costs was reported, whereas the information on resource consumption was less clear. The costs were treated deterministically, but the impact of using alternative cost estimates was investigated in the sensitivity analysis. The price year was provided, which will facilitate reflation exercises in other time periods. The authors stated that patterns of care were estimated from a physician survey, which should reflect typical resource consumption in the
USA.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, the use of extensive sensitivity analyses enhances the external validity of the analysis. The authors stated that adjustments in quality of life, to account for the effect the test may have on decision-making for patients and physicians, were not considered. Thus, the benefits might have been underestimated.

Implications of the study
The study results suggested that the societal benefits and costs of the test are highly influenced by two factors. More specifically, how patients and physicians interpret and use the results of the assay, and whether the assay would be used in all patients with LN-, ER+ ESBC or would be restricted to a sub-set of patients. The authors stated that recent studies have been assessing the prognostic and predictive ability of the RS. Further, since the 21-gene RT-PCR assay is a first-generation test, the development of second-generation assays including more genes could further improve the prognostic and predictive accuracy of the assay.

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Other publications of related interest


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