Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation studies

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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 compared three adjuvant treatment strategies in early-stage breast cancer (ESBC). These were tamoxifen alone, chemotherapy followed by tamoxifen, and recurrence score (RS)-guided therapy based on the results of the 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR) assay. In the RS-guided group low-risk patients were treated with tamoxifen, while intermediate- and high-risk patients received chemotherapy and tamoxifen. For the treatment strategies that included chemotherapy, the following regimens were accounted for and compared:

doxorubicin and cyclophosphamide (AC) every 3 weeks x 4 cycles;

AC every 2 weeks x 4 cycles with colony-stimulating factor (CSF) support;

AC followed by paclitaxel (AC-T) every 3 weeks x 8 cycles;

AC-T every 2 weeks x 8 cycles with CSF support; and

docetaxel, doxorubicin, and cyclophosphamide (TAC) every 3 weeks x 6 cycles with CSF support.

Type of intervention
Treatment.

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

Study population
The study population comprised women with lymph node-negative, estrogen receptor-positive ESBC, eligible to provide RNA for RT-PCR analysis. Eligibility was based on the primary tumour block and the availability of the tumour. The study population appear to have comprised patients from the National Surgical Adjuvant Breast Cancer (NSAB) Program B-20 and B-14. Further details of the study population were reported in the two parent clinical studies from which clinical data were obtained (Paik et al. 2004 and 2006, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was not explicitly stated, but it appears to have been secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were mainly derived from the two parent clinical studies published in 2004 and 2006. Resource use and cost data were derived from the studies published in 2005. The price year was not explicitly reported.
Source of effectiveness data
The clinical data included 10-year distant recurrence-free survival for each treatment group, depending on whether women with node-negative receptor-positive ESBC were classified as high risk (RS \( \geq 31 \)), intermediate risk (RS 18 to 30), or low risk (RS < 18) of distant recurrence at 10 years.

Modelling
Based on data from the clinical trials, an RS (OncotypeDx) ranging from 0 to 100 was generated from each patient’s gene expression results. Data were analysed using a time-varying piece-wise log-hazard ratio model, and the RS score was estimated as a continuous measure. The 10-year distant recurrence rate was calculated using a Breslow-type estimator. In addition, a decision analytic model was constructed to compare clinical outcomes, costs and quality of life of the three treatment strategies. The time horizon and the most important clinical probabilities that populated the model were reported.

Sources searched to identify primary studies
The clinical effectiveness data were derived from two published randomised trials (Paik et al. 2004 and 2006). The design and methodology of the two studies were not reported in detail.

Methods used to judge relevance and validity, and for extracting data
The process used to identify the data was not reported. No inclusion criteria for any parameters were specified. However, the authors appear to have derived estimates of effectiveness from large trials referring to the NSAB Program that directly assessed the prognostic accuracy, and its impact on treatment, of the 21-gene expression signature in women with lymph node-negative estrogen receptor-positive ESBC.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years saved and quality-adjusted life-years (QALYs). The utility values were derived from published studies. It was reported that patients’ values were evaluated using the time trade-off technique. Although the time horizon of the analysis exceeded 2 years, meaning that discounting was relevant, the benefits were not discounted.

Direct costs
The costs of adjuvant chemotherapy, surveillance without recurrence, the OncotypeDx assay and recurrent treatment costs (reported as summary costs per patient) were reported to have been included in the analysis. The authors reported limited information on the costing in the current paper, referring instead to two separate papers (Hornberger et al. 2005 and Oestreicher et al. 2005, see ‘Other Publications of Related Interest’ below for bibliographic details). It was reported that drug costs were included only for chemotherapy, while further treatment-related direct costs, administration costs, laboratory testing costs, professional fees, the patients’ transportation costs and relevant out-of-pocket expenses were not included in the analysis. The costs were not discounted and the price year was not reported.

Statistical analysis of costs
The authors provided descriptive statistics of the cost data (mean values, range and shape of distribution). Further statistical analysis of the costs was not reported.

Indirect Costs
Productivity costs were not included in the analysis.

Currency
US dollars ($).
Sensitivity analysis
Parameter uncertainty was investigated through a probabilistic sensitivity analysis, using Monte Carlo simulations based on 1,000 replicates. Distant recurrence-free survival and cost parameters in the model were assigned probability distributions. In addition, one-way sensitivity analyses in conjunction with threshold analyses appear to have been performed to assess the robustness of the results to variation in the input parameters (e.g. healthy life expectancy, utilities). The ranges used were obtained from published literature.

Estimated benefits used in the economic analysis
Life expectancy at 10 years did not differ significantly between the RS-guided strategy and the combination of chemotherapy and tamoxifen. Compared with tamoxifen alone, RS-guided therapy resulted in 2.2 life-years gained.

It was reported that at a utility value of 0.90 assigned to adjuvant chemotherapy, the RS-guided strategy resulted in 0.97 incremental QALYs compared with tamoxifen alone, and 1.71 QALYs compared with a combination of tamoxifen and chemotherapy.

Cost results
The mean and incremental costs were reported for each treatment strategy. The tamoxifen alone strategy resulted in a cost of $11,890 per patient, the RS-guided strategy in a cost of $16,162, and the combination of chemotherapy and tamoxifen in $18,418. When the cost of recurrence exceeded $100,759, the RS-guided strategy resulted in cost-savings in comparison with any other strategy.

The authors reported that for all chemotherapy regimens with a cost higher than $5,822, the RS-guided strategy resulted in cost-savings in comparison with the chemotherapy and tamoxifen strategy. The cost-savings with the RS-guided strategy ranged from $458 when AC-T every 3 weeks x 8 cycles was used, to $9,810 when TAC every 3 weeks x 6 cycles with CSF support was used. When chemotherapy consisted of AC every 4 weeks x 4 cycles, the chemotherapy and tamoxifen strategy appear to have incurred the lowest cost.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was performed and each treatment option was compared with tamoxifen alone. The RS-guided strategy resulted in an incremental cost of $1,944 per life-year gained, while the combination of chemotherapy and tamoxifen resulted in an incremental cost of $3,385 per life-year gained.

When adjuvant chemotherapy was assigned a utility value of 0.90, the RS-guided strategy resulted in an incremental cost of $4,432 per QALY gained.

Monte Carlo simulations demonstrated that, when the RS-guided strategy was compared with tamoxifen alone, the mean incremental cost-effectiveness ratio was $2,769 per life-year saved and the median 1,784 per life-year saved. The willingness-to-pay (WTP) analysis demonstrated that tamoxifen alone was the preferred strategy at a WTP value of zero, while the RS-guided strategy became equally preferable at a WTP of $7,500 per life-year saved. When the WTP exceeded $15,000, the RS-guided strategy remained the preferred strategy with a probability of 70%.

Authors’ conclusions
The analysis demonstrated that the recurrence score (RS)-guided treatment strategy resulted in greater efficacy at an acceptable cost-effectiveness ratio when compared with tamoxifen alone, while incurring lower costs and similar efficacy when compared with the combination of chemotherapy and tamoxifen for the treatment of patients with lymph node-negative estrogen receptor-positive early-stage breast cancer (ESBC).

CRD COMMENTARY - Selection of comparators
A justification was provided for the comparators used. Adjuvant chemotherapy and tamoxifen seemed to represent the
most commonly used treatment options in the authors’ setting, while treatment decisions (tamoxifen and/or chemotherapy) based on a 21-gene RT-PCR test represented a newly developed strategy. In addition, the chemotherapy modules accounted for in the analysis represented commonly used chemotherapy regimens in the authors’ setting. You should decide if these represent valid technologies in your own setting.

Validity of estimate of measure of effectiveness
The parameters of the model were obtained from two published studies (Paik et al. 2004 and 2006). Although the description of the analysis indicates that some synthesis of the data had taken place, no details of the methods used were provided.

Validity of estimate of measure of benefit
The authors used life-years gained and QALYs as measures of benefit in the economic analysis, these being derived from published literature. The benefits were not discounted when they could have been.

Validity of estimate of costs
The authors stated that they had adopted a societal perspective, but the costing reported in the paper would suggest that the perspective was actually that of the third-party payer. However, some relevant categories of costs, namely drug administration, professional fees, laboratory testing and adverse events, were not included in the analysis. The resource quantities and the prices were not reported separately. These facts will limit the generalisability of the authors’ results. In addition, although the time horizon of the analysis was 10 years, the authors did not carry out discounting. The price year was not explicitly reported, which will hinder future reflation exercises.

Other issues
The authors did not compare their findings with those from other studies so it is not possible to objectively assess the degree to which their results agree with other published studies. The issue of the generalisability of the results to other settings was not directly addressed, but a sensitivity analysis was performed which improves the external validity of the study. The authors do not appear to have presented their results selectively, but the methods used in their study were not described in detail and the results were not presented satisfactorily. For example, the authors did not fully report the results of the sensitivity analyses they performed. The authors reported limitations to their costing analysis, which have already been highlighted in this abstract.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice. Further research on the development and validation of assays with higher accuracy in estimating disease prognosis and treatment effectiveness in women with ESBC is recommended.

Source of funding
Supported by Genomic Health and Amgen.

Bibliographic details

PubMedID
17311307

DOI
10.1002/cncr.22506
Other publications of related interest
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Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents, Hormonal /therapeutic use; Breast Neoplasms /diagnosis /drug therapy /pathology; Chemotherapy, Adjuvant; Cost-Benefit Analysis; Disease-Free Survival; Female; Gene Expression; Humans; Lymph Nodes /pathology; Monte Carlo Method; Neoplasm Recurrence, Local /diagnosis /pathology; Prognosis; RNA, Messenger /analysis; Reverse Transcriptase Polymerase Chain Reaction /economics /methods; Tamoxifen /therapeutic use; Treatment Outcome

AccessionNumber
22007000872

Date bibliographic record published
30/11/2007

Date abstract record published
30/11/2007