Cost-effectiveness analysis of strategies for HER2 testing of breast cancer patients in France
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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 investigated strategies involving the use of immunohistochemistry (IHC) and/or fluorescent in situ hybridisation (FISH) techniques for diagnosing the HER2 status of invasive breast carcinoma.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The target study population comprised patients with infiltrating breast cancer. No further details were given.

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

Dates to which data relate
The dates when the effectiveness data were collected were not explicitly stated. The dates when the cost data were collected were unclear. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published literature and a multi-centric study that was not referenced.

Modelling
A decision analysis model, in the form of a decision tree, was created using Data 4.0 (TreeAge Software, Williamstown, MA) to compare the five diagnostic strategies. The tree modelled patients from initial diagnosis of infiltrating breast cancer to potential metastatic relapse. The time horizon of the model was 20 years from diagnosis.

Outcomes assessed in the review
The authors assessed the probabilities of events defining the decision model:

- the metastatic relapse rate within 10 years;
- the probability of mortality from other causes;
- the probability that HER2 tests were impossible, possible and performed, or not performed due to premature death or
inappropriate HER2 testing.

The authors also estimated, from a database derived from the unreferenced multi-centric study, the sensitivity and specificity of IHC as used in France.

**Study designs and other criteria for inclusion in the review**

The criteria for inclusion were not reported. One major source of evidence was unpublished. The rest were published studies.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

Not reported.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

The total number of studies included was unclear. There appears to have been at least six studies.

**Methods of combining primary studies**

The studies were combined using narrative methods. The authors used the primary studies to create databases from which to derive parameter estimates.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

At metastatic relapse, HER2 testing was never reported as being impossible. Therefore, the only reason for patients with HER2 amplified tumour not be given trastuzumab at first metastatic relapse was because they were identified as false negatives.

Seventy-four per cent of IHC scores were 0 or 1+, 2% were 2+ and 24% were 3+ for patients who relapsed within 10 years after diagnosis.

All scores were 0 or 1+ when relapse occurred after 10 years.

The sensitivity of IHC compared with FISH was 0.88 and the specificity was 0.91.

**Measure of benefits used in the economic analysis**

Two summary measures of health outcome were used in the economic analysis. The first was the number of patients correctly managed (defined as the false-negatives avoided) and the second was the number of patients correctly managed (false-positives avoided).
Direct costs
The authors did not report a perspective for the analysis, but did report that only direct costs likely to be influenced by the five defined strategies were taken into consideration. Such direct costs would differ according to the perspective actually adopted. Nevertheless, the authors reported including data on the working time of each staff category involved (as recorded by the hospitals) and data on reagents, consumables, equipment and maintenance provided by the hospitals and manufacturers. Catalogue prices were used to inform unit prices. Resource use data were taken from the multi-centric, unpublished study on diagnosis and HER2 status. The costs were not discounted in the base-case, but were discounted at 3% and 5% in sensitivity analyses to “account for the distribution over time of recurring metastases”. The authors did not provide a breakdown of the unit costs and quantities involved in the study. The price year was 2002.

Statistical analysis of costs
The authors did not report a statistical analysis of the costs beyond the simulation of 10,000 patients. It was uncertain how variability entered the decision model as the authors did not report defining probability distributions for variables.

Indirect Costs
The indirect costs were not considered relevant to the study.

Currency
Euros (EUR).

Sensitivity analysis
The authors used sensitivity analysis to explore the impact of the discount rate, the cost of the FISH test, and the proportion of samples fixed using formalin. It was unclear whether one-way or multi-way analyses were used. The authors used narrative descriptions to define sensitivity ranges.

Estimated benefits used in the economic analysis
Given that false negatives were the only cause of patients with HER2 amplified tumour not being given trastuzumab at first metastatic relapse, strategies S1 to S5 correctly managed 0 patients (S1 and S2), 44 patients (S3) and 9 patients (S4 and S5).

With HER2 non-amplified tumour and improper trastuzumab use at first metastatic relapse, strategies S1 to S5 correctly managed (that is, false-positives avoided) 0 (S1, S2 and S4), 16 patients (S3) and 16 patients (S5).

Cost results
The average cost per patient was EUR 43 using IHC and EUR 283 using FISH.

The authors noted that reagents accounted for 61% of this cost.

The average cost of retrieving a tumour action from the archive was EUR 14, and the calculated cost of performing a metastatic biopsy was EUR 893.

Synthesis of costs and benefits
Given that false negatives were the only cause of patients with HER2 amplified tumour not being given trastuzumab at first metastatic relapse, "efficient strategies” were S1 and S4 with an incremental cost-effectiveness ratio (ICER) of EUR 722, and S3 with an ICER of EUR 6,127.

With HER2 non-amplified tumour and improper trastuzumab use at first metastatic relapse, the most efficient strategies were S1 and S5, which had an ICER of EUR 4,725.
The results were relatively robust to changes in the discount rate. They were more sensitive to changes in the cost of the FISH test and the proportion of samples fixed using formalin. Although, for the latter, the relative results remained unchanged.

Authors' conclusions
All strategies were more expensive, but at least as effective, in comparison with current practice.

CRD COMMENTARY - Selection of comparators
The authors compared five interventions. One represented current practice and the others were scenarios that would be appropriate whether or not the tumour block was fixed with formalin. The reader must judge whether these scenarios represent possible and/or all scenarios within their own setting.

Validity of estimate of measure of effectiveness
Clinical data for the model were derived from the literature and from an unpublished study. There was nothing to suggest that the search for clinical data was systematic and the authors did not state why specific studies were selected.

Validity of estimate of measure of benefit
The authors used two proxy measures of health benefit. These were the number of false-negatives avoided and the number of false-positives avoided. The outcomes need to be considered together and therefore caution is recommended when interpreting the ICERs based on partial proxy benefits.

Validity of estimate of costs
The authors did not state the perspective from which the costing analysis was carried out (i.e. that of the third-party payer or the health care provider). Since the authors reported that only the direct costs were included and the work was funded by the French government, the perspective is likely to have been that of the health care system. Little detail (unit costs and quantities were not reported separately) was provided, making it difficult to fully understand the analysis and judge the key drivers.

Other issues
The authors drew some comparisons with the findings of other studies, stating that their conclusions echoed some that had been published. They also noted that differences between these studies were generated by the relative setting (and hence price differences), and the difference in outcome measures used. The authors did not explain why they did not try to estimate quality-adjusted life-years, as was done in the comparison study. The issue of generalisability to other settings was not addressed, although it was improved by a sensitivity analysis around the cost of the test and the proportion of samples fixed using formalin. The generalisability could have been improved further by reporting in greater detail and using wider sensitivity analyses. The authors did not note any specific limitations of the study.

Implications of the study
The authors did not make any recommendations for policy or practice following on from their study.

Source of funding
Funded by the French Ministry of Health.

Bibliographic details
Health Care 2006; 22(3): 396-401

PubMedID
16984069

Other publications of related interest
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /therapeutic use; Antibodies, Monoclonal, Humanized; Antineoplastic Agents /therapeutic use; Breast Neoplasms /drug therapy /genetics; Cost-Benefit Analysis; Decision Trees; Female; France; Genetic Testing /economics /methods; Humans; Immunohistochemistry /economics; In Situ Hybridization, Fluorescence /economics; Prospective Studies; Receptor, ErbB-2 /biosynthesis; Recurrence; Trastuzumab

AccessionNumber
22006008316

Date bibliographic record published
31/03/2007

Date abstract record published
31/03/2007