Cost-effectiveness of HER2 testing and 1-year adjuvant trastuzumab therapy for early breast cancer
Lidgren M, Jonsson B, Rehnberg C, Willking N, Bergh J

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.

CRD summary
This study compared the costs and effects of one year of adjuvant trastuzumab with standard care for women, with early-stage breast cancer, who had successfully completed standard adjuvant chemotherapy. The authors concluded that fluorescence in-situ hybridisation testing for all patients followed by one year of adjuvant trastuzumab for those who tested positive was a cost-effective treatment option from a societal perspective. The methods were appropriate and were mostly well reported. Overall, the authors’ conclusions appear to be reasonable.

Type of economic evaluation
Cost-utility analysis

Study objective
The purpose was to assess the cost-effectiveness of the addition of one year of adjuvant trastuzumab therapy after adjuvant chemotherapy in women with early breast cancer.

Interventions
The four strategies were compared with strategy one, which was the standard care and consisted of no testing and no adjuvant trastuzumab therapy.

Strategy two was immunohistochemical (IHC) test followed by one year of adjuvant trastuzumab for those patients with a IHC +3 result and standard care for all other patients.

Strategy three was IHC test followed by one year of adjuvant trastuzumab for patients with IHC +2 and +3 results and standard care for all other patients.

Strategy four was IHC test followed by fluorescence in-situ hybridisation (FISH) test confirmation for patients with IHC +2 and +3 results followed by one year of adjuvant trastuzumab for FISH positive patients and standard care for all other patients.

Strategy five was FISH test followed by one year of adjuvant trastuzumab for FISH positive patients and standard care for all other patients.

Trastuzumab was administered using an 8mg/kg loading dose, followed by 6mg/kg every third week for a total of 17 doses. Women in the hypothetical cohort were assumed to have completely excised the breast cancer, completed at least four cycles of adjuvant chemotherapy, and were aged 55 years.

Location/setting
Sweden/secondary care.

Methods
Analytical approach:
A Markov model was developed using published sources to compare the alternative strategies over a lifetime. The authors stated that a societal perspective was adopted, in a Swedish setting.
Effectiveness data:
The effectiveness data were derived from a synthesis of published literature. However, a single randomised controlled trial (the Herceptin Adjuvant, HERA, trial) formed the key source of effectiveness data (Piccart-Gebhart, et al. 2005, and Smith, et al. 2007, see ‘Other Publications of Related Interest’ below for bibliographic details). A large data set of Swedish breast cancer patients (20,624) was used to assess the risk of recurrence and mortality estimates. Human epidermal growth factor receptor 2 protein (HER2) overproduction prevalence and conditional probabilities for HER2 testing were also reported. The clinical outcomes in the analysis were disease recurrence, including locoregional, contralateral and distant metastases, no recurrence, and deaths. Several assumptions, supported with references, were made where relevant.

Monetary benefit and utility valuations:
The utilities were based on the Swedish population health related quality of life (HRQoL, Burstrom, et al. 2006, see ‘Other Publications of Related Interest’ below for bibliographic details) these were adjusted for a reduction in HRQoL due to breast cancer, using data from a published study (Lidgren, et al. 2007, see ‘Other Publications of Related Interest’ below for bibliographic details).

Measure of benefit:
The measure of benefit used was quality-adjusted life-years (QALYs) and these were discounted at 3%.

Cost data:
Both direct and indirect costs were included in the analysis. The resource use estimates were based on those obtained in the HERA trial. The resources included pharmaceuticals, outpatient visits, cardiac monitoring, and hospitalisations from adverse events. The cost of chemotherapy prior to adjuvant trastuzumab was omitted as it was assumed to be the same for both strategies. Indirect costs were the loss of productivity using the human capital approach, the morbidity of breast cancer at various stages, and the future costs of additional years of life. The prices were from various sources such as the Swedish pharmaceutical clinical charges and published studies including a prior naturalistic cost study by the authors (Lidgren, et al. 2007). The IHC and FISH test prices were from a large hospital. All prices were adjusted to Euros (EUR) for 2005 and converted from Swedish kronor (SEK) at a rate of one EUR equals SEK 0.9282. All costs were discounted at 3%

Analysis of uncertainty:
One-way sensitivity analyses investigated variations in the key parameters of from minus 30% to plus 30% of the base values. Two-way sensitivity analyses tested the specificity and sensitivity of the IHC test and FISH test for HER2. A probabilistic sensitivity analysis was also conducted and a cost-effectiveness acceptability curve was presented.

Results
The mean costs ranged from EUR 115,151 for strategy one to EUR 129,188 for strategy three. The QALYs gained ranged from 11.020 for strategy one to 11.304 for strategy five.

Strategy one was the least effective and the least costly. Strategies three and two were dominated (less effective and more costly) and extendedly dominated (incremental cost-effectiveness ratio, ICER, was higher than the next most effective non-dominated strategy). The ICER for strategy four was EUR 35,975 when compared with strategy one and the ICER for strategy five was EUR 41,471 when compared with strategy four.

The sensitivity analysis showed that these results were sensitive to changes in the age at the start of therapy with lower ICERs for younger women, but strategies four and five remained below EUR 65,000 when patients were 65 years or younger at the start of trastuzumab therapy. The ICERs were robust to changes of plus or minus 30% in selected parameters except for the risk reduction ratio, duration of treatment effect, and the inclusion of future costs, where the ratios were between EUR 54,600 and EUR 97,000 for strategies four and five.

The results from the probabilistic sensitivity analyses, which were presented as a cost-effectiveness acceptability curve, showed that a willingness to pay of EURO 72,000 strategies four and five would be cost-effective in more than 90% of simulations.
Authors' conclusions
The authors concluded that FISH testing for all patients, followed by one year of adjuvant trastuzumab for those who tested positive, was a cost-effective treatment option from a societal perspective.

CRD commentary
Interventions:
The five strategies and the profile of the intended patient population were clearly described and appropriately included the standard care in the authors’ setting.

Effectiveness/benefits:
The effectiveness data were derived from various published studies which appeared to be of high quality. However the methods used to find and select these studies were not stated. Therefore it is not possible to ascertain if the best available evidence was used. The baseline inputs, along with their sources, were fully presented. The utility reductions were also presented, which allows the reader to determine whether these are appropriate to their own setting.

Costs:
The costs appeared to reflect those of the societal perspective. The methods were reported in detail and the sources and references were clearly documented. Base-case cost parameters and the corresponding confidence intervals were presented.

Analysis and results:
An illustration of the model structure was given and a thorough description of the health states and possible transitions between them were described. An incremental analysis was appropriately conducted and the results were clearly presented. Probabilistic sensitivity analyses were used to test for uncertainty in utilities, costs and effectiveness estimates. However, the details of the distributions assigned were not reported and the results were presented, using cost-effectiveness acceptability curves, only for the two strategies which were not dominated. The authors identified and discussed a number of limitations of their study alongside comprehensive comparisons with similar studies which also concluded that adjuvant trastuzumab was cost-effective.

Concluding remarks:
In general, with the exception of the limitations mentioned, the methods were satisfactory and the results were reasonably transparent. The authors’ conclusions appear to be a fair assessment of the analysis undertaken.

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Other publications of related interest

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