Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis

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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 several testing strategies to identify women with an over-expression of the human epidermal growth factor receptor-2 (HER2) gene, a breast cancer (BC) marker. The seven strategies investigated were based on the combination of two diagnostic tests, that is, immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH). IHC uses polyclonal or monoclonal antibodies that recognise and bind to HER2 protein in the tissue section, thus enabling the tester to visualise the location and relative amount of HER2 protein. FISH uses fluorescent-labelled probes that recognise and bind to the HER2 gene in cell nuclei, thus enabling the tester to visualise and count the copies of HER2 per cell. Seven diagnostic strategies were considered (criteria for HER2-positive status in brackets):

Strategy 1 was the base strategy. It consisted of IHC plus confirmation of 2+ scores with FISH (HER2-positive if 3+ score or positive result of FISH).

Strategy 2 was IHC (HER2-positive if 2+ or 3+ score).

Strategy 3 was IHC (HER2-positive if 3+ score).

Strategy 4 was IHC plus confirmation of 1+ and 2+ scores with FISH (HER2-positive if 3+ score or positive result of FISH).

Strategy 5 was IHC plus confirmation of 2+ and 3+ scores with FISH (HER2-positive if positive result of FISH).

Strategy 6 was IHC plus confirmation of 1+, 2+ and 3+ scores with FISH (HER2-positive if positive result of FISH).

Strategy 7 was FISH (HER2-positive if positive result of FISH).

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of women with BC.

Setting
The setting was a laboratory centre. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2005. No dates for the resource use data were reported. The price year was 2006.
Source of effectiveness data
The clinical data used in the economic analysis were the IHC scores (percentages of patients with 0+, 1+, 2+ and 3+ scores) and the rate of positive results of FISH.

Sources searched to identify primary studies
For each study selected, the sample size and results (in terms of IHC scores and positive FISH findings) were reported. Information on the design and other characteristics of the primary studies was not provided. FISH was assumed to be the 'gold' standard, with 100% accuracy.

Methods used to judge relevance and validity, and for extracting data
A systematic review of the literature was undertaken with commonly used databases such as MEDLINE and EMBASE. In addition, the bibliographies of retrieved articles were checked for other possibly eligible papers. The inclusion and exclusion criteria for the review were reported. A Bayesian meta-analysis was carried out to estimate the distribution of IHC scores (0, 1+, 2+, 3+) and the probability of obtaining a positive result of FISH for each category of IHC score.

Measure of benefits used in the economic analysis
The summary benefit measure used was the percentage of cases with accurately determined HER2 status. This was estimated using the Bayesian meta-analysis approach. No discounting was necessary.

Direct costs
The analysis of the costs was carried out from the perspective of the third-party payer. It included the costs of testing. In a separate analysis, the annual cost of trastuzumab therapy was calculated on the basis of the test results. A breakdown of the cost items was not presented. The unit costs and the resource quantities were not presented separately. The costs were derived from billing information maintained by the provincial health insurance agency in Quebec. The sources of resource use were unclear. Discounting was not performed as only short-term costs were included in the analysis. The price year was 2006.

Statistical analysis of costs
The costs and quantities were treated stochastically.

Indirect Costs
The productivity costs were not included.

Currency
Canadian dollars (CAD).

Sensitivity analysis
A probabilistic sensitivity analysis was performed to assess the robustness of the cost-effectiveness analysis by varying all parameters of the economic evaluation simultaneously over plausible ranges. The distributions of the IHC scores and the rate of positive results of FISH were determined from the meta-analysis. For the distribution of the cost of each test, a uniform distribution over the interval (defined by +/- 20% around the cost) was used. Credible intervals (CIs) were generated.

Estimated benefits used in the economic analysis
The median percentage of accurately identified cases was:
96.4% (95% CI: 94.7 to 97.5) with strategy 1 (base-case strategy);
88.2% (95% CI: 80.8 to 93.9) with strategy 2;
92.9% (95% CI: 87.9 to 95.7) with strategy 3;
98.2% (95% CI: 96.9 to 99.1) with strategy 4;
97.6% (95% CI: 96.4 to 98.4) with strategy 5;
99.4% (95% CI: 98.7 to 99.9) with strategy 6; and
100% with strategy 7.

**Cost results**
The median cost of the test per 1,000 women was (in CAD thousands):

CAD 164 (95% CI: 124 to 208) with strategy 1;
CAD 108 with strategies 2 and 3;
CAD 331 (95% CI: 198 to 480) with strategy 4;
CAD 240 (95% CI: 208 to 277) with strategy 5;
CAD 406 (95% CI: 275 to 555) with strategy 6; and
CAD 467 with strategy 7.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios (ICERs; i.e. the incremental cost per case with accurately determined HER2 status) were calculated in order to combine the costs and benefits of the alternative strategies.

After removing dominated or extended dominated strategies (i.e. strategies 2, 3 and 4), the ICERs over the next less effective strategy were:

CAD 6,175 (95% CI: 3,630 to 12,140) with strategy 5 (over strategy 1);
CAD 8,061 (95% CI: 3,972 to 13,570) with strategy 6 (over strategy 5); and
CAD 8,401 (95% CI: 5,879 to 11,970) with strategy 7 (over strategy 6).

In a budget impact analysis the authors stated that about 20,000 women receive a diagnosis of BC every year in Canada. Of these women, an estimated 4,218 would truly be HER2 positive and about 240 would receive a false-positive result with the base strategy (strategy 1). If the HER2 status of these 240 women was correctly determined and no trastuzumab therapy was given, the cost of this therapy would be reduced by about US$12 million across the country each year.

**Authors' conclusions**
The strategy with the lowest cost-effectiveness ratio for human epidermal growth factor receptor-2 (HER2) gene testing, compared with current practice, was to screen all breast cancer (BC) patients with immunohistochemistry (IHC) and to confirm 2+ and 3+ scores with fluorescence in situ hybridisation (FISH) (i.e. strategy 5).
CRD COMMENTARY - Selection of comparators
The authors provided a justification for the choice of the comparators, which were appropriately selected and described. Several options were considered, based on the two main tests and different criteria for establishing HER2-positive patients. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a systematic review of the literature, the methods and conduct of which were reported in detail. The results of the review and the reasons for excluding primary studies were extensively reported. The approach used to combine the primary estimates was described. The use of a Bayesian meta-analysis allowed the heterogeneity and variability in the primary studies to be taken into account. Some details of the primary studies were also reported. Therefore, the analysis of effectiveness appears to have been carried out credibly.

Validity of estimate of measure of benefit
The summary benefit measure used in the analysis represents a typical outcome of a diagnostic strategy. The impact on a final measure such as life-years was not investigated.

Validity of estimate of costs
Limited information on the analysis of the costs was reported. Only the perspective, the source of the costs, and the price year were reported. A breakdown of the cost categories was not presented, which will limit the possibility of replicating the analysis in other settings. A probabilistic distribution was given to the costs in order to address the issue of uncertainty in the economic estimates.

Other issues
The authors stated that their findings were similar to those found in a previous economic evaluation of diagnosis in women with advanced BC. The issue of the generalisability of the study results to other settings was not explicitly addressed, although a probabilistic sensitivity analysis was performed. The authors noted that one limitation of the analysis was that the study was cross-sectional and did not account for the longitudinal costs and benefits of trastuzumab treatment in eligible women.

Implications of the study
The study results support HER2 testing of all BC patients using IHC, with further confirmation of 2+ and 3+ scores by FISH.

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None stated.

Bibliographic details

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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.

Elkin EB, Weinstein MC, Winer EP, et al. HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-

Norum J, Risberg T, Olsen JA. A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a


Hicks DG, Tubbs RR. Assessment of the HER2 status in breast cancer by fluorescence in situ hybridization: a technical

Indexing Status
Subject indexing assigned by NLM

MeSH
Breast Neoplasms /diagnosis /genetics; Canada; Cost-Benefit Analysis; False Positive Reactions; Female; Genes,
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