Published in final edited form as:

Per Med. 2009 March ; 6(2): 193–215. doi:10.2217/17410541.6.2.193.

Looking back at 10 years of trastuzumab therapy: what is the role of HER2 testing? A systematic review of health economic analyses

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Abstract

Trastuzumab is a targeted therapy for human EGF receptor-2 (HER2)-positive breast cancer. The effectiveness and cost-effectiveness of trastuzumab hinges not only on its clinical efficacy in responding patients, but on the ability to accurately identify appropriate therapeutic candidates. We sought to systematically review the cost-effectiveness of trastuzumab with a focus on the impact of the test(s) used for HER2 diagnosis. Our review included 17 economic evaluations or health technology assessments of trastuzumab therapy or HER2 testing. Trastuzumab was considered cost-effective in all early-stage disease studies, while one author concluded that trastuzumab was not cost-effective for metastatic disease. Only two papers considered the joint effects of test accuracy and sequencing with trastuzumab therapy. These demonstrated that trastuzumab cost-effectiveness is sensitive to HER2-test properties.

Keywords

cost-effectiveness; cost-utility; HER2; herceptin; sensitivity; specificity; targeted therapy; trastuzumab

Breast cancer is the second most common malignancy and the second most common cause of cancer death in women in the USA. The overexpression of human EGF receptor-2 protein (HER2/*neu* or HER2) is prevalent in approximately 20–30% of breast cancer cases [1].

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Financial & competing interests disclosure

This research was funded in part by an award from the Ontario Council on Graduate Studies; it was also funded by two grants from the National Cancer Institute (R01CA101849 and P01CA130818). Deborah Marshall provides ad hoc consulting for i3 Innovus, a global health economics and outcomes research company. Natasha Leighl has previously received honoraria from Hoffmann-La Roche within the last 2 years for continuing medical education lectures that were not related to this project or herceptin. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

HER2 positivity is associated with increased rates of tumor growth and post-surgical disease recurrence, reduced survival and poorer response to standard chemotherapy [1,2].

Trastuzumab (Herceptin®) is a breast cancer therapy specifically targeted for women who overexpress HER2, and may only be provided to patients with evidence of HER2 overexpression [3]. It was first approved for the treatment of HER2-positive metastatic breast cancer in 1998 and has been commercially available for 10 years. Treatment with trastuzumab was linked to the concomitantly approved use of two commercially available tests for HER2 determination in that same year. FISH detects *HER2* gene amplification in paraffin-embedded tissue samples. It is considered the gold standard of HER2 testing but is not perfect; it is quite costly at US\$300–400 per test and requires skilled laboratory personnel [4]. In contrast, immunohistochemistry (IHC) detects HER2 protein expression and has experienced widespread adoption owing to the ease of test conduct and its lower cost (<US\$100). However, IHC is less accurate than FISH due to the susceptibility of proteins to damage when handling paraffin-embedded tissue samples [4]. The interpretation of IHC test results can also be subjective [5], and variations in inter-rater reliability, within and between analytic centers, are well documented [4]. Still, trastuzumab is considered a highly successful example of targeted therapy with worldwide sales in 2007 of US\$1.48 billion over the 12 months ending in March 2008 [101]. Its efficacy was recently summarized in a systematic review of adjuvant therapy, and is associated with a combined 0.62 relative risk of disease-free survival and 0.56 relative risk of overall survival compared with those taking no trastuzumab [6].

Countries with single payer systems, such as the UK, have questioned the value of including trastuzumab in their formularies and decision-makers have demanded a better understanding of the clinical and cost-effectiveness of trastuzumab [7,8]. In Canada, patient demand and political pressure were reported to have pushed forward the approval of trastuzumab in the adjuvant setting, ahead of complete efficacy and safety data reports [9]. Other jurisdictions such as New Zealand [10–14] and the USA [15] have also debated the high cost of trastuzumab therapy. Given this decidedly publicized controversy, this paper examines evidence from cost-effectiveness analyses of trastuzumab treatment using systematic review methods. Cost-effectiveness analysis quantifies the consequences of two or more health interventions in terms of both health outcomes and associated costs in an incremental fashion [16]. However, the effectiveness of trastuzumab as a targeted therapy hinges not only on its clinical efficacy in responding patients, but on the ability of clinicians to accurately identify the appropriate therapeutic candidates. In the case of trastuzumab, it is particularly important to investigate the impact of testing given that two commercially available tests are widely used, allowing different strategies for initial or confirmatory testing. If economic analysis and decision analytic modeling are used to inform decision making, it is important that all relevant variables to that decision are included. For example, the strategy used to identify HER2-positive patients could significantly impact the predicted cost-effectiveness of trastuzumab therapy if the rates of false-positive and false-negative diagnoses are high. However, repeated or confirmatory testing is associated with additional costs that may not justify the incremental gain in accurate diagnoses. Individual models of testing or treatment can isolate the most cost-effective treatment or diagnosis strategies, but will ignore the influence that inaccurate diagnosis has on the incremental cost-effectiveness of therapy. Moreover, decision makers could reach erroneous conclusions if the selection of patients in clinical practice differs from the clinical trial setting. We therefore sought to characterize the cost-effectiveness of trastuzumab in the context of HER2 testing.

Cardiotoxicity has emerged as a rare but serious side-effect in trastuzumab-treated patients [17]. This bears particular clinical importance in the early-stage breast cancer population given that a majority of patients can be expected to experience remission and live full lives.

This issue is also particularly important in light of HER2 testing; an inaccurate test result places false-positive patients at a potentially higher risk of developing cardiotoxicity without actually experiencing any therapeutic benefit. Development of symptomatic or asymptomatic heart failure may also affect health-related quality of life. Therefore, we also examined how cardiotoxicity was addressed in the papers identified in the search.

Methods

Data sources & search strategy

A systematic search was undertaken to identify economic analyses and health technology assessments which included an economic analysis of trastuzumab in the treatment of breast cancer or HER2 testing. The search included publications from up to, and including, October 2008 indexed in BIOSIS, Cochrane, CRD, EconLit, the Excerpta Medica Database (EMBASE), the Health Economic Evaluations Database (HEED), MEDLINE and PubMed electronic databases. The BIOSIS database was included specifically due to its coverage of conference proceedings and abstracts. Our search strategy allowed for the inclusion of analyses conducted prior to the 1998 market approval of trastuzumab in the USA.

The search strategy used three filters to identify relevant publications: economic (cost and cost-analysis, health economics, economic evaluation, pharmacoeconomics, cost-effectiveness, cost-benefit, cost-utility); breast cancer (breast tumor, breast carcinoma, breast neoplasm, mammary AND [tumor or carcinoma or neoplasm or cancer]); and trastuzumab or HER2/*neu* (ERBB2 receptor, epidermal growth factor receptor, herceptin, trastuzumab, HER2). A detailed description of the search strategies used in each database is provided in Appendix 1. Due to the high potential for relevance to this review, abstracts from the San Antonio Breast Cancer Symposium (SABCS) published between 2004 and 2007 were hand-searched. Technology appraisals produced by NICE in the UK were also hand-searched as they were published in the English language from a country where the trastuzumab controversy is well-documented. Finally, the reference lists of key topical reviews and retrieved articles were also hand-searched.

Inclusion criteria

Among the English language publications meeting the search strategy criteria were (a citation was included if it met the following criteria):

- A paper detailing original research, defined as any study reporting findings based on a collection of new data or assembly of existing data in a new context with a new result;
- An analysis – an economic evaluation considering two or more alternatives and presenting results in an incremental ratio (this included cost-minimization, cost-effectiveness, cost-utility, cost-benefit and health technology assessments containing any of the aforementioned analyses);
- A study considering breast cancer as the primary focus;
- An analysis evaluating either HER2 testing strategies (consisting of IHC or FISH tests to identify HER2-overexpressing patients) or trastuzumab treatment of HER2-positive breast cancer.

Conference abstracts and presentations were included in the initial phase of the review and authors were contacted to determine whether fully reported results had been published in a peer-reviewed setting. Only peer-reviewed analyses were included in this review.

Study selection

The abstracts and titles of all search hits were reviewed independently by two reviewers (Ilia Ferrusi and Deborah Marshall), and each potentially relevant article was obtained in full for further review. Consensus was reached via discussion between the two reviewers to obtain agreement on any conflict during the title and abstract review process. Cohen's unweighted κ [18] was calculated to reflect the agreement between reviewers in the title and abstract review process. Selection of studies based on full article review was conducted by a single reviewer (Ilia Ferrusi) and verified by an independent reviewer (Deborah Marshall).

Data abstraction

Data abstraction characterized the following features of each economic evaluation:

- The aim of each economic analysis;
- The method of analysis (i.e., cost-effectiveness, cost-utility, cost-benefit or cost-minimization analysis; Markov, decision-tree model etc.);
- The population of interest;
- Testing and treatment alternatives examined;
- How the potential for cardiotoxicity and its management was modeled;
- The primary findings of the analysis (i.e., incremental cost-effectiveness ratio) converted to 2007 US dollars using annual average exchange rates [102–105] and the medical component of the consumer price index [106];
- Characterization of parameter uncertainty;
- The author's conclusions.

Results

Search results

Search results are shown in Figure 1. The search strategy identified 958 relevant citations from the following databases: Cochrane (13), CRD (27), EMBASE (677), HEED (7), MEDLINE (119) and PubMed (115). Searches conducted in BIOSIS and EconLit were not fruitful. Hand-searching identified an additional ten citations. Among the 968 total hits, 199 were duplications leaving 769 titles and abstracts for review. A total of 75 citations were selected for full review based on the inclusion criteria (Cohen's unweighted $\kappa = 0.86$), and 58 were excluded after further application of the exclusion criteria. This left 17 studies for abstraction. Among those, 12 considered trastuzumab therapy only, two examined HER2 testing and trastuzumab treatment and three considered HER2 testing exclusively.

Several relevant conference abstracts and letters were identified during the literature search, but personal communication with the authors revealed that full analyses were not yet published in a peer-reviewed journal [19–22].

The majority of models were hypothetical cohort simulations (16/17). Models of trastuzumab efficacy were most sensitive to the drug cost (7/14), duration of survival benefit (6/14), discount rate (5/14) and the relative risk reduction (4/14) associated with trastuzumab. In models that considered HER2 testing, we noted that only models considering test-treat scenarios were sensitive to changes in IHC or FISH sensitivity or specificity (2/5). We also rated study quality per the Drummond criteria, which considers a well-defined study question and perspective, comprehensive description of treatment alternatives, evidence of effectiveness, inclusion of all relevant costs and consequences,

appropriate units for costs and consequences, credible valuation of costs and consequences, temporal adjustment, incremental analysis and uncertainty analysis [16]. Each study specified a clear research question, and most (14/17) stated the perspective. While all studies did an excellent job of explaining the treatment alternatives, the reasons for selection and exclusion of other alternatives were generally poorly described. Evidence of effectiveness was only demonstrated in a single study, while the remainder (13/14) employed evidence from randomized, controlled trials to inform trastuzumab efficacy. Elements of costing were difficult to evaluate given the limited space permitted in publications. This element was quite variable in quality, although some authors gave a very thorough and detailed description [23,24]. Discounting was always reported and conducted appropriately per the context of the analysis, although discounting was not warranted in a cross-sectional analysis of trastuzumab and all testing-only analyses. Uncertainty analysis was the most poorly performed or reported element in this review. A total of five of the 17 studies were supported, at least in part, by the drug manufacturer (either Hoffmann-La Roche [NJ, USA] or Genentech [CA, USA]), while the remaining studies were supported by public funding agencies (6/17) or did not report a funding source (6/17).

Metastatic breast cancer

The four metastatic studies were conducted in European (3/4) and North American settings; these are shown in TABLE I. Elkin *et al.* conducted a unique analysis in which the costs and consequences of HER2 testing and treatment were considered [25]. This study examined alternative test–treat strategies whereby patients were tested with IHC only, IHC with FISH confirmation under various circumstances, or FISH alone (see TABLE 1). It demonstrated that the choice of test–treat strategy has a significant impact on the cost–effectiveness of therapy. By quantifying the additional expense of treating false-positive patients and the opportunity lost by not treating false-negative patients, this study presented crucial evidence of test–treat interdependency on cost–effectiveness. The use of testing and the shorter time horizon of the metastatic analysis is likely to have produced the single largest incremental cost–effectiveness ratio (ICER) for trastuzumab therapy identified in this review at US \$153,648–178,231 per quality adjusted life year (QALY) depending on the testing strategy. Norum *et al.* reported a similar ICER (US\$92,584–217,264 per life year saved [LYS]) but concluded that trastuzumab was not cost-effective against standard chemotherapy [26]. The analysis by Poncet *et al.* was informed by a pragmatic evaluation of trastuzumab in French hospitals against matched geographic controls [27]. This study predicted a much lower ICER for trastuzumab of US\$17,861 per LYS over nontrastuzumab in a 2-year time frame. The authors concluded that trastuzumab was an ‘affordable’ treatment option. The NICE technology assessment considered trastuzumab in combination and as monotherapy [28]. The assessment of monotherapy modeled an indirect comparison of trastuzumab with vinorelbine, but NICE reviewers were not confident with these findings given the indirect comparison and small size of the trials.

A single metastatic study considered the consequences of cardiotoxicity [25]. Poncet’s pragmatic analysis [27] accounted for the exclusion of cardiac toxicities, as none were observed in the study population. Norum, Elkin and Poncet *et al.* included the costs of HER2 testing, and Norum and Elkin both estimated trastuzumab benefit from the same clinical trial [29], but only Elkin modeled test characteristics and repeated the testing. Studies of metastatic breast cancer were only sensitive to estimates of trastuzumab effectiveness when testing was not modeled. In fact, Elkin demonstrated that the cost–effectiveness of trastuzumab in metastatic disease was insensitive to treatment benefit when testing was considered; instead, the ICER was predominantly affected by changes in test properties. Moreover, Elkin revealed that a strategy combined of the two different tests

resulted in more accurate patient identification and subsequently better therapeutic outcomes.

Early-stage breast cancer

A total of eight out of the 10 analyses of trastuzumab in early-stage disease concluded that it was a cost-effective treatment option against comparators, as outlined in TABLE 2. Authors were only uncertain of the cost-effectiveness when 52- and 9-week regimens were compared [23,24,30]. These studies suggested that the ICER for trastuzumab was smaller under the 9-week course, but were reluctant to state this conclusively due to the short-term results and the small size of the Finland Herceptin (FinHer) 9-week trial [1]. Trastuzumab benefit was usually assumed to last for 5 years (6/10) following therapy, while others assumed that benefit occurred only for the duration of trial data (2/10) or did not state this assumption (2/10). We found that cost-effectiveness estimates in early-stage disease were more favorable than those in the metastatic breast cancer setting. Some variation was noted across geographical regions; European estimates ranged from \$6,783 per life years gained (LYG) to US\$65,250/QALY, North American estimates ranged from US\$20,065 to US\$43,330/QALY, while all other regions ranged from US\$14,083/QALY to US\$23,309/LYG. When comparing within outcome type, the ranges between estimates were more similar: US\$13,361–65,250/QALY and US\$6,783–51,976/LYG. Some of this variation can be explained by the choice of trastuzumab regimen. Estimates for 52-week therapy ranged from US\$13,361–65,250/QALY, while estimates for the 9-week regimen were US\$6,783/LYG to US\$14,083/QALY.

Very few early-stage studies assessed the impact of HER2 testing strategies on the cost-effectiveness of trastuzumab, despite the greater potential of the patient population and Elkin's previous findings in the metastatic setting. Lidgren and colleagues conducted the only analysis to consider test accuracy and alternate testing strategies, including confirmatory testing (TABLE 2) [31]. Garrison and colleagues [32] attempted to account for test accuracy by assuming that five tests were performed for every HER2-positive patient, and in estimating test costs, that 30% of tests were FISH. While Garrison's model did not actually model test accuracy, Lidgren's examination of various test-treat strategies demonstrated that the choice of test strategy affected the ICER. Lidgren concluded that FISH testing for all patients was the preferred strategy because it resulted in the greatest gain in QALYs while falling below a willingness-to-pay threshold of \$56,116 (€41,500 in 2005). However, if cost-effectiveness is the sole criterion, then confirmatory FISH for IHC2⁺ and 3⁺ would be the strategy of choice. In univariate, sensitivity analysis, Lidgren's model was sensitive to the trastuzumab-related risk reduction of an event, the duration of trastuzumab benefit and future costs. However, in a multivariate, sensitivity analysis, the model was sensitive to changes in the sensitivity and specificity of IHC, and the strategy of initial IHC with FISH confirmation of IHC2⁺ and 3⁺ was the only nondominated strategy.

Modeled rates of cardiac toxicity varied considerably. Some of this variation can be attributed to the different rates observed in the FinHer and Herceptin Adjuvant (HERA) trials; indeed, models considering FinHer and HERA modeled both rates (2/2). The HERA cardiotoxicity rate of 1.67% was most frequently modeled (5/10); others modeled cardiotoxicity at a rate of 2% (2/10) and rates of 2.9 and 3%. Cardiac side effects were modeled using various methods in all early-stage studies. Most analyses modeled the costs of monitoring (9/10) and treatment (10/10) of cardiotoxicity-related events, such as congestive heart failure, based on the rates observed in clinical trials. Three studies modeled actual health states [33–35] associated with cardiotoxicity, and two overtly assumed that death rates due to cardiac toxicity were negligible. Lidgren's analysis of test-treat strategies was the only one to model a utility decrement for patients developing cardiotoxicity.

Testing

The search strategy included economic analyses of HER2 testing outside the context of trastuzumab treatment (TABLE 3). Testing studies tended to vary widely in methodology and alternatives examined, which we believe is related more to regional practice patterns than was observed in analyses of treatment. For example, both Morelle *et al.* [36] and Dranitsaris *et al.* [37] considered the timing of HER2 testing, although each framed the analysis differently. Morelle's motivation behind the choice of alternative strategies and test timing was driven by the inconsistent practice of paraffin-embedding tissue samples under local recommendations at the time [36]. However, Dranitsaris' cost-minimization analysis sought to determine whether HER2 testing at initial diagnosis in stages I, II or III would save the cost of tissue retrieval when testing at the time of metastatic relapse [37]. This indicates that local practice and test availability are key considerations.

The findings of Dendukuri *et al.* echoed Elkin *et al.* [25] and Lidgren *et al.* [31], demonstrating that it was more cost-effective to either use FISH to confirm equivocal and positive IHC tests (see TABLE 4), or to test all patients with FISH up front. This lends support to the use of confirmatory testing for equivocal IHC test results, but does not fully capture the impact of false-negative or -positive results in the consideration of subsequent patient outcomes and treatment.

TABLE 5 provides a summary of test properties modeled in analyses considering testing and treatment. We found that models of therapy did not consider test timing (i.e., to test upon initial diagnosis at early-stage, at the time of metastasis or both). Test timing was probably not a concern in Lidgren's analysis, given the evidence demonstrating concordance between HER2 overexpression in early and later disease stages [31]. There are emerging data that suggest the rate of discordance in HER2 expression between initial diagnosis and relapse may be 6–8% [38,39]. However, the question of test timing may have been relevant in Elkin's analysis of metastatic therapy [25]. Interestingly, repeat IHC testing was not considered in either analysis. Indeed, IHC tests tend to be used as a first-line test owing to the ease of conduct despite well-documented inaccuracies. All studies considered FISH as the only test for confirmatory purposes in all stages of disease. The literature clearly demonstrates that the testing strategy is an influential factor when considering the cost-effectiveness of trastuzumab therapy.

Discussion

We have demonstrated that trastuzumab is widely considered cost-effective across a range of international settings, economic perspectives and clinical settings. Therapy was more cost-effective in early-stage disease due to the substantial gain in life expectancy observed with adjuvant therapy, allowing the additional cost of trastuzumab therapy to be distributed over a larger period. However, studies taking a societal or partial societal perspective, noted that the incremental life years obtained with trastuzumab resulted in additional costs accrued over the lifetime of patients. Studies that concluded that trastuzumab was not cost-effective against comparators were conducted in the metastatic setting. A few studies concluded that trastuzumab might be cost-effective given the difference in costs accrued over 52- and 9-week regimens and the uncertainty around optimal duration of adjuvant trastuzumab therapy. This discrepancy may well be clarified when long-term results of the FinHer and HERA trials become available. Our findings are consistent with a recent systematic review of 52-week trastuzumab in the early-stage setting [40]. McKeage *et al.* reviewed adjuvant trastuzumab and do note the importance of testing, but do not compare findings from studies that consider testing alone. Younis *et al.* also conducted a literature review of trastuzumab economic analyses and emphasized the clinical issues, particularly around concurrent or

consecutive administration and duration of therapy [41]. This review also acknowledged the significance of HER2 testing within the context of trastuzumab treatment.

Testing emerged as an important influence on the cost-effectiveness of therapy. When test-treat strategies were considered in the metastatic or early-stage settings, the message was consistent – the choice of testing strategy can ‘make or break’ the cost-effectiveness of trastuzumab therapy in the adjuvant or metastatic setting. This was linked to the minimization of false-positive and false-negative diagnoses through the use of either alternative test-treat strategies, which favored initial IHC with FISH confirmation of equivocal and positive cases, or the alternative, FISH testing for all patients. The impact of testing was most apparent in Elkin’s metastatic analysis, where trastuzumab was modeled in a population with a much shorter life expectancy. Lidgren’s model was not as sensitive to test properties in univariate analysis, but two-way analysis of IHC sensitivity and specificity did result in the exclusion of the FISH testing alone strategy by dominance. This suggests that the accuracy of diagnostic tests and the resultant mistreatment of false-positive and false-negative patients can have a profound impact on the cost-effectiveness of subsequent therapy. However, it is important to note that all testing studies assumed FISH to be the gold standard despite the fact that its not 100% specific or 100% sensitive. A recent study of central laboratory testing found that FISH and IHC showed 100% and 84.2% sensitivity in predicting patient response to trastuzumab monotherapy [42]. Dendukuri’s systematic review estimated the probability of a positive FISH result within each IHC result category (TABLE 4), and used those probabilities to inform the cost-effectiveness analysis. Similarly, Elkin estimated a weighted average probability of each IHC result category conditional upon FISH results from several studies; this weighted average informed Lidgren’s analysis as well.

The Canadian meta-analysis and cost-effectiveness analysis of HER2 testing strategies [4] echoed the results demonstrated in the treatment setting: initial testing with IHC followed by confirmatory FISH for IHC2⁺ and 3⁺ results was the most cost-effective strategy. Garrison’s analysis provided indirect support for the importance of modeling HER2 test characteristics. His analysis attempted to capture the impact of testing by assuming that five tests must be performed per accurate diagnosis. This approach only captures the cost of additional testing, and does not estimate the impact of improper diagnosis. Moreover, the assumption that one in five tests leads to an accurate diagnosis actually represents population-wide testing, in which optimistic estimates of HER2 prevalence are about 20%. This assumes that all 20% (1/5) of prevalent cases will be identified with a single test, while the remaining 80% of HER2-negative patients (4/5) will also be identified with a single test. Local practice patterns significantly influenced the selection of alternatives and analytic approach in testing-focused analyses, probably accounting for the greater variability in the findings of these studies. Unfortunately, local testing practices were not modeled in conjunction with treatment. Therefore, future analyses would benefit from a more ‘real-world’ reflection of testing practice in a model considering the joint effects of testing and treatment. We also found that IHC was only considered as the first test in all studies evaluating test sequencing; it is likely that this reflects the well-documented inaccuracy of this test.

Cardiac toxicity was considered in all analyses of early-stage disease, and compared to only one analysis of metastatic breast cancer. This probably reflects the better characterization of cardiac toxicity rates and the nature of this side effect after years of careful study. While several analyses captured the economic consequences of cardiac toxicity by modeling the costs associated with monitoring and treatment, only Elkin’s and Lidgren’s test-treat designs were able to capture the consequences of cardiotoxicity in light of the potential for inappropriate treatment. Lidgren’s design further attempted to estimate changes in quality of life due to development of congestive heart failure. Although none of the models included in

this review were sensitive to cardiac toxicity rates or associated costs, it is important to note that the ability to capture all effects of improper treatment can only be achieved through consideration of test–treat strategies. This may become a very important consideration for future targeted therapies.

Any decision regarding the cost–effectiveness of trastuzumab should consider the context of its application in conjunction with the evidence. This systematic summary of the evidence suggests that trastuzumab is a cost-effective treatment option in early-stage breast cancer and may be cost-effective in metastatic disease as well. This conclusion was consistent in early-stage disease across a variety of international viewpoints and economic perspectives. Moreover, all ICER estimates detailed herein, fall within the range of other accepted cancer treatments. Most models were sensitive to the efficacy and cost of trastuzumab therapy. The ability of clinicians to accurately identify appropriate therapeutic candidates using HER2 testing emerged as an important factor in determining the effectiveness and cost–effectiveness of trastuzumab therapy. This review has also demonstrated that the choice of test and test sequencing can influence how cost-effective trastuzumab treatment is by reducing the number of false-positive and false-negative HER2 diagnoses. In this regard, initial testing with IHC followed by FISH confirmation of IHC2⁺ and 3⁺ patients was associated with the lowest ICERs, while FISH testing was also cost-effective. Again, the choice of test–treat strategy in practice must take the local context into account. Nevertheless, these findings are generally consistent with the guidelines for HER2 testing issued by the College of American Pathologists (IL, USA)/American Society for Clinical Oncology (VA, USA) [5]. Future analyses would benefit from further exploration of testing factors, particularly the accuracy of testing in the community versus testing in reference laboratories, and whether trastuzumab is provided within the context of testing guidelines. The impact of these factors has not been examined using decision–analytic modeling. Additional exploration of the recently approved chromogenic *in situ* hybridization (CISH) test [107] for HER2 status determination is also warranted.

Future perspective

As the application of personalized medicine through targeted therapies continues to expand in medicine, it will be imperative to consider test accuracy and sequencing (where more than one test is available) when analyzing the effectiveness and cost–effectiveness of future targeted therapies. Only through careful consideration of test–treat strategies will analysts be able to capture the impact of improper diagnosis as it relates to missed therapeutic opportunities and needless exposure to treatment-related side effects.

Executive summary

The clinical scenario

- Trastuzumab is a targeted therapy for human EGF receptor-2 (HER2)-positive breast cancer.
- HER2-positive patients may be identified using immunohistochemistry or FISH testing; these tests differ in their associated costs, sensitivity and specificity.
- The cost–effectiveness of trastuzumab may therefore be linked to the accuracy of the strategy used to identify patients in addition to the clinical efficacy of the drug.
- We therefore aimed to identify and review the current evidence of cost–effectiveness of trastuzumab and HER2 testing.

Analytic approach

- Systematic review of economic evaluations or health technology assessments (containing economic evaluations) of trastuzumab therapy or HER2 testing.
- Electronic searches conducted in BIOSIS, Cochrane, CRD, EconLit, Excerpta Medica Database (EMBASE), Health Economic Evaluations Database (HEED), MEDLINE and PubMed.
- Data extraction included study aim, analytic methods, patient population, alternatives examined, primary findings, uncertainty analysis and conclusions.

Results

- A total of 17 economic evaluations were included in the review; 12 considered trastuzumab therapy alone, two considered HER2 testing and subsequent trastuzumab treatment and three considered HER2 testing alone.
- All studies examining trastuzumab in the early-stage setting (n = 10) considered trastuzumab to be a cost-effective treatment option.
- One study of trastuzumab in the metastatic setting concluded that trastuzumab was not cost-effective.
- HER2 testing studies tended to focus on test sequencing or timing relative to jurisdictional constraints, and therefore demonstrated greater discordance in their conclusions.
- Studies that examined testing and treatment (n = 2) reported that initial testing with immunohistochemistry followed by confirmatory FISH testing with trastuzumab provided to FISH positive patients, was the most cost-effective test–treat strategy.
- The same conclusion regarding test sequencing was reached in another study that considered testing exclusively.
- Use of FISH testing alone was also cost-effective.
- Studies that considered testing and treatment noted that test characteristics were influential model parameters.
- Costs associated with trastuzumab-induced cardiotoxicity were modeled in all analyses of early-stage disease compared to a single metastatic study.
- The methods used to model cardiotoxicity varied and rarely included health states (3/10) in early-stage disease.

Conclusion

- Trastuzumab was considered cost-effective in the early-stage setting because the significant up-front costs of therapy were offset by the significant gain in life for this patient population.
- Testing is an important factor in determining the cost–effectiveness of trastuzumab therapy and the choice of test strategy is key.
- Initial testing with IHC and confirmatory FISH testing has the lowest incremental cost–effectiveness ratio, as it reduces the excess cost associated with treating false-positive patients while minimizing the lost opportunity of not treating false-negative patients. FISH testing alone is also cost-effective.
- Studies that model test–treat strategies were also able to capture the consequences of improper diagnosis in terms of cardiotoxicity.

- Economic evaluations must consider testing in conjunction with trastuzumab treatment for breast cancer.

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Figure 1. Quorum diagram depicting the flow of studies through the review process
HER2: Human EGF-2 receptor.

Table 1

Summary of economic analyses of trastuzumab in metastatic breast cancer.

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
Poncet <i>et al.</i> (2008) (France) (Hospital) (2 years) (None)	To estimate the ICER of trastuzumab + paclitaxel as first-line CTX compared to standard CTX using data from a local prospective trial	<ul style="list-style-type: none"> Pragmatic open-controlled clinical trial; four hospitals provided trastuzumab + paclitaxel, while six control hospitals provided any CTX without trastuzumab CEA Threshold analysis also conducted 	IHC3+ MBC patients 18 years or older	Trastuzumab + paclitaxel versus range of standard CTX chosen at the investigator's discretion	\$17,861/LYS	Not conducted	Trastuzumab-associated costs seem affordable within the French healthcare system	[27]
Norum <i>et al.</i> (2005) (Norway) (Payer) (Lifetime) (5%)	To compare expected health outcomes of trastuzumab in advanced BC with costs in a model-based CEA	<ul style="list-style-type: none"> CEA Modeling method not stated Costs of cardiac monitoring and cardiologist visits included 	IHC2+ and 3+ MBC patients	Trastuzumab + standard chemotherapy versus standard chemotherapy alone	\$92,584–\$217,264/LYS depending on survival benefit	<ul style="list-style-type: none"> Multivariate examining: HER2 prevalence, IHC costs, outpatient costs, pharmacy administration costs, trastuzumab costs and survival benefit Survival benefit and drug costs impacted CE 	Trastuzumab not CE	[26]
Elkin <i>et al.</i> (2004) (USA) (Not stated, but partial societal costs included) (Lifetime) (3%)	To estimate ICER of alternative testing and trastuzumab treatment strategies in MBC patients	<ul style="list-style-type: none"> CUA Markov model + Monte Carlo simulation Costs of cardiac monitoring and treatment modeled 	Hypothetical cohort of 65-year-old women with newly diagnosed with MBC	<ul style="list-style-type: none"> S1: no testing; CTX for all S2: IHC only; trastuzumab for IHC3+ only S3: IHC only; trastuzumab for IHC2+ and IHC3+ S4: IHC, FISH confirmation of IHC2+ and HC3+; trastuzumab for FISH+ S5: IHC, FISH confirmation of IHC2+; trastuzumab for FISH+ or IHC3+ S6: FISH only; trastuzumab for FISH+ 	<ul style="list-style-type: none"> Only two ICERS were not dominated: S4: \$153,648/ QALY for IHC With FISH confirmation of all positives versus S1; S6: \$178,231/ QALY for initial FISH versus S1 All other strategies not CE 	<ul style="list-style-type: none"> Univariate and multivariate Ranges generally from published literature Only changes in test characteristics influenced results 	It was more CE to use FISH alone or as confirmation of all positive IHC results, rather than using FISH to confirm only weakly positive results or using IHC alone	[25]

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
				– S7: no testing, trastuzumab for all (chemotherapy = paclitaxel)				
NICE (2002) (UK) (NHS) (Lifetime) (3.5%)	To provide guidance on the use of trastuzumab in advanced BC	– CUA within HTA that included data from an unpublished Roche (2000) submission to NICE	MBC patients with IHC3+	– S1: trastuzumab + paclitaxel versus paclitaxel alone – S2: trastuzumab monotherapy versus vinorelbine monotherapy	– S1: \$90,118/ QALY for trastuzumab in combination with paclitaxel – S2: \$18,024/ LYG for trastuzumab as monotherapy	– Methods not described – Sensitive to survival estimates in combination therapy	– Study S1 was well conducted while study S2 was less so – Trastuzumab recommended as a cost-effective treatment option for MBC	[28]

BC: Breast cancer; CE: Cost-effective; CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis; CTX: Chemotherapy; HER2: Human EGF receptor-2; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio; IHC: Immunohistochemistry; LYG: Life years gained; LYS: Life years saved; MBC: Metastatic breast cancer; S1–7: Strategy 1–7; QALY: Quality adjusted life year.

Table 2

Summary of economic analyses of trastuzumab in early-stage breast cancer.

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
Lidgren <i>et al.</i> (2008) (Sweden) (Societal) (Lifetime) (3%)	<ul style="list-style-type: none"> To carry out a CEA of the addition of 1-year of trastuzumab after adjuvant CTX for patients with early BC Five testing strategies examined 	<ul style="list-style-type: none"> CUA Markov model 1-year cycles Monte Carlo simulation Costs of cardiac monitoring and treatment modeled Modeled utility decrement for congestive heart failure 	Hypothetical cohort of 55-year-old women with completely excised BC, treated with at least four cycles of adjuvant CTX	<ul style="list-style-type: none"> S1: no testing, no trastuzumab for all S2: IHC for all, trastuzumab for IHC3+ S3: IHC for all, trastuzumab for IHC2+ and 3+ S4: IHC for all, FISH S5: confirmation of IHC2+ and 3+, trastuzumab for FISH+ S6: FISH for all, trastuzumab for FISH+ 	<ul style="list-style-type: none"> S2 and 3 ruled out by classic or extended dominance ICERs per QALY: S4 over S1: \$48,645; S5 over S4: \$56,077 	<ul style="list-style-type: none"> Univariate analysis of several model parameters $\pm$ 30%; trastuzumab risk reduction, duration of treatment effect and future costs had the greatest impact Multivariate analysis of IHC sensitivity and specificity; ICER of \$5 affected PSA of costs, utilities and trastuzumab efficacy; CEACs provided 	<ul style="list-style-type: none"> 1-year adjuvant trastuzumab is a cost-effective treatment option compared to observation FISH testing for all is a preferable strategy due to higher QALY gains and an ICER below many common WTP thresholds 	[31]
Neyt <i>et al.</i> (2008) (Belgium) (Payer) (Lifetime) (3 and 1.5%)	<ul style="list-style-type: none"> To estimate the cost-effectiveness of 9-week (FinHer)* and 1-year (HERA)[†] trastuzumab therapy compared to standard adjuvant treatment 	<ul style="list-style-type: none"> CEA Budget impact analysis Model type not indicated Incremental risk of heart failure with HERA and FinHer modeled Costs of cardiac monitoring modeled Mean cost of heart failure modeled 	Hypothetical cohort of HER2+ patients	<ul style="list-style-type: none"> S1: 9-week trastuzumab therapy (FinHer) S2: 1-year trastuzumab therapy (HERA) S3: standard adjuvant therapy 	<ul style="list-style-type: none"> S1: \$11,719/LYS over standard therapy for all stages of disease; dominant strategy for stage II and III disease S2: \$54,976/LYS over standard therapy for all stages of disease 	<ul style="list-style-type: none"> Scenario analysis, subgroup analysis and PSA Model most sensitive to the cost discount rate, progression to metastatic disease and trastuzumab efficacy 	<ul style="list-style-type: none"> After accounting for medical, patient, budgetary and societal 'arguments', FinHer regimen is preferred; large-scale multinational trial results are needed to confirm the benefits of the FinHer trial 	[24]
Shiroiwa <i>et al.</i> (2008) (Japan) (Payer) (50 years) (3%)	<ul style="list-style-type: none"> To estimate the cost-effectiveness of adjuvant trastuzumab compared to standard adjuvant CTX based on the results of the HERA[†] trial in a Japanese population 	<ul style="list-style-type: none"> CEA Markov model 1-month cycle Budget impact analysis Rates of severe, a/symptomatic heart failure modeled Cardiotoxicity treatment costs modeled 	Hypothetical cohort of patients, median 49 years old	<ul style="list-style-type: none"> Standard adjuvant CTX versus standard adjuvant CTX with trastuzumab 	<ul style="list-style-type: none"> \$23,309/LYS over standard assuming trastuzumab benefit lasts 5 years 	<ul style="list-style-type: none"> Univariate analysis of all model assumptions PSA of all transition probabilities and costs Model was most sensitive to the duration of trastuzumab efficacy 	<ul style="list-style-type: none"> 1-year trastuzumab therapy is superior to standard adjuvant CTX in terms of cost-effectiveness 	[44]

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
Dedes <i>et al</i> (2007) (Finland) (Provider) (5, 10 and 15 years) (Costs: 3%, outcomes: 0%)	CEA taking into account the long-term clinical benefits and adverse effect profile of trastuzumab based on interim results of HERA [‡] and FinHer [*] trials	<ul style="list-style-type: none"> CEA Markov model 1-year cycle Costs of cardiac monitoring and treatment modeled 	<ul style="list-style-type: none"> Hypothetical cohort of 10,000 post-surgery women aged 50 years ER⁺ patients included (50%) 	Standard adjuvant CTX versus standard adjuvant CTX with trastuzumab	<ul style="list-style-type: none"> HERA: \$25,807/LYS over 15 years FinHer: \$6,783/LYS over 15 years 	<ul style="list-style-type: none"> Univariate analysis of: <ul style="list-style-type: none"> trastuzumab price, yearly cost of MBC, clinical efficacy of trastuzumab, cost of treating local-regional recurrence and discount rate Results sensitive to the price of trastuzumab, trastuzumab efficacy and regimen 	<ul style="list-style-type: none"> Adjuvant trastuzumab may be CE in a long-term perspective based on HERA data FinHer 9-week regimen may save costs compared to no adjuvant trastuzumab 	[30]
Garrison <i>et al</i> (2007) (USA) (Payer, partial societal) (Lifetime, 20 years) (3%)	To develop a model to estimate the incremental CE of adjuvant trastuzumab for early-stage HER2 ⁺ BC in the USA	<ul style="list-style-type: none"> CUA Markov model Costs of cardiac monitoring and treatment of cardiac events modeled Assumed that five tests were performed for every HER2⁺ patient and that 30% of tests were FISH 	<ul style="list-style-type: none"> Hypothetical cohort of 50-year old women HER2⁺ status defined as IHC3⁺ or FISH⁺ 	Adjuvant trastuzumab + standard of care versus standard of care alone	<ul style="list-style-type: none"> Payer perspective: \$27,584/QALY Partial societal perspective: \$28,858/QALY 	<ul style="list-style-type: none"> Univariate and multivariate for all parameters except control arm survival Most sensitive to discount rate, drug price, probability of metastasis and time horizon, but findings are generally robust Best case: \$9,506; worst case: \$72,404 	<ul style="list-style-type: none"> Cost-effective over projected life-time horizon Lower CE ratio than many accepted oncology treatments 	[32]
Kurian <i>et al</i> (2007) (US) (Partial societal) (40 years) (3%)	To analyze costs and health benefits of anthracycline-based trastuzumab regimen with anthracycline and nonanthracycline regimens	<ul style="list-style-type: none"> Markov model 1-month cycle Monte Carlo simulation Cardiotoxicity states modeled Costs of cardiac monitoring and treatment modeled Assumed death due to cardiotoxicity is negligible 	<ul style="list-style-type: none"> Hypothetical cohort of post-surgery women aged 49 years, similar to those enrolled in NSABP B-31, N9831 and BCIRG 006 trials 	<ul style="list-style-type: none"> S1: no trastuzumab S2: trastuzumab with nonanthracycline chemotherapy S3: trastuzumab with anthracycline chemotherapy 	<ul style="list-style-type: none"> S2 regimen dominated S3 regimen ICER of \$43,330/QALY versus S1 	<ul style="list-style-type: none"> Univariate and PSA Varied $\pm$ 20%; results most sensitive to: discount rate, cost of S3, cost of treatment and median survival after recurrence 	<ul style="list-style-type: none"> Trastuzumab in combination with anthracycline CTX is cost-effective and trastuzumab with nonanthracycline CTX is dominated in base case and PSA 	[33]
Liberate <i>et al</i> (2007) (Italy) (Health care system) (15 years) (3%)	To evaluate the CE of 12-month adjuvant trastuzumab in women with HER2 ⁺ early BC	<ul style="list-style-type: none"> CUA Decision tree + Markov model Monte Carlo simulation Joint analysis of NSABP B-31 and N9831 trials Cardiotoxicity states 	<ul style="list-style-type: none"> Hypothetical cohort aged 50 years and clinically similar to those enrolled in NSABP B-31 and N9831 trials 	CTX alone versus weekly trastuzumab for 1 year	<ul style="list-style-type: none"> \$20,095/QALY or $\leq$ \$27,044 (€20,000)/QALY with 91% likelihood in Italian setting \$20,605/QALY $\leq$ \$25,000/QALY with 91% likelihood in USA 	<ul style="list-style-type: none"> PSA for all parameters Multivariate SA with results of HERA[‡] Less CE in elderly, low-risk patients CEAC provided 	<ul style="list-style-type: none"> In the subgroup of patients analyzed, trastuzumab amplified clinical advantage of adjuvant therapy at a cost generally considered appropriate for 	[34]

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
		modeled – Assumed death due to cardiotoxicity is negligible – Costs of cardiac monitoring and treatment modeled			setting		the added value produced – Highly CE in medium to high-risk patients of up to 70 years	
Millar <i>et al</i> (2007) (Australia) (Payer) (51 years) (3%)	To estimate the CE of trastuzumab for early BC from an Australian health system perspective	– CUA – Markov model – 1-year cycle length – Calibrated disease model – Joint analysis of NSABP-31 and HERA* trials to estimate 52-week trastuzumab efficacy – Costs of cardiac monitoring and treatment modeled – Assumed cardiotoxicity cured 3 years after CTX	– Hypothetical cohort aged 50 years at diagnosis – 35- and 65-year-old cohorts examined	9- (FinHer*) and 52- (HERA*) week trastuzumab treatment versus no trastuzumab	– \$18,882/QALY for 52-week regimen – \$14,083/QALY for 9-week regimen (FinHer)	– Univariate and multivariate analysis of: efficacy, recurrence, trastuzumab price, cost of MBC, noncancer illness treatment and duration of trastuzumab benefit – Model was most sensitive to drug cost, duration of treatment benefit and discount rate	– Adjuvant trastuzumab may be CE – Trastuzumab group incurs greater costs due to increased survival later in life – Substantially improved CE with 9-week trastuzumab regimen	[23]
Nortum <i>et al</i> (2007) (Norway) (Societal) (Lifetime) (3%)	To explore CE of including trastuzumab in adjuvant BC treatment in Norway	– Decision-analytic model – Assumed 10% and 20% improvements in survival – Costs of cardiac monitoring and treatment modeled	Hypothetical cohorts of women aged 50–60 years and 60–70 years	Trastuzumab + current treatment (FEC ₁₀₀) versus current treatment alone per November 2005 Norwegian Breast Cancer Group guideline	– 10% survival gain: \$49,668–\$63,480/QALY – 20% survival gain: \$13,361–\$27,171/QALY	– Univariate analysis of all parameters – Changes in LYG, trastuzumab price, production gained and disease recurrence all affected ICER	– Under Norwegian €50,000/LYG threshold for CE, adjuvant trastuzumab appears CE – A minimum of 8% improvement in survival over 10 years is needed for CE	[45]
NICE (2006) (UK) (NHS) (Lifetime) (3.5%)	To provide guidance on the use of trastuzumab in adjuvant therapy	– Manufacturer CUA within HTA – Markov cohort model based on results of HERA* trial – Assumed all patients tested with IHC and FISH for confirmation of IHC2+	– Women who had surgery and completed standard CTX – LVEF >55%	Standard adjuvant CTX (HERA) versus weekly trastuzumab for 1 year	NICE: with cardiotoxicity events in a clinical setting, new ICER ranged from \$31,637–65,250/QALY – \$11,254/QALY proposed by manufacturer is an underestimate	– Univariate, multivariate and PSA – Discount rate, trastuzumab cost and RRR have greatest impact – CEAC provided	– Adjuvant trastuzumab is cost-effective – NICE estimate assumes 100% of relapsed MBC patients are retreated with trastuzumab	[35]

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Author's conclusions	Ref.
		<div><div>– Cardiotoxicity states modeled</div><div>– Cost of cardiac monitoring and management of minor and severe cardiac events modeled</div></div>						

* See ref [1].

[‡] See ref [43].

BC: Breast cancer; BCIRG: Breast Cancer International Research Group; CE: Cost-effectiveness; CEA: Cost-effectiveness analysis; CEAC: Cost-effectiveness acceptability curve; CUA: Cost-utility analysis; CTX: Chemotherapy; ER: Estrogen receptor; FinHer: Finland Herceptin; FEC: 5-fluorouracil, epirubicin and cyclophosphamide; HERA: Herceptin adjuvant; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio; IHC: Immunohistochemistry; LVEF: Left ventricular ejection fraction; LYS: Life years saved; LYG: Life years gained; MBC: Metastatic breast cancer; N9831: North Central Cancer Treatment Intergroup Trial N9831; NSABP: National Surgical Adjuvant Breast and Bowel Project; S1-5: Stragety 1-5; SA: Sensitivity analysis; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year; WTP: Willingness to pay

Table 3

Summary of economic analyses considering HER2 testing only.

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Conclusions	Ref.
Dendukuri <i>et al</i> (2007) (Canada) (3rd party payer) (Cross-sectional) (N/A)	Meta-analysis of studies published between 2000 and 2005, to estimate the percentage of HER2 ⁺ patients whose status was accurately determined by IHC and CEA of seven alternative strategies to test HER2 status	<ul style="list-style-type: none"> – Cross-sectional Bayesian meta-analysis to estimate the distribution of IHC scores and the probability of a positive FISH result in each IHC score category from a systematic review of IHC and FISH studies – CEA of screening strategies 	Hypothetical cohort of BC patients tested with assays licensed by Health Canada	<ul style="list-style-type: none"> – S1: IHC + FISH confirmation of IHC2⁺; HER2⁺ defined as IHC3⁺ or FISH⁺ (base case) – S2: IHC only; HER2⁺ defined as IHC2⁺ or 3⁺ – S3: IHC only; HER2⁺ defined as IHC3⁺ – S4: IHC + FISH confirmation of IHC1⁺ or 2⁺; HER2⁺ defined as IHC3⁺ or FISH⁺ – S5: IHC + FISH confirmation of IHC2⁺ and 3⁺; HER2⁺ defined as FISH⁺ – S6: IHC + FISH confirmation of IHC1⁺, 2⁺ and 3⁺; HER2⁺ defined as FISH⁺ – S7: FISH only 	<p>Strategies 2, 3 and 4 were ruled out by classic or extended dominance. The incremental costs per accurately determined HER2 status (ICERs) for the remaining nondominated strategies were:</p> <p>S5 over S1: \$5,686; S6 over S5: \$7,423; S7 over S6: \$7,736.</p>	<ul style="list-style-type: none"> – PSA performed by varying all parameters of the economic evaluation – Simultaneously over plausible ranges – The cost of FISH did effect CEA results 	The strategy with the lowest ICER compared to current practice is to screen all BC patients with IHC plus confirmation of IHC2 ⁺ and 3 ⁺ by FISH (S5)	[4]
Morelle <i>et al</i> (2006) (France) (Not stated) (20 years after first diagnosis) (0%)	To examine the CE of five different testing strategies to direct trastuzumab therapy at metastatic relapse in secondary care	<ul style="list-style-type: none"> – CEA – A decision tree modeled the five diagnostic strategies in a cohort of 10,000 patients. Test characteristics were adapted to French context using local laboratory testing guidelines, local fixatives and the accessibility of paraffin-embedded samples at time of relapse. 	Hypothetical cohort of 10,000 infiltrating BC patients were used in the model. A prospective, multicentric study followed 2045 invasive BC patients from initial diagnosis to ascertain local diagnostic test characteristics	<ul style="list-style-type: none"> – S1: IHC at first MBC relapse (base case) – S2: systematic IHC at diagnosis – S3: FISH at first MBC relapse when IHC is not possible due to fixation – S4: FISH at first MBC relapse + IHC to clarify status of IHC2⁺ – S5: FISH at first MBC relapse + IHC to clarify the status of IHC2⁺ and 3⁺ – IHC was only used in S4 and S5 when the tumor was fixed in formalin 	<ul style="list-style-type: none"> – All strategies were more expensive but at least as effective, in comparison with the base case – ICER per criterion 1: S4 \$839/false-negative avoided – ICER per criterion 2: S5 \$5,491/false-positive avoided 	<ul style="list-style-type: none"> – Methods unclear; authors varied the discount rate (3, 5%), FISH test cost and proportion of samples fixed in formalin – Results not sensitive to any of above 	<ul style="list-style-type: none"> – Given that false-negatives were the only cause of patients with HER2 amplified tumor not being given trastuzumab at the first metastatic relapse, efficient strategies' were S1 and S4 – Determining HER2 status at diagnosis, as an indication for trastuzumab at metastatic relapse, incurs substantial incremental costs which do not 	[36]

Study (Country) (Perspective) (Time horizon) (Discount rate)	Study aim	Methods	Population	Alternatives examined	Results (2007 US\$)	Sensitivity analysis	Conclusions	Ref.
Dranitsaris <i>et al</i> (2003) (Canada) (payer) (5 years) (3%)	To assess the economic benefit of undertaking HER2 testing at diagnosis or disease recurrence	<ul style="list-style-type: none"> - CMA - Decision tree - Trastuzumab treatment not modeled - IHC3+ for HER2+ with FISH; FISH+ for HER2+ - Likelihood of disease recurrence at 5 years modeled 	<ul style="list-style-type: none"> - Pre- and post-menopausal women diagnosed with stages I-III BC - Stage IV not included as HER2 diagnosis is standard of care at that stage 	<ul style="list-style-type: none"> - S1: HER2 test at diagnosis (stages I-III) - S2: HER2 test at MBC recurrence (base case) 	ICERS of testing at stages I-III versus MBC recurrence: - I: \$30,369 additional costs - II: \$66,296 savings - III: \$53,616 savings Net savings of \$89,543 if tested at first diagnosis versus recurrence	One-way analysis of incidence of inconclusive results, effect of various adjuvant CTX protocols on survival and 5 year recurrence rates	HER2 testing of all newly diagnosed stage I-III BC patients would result in cost-savings for the Canadian healthcare system	[37]

BC: Breast cancer; CE: Cost-effectiveness; CEA: Cost-effectiveness analysis; CMA: Cost-minimization analysis; CTX: Chemotherapy; HER2: Human EGF receptor-2; ICER: Incremental cost-effectiveness ratio; IHC: Immunohistochemistry; MBC: Metastatic breast cancer; PSA: Probabilistic sensitivity analysis; S1-7: Strategy 1-7.

Table 4

Description of HER2 status determination by immunohistochemistry testing.

IHC grade	Description
0	Negative test; no staining
1 ⁺	Negative test; weak, incomplete membrane staining in any proportion of tumor cells
2 ⁺	Equivocal test; complete membrane staining that is either nonuniform or weak in intensity but with obvious circumferential distribution in at least 10% of cells
3 ⁺	Positive test; uniform intense membrane staining of >30% of invasive tumor cells

IHC: Immunohistochemistry; HER2: Human EGF receptor-2.

Table 5

Summary of economic analyses of trastuzumab considering the choice or sequence of HER2 test used to identify potential responders

Author, date (Country) (Perspective) (Time horizon) (Discount rate)	How were test properties modeled?	Was test timing considered?	Were alternative test sequences considered?	What impact did test properties have on the results?	Ref.
Lidgren <i>et al.</i> (2008) (Sweden) (Societal) (lifetime) (3%)	Test properties were modeled according to Elkin <i>et al.</i> *	No; only testing at diagnosis of early-stage BC was considered	Yes; authors considered primary testing with IHC followed by FISH confirmation under various circumstances, or FISH testing alone (see TABLE 2 for test-treat strategies)	The CE of trastuzumab therapy was highly dependent on testing strategy; trastuzumab therapy was only CE in early BC if FISH testing was used to confirm all IHC-positive patients (\$36,112/QALY), or if FISH was the only test used (\$41,629/QALY)	[31]
Elkin <i>et al.</i> (2004) (USA) (Not stated) (Lifetime) (3%)	A total of ten studies of IHC and FISH test properties were reviewed and weighted averages were calculated to inform model transition probabilities	No; only testing at MBC was considered	Yes; authors considered primary testing with IHC followed by FISH confirmation under various circumstances, or FISH testing alone (see TABLE 1 for test-treat strategies)	<ul style="list-style-type: none"> - Testing had an important impact on the cost-effectiveness of trastuzumab therapy; Strategy 4 (IHC with FISH confirmation of IHC2+ and 3+; trastuzumab for FISH+) has an ICER of \$153,648/QALY, while Strategy 6 (FISH only; trastuzumab for FISH+) had an ICER of \$178,231/QALY - The authors concluded that society must be willing to pay for CE testing strategies if it is willing to pay for trastuzumab at all. 	[25]

* See ref. [25].

BC: Breast cancer; CE: Cost-effectiveness; HER2: Human EGF receptor-2; ICER: Incremental cost-effectiveness ratio; IHC: Immunohistochemistry; MBC: Metastatic breast cancer; QALY: Quality adjusted life year.

Appendix 1

Search strategies.

No.	Database: BIOSIS previews <i>Search history</i>
1	TS=((Economic Impact OR Economic Value OR Pharmacoeconomics OR Health Care Cost OR Economic Factors OR Economics OR Cost Analysis OR Cost OR Economic Analysis OR Cost-Effectiveness OR Costs OR "Quality of Life" OR Health Care Costs OR Medical Costs OR Quality-of-life).mp.)
2	TS=((Trastuzumab or Herceptin or Epidermal Growth Factor Receptor 2 or her2 or Oncogene Neu or erbB-2 Receptor).mp.)
3	TS=(Trastuzumab or Herceptin or Epidermal Growth Factor Receptor 2 or her2 or Oncogene Neu or erbB-2 Receptor)
4	TS=(((((Breast or Mammary) and (Neoplasm* or Cancer* or Carcinoma* or Tumour* or Tumor* or Metastas*)) or (Breast Neoplasm* or Breast Cancer* or Breast Carcinoma*))).mp.)
5	TS=(((((Breast or Mammary) and (Neoplasm* or Cancer* or Carcinoma* or Tumour* or Tumor* or Metastas*)) or (Breast Neoplasm* or Breast Cancer* or Breast Carcinoma*)))
6	#4 AND #2 AND #1
7	#5 AND #3 AND #1
<i>DocType: All document types; LitType: All literature types; Language: English; Taxa Notes: All Taxa Notes.</i>	
No.	Database: Cochrane via Wiley (Cochrane reviews, technology assessments, NHS Economic evaluation database [NHS EED]) <i>Search history</i>
1	MeSH descriptor Breast Neoplasms explode all trees
2	((breast* or mammar*) near/3 (neoplasm* or metastas* or carcinoma* or tumour* or tumor* or cancer*)):ti,ab,kw
3	(#1 OR #2)
4	(trastuzumab* or herceptin*):ti,ab,kw
5	(cost effective* or cost benefit* or cost utility*):ti,ab,kw
6	MeSH descriptor Costs and Cost Analysis explode all trees
7	MeSH descriptor Economics, Pharmaceutical explode all trees
8	(#5 OR #6 OR #7)
9	(#3 AND #4 AND #8)
No.	Database: Centre for reviews & dissemination (Database of Abstracts of Reviews of Effects [DARE], NHS EED, Health Technology Assessment Database [HTA]) <i>Search history</i>
1	MeSH Breast Neoplasms
2	MeSH Breast
3	mammary
4	#2 OR # 3
5	MeSH Neoplasms
6	metastas*
7	MeSH Carcinoma
8	carcinoma*
9	tumour*
10	cancer*
11	tumor*
12	neoplasm*

No.	Database: BIOSIS previews
	<i>Search history</i>
13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	breast OR mammary NEAR neoplasm OR tumor OR tumour OR cancer OR carcinoma
15	#4 and #13
16	#1 or #15
17	#1 or #14
18	trastuzumab
19	herceptin
20	MeSH Receptor, erbB-2 EXPLODE 2
21	her2
22	or/21-24
23	#18 or # 22 or # 23 or #21
24	#16 and #23
25	#17 and #23
26	#17 or #16
27	#26 and #23
28	MeSH Costs and Cost Analysis EXPLODE 1
29	(value AND of AND life OR economics, AND medical OR economics, AND pharmaceutical OR models, AND economic OR markov AND chains OR monte AND carlo AND method OR uncertainty) AND .sh.
30	(“value of life” OR economics, AND medical OR economics, AND pharmaceutical OR models, AND economic OR “markov chains” OR “monte carlo method” OR uncertainty) AND .sh.
31	“value of life” OR economics
32	economics
33	“medical economics”
34	“markov chain”
35	“markov chain*”
36	“monte carlo”
37	uncertainty
38	(quality NEAR life) OR (willingness NEAR pay) OR (quality NEAR “adjusted life year*”) OR (sensitivity NEAR analysis)
39	QOL OR QOLY* OR HRQOL OR QALY*
40	decision NEAR tree* OR analy* OR model*
41	MeSH Cost-Benefit Analysis EXPLODE 1
42	MeSH Economics, Pharmaceutical EXPLODE 1
43	#28 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
44	#24 and #43
45	#25 and #43
46	english:la
47	#44 and #46
48	#45 and #46
No.	Database: EconLit (earliest to 2008)
	<i>Search history</i>

No.	Database: BIOSIS previews
	<i>Search history</i>
1	((Economic Impact) or (Economic Value) or Pharmacoeconomic*) or ((Health Care Cost) or (Economic Factor*) or Economic*) or ((Cost Analysis) or Cost* or (Economic Analysis)) or (Cost-Effectiveness or (Quality of Life) or (Health Care Cost*)) or ((Medical Cost*) or Quality-of-life or Cost-Benefit) or (discount* or HRQOL or QOL) or (QALY* or (sensitivity analysis) or (Health Economic*)) or ((Economic Evaluation) or (willingness to pay))
2	(breast cancer) or (breast carcinoma) or (breast tumour)
3	(herceptin or trastuzumab or (epidermal growth factor receptor 2)) or (erbB-2 or Her2 or Her2/neu) or ((erbB-2 receptor\$) or (neu oncogene))
4	#1 and #2 and #3
	<i>Terms searched 'anywhere'.</i>
No.	Database: The Excerpta Medica Database (EMBASE)
	<i>Search history</i>
1	exp Breast Tumor/
2	((breast\$ or mammar\$) adj3 (neoplasm\$ or metastas\$ or carcinoma\$ or tumour\$ or tumor\$)).ti,ab.
3	Trastuzumab/ or 180288-69-1.rn.
4	herceptin\$.ti,ab,tn.
5	(cost effective\$ or cost benefit\$ or cost utility\$).ti,ab.
6	exp Health economics/ or exp Economic Evaluation/ or exp Pharmacoeconomics/ or exp Economic Aspect/ or pe.fs.
7	(1 or 2) and (3 or 4) and (6 or 5)
8	limit 7 to english language
No.	Database: Health Economic Evaluations Database ([HEED] online) 2008
	<i>Search history</i>
1	((breast* OR mammar*) AND (neoplasm* OR metastas* OR carcinoma* OR tumour* OR tumor*)) AND (Trastuzumab OR herceptin); all fields
No.	Database: Ovid MEDLINE®in-process & other nonindexed citations & Ovid MEDLINE® 1950 to present
	<i>Search history</i>
1	exp "Costs and Cost Analysis"/
2	(value of life or economics, medical or economics, pharmaceutical or models, economic or markov chains or monte carlo method or uncertainty).sh.
3	economics.fs.
4	(quality of life or quality-adjusted life years).sh.
5	economics.sh.
6	((econom\$ or cost or costly or costing or costed or prices or pricing or discount or discounts or discounted or discounting or budget\$ or afford\$ or pharmacoeconomic\$ or pharmaco) adj1 economic\$).ti,ab.
7	(decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.
8	((value or values or valuation) adj2 (money or monetary or life or lives)).ti,ab.
9	(QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab.
10	((quality adj1 life) or (wilingness adj1 pay) or (quality adj1 adjusted life year\$) or (sensitivity adj analysis) or quality adjusted life expectanc\$).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	*Breast Neoplasms/
13	*Breast/
14	mammary.mp.
15	13 or 14

No.	Database: BIOSIS previews
	Search history
16	*Neoplasms/
17	metastas\$.mp.
18	*Carcinoma/
19	tumour\$.mp. [mp=ti, ot, ab, nm, hw]
20	cancer\$.mp. [mp=ti, ot, ab, nm, hw]
21	tumor\$.mp. [mp=ti, ot, ab, nm, hw]
22	neoplasm\$.mp. [mp=ti, ot, ab, nm, hw]
23	neoplasm\$.mp. [mp=ti, ot, ab, nm, hw]
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	15 and 24
26	12 or 25
27	trastuzumab.mp. [mp=ti, ot, ab, nm, hw]
28	herceptin.mp. [mp=ti, ot, ab, nm, hw]
29	Receptor, erbB-2/
30	Receptor, Epidermal Growth Factor/
31	her2.mp.
32	27 or 28 or 29 or 30 or 31
33	26 and 32
34	11 and 33
35	limit 34 to english language
No.	Database: PubMed
	Search history
23	Search ("1"[Publication Date] : "2008/10/31"[Publication Date]) AND (#22)
22	Search #21 Limits: English
21	Search #20 Limits: Humans
20	Search #19 and #16 and #7
19	Search #17 or #18
18	Search "receptor, erbB 2"[MeSH Terms]
17	Search herceptin or trastuzumab or her2[Text Word]
16	Search "breast neoplasms"[MeSH Terms] or #15
15	Search #10 and #14
14	Search #11 or #12 or #13
13	Search metastas* OR tumour* OR tumor* OR cancer* OR neoplasm* OR carcinoma*[Text Word]
12	Search "carcinoma"[MeSH Terms]
11	Search "neoplasms"[MeSH Terms]
10	Search #8 or #9
9	Search mammary[Text Word]
8	Search "breast"[MeSH Terms]
7	Search #1 or #2 or #3 or #4 or #5 or #6

No.	Database: BIOSIS previews <i>Search history</i>
6	Search QOL or HRQOL or QALY*
5	Search cost effectiveness or cost benefit or cost utility
4	Search “cost*effectiveness” or “cost*benefit” or “cost*utility”
3	Search “value of life” or economics or “medical economic*” or “pharmaceutical model*” or economic or “markov chain*” or “monte carlo” or “uncertainty analys*”[Text Word]
2	Search “quality of life”[All Fields] AND “quality adjusted life”[All Fields] AND “health related quality of life”[All Fields]
1	Search “cost benefit analysis”[MeSH Terms] OR “cost control”[MeSH Terms] OR “cost of illness”[MeSH Terms] OR “cost savings”[MeSH Terms] OR “costs and cost analysis”[MeSH Terms].