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EPIDEMIOLOGY

Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost–effectiveness analysis of different predictive assay strategies

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Abstract Trastuzumab has conferred significant clinical benefits in HER-2-positive breast carcinomas. HER-2 status is determined by immunohistochemistry (IHC) and/or fluorescence in situ hybridisation (FISH), but appropriate assessment of HER2 status remains subject to considerable debate. Data on the health economic impact of HER-2 test strategies are limited. A life-long Markov state transition model was used to assess costs and effectiveness of HER-2 assay strategies (based on IHC, FISH, both combined or FISH confirmation of IHC2+) for a hypothetical cohort of early breast cancer patients from the perspective of the Swiss health system. We compared clinically relevant strategies of predictive testing and subsequent trastuzumab treatment of HER-2-positive patients only. FISH testing was the most cost–effective strategy with an incremental cost–effectiveness ratio of €12,245 per additional quality-adjusted life-year (QALY) gained, compared to no trastuzumab treatment. The next best strategy was parallel IHC and FISH, with costs of €400,154/QALY gained compared to FISH alone. FISH as primary HER-2 testing modality remained the preferred option in deterministic and probabilistic sensitivity analysis. Predictive testing to identify adjuvant breast cancer patients who benefit from trastuzumab treatment is a clinical and economic necessity. Our model identifies FISH as the most cost–effective approach.

Keywords Cost–effectiveness · Adjuvant · Breast cancer · Predictive tests · Trastuzumab

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Introduction

Human epidermal growth factor receptor 2 (HER-2/neu, hereafter referred to as HER-2), is a transmembrane receptor tyrosine kinase expressed in epithelial cells including the breast. Approximately 20–25% of breast cancers patients show HER-2 protein overexpression and/or HER-2 oncogene amplification [1–4]. Both are markers for aggressive disease [5, 6] and the molecular targets of trastuzumab (Herceptin®, Roche Pharma, Switzerland) and lapatinib (GlaxoSmithKline, London, UK). Trastuzumab, a humanized monoclonal antibody, is used successfully in the therapy of HER-2-positive invasive breast carcinomas [7–10]. In the adjuvant setting, it substantially reduces recurrence rates and overall mortality in combination with chemotherapy [11–14]. There is now consensus on a life-prolonging effect in metastatic, early node-positive and node-negative HER-2 positive invasive breast cancers. Trastuzumab has also dramatically increased treatment costs [15].

Gene amplification and protein overexpression can be identified by immunohistochemistry (IHC) or fluorescence in situ hybridisation (FISH), respectively [7]. Despite a long history of predictive HER-2 testing in breast cancer

patients, there is still no consensus on the most appropriate testing approach. Selection criteria include accuracy, reproducibility and precision but also cost [16]. Published results comparing HER-2 status determined by FISH or IHC in formalin fixed, paraffin embedded (FFPE) tissues are contradictory. Standardization of IHC in FFPE tissue samples is difficult due to pre-analytical problems and high subjectivity in interpretation. Concordance rates range between 80 and 90%, depending on the methodology, instrumentation and experience of the laboratories carrying out the tests [17]. This implies significant numbers of false negative test results, which may have dramatic consequences for the affected patients [18]. Current American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) guidelines recommend the use of IHC for initial evaluation of HER-2 status but initial use of FISH is also discussed [19]. Arguments for FISH include better reproducibility and accuracy, although FISH is more expensive than IHC [20].

Expensive new cancer therapies are usually regarded as appropriate if trial data show clinically relevant improvements [21, 22]. Several publications have addressed the cost–effectiveness of trastuzumab in HER-2-positive breast cancer patients [23–25]. Markov models have been used to evaluate the cost–effectiveness of HER-2 testing strategies in the adjuvant and metastatic settings [26–28] but comprehensive cost–effectiveness analysis comparing alternative assay strategies are limited.

Using a life-long Markov state transition model, we evaluated the health economic impact of trastuzumab treatment of adjuvant breast cancer in Switzerland and the influence of different HER-2-testing strategies (IHC, FISH, both combined or FISH confirmation of IHC2+ status) [29]. The model can also be used for similar decision problems arising with other predictive tests in pathology.

Methodology

Overview of breast cancer disease model

A Markov model with a cycle length of 1 year was used to reproduce the disease process and economic consequences. Economic endpoints were the costs associated with each strategy. Effectiveness was assessed as quality-adjusted life-years (QALYs). Incremental cost–effectiveness ratios (ICERs) were planned to be calculated if applicable, i.e. in non-dominant situations. The time horizon of the analysis was life-long (50 years).

Costs were assessed from the perspective of the Swiss health care system. Consequently, non-medical and indirect costs were disregarded. Direct medical costs included drug costs, costs for predictive testing (where applicable), gynaecological examinations, diagnostic procedures and hospitalization (Table 3). Costs and effects were discounted at 3% [21]. Costs are shown in Euros (€). In March 2009, €1.00 equalled Swiss Francs (CHF) 1.50.

Patient populations studied

The model assessed a hypothetical cohort of female breast cancer patients aged 50 years, of whom 20% were HER-2-positive. The HER-2-positive patient population was defined by the eligibility criteria of the HERA trial [12]. In brief, patients had centrally validated HER-2-positive early stage invasive breast cancer with either node-positive or node-negative disease status (disease-free status). They completed local regional therapy and at least four courses of predefined standard adjuvant or neoadjuvant chemotherapy. Eligibility criteria for disease-free HER-2-negative patients were WHO performance status 0–1 with a confirmed HER-2-negative status. They had undergone breast surgery with axillary-node dissection or sentinel-node biopsy for invasive breast carcinoma [11].

Strategies compared

We assessed the following testing strategies: IHC alone, FISH alone, parallel IHC and FISH, sequential testing with FISH confirmation of IHC2+. Patients with positive IHC (2+ or 3+) and/or positive FISH received adjuvant trastuzumab treatment. Patients with no or a very low HER-2 expression levels (IHC 0 or 1+ or negative FISH) received standard treatment. Costs and effects of no trastuzumab treatment and a strategy of trastuzumab treatment of all patients with no predictive testing were used as reference values. The latter does not represent a clinically relevant option but was added to demonstrate the overall magnitude of the benefits achieved with predictive testing.

False positive and false negative test results lead to inadequate treatment of the affected patients. Sensitivity and specificity of IHC and FISH was assessed from published literature [30]. Sensitivity and specificity of the parallel testing strategy were calculated according to the "believe-the-positive" approach, i.e. the combined result was positive if one test indicated a positive result. Both tests were regarded as conditional independent (Table 1) [31].

Disease stages

The simulated population moved through distinct disease states, namely, disease-free survival, local recurrence, regional recurrence, metastatic disease and death (Fig. 1).

Table 1 Testing strategies and test characteristics

	Test strategy	Test	Cut-off for HER-2 positivity	Sensitivity (±95% CI)	Specificity (±95% CI)	Ref.
1.	All	IHC	2+ and 3+	0.91 (0.88–0.94)	0.75 (0.72–0.77)	[30]
2.	All	FISH	≥2.0[b]	0.98 (0.87–1.0)	0.9 (0.82–0.95)	[30]
3.	All, parallel testing[a]	IHC	2+ and 3+	0.9982 (0.9844–1.0)	0.675 (0.5904–0.7515)	[30, 31]
		FISH[a]	≥2.0[b]			
4.	First all	IHC	3+	0.905 (0.893–0.933)	0.987 (0.976–0.992)	[17]
	Second: If IHC2+	FISH	≥2.0[b]			
5.	No test, all trastuzumab					
6.	No test, no trastuzumab[c]					

NB: sensitivity and specificity of the combined tests remain in sequential or parallel testing order the same [58]

[a] *BTP* belief the positive. 1 positive test is enough for + results. Negative result if both test −

[b] Ratio HER-2/CEP17 signal

[c] Reference strategy

Local recurrence was defined according to the American Joint Committee on Cancer (AJCC) as isolated ipsilateral in-breast cancer recurrence after breast-conserving therapy of a stage 0–III breast carcinoma [32]. Regional recurrence included patients with cancer recurrence in the axilla with or without in-breast recurrence after breast-conserving therapy of stage 0–II breast carcinoma [33]. Metastatic disease implied women with progressive metastatic breast cancer without previous chemotherapy treatment for metastatic disease [7].

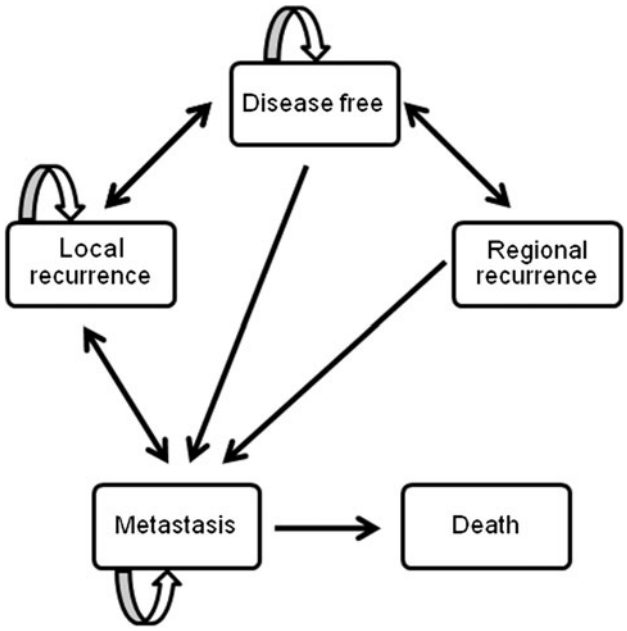

Fig. 1 Markov model starting with the disease-free health state. Diagram of model structure, comprising five health states: disease free, local recurrence, regional recurrence, metastasis (distant recurrence) and death

Clinical data sources

Clinical model inputs, namely, state transition probabilities for patients with HER-2-positive and HER-2-negative breast carcinomas (Table 2), were derived from the literature. We disregarded phase II trials, studies only presented as conference abstracts, studies with very low sample size, and studies with insufficient information for being used in our model. Efficacy results from studies of monoclonal antibodies targeted against HER-2 other than trastuzumab were not taken into account. Modelling of disease-free survival was based on HERA [12]. We assumed that HER-2-positive individuals with trastuzumab treatment would have the same transition probabilities as the patients receiving adjuvant trastuzumab in HERA. The recurrence rates seen in the HERA comparator group were applied to our HER-2-positive group without trastuzumab treatment. In the HER-2-negative situation, transition probabilities were assumed to be unaffected by trastuzumab treatment [11].

The future history of patients entering the local and regional recurrence states was derived from published retrospective reviews of medical records and was not dependent on HER-2 status [34, 35]. One-year survival rates in metastatic breast cancer patients stemmed from two phase III trials of standard treatment plus trastuzumab versus best supportive care [7, 36]. It was assumed that after 5 years, the risk of reappearing metastasis would decline by 10% annually [37].

Overall mortality rates of the Swiss female population was taken from published Swiss life tables [38].

Utilities

Utilities were based on a study using the self-administered EQ-5D questionnaire [39]. Responses were combined with

Table 2 Annual transition probabilities

HER-2 status Trastuzumab		+ Yes	+ No	− Yes	− No	Ref.
Disease state	Transition to					
Disease free	Disease free	0.934	0.879	0.975	0.975	[11, 12, 59]
	Local recurrence	0.01	0.022	0.004	0.004	
	Regional recurrence	0.006	0.008	0.004	0.004	
	Metastatic disease[a]	0.05	0.091	0.017	0.017	
Local recurrence	Disease free	0.878	0.878	0.878	0.878	[35]
	Local recurrence	0.028	0.028	0.028	0.028	
	Metastatic disease[a]	0.094	0.094	0.094	0.094	
Regional recurrence	Disease free	0.895	0.895	0.895	0.895	[34]
	Metastatic disease[a]	0.105	0.105	0.105	0.105	
Metastatic disease	Metastatic disease[a]	0.78	0.67	0.788	0.788	[7, 36]
	Death	0.22	0.33	0.212	0.212	

[a] Transition probabilities only shown for first 5 years. In the subsequent cycles, the model assumed a declined recurrence rate of 10% after each cycle

visual analogue scale-based population preference values. Utilities per disease stage were: first year after primary breast cancer, 0.696 (95% confidence interval (CI) 0.634–0.725); first year after recurrence, 0.779 (CI 0.700–0.849); second and subsequent years after primary breast cancer/recurrence, 0.779 (CI 0.745–0.811); metastatic disease state, 0.685 (CI 0.620–0.735) [39].

Medical resource use

HER-2-positive group

Disease-free status

HER-2-positive patients received trastuzumab after excision of early stage breast cancer and completion of chemotherapy. Trastuzumab dosing and planned treatment duration corresponded to the regimen used in HERA, with a 8 mg/kg loading dose and 6 mg/kg dose every 3 weeks during 1 year [12]. We assumed that 15% of the patients would receive an additional 150 mg vial due to higher weight (>74 kg). Echocardiography was performed quarterly during trastuzumab treatment [12]. All patients received gynaecological examinations [40]. During 5 years, half of HER-2-positive patients were treated with aromatase inhibitors (letrozol 2.5 mg/day or anastrozol 1 mg/day) [12].

Local and regional recurrence

Mammography, gynaecological examinations, diagnostic ultrasound, radiotherapy and surgery including hospitalization, and aromatase inhibitors (as described above) were used in these patients [25]. Local recurrence was assumed to be localized in the thoracic wall (40%) or in the breast (60%) [41].

Metastatic state

Chemotherapy, radiotherapy, diagnostic ultrasound and palliative surgery including hospitalization, and aromatase inhibitors (as described above) were used in these patients [25]. We assumed that 80% of the patients responded to trastuzumab treatment in the first-line therapy and that half of these patients were re-treated with trastuzumab for an additional year when metastases were diagnosed [7].

Untested group

Untested patients all received trastuzumab treatment as described for the HER-2-positive group. Aromatase inhibitor was given to 70% of these patients for 5 years [12, 42, 43].

HER-2-negative group

Patients with no HER-2 overexpression did not receive trastuzumab but were otherwise treated as described for the HER-2-positive group. During 5 years, 70% were assumed to receive hormone therapy [42, 43].

Unit costs

Unit costs (Table 3) for laboratory and diagnostic interventions were derived from the official Swiss tariff list [44]. Hospital case-based flat rates and day rates were

based on Swiss Diagnosis Related Groups (DRGs) [45]. Length of hospital stay was based on data provided by the Swiss Federal Statistic Office [46]. Drug costs based on official Swiss pharmacy prices [47]. Costs of diagnostics and therapeutic interventions in each state were assessed on this basis. However, as the adjuvant therapy was assumed to be the same for all patients, costs of initial treatment (primary breast surgery and adjuvant chemotherapy) were not included.

Sensitivity analysis

Deterministic sensitivity analysis tested the precision and robustness of the results. Parameters with a direct impact on incremental costs were varied by ±30% (price of trastuzumab, price of predictive tests, costs of local and regional recurrence and metastatic disease). Medical resource use was not varied separately as it was assumed that any related uncertainty would be covered by the variation of unit costs. The discount rate was set to 0 and 6%.

In addition, variables subject to statistical uncertainty (sensitivity and specificity of IHC and FISH, metastatic, local and regional recurrence rates, utilities) were varied within their 95% confidence intervals (CIs) [48]. The prevalence of a normal (negative) HER-2 expression pattern was varied between 75 and 85%.

Probabilistic sensitivity analysis

Uncertainty around the base case results was additionally assessed by probabilistic sensitivity analysis (PSA), using 10,000 sets of parameter values randomly sampled from beta distributions reflecting the ranges of variation used in deterministic sensitivity analysis [49]. Parameters covered included HER-2 prevalence, utilities, transition probabilities, and test sensitivity and specificity. Unit costs were not subject to uncertainty and therefore not included in the PSA [44].

Model implementation

The Markov model was implemented in TreeAge Pro® 2009 (TreeAge Software Inc, Williamstown, MA, USA).

Table 3 Cost per type of resource use (per first year in € per patient)

Type of resource	Duration/amount	Unit cost (€)	Ref.
Hormonal therapy	1 year	2,233	[44, 47]
Trastuzumab price (Herceptin®, Roche, Switzerland)	1 vial per 150 mg	860	[47]
	1 vial per 440 mg	2,341	
Trastuzumab treatment (Incl. Infusion and 4× echocardiography)	1 year	42,588	[44, 47]
IHC test	1 test	53	[44]
FISH test[a]	2 test probes	686	[44]
Gynaecological examination[b]	1	142	[44]
Mammography	1	107	[44]
Sonography	1 year	100	[44]
Surgery	1 year	1,275[c]	[44]
		2,778[d]	
Material	1 year	167	[44]
Anaesthesia	1 year	540	[44]
Radiotherapy	1 year	4,688[e]	[44]
		8,467[f]	
Hospitalization	7.6 days	2,281[g]	[60]

[a] Based on the resource use in Swiss laboratories

[b] According to the Swiss Consortium for Gynaecological Oncology and Obstetrics (AGO) [40]: four examinations per year in the years 1–3, two examinations in the years 4–5, one examination in the years 5–10 and biennial examinations thereafter

[c] Local recurrence in the breast

[d] Thoracic local recurrence and regional recurrence

[e] For thoracic local recurrence

[f] For regional recurrence

[g] Average duration of stay of C500 to C509 (ICD10 classification) during 2005 in Switzerland

Results

Base case analysis

Effect

Differences in effectiveness between the strategies involving trastuzumab treatment arose from imperfect sensitivity and specificity of the testing strategies (Table 1). Some HER-2-positive patients had false negative test results and hence did not receive trastuzumab, which lead to a loss of QALYs. Therefore, the no testing strategy (where all patients received trastuzumab) accrued most QALYs (12.751 QALYs per patient). The testing strategies accrued between 12.741 and 12.750 QALYs. At the lower end, the no trastuzumab strategy resulted in 12.254 QALYs (Table 4).

Costs

Trastuzumab substantially increased costs in both the testing and non-testing strategies, compared to no trastuzumab treatment. However, the increase was distinctly lower in the testing strategies. Here, trastuzumab costs were strongly reduced as therapy was targeted to those patients who profited most (Table 4).

Per-patient total lifetime costs in the predictive testing strategies ranged from €38,153 (FISH confirmation of IHC2+) to €41,830 (parallel IHC and FISH). FISH confirmation of IHC2+ saved €62 in comparison to FISH alone. If FISH alone was used, per-patient savings compared to IHC alone and parallel IHC and FISH would be €1,736 and €3,615, respectively.

Incremental cost–effectiveness

The reference (no trastuzumab) strategy was least costly and least effective (€32,258 and 12.254 QALYs per patient) (Table 4). FISH alone testing was associated with a per-patient cost of €38,215 and resulted in 12.741 QALYs, corresponding to an ICER of €12,245/QALY when compared with the no trastuzumab strategy. This was the most favourable ICER observed. FISH alone testing dominated IHC alone and FISH confirmation of IHC2+. In the latter comparison, FISH alone was in a situation of extended dominance [50], e.g.it was slightly more expensive but showed a better incremental cost–effectiveness ratio than the comparator. Superior characteristics of the FISH test lead to a gain in clinical effectiveness and hence, clinical savings that over-compensated or near-compensated much higher test costs. The ICER of parallel IHC and FISH was €400,154/QALY compared to FISH alone. ICERs for the non-testing approach were prohibitively high. Figure 2 summarizes cost–effectiveness results.

Current Swiss data show an annual average of 5,091 incident breast cancer cases between 2001 and 2005 [51]. On this basis, FISH confirmation of IHC2+ versus FISH alone would lead to cost savings of €315,642, and lose 245 QALYs, per year. FISH alone compared to IHC alone would save €8,837,976, and gain 177 QALYs, per year. FISH alone compared to parallel IHC and FISH would lead to savings of €18,403,965 and a loss of 46 QALYs.

Table 4 Base case cost–effectiveness analysis (CEA) of different testing strategies (reference: no trastuzumab)

Test strategy	Lifetime cost per person	Lifetime efficacy	*C/E*	Incremental costs[a]	Incremental efficacy[b]	ICER
Unit	€	QALY	€/QALY	€	QALY	€/QALY
No trastuzumab[c]	32,258	12.254	2,632	–	–	–
IHC first (FISH only for IHC2+)	38,153	12.693	3,006	(5,895)[d]	(0.4384)[d]	Dominated[d]
FISH alone	38,215	12.741	2,999	5,957[e]	0.4865[e]	12,245[e]
IHC alone	39,951	12.706	3,144	(1,736)[f]	(−0.0348)[f]	Dominated[f]
Parallel IHC and FISH	41,830	12.750	3,281	3,615[g]	0.0090[g]	400,154[g]
NO test	53,860	12.751	4,224	12,030[h]	0.0009[h]	13,456,577[h]

[a] Relative to the strategy with the next lower cost

[b] Relative to the strategy with the next lower efficacy

[c] Reference strategy

[d] Compared to the reference strategy (no trastuzumab)

[e] Extendedly dominated by FISH alone (extended dominance: is applied to remove from consideration strategies whose cost–effectiveness is inferior in comparison with at least one more expensive strategy)

[f] Dominated by FISH alone (simple dominance: a strategy is dominated by another if the former both costs more and is less effective)

[g] Compared to FISH alone

[h] Compared to parallel IHC and FISH

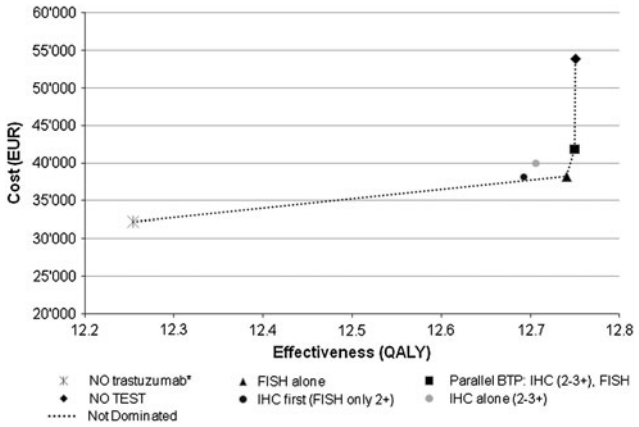

Fig. 2 Cost–effectiveness analysis. Graphical representation of incremental cost–effectiveness results. IHC alone (2–3+) is dominated by FISH alone, i.e. less effective and more expensive. IHC first (FISH only 2+) is extendedly dominated by FISH alone, i.e. less expensive but also less cost–effective. For the remaining strategies, the slope of the *dotted line* represents incremental cost–effectiveness

Sensitivity analysis

In deterministic sensitivity analysis, varying the price of trastuzumab and the discount rate had substantial influence on the results. Variation of other unit costs (apart from trastuzumab), cancer recurrence rates, test sensitivity or specificity, utilities or the HER-2 overexpression pattern did not influence the ranking of strategies. The ICERs for the non-dominated strategies were essentially sustained in all situations analyzed (Fig. 3, Table 5). The rank order of the testing strategies was also robust (Table 5). However, if the specificity of FISH alone was set a low value of 0.82 (while specificity was left unchanged for the other strategies), FISH confirmation of IHC2+ would become the preferred strategy due to its much higher specificity value. None of the other analyses performed affected the preferability of FISH alone (Fig. 3).

At a willingness to pay per QALY gained of €13,333, the FISH testing approach became dominant until at €380,000, parallel FISH and IHC became the preferred strategy (Fig. 4a). Further PSA results are shown in Fig. 4b.

Discussion

We modelled the cost–effectiveness of different predictive HER-2 testing strategies, prior to trastuzumab treatment of adjuvant breast cancer patients, from a Swiss health system perspective. FISH alone testing with subsequent trastuzumab treatment of HER-2-positive patients was identified as the most cost–effective approach, with an ICER of €12,245 per QALY gained compared to no trastuzumab use. It dominated other testing strategies or these showed unfavourable cost–effectiveness ratios. Sensitivity analysis showed these results to be robust over a wide range of assumptions. As a limitation, we did not take into account a possible

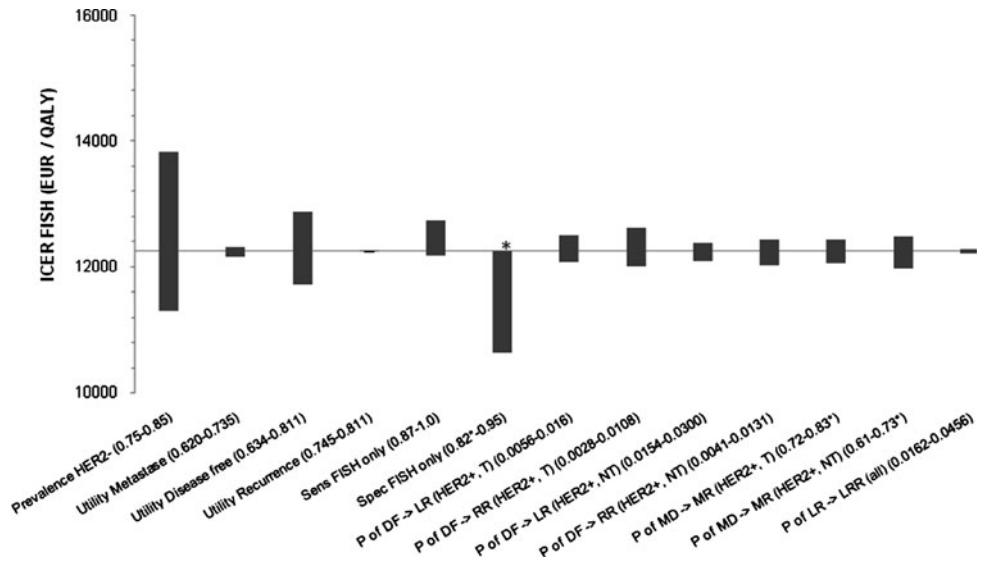

Fig. 3 Plot of the deterministic sensitivity analyses for parameter uncertainty with regard to the ICER of FISH testing compared with no trastuzumab. *Larger bars* indicate stronger sensitivity of the base case ICER of FISH testing versus the reference strategy to uncertainty around the respective parameters. *DF* disease free, *FISH* fluorescence in situ hybridisation, *ICER* incremental cost–effectiveness ratio, *IHC* immunhistochemistry, *LLR* local/regional recurrence, *LR* local recurrence, *MD* metastatic disease, *MR* metastatic recurrence, *NT* no trastuzumab, *P* probability, *RR* regional recurrence, *Sens* sensitivity, *Spec* specificity, *T* trastuzumab. *In this sensitivity analysis, FISH confirmation of IHC2+ becomes the preferred strategy with an ICER of €13,448 compared to reference strategy

Table 5 One-way sensitivity analysis of incremental costs (€) per QALY gained (ICER) without dominated strategies

Testing strategy	FISH alone vs. no trastuzumab	Parallel testing[c] vs. FISH alone	NO TEST vs. parallel testing
Baseline	12,245	400,154	13,456,577
Price trastuzumab +30%	15,982	531,788	17,377,558
Price trastuzumab −30%	8,507	268,544	9,549,342
Price all predictive tests +30%	12,398	398,547	13,396,396
Price all predictive tests −30%	12,091	401,785	13,530,503
Cost of FISH test probe −50%	11,892	400,129	13,655,867
Cost metastatic basis treatment +30%[a,b]	11,806	399,727	13,463,011
Cost metastatic basis treatment −30%[a,b]	12,683	400,605	13,463,889
Cost local recurrence +30%[a]	12,181	400,102	13,463,386
Cost local recurrence −30%[a]	12,308	400,230	13,463,514
Cost regional recurrence +30%[a]	12,243	400,164	13,463,448
Cost regional recurrence −30%[a]	12,246	400,168	13,463,451
Discount rate 6%	18,721	636,009	21,215,854
Discount rate 0%	7,644	230,451	7,818,473

[a] Without consideration of hormone therapy

[b] Price for trastuzumab not included

[c] Parallel both tests (BTP): either IHC (2–3+) or FISH+ test result needed for HER-2+ status

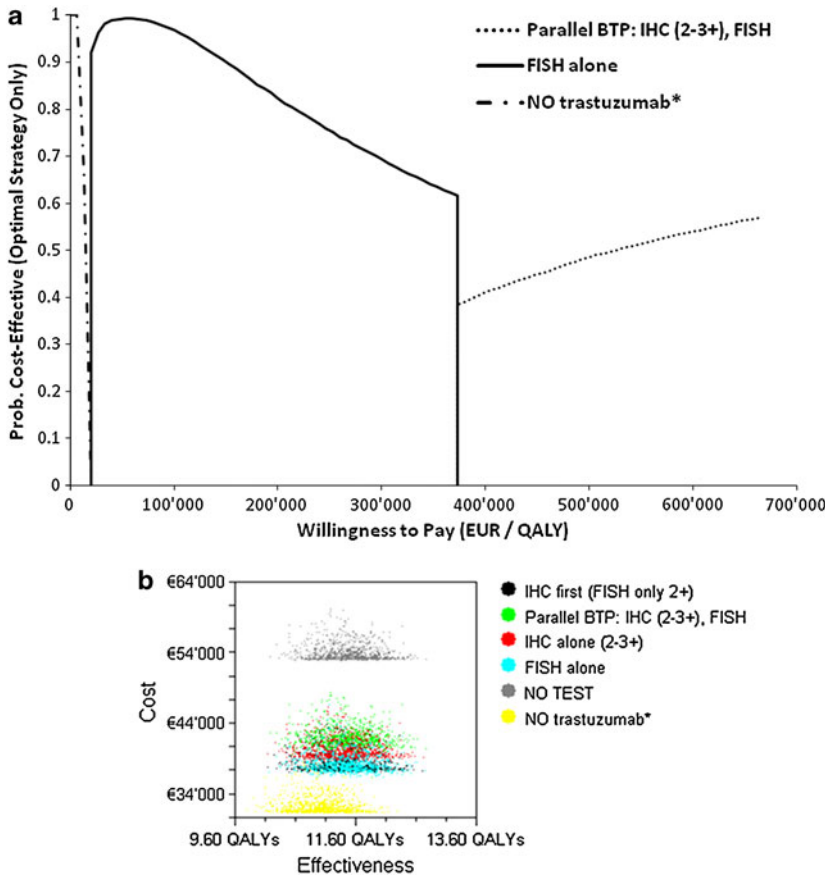

Fig. 4 Results from the probabilistic sensitivity analysis (PSA). **a** Acceptability frontier. The cost–effectiveness acceptability frontier shows the PSA-based probability of testing strategies of being cost–effective. For different willingness to pay thresholds, different strategies are optimal. For each threshold, only the probability for the optimal strategy is shown. **b** Incremental cost (€)–effectiveness scatter plot of all testing options. The cost–effectiveness scatter plot uses the cost–effectiveness plane to plot a test cost and effectiveness pair for each recalculation of the model (10,000 runs)

influence of false positive and false negative test results on the event risks reported in HERA and in the other trials used for deriving transition probabilities in this modelling study. This would have required complex correction procedures and tentative assessments indicated a minor impact.

In routine practice, many local laboratories only use IHC. Central laboratories often use FISH to confirm IHC2+, as was the case in the HERA study [12]. Both of these strategies were dominated by the FISH alone strategy in our model. The inferiority (extended domination) of FISH confirmation of IHC2+ was due to this strategy, clinical characteristics, although it was cheaper than FISH alone.

In Switzerland, many central laboratories have started to use primary FISH assays. However, IHC may be added in unclear cases. The implications were difficult to assess as no sensitivity or specificity data for FISH equivocal samples (HER-2/CEP17 ratio signal between 1.8 and 2.2) were available from the literature. A tentative assessment assuming a hypothetical sensitivity of 0.892 (CI 0.766–0.94 [30, 31]) indicated a quality-adjusted survival of 12.470 QALYs and hence no further gain in clinical effectiveness.

In a recent cost–effectiveness analysis in the metastatic setting, conducted by Elkin et al., trastuzumab treatment without predictive testing was dominated by a testing strategy not covered here, namely, the confirmation of IHC2+ or 3+ with FISH [26]. Only patients with a positive result in both tests received trastuzumab, i.e. considerably fewer than in our combined IHC and FISH strategy. It may indeed make sense to use stricter criteria for trastuzumab treatment in the metastatic than in the adjuvant setting. However, the strategy of FISH confirmation of IHC 2–3+ was also assessed for non-metastatic patients. In a meta-analysis by Dendukuri et al. [17], focusing on invasive breast cancer patients, and in a Swedish cost–effectiveness analysis studying adjuvant breast cancer patients [27], it was again identified as the strategy with the best ICER. Of note, the former study only took into account diagnostic costs; it disregarded trastuzumab costs [17]. The latter estimated IHC scores from FISH results, based on Elkin et al. [26], and thus made an implicit assumption of dependency of IHC and FISH. In a separate implementation of the model, we estimated the lifetime costs and effects of the strategy defined by Elkin et al. in the adjuvant setting. After reducing sensitivity (0.892, CI 0.766–0.94) and increasing specificity (0.975, CI 0.950–0.989) [30, 31], costs summed up to €36,706 in combination with 12.697 QALYs gained. Indeed, this would imply a favourable ICER. However, due to a low practical relevance in the adjuvant setting, and presumable lack of acceptability in a resource-rich setting, we did not incorporate this strategy into the main analysis.

Recent evidence suggests that HER-2 expression in primary and advanced tumour tissue may be discordant by 5–10% [52–57]. HER-2 status may therefore be re-assessed before starting trastuzumab treatment in metastatic breast cancer patients experiencing disease progression. However, our model focuses on adjuvant therapy and we did not attempt to assess the economic implications of this approach, as currently, this is not routine practice.

A recent review favours FISH over IHC for accuracy, reproducibility and precision reasons [16]. According to this source, 15–48% of equivocal IHC2+ breast cancers show HER-2 gene amplification. In addition, 2–8% of IHC 0/1+ breast cancers are FISH amplified. Around 5–22% of IHC 3+ breast cancers have no gene amplification (false negativity) [16]. In addition, a positive FISH status points towards a stronger responsiveness to trastuzumab. The use of FISH testing diminishes the number of patients eligible for trastuzumab therapy due to both superior sensitivity and specificity compared to IHC [16]. These findings favour primary FISH testing and are consistent with our health economic result.

Conclusion

Clinically useful predictive tests with reasonable sensitivity and specificity to predict drug-response are one cornerstone in achieving a cost–effective implementation of new treatment strategies in oncology. Currently, many novel predictive assays (e.g. *k-ras* testing in colorectal cancer, *EGFR* mutation analysis in lung cancer) are being introduced. Results from carefully conducted health economic analyses should inform future guidelines on the use of such tests. In the adjuvant breast cancer setting, primary FISH testing with subsequent trastuzumab treatment of HER-2-positive patients is a cost–effective and preferable approach.

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Conflict of interest No conflict of interest to declare.

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