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Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer

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ABSTRACT

Background: The 70-gene signature (MammaPrint®) is a prognostic test used to guide adjuvant treatment decisions in patients with node-negative breast cancer. In order to decide upon its use, a systematic comparative analysis of the effects of the 70-gene signature, the Sankt Gallen guidelines and the Adjuvant Online Software for these patients on survival, quality of life and costs is warranted.

Methods: A Markov decision model was used to simulate the 20-year costs and outcomes (survival and quality-of-life adjusted survival (QALYs)) in a hypothetical cohort of node-negative, estrogen receptor positive breast cancer patients. Sensitivity and specificity of the three prognostic tools were based on 5 and 10 years breast cancer specific survival and distant metastasis as first event, derived from a pooled analysis consisting of 305 tumour samples from 3 previously reported validation studies concerning the 70-gene signature.

Results: Small differences in survival, but substantial differences in quality-adjusted survival between the prognostic tools were observed. Quality-adjusted survival was highest when using the 70-gene signature. Based on costs per QALY, the 70-gene has the highest probability of being cost-effective for a willingness to pay for a QALY higher than €4600.

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Sankt Gallen showed the highest survival rates compared to the 70-gene signature, but leads to a substantial larger amount of adjuvant chemotherapy and hence higher costs, thus demanding a willingness to pay of €29.326 to save a life year.

Conclusions: When deciding upon the cost-effectiveness of the prognostic tests, the 70-gene signature improves quality-adjusted survival and has the highest probability of being cost-effective.

1. Introduction

Adjuvant systemic therapy for early breast cancer improves disease-free and overall survival.[1] The majority of early breast cancer patients, particular with lymph node-negative disease (60–70%), has a fairly good 10-year overall survival with loco-regional treatment alone, with 30–40% developing distant metastasis.[1] Nevertheless, according to current guidelines, most lymph node-negative patients are offered chemotherapy, likely causing an important proportion of over-treatment.[2] Since this treatment has severe side-effects, and is very costly, a careful selection of patients is important. In order to choose the optimal prognostic test, a trade-off between survival, quality of life adjusted survival and costs is inevitable.

In 2002, the 70-gene prognosis signature (MammaPrint®) was identified using microarray analysis for lymph node-negative breast cancer patients.[3] This prognosis signature has been validated in several retrospective patient series.[4–6] These studies confirmed that the 70-gene signature accurately discriminates between patients with a high and low risk of developing distant metastasis. The usual path of adoption in clinical practice would include a prospective randomized trial; however, this would take at least 8–10 years. Therefore, it was decided that it was appropriate to evaluate this technology in a non-randomized feasibility study. The Dutch Health Care Insurance Board sponsored this controlled introduction study, the multicenter microarRAy prognoSTics in breast cancER (acronym RASTER)-study. The main aim was to analyse the differences between adjuvant systemic treatment advice for breast cancer based on Dutch guidelines and the 70-gene signature, taking into account patients' preferences.[7] However, a need for level I evidence of the performance of the 70-gene signature remained. Therefore, the currently ongoing randomized phase III clinical trial, the MINDACT-trial (Microarray In Node-negative Disease may Avoid ChemoTherapy), was designed.[2,8] Alongside both studies a Constructive Technology Assessment is performed[9], of which the cost-effectiveness analysis (CEA) underlying this paper takes part. The CEA provides a systematic comparative analysis of the available prognostic tests for node-negative breast cancer patients, that is not only based on test performance and long-term survival, but also on quality of life and costs. The results of this analysis are important to the decision to implement the 70-gene signature.

Earlier, in a cost-effectiveness analysis of the 70-gene signature performed by Oestreicher and colleagues, 2005[10], the conclusion was that although gene expression profiling in breast cancer holds great promise, additional refinement and validation are needed before implementation in clinical practice. This analysis was performed on one retrospective validation series of Buyse and colleagues, 2006.[5] Hornberger and colleagues, 2005 and Lyman and colleagues, 2007 performed a cost-effectiveness analysis concerning the 21-gene RT_PCR assay (Oncotype DX).[11,12] They concluded that the gene expression profile predicted more accurately than current guidelines, and if applied appropriately, the assay was predicted to increase quality-adjusted survival and save costs.

The goal of our analysis was to show the expected cost-effectiveness of the use of the 70-gene signature compared to the currently used clinical guidelines Sankt Gallen and Adjuvant Online software, using a pooled database of three retrospective validation series. For this analysis, we developed a Markov model to compare long-term consequences of the use of three prognostic tools in patients with node-negative breast cancer: (1) the 70-gene signature (70-gene), (2) clinical pathological test result using the Sankt Gallen guidelines (SG),[13] (3) clinical pathological test result using the Adjuvant Online Software (AO).[14]

2. Materials and methods

2.1. Procedures

This cost-effectiveness analysis was approved by the Institutional Review Board of the Netherlands Cancer Institute.

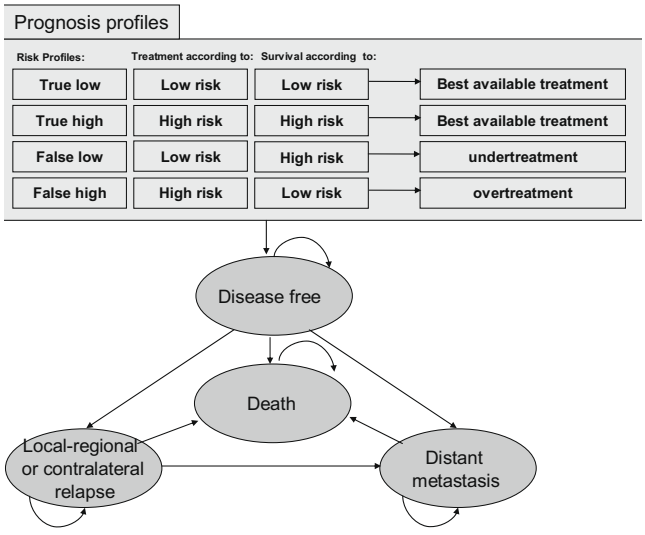

Fig. 1 – Model structure.

2.2. Model description

A Markov model was constructed with four mutually exclusive health states: disease free survival, relapse (including local and regional recurrences, secondary primary and contralateral breast cancer), distant metastasis, and death (Fig. 1). The study adopts a health care perspective. The model simulated the course of events in a hypothetical cohort of 1000 patients aged 50 years with early, operable node-negative, estrogen receptor (ER)-positive breast cancer for three strategies: 70-gene signature, Sankt Gallen and Adjuvant Online. The specific selection of ER positive patients was made because the 70-gene signature is proven to have less additional clinical value for ER negative patients due to the high rates of high risk.[15] In each strategy, based on the sensitivity and specificity of the prognostic test, patients were classified as having a true low, true high, false low, or false high risk of developing metastasis. It was assumed that both the prognostic test result and the treatment guidelines would be followed in all cases. We simulated in the model that all patients received endocrine treatment (ET); a second generation ET regimen: 2.5 years of Tamoxifen followed by 2.5 years of an Aromatase Inhibitor (mean of Anastrazol, Letrozol and Exemestane), and the 80% of high risk patients were assumed to receive six cycles of 5-Fluorouracil, Epirubicine, Cyclofosfamide (FEC 6*100), 10% was assumed to receive six cycles of Docetaxel, Doxorubicine, Cyclofosfamide (TAC) and 10% Doxorubicine, Cyclofosfamide (AC) and Paclitaxel (4 + 12), in combination with Trastuzumab, according to the European guidelines.[13,16] Trastuzumab (Herceptin) was given to 10% of the high risk patients, according to the proportion of HER2-neu positive patients in the node negative, ER positive group.[17] Chronic congestive heart failure was modelled as an adverse event due to the administration of Trastuzumab in combination with anthracyclines and anthracyclines alone. Furthermore, consequences of congestive heart failure in terms of both costs and quality of life utility are incorporated, only modelled in relation to the adjuvant treatment. These model inputs are based on Keefe, 2002.[18] (Table 2). The duration of the mean post-operative treatment (radiotherapy plus chemotherapy) was assumed to be finished within the first year. It was assumed that patients could only have one relapse, for which they received the best available treatment with the same costs, regardless which kind of

Table 1 – Sensitivity and specificity of the diagnostics strategies, based on the pooled database.

			70-g			SG			AO		
Outcome	Follow up	Event	Low	High	Total	Low	High	Tot	Low	High	Total
Breast cancer specific survival[a]	10[b]	No	153	110	263	29	234	263	141	122	263
			93%	78%	86%	94%	85%	86%	89%	84%	86%
		Yes	11	31	42	2	40	42	18	24	42
			7%	22%	14%	6%	15%	14%	11%	16%	14%
		Total	164	141	305	31	274	305	159	146	305
			100%	100%	100%	100%	100%	100%	100%	100%	100%
		Se	0.74			0.95			0.57		
		Sp	0.58			0.11			0.54		
	5	No	161	126	287	30	257	287	153	134	287
			98%	89%	94%	97%	94%	94%	96%	92%	94%
		Yes	3	15	18	1	17	18	6	12	18
			2%	11%	6%	3%	6%	6%	4%	8%	6%
		Total	164	141	305	31	274	305	159	146	305
			100%	100%	100%	100%	100%	100%	100%	100%	100%
		Se	0.83			0.94			0.67		
		Sp	0.56			0.10			0.53		
Distant metastasis as first event[a]	10	No	148	104	252	27	225	252	135	117	252
			90%	74%	83%	87%	82%	83%	85%	80%	83%
		Yes	16	37	53	4	49	53	24	29	53
			10%	26%	17%	13%	18%	17%	15%	20%	17%
		Total	164	141	305	31	274	305	159	146	305
			100%	100%	100%	100%	100%	100%	100%	100%	100%
		Se	0.7			0.92			0.55		
		Sp	0.59			0.11			0.54		
	5	No	158	116	274	30	244	274	150	124	274
			96%	82%	90%	97%	89%	90%	94%	85%	90%
		Yes	6	25	31	1	30	31	9	22	31
			4%	18%	10%	3%	11%	10%	6%	15%	10%
		Total	164	141	305	31	274	305	159	146	305
			100%	100%	100%	100%	100%	100%	100%	100%	100%
		Se	0.81			0.97			0.71		
		Sp	0.58			0.11			0.55		

Se: sensitivity, Sp: specificity.

[a] In this population 62% was T-stage 1, 38% T-stage 2/3, 19% grade 1, 54% grade 2, 26% grade 3.

[b] Base case analysis.

adjuvant treatment the patient originally received for the primary tumour. However, after experienced a relapse, the patient has a higher risk to develop distant metastasis. The calculations are performed per year, with a total simulated time horizon of 20 years.

2.3. Probabilities

The sensitivity and specificity of each prognostic test were calculated from a pooled analysis consisting of 3 previously reported validation studies: van de Vijver and colleagues, 2002, Buyse and colleagues, 2006 and Bueno de Mesquita and colleagues, 2008.[4–6] From this database, a total of 305 untreated, node negative and ER-positive tumour samples were selected and classified by the 70-gene signature and the clinical pathological guidelines as low or high risk of developing distant metastasis. In the series of van de Vijver and colleagues, 2002, the 61 samples of the original development series were excluded.[4,19] We calculated the sensitivity and specificity of the three strategies for breast cancer specific survival (BCSS) at 10 years (Table 1). Patients were evaluated as low clinical-pathological risk, if their 10-year disease

Table 2 – Base case parameters.

Parameter				Base case (mean)	SE	Distribution	Source
Test performance							
70-gene	Low risk		True	0.502	+/−0.03	Dirichlet	[4–6]
			False	0.036	+/−0.03	Dirichlet	
	High risk		True	0.102	+/−0.07	Dirichlet	
			False	0.361	+/−0.03	Dirichlet	
SG	Low risk		True	0.095	+/−0.06	Dirichlet	
			False	0.007	+/−0.01	Dirichlet	
	High risk		True	0.131	+/−0.03	Dirichlet	
			False	0.767	+/−0.02	Dirichlet	
AO	Low risk		True	0.462	+/−0.03	Dirichlet	
			False	0.059	+/−0.03	Dirichlet	
	High risk		True	0.079	+/−0.08	Dirichlet	
			False	0.400	+/−0.03	Dirichlet	
Transition probabilities							
Chronic congestive heart failure due to							
Trastuzumab	Year 1			0.160	+/−0.03	Beta	[18]
	Year 2–20			0.060	+/−0.02	Beta	
Anthracyclines	Year 1			0.030	+/−0.01	Beta	
	Year 2–20			0.007	+/−0.01	Beta	
DFS to relapse	Low risk	True		0.000	Fixed		Assumption
		False		0.000	Fixed		Assumption
	High risk	True	5y	[a]0.016	+/−0.00088	Beta	[21]
			10y	0.014	+/−0.00082	Beta	
			20y	0.013	+/−0.00080	Beta	
		False		0.000	Fixed		Assumption
DFS to distant metastasis	Low risk	True		0.000	Fixed		Assumption
		False		0.499	+/−0.03	Beta	Assumption
	High risk	True	5y	[b]0.020	+/−0.00096	Beta	[21]
		Her2–	10y	0.013	+/−0.00077	Beta	
			20y	0.010	+/−0.00069	Beta	
		False		0.000	Fixed		Assumption
Relapse to distant metastasis	Low risk	True		0.000	Fixed		Assumption
		False		0.499	+/−0.03	Beta	Assumption
	High risk	True	5y	[b]0.103	+/−0.00212	Beta	[21]
		Her2–	10y	0.054	+/−0.00158	Beta	
			20y	0.039	+/−0.00135	Beta	
		False		0.000	Fixed		Assumption
Hazard ratio Trastuzumab				0.640	+/−0.0988	Beta	[21]
Distant metastasis to death 1–5 years				0.310	+/−0.0032	Beta	[21]
Distant metastasis to death 5–10 years				0.025	+/−0.0011	Beta	
Distant metastasis to death 10–20 years				0.004	+/−0.0004	Beta	
Background mortality				Age specific mortality figures			[23]
Adjuvant treatment high risk patients							
Chemotherapy and endocrine therapy					0.90	(ER+, Her2– patients)	[13]
Chemotherapy and endocrine therapy and Trastuzumab					0.10	(ER+, Her2+ patients)	[17]
Adjuvant treatment low risk patients							
Endocrine therapy					1.00		Assumption

[a] False low patients were assumed to have a risk twice as high compared with true high patients.
[b] Her2+ patients were assumed to have a risk twice as high as the Her2– patients.

Table 3 – Base case costs per year.

	Unit cost €	Units	Base case €	%	(95% CI)	References
FEC-regime				80%		25,26
FEC100[a]	261	6	1569			
Day care costs	236	6	1414			
Laboratory/imaging	1200	1	1438			
Subtotal per patient			4421	3537	Fixed	
TAC-regime				10%		25,26
TAC[b]	1428	6	8571			
G-CSF	1319	6	7917			
Day care costs	236	6	1414			
Laboratory/imaging	1200	1	1438			
Subtotal per patient			19.340	1934	Fixed	
PAC-regime				10%		25,26
Paclitaxel[c]	626	12	7513			
G-CSF	1319	12	15.828			
Day care costs	236	12	1414			
Laboratory/imaging	1200	1	1438			
AC[c]	315	4	1260			
Day care costs	236	4	1414			
Laboratory/imaging	1200	4	1438			
Subtotal per patient			31.257	3126	Fixed	
Total per patient				8596	Fixed	
Tamoxifen				50%		25,26
Cost of 20 mg Tamoxifen tablet	0.17	365	62			
Additional costs[d]			153			
Subtotal per patient			216	108	Fixed	
Anastrozol				17%		25,26
Cost of 1 mg Anastrozol tablet	3.38	365	1235			
Additional costs			153			
Subtotal per patient			1388	231	Fixed	
Letrozol				17%		25,26
Cost of 2.5 mg Letrozol tablet	3.39	365	1239			
Additional costs			153			
Subtotal per patient			1392	232	Fixed	
Exemestane				17%		25,26
Cost of 2.5 mg Exemestane tablet	3.71	365	1353			
Additional costs			153			
Subtotal per patient			1506	251	Fixed	
Switch 2.5 years Tam/2.5 years A.I				822	Fixed	
Trastuzumab			36.298		Fixed	21
Chronic congestive hart failure			3453		Fixed	21
Follow-up costs low risk			[e]1179		Fixed	Assumption
Follow-up costs high risk			2359			21
In- and outpatient costs			2294		1751–3200	
Drug costs			65		Fixed	
Relapse first year			12.181			21
In- and outpatient costs			10.263		8307–12.986	
Drug costs			1918		Fixed	
Relapse after first year			2359			21
In- and outpatient costs			2294		1751–3200	
Drug costs			65		Fixed	
Distant metastasis state			14.303			21
In- and outpatient costs			9563		8060–11.730	
Drug costs			4740		Fixed	
Distant metastasis last year of life			6813		Fixed	21
70-Gene signature			2675		Fixed	Agendia

Assumes a mean body surface area of 1.7 m^2 and a weight of 70 kg.

[a] Fluorouracil (500 mg/m^2), Epirubicine (100 mg/m^2), Cyclofosfamide (500 mg/m^2).

[b] Docetaxel (75 mg/m^2), Doxorubicine (60 mg/m^2), Cyclofosfamide (600 mg/m^2).

[c] Paclitaxel (80 mg/m^2), Doxorubicine (60 mg/m^2), Cyclofosfamide (600 mg/m^2).

[d] Additional costs includes DEXA scan, consultation, laboratory, imaging.

[e] Assumed twice as low as follow-up costs high risk.

specific survival (without chemotherapy or endocrine therapy) is estimated by 'Adjuvant! Online' as greater than 88% for ER-positive patients.[14] According to the Sankt Gallen guidelines, a low clinical risk was defined as estrogen and/

or progesteron positive, and the following features: tumour size smaller or equal to 2 cm, grade 1 (Elston and Ellis), and equal or above 35 years.[20] All others were considered as high risk. It was simulated that patients classified as true low or false high risk had a zero probability to experience a relapse or distant metastasis. (Table 2) For the true high patients, yearly transitions (constant in year 1–5, 5–10 and 10–20) from disease free survival to relapse and distant metastasis, and from relapse to distant metastasis, were based on a sample of 20,624 Swedish breast cancer patients, derived from the study of Lidgren and colleagues, 2008.[21] For the patients receiving Trastuzumab, a relative risk reduction with the hazard ratio of 0.64 (95% confidence interval 0.54–0.76) was applied.[21] Furthermore, the risk of distant recurrence for Her2neu-positive patients was assumed to be twice as high compared with Her2neu-negative patients.[21,22] It was assumed that the false low patients had a 100% probability to experience a distant metastasis (corresponding with an annual probability of 0.499) and the risk of a relapse after the disease free state was modelled assumed to be twice as high compared with true high patients. Background mortality was based on age-specific death rates from the Central Bureau of Statistics of the Netherlands.[23] All statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

2.4. *Health effects*

Quality of life was modelled by assigning utilities to the different health states. These utilities were based on Lidgren and colleagues[24] (Table 4). In Lidgren and colleagues, to calculate utility weights the EQ5D norm values for the general population were used. For patients who received adjuvant treatment, the utilities were calculated as long as they received the treatment; in the first year for CT and over 5 years for ET.

2.5. *Costs*

The costs of the health states DFS, relapse and distant metastasis (health states costs and one time costs of patients dying of breast cancer) were based on Lidgren and colleagues 2008, except the costs of chemotherapy and hormonal therapy[21] (Table 3). The total Trastuzumab costs consist of the costs of Trastuzumab and administration costs (€36.298).[21] The costs of chemotherapy and hormonal therapy were not reported by Lidgren and colleagues, and therefore based on Dutch sources.[25,26] Chemotherapy costs consisted of drug costs, day care costs (including administration), laboratory and diagnostic imaging costs (including mammography, tumormarkers) and prevention as the granulocyte colony stimulating factor (G-CSF, Neulasta) administration in combination of the taxane-containing therapies. The costs of the 70-gene signature were provided by Agendia BV; full costs including transport, additional specimen processing at the local hospital and Value Added Tax (VAT). Costs were expressed in 2005 Euros.

2.6. *Uncertainty analysis*

We programmed the model in Microsoft Excel (Microsoft, Redmond, WA) and validated it using various sensitivity analyses. Future costs and effects were discounted to their present value by a rate of 4% and 1.5% per year respectively, according to Dutch guidelines.[25] Incremental cost-effectiveness ratios (ICERS) were calculated by dividing the incremental costs by incremental life years (LYs) and by incremental quality adjusted life years (QALYs). Uncertainty in the input parameters was handled probabilistically, by assigning distributions to parameters (Table 2).[27] Parameter values were drawn at random from the assigned distributions, using Monte Carlo simulation with 1000 iterations. The results of the simulation of the hypothetical cohort of 1000 patients are illustrated in a cost-effectiveness (CE) plane, each quadrant indicates whether a strategy is more or less expensive and more or less effective.[28] To show decision uncertainty, cost-effectiveness acceptability curves (CEACs) are presented. CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, given different cost per QALY ratios. Whether a strategy is deemed efficient depends on how much society is willing to pay for a gain in effect, which is referred to as the ceiling ratio.[28] In the Netherlands an informal ceiling ratio of €80.000 per QALY exists (Dutch Council for Public Health and Health Care 2006). This is a maximum ceiling ratio which applies when there is a high burden of disease. This is certainly the case for breast cancer. The National Institute for Health and Clinical Excellence in the United Kingdom uses a ceiling ratio between £20,000 and £30,000 per QALY.

2.7. *Sensitivity analyses using different scenarios*

In addition, we performed four one-way sensitivity analyses, using different scenarios. Firstly, we used DM as first event instead of BCSS as final outcome to determine the sensitivity

Table 4 – Base case utilities for health states.

Utilities		Mean	95% CI	Distribution	Source
Disease free survival	No adjuvant systemic treatment first year	0.935	+/−0.02	Beta	[21,24]
	Disease free survival year 2–20	0.935	+/−0.02	Beta	
	Chemotherapy year 1	0.620	+/−0.04	Beta	
	Endocrine therapy year 1–5	0.744	+/−0.05	Beta	
	Trastuzumab year 1	0.620	+/−0.04	Beta	
	Chronic congestive heart failure	0.700	+/−0.05	Beta	Assumption
Relapse		0.779	+/−0.04	Beta	
Distant metastasis		0.685	+/−0.03	Beta	

Table 5 – Incremental cost-effectiveness results (mean (95% confidence interval)).

Diagnostic strategy	LYs	Costs	Incremental LYs	Incremental costs	Incremental CE-ratio	% More effective		% Less effective	
						More costs	Less costs	More costs	Less costs
Sankt Gallen	16.14	€ 35.475							
70-Gene signature	15.88	€ 28.045	0.25 (−0.38 to +0.88)	€ 7430 (+3880 to +11.757)	€ 29.326/LY[a]	78%[a]	0%[a]	0%[a]	22%[a]
Adjuvant Online	15.68	€ 26.915	0.20 (−0.13 to +0.52)	€ 1130 (−2003 to +4037)	€ 5736/LY[b]	65%[b]	24%[b]	1%[b]	10%[b]
Diagnostic strategy	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental CE-ratio	% More effective		% Less effective	
						More costs	Less costs	More costs	Less costs
70-Gene signature	12.44	€ 28.045							
Adjuvant Online	12.20	€ 26.915	0.24 (−0.09 to +0.58)	€ 1130 (−2003 to +4037)	€ 4614/ QALY[b]	68%[b]	25%[b]	0%[b]	7%[b]
Sankt Gallen	11.24	€ 35.475	1.20 (+0.39 to +1.54)	–€ 7430 (−11.757 to −3880)	Dominant[c]	0%[c]	0%[c]	100%[c]	0%[c]

[a] Sankt Gallen compared to 70-gene.
[b] 70-Gene compared to Adjuvant Online.
[c] 70-Gene compared to Sankt Gallen.

and specificity of the diagnostics tests. In addition, we used 5 years of follow-up to final end-point instead of 10 years for both outcomes. Secondly, we computed sensitivity and specificity separately for the three series. Thirdly, because using QALY as an outcome in cost-effectiveness analyses in oncology is a debated issue, as this has proven to be difficult to estimate health state utilities among cancer patients.[29], we used different QoL-scores (utilities) for disease free survival with and without adjuvant systemic therapy.[11,30] Fourthly, because the costs of chemotherapy are likely to become higher with the increase of novel regimens, the costs of chemotherapy were varied to €20.000. Cost-effectiveness acceptability curves (CEACs) are used to show the impact of these changes in model input on the probability that the 70-gene is cost-effective.

3. Results

3.1. *Mean results*

The strategies were found to be on average equally effective, but the St. Gallen strategy was more costly than the 70-gene and Adjuvant Online strategy. The total health care costs per patient were: €28.045 (70-gene), €35.475 (SG) and €26.915 (AO) (Table 5). The number of life years amounted to: 15.88 (70-gene), 16.14 (SG) and 15.68 (AO). The difference in costs per life year gained of the Sankt Gallen compared to the 70-gene strategy resulted in €29.326/LY. Subsequently the 70-gene strategy was compared to the Adjuvant Online strategy, to assess the results in case the St. Gallen strategy would not be accepted, which resulted in €5.736 per life year gained.

The 70-gene strategy yielded more quality adjusted life years (12.44) than the AO strategy (12.20), and the SG strategy (11.24). Compared to the AO strategy the 70-gene strategy costs €4.614 per QALY gained. In comparison to the SG strategy, the 70-gene strategy yielded more QALYs and was less costly.

3.2. *Uncertainty analysis of mean results (probabilistic)*

The plots indicate that the strategies differ more in terms of quality-adjusted survival than in terms of survival (Fig. 2). When focusing on survival, the Sankt Gallen strategy has the highest probability of being cost-effective if the maximum willingness to pay for one life year exceeds €29.326. In case of costs and QALYs, the 70-gene signature has the highest probability of being cost-effective for ceiling ratios of 4614 Euro/QALY and higher.

3.3. *Different scenarios in sensitivity analyses*

For the first sensitivity analyses, the CEACs 1 and 2 showed that, when comparing costs and life years, the 70-gene signature has the highest probability of being cost-effective in case of BCSS and DM at 5 years; however the Sankt Gallen strategy appears to be more cost-effective in case of BCSS and DM at 10 years. When comparing costs and quality adjusted life years, the 70-gene signature remains the most cost-effective strategy. The sensitivity analyses for the Buyse-series sepa-

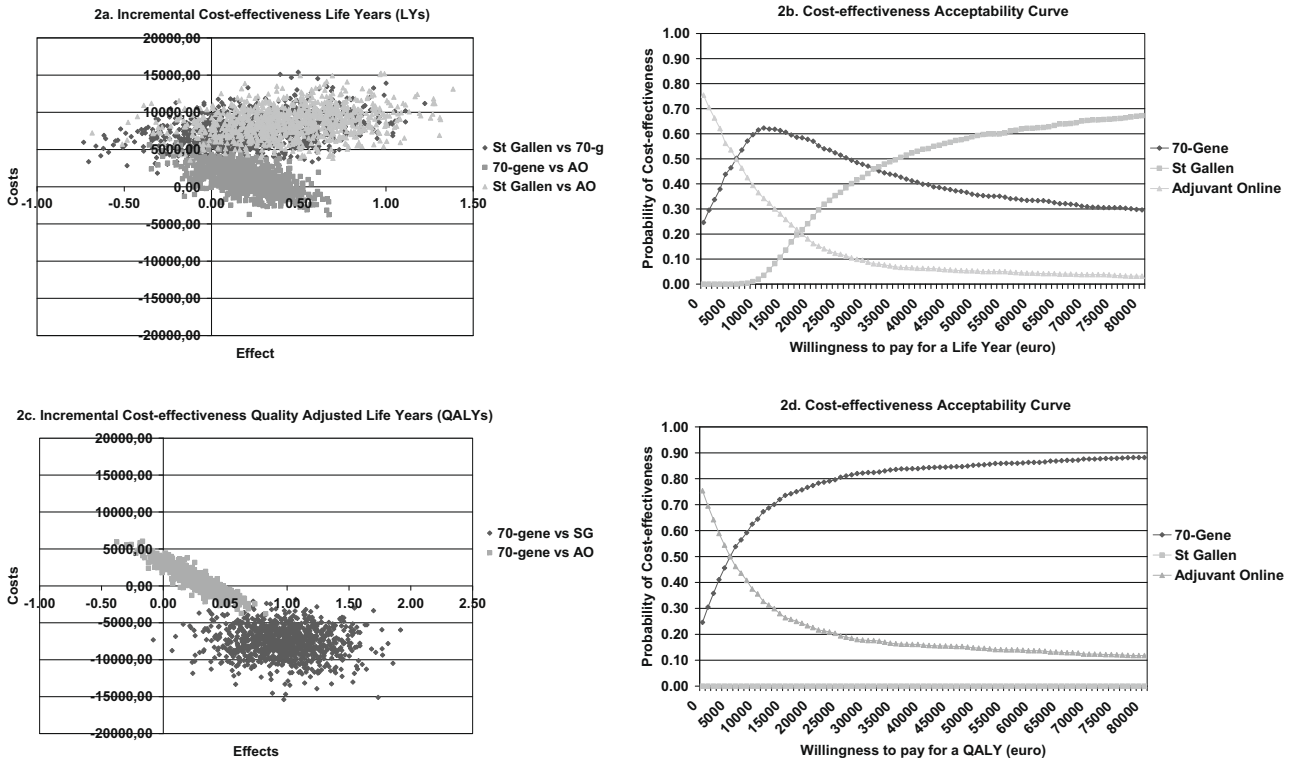

Fig. 2 – Cost-effectiveness (CE)-planes and cost-effectiveness acceptability curves (CEAC). (a) Cost-effectiveness-plane, incremental cost per LYs, (b) cost-effectiveness acceptability curve, incremental cost per LYs, (c) cost-effectiveness-plane, incremental cost per QALYs, (d) cost-effectiveness acceptability curve, incremental cost per QALYs.

rately showed no difference in results, however, the van de Vijver-series and the Bueno-de-Mesquita-series showed a slightly higher specificity of the Adjuvant Online compared to the 70-gene signature, which resulted in a more effective and less costly situation for the Adjuvant online. Using other utility inputs did not change the results substantial, however using higher costs for chemotherapy resulted in more beneficial outcomes for the 70-gene strategy, for both survival and quality-adjusted survival (Appendix tables and figure).

4. Conclusions and discussion

The model-based CEA showed that the three prognostic tests (70-gene, SG and AO) in node-negative, estrogen receptor positive breast cancer patients are very comparable in terms of their long-term effect on survival, but vary substantial in costs and quality adjusted life years. The 70-gene strategy is more costly than the AO strategy, but less costly than the SG strategy. Furthermore, the 70-gene strategy results in substantial more QALYs than both clinical prognostic tests. When comparing costs and quality adjusted life years, the 70-gene signature has the highest probability of being cost-effective. When comparing costs and life years, the 70-gene signature has the highest probability of being cost-effective in case of BCSS and DM at 5 years, however the Sankt Gallen strategy appears to be more cost-effective in case of BCSS and DM at 10 years. This result is not surprising since the 70-gene signature was validated for BCSS and DM at 5 years.

It would be ideal to perform this analysis on a direct randomized comparison of the three prognostic tools. However, the MINDACT-trial is still ongoing, and at the moment policy makers request information regarding the expected cost-effectiveness of the 70-gene signature. Therefore the Markov modelling technique has been used to integrate the currently available evidence. Using QALY as an outcome in cost-effectiveness analyses in oncology is a debated issue, as it has proven to be difficult to estimate health state utilities among cancer patients.[29] However, when applying a test aiming to focus and thus reduce chemotherapy over-treatment, as in this study, it seems inevitable to somehow quantify the effects of treatment on the quality of life of patients with cancer. This emphasises the need for more data on the quality of life of cancer patients, and the importance of research directed at possible biases and innovative methodologies in measuring quality of life. The specific impact of the 70-gene signature and the consequences of this test on the quality of life of breast cancer patients are currently investigated in the MINDACT-trial. These data are however not yet available. Besides for the utility input, the cost-effectiveness outcomes also are sensitive to changes in the cost inputs. It would be ideal to measure the costs and utilities alongside the multinational randomized controlled trial.

We have chosen to model only one relapse per patient as this is a common assumption in breast cancer patients.[31–33] Because we modelled only one relapse probability per patient, there could be an underestimation of the costs of a relapse (around 30% of the patients develop more than one relapse). As we only included health care costs, another underestimation of costs can be caused by not including productivity loss in case of chemotherapy. Possible carry-over effects for the

specific treatments were not considered in the model, this can cause an underestimation of the effects. We included 10% administration of Docetaxel, however this is regimen is currently being discussed for this, in principal, low risk group.[16]

As we compare our results to the three other CEAs with regard to the cost-effectiveness of gene expression profiling in breast cancer,[10–12] our conclusion agrees with the fact that the use of the 70-gene signature increases quality-adjusted survival and is potentially cost saving.

In this study, it was assumed that both physicians and patients would be 100% compliant to the prognostic test result and the treatment guideline. Therefore, the results of this study indicate the cost-effectiveness of the diagnostic tests assuming perfect implementation. This may not be feasible in real life. Currently, in a continuous CTA-study alongside the MINDACT-trial, different (technical, societal and medical) scenarios are being constructed which show the possible implementation of the 70-gene signature in daily practice. These scenarios will be used as input for the Markov model underlying the current study and would result in more 'real world' cost-effectiveness estimates.[34] Furthermore, there is discussion on what will be the best way to use the 70-gene signature, and in which different subgroups the 70-gene signature has an added value. According to new insights, Knauer and colleagues, 2008 distinguished more subgroups according to the HER2 status and ER status, which could influence the cost-effectiveness as well.[35] Mook and colleagues, 2008 suggests to include also the 1–3 node positives besides the node negatives, which could cause a shift in the adjuvant treatment in the high risk groups.[36] Further research into the effectiveness and cost-effectiveness of the 70-gene signature in other populations or subtypes is certainly warranted.

To conclude, according to our analyses using the 70-gene signature or clinical prognostic tests (SG or AO) in node-negative breast cancer patients results in comparable survival. In terms of quality-adjusted survival, using the 70-gene signature is cost-effective compared to AO and is more effective and less costly than SG. When deciding upon the cost-effectiveness of the prognostic tests, the 70-gene signature has the highest probability of being cost-effective.

Conflicts of interest statement

W.H. van Harten is a non-remunerated, non-stakeholding member of the supervisory board of Agendia BV. All other authors declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.02.035.

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