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Original Research

Cost-effectiveness analysis of the 70-gene signature compared with clinical assessment in breast cancer based on a randomised controlled trial

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KEYWORDS
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Abstract ***Background:*** The clinical utility of the 70-gene signature (MammaPrint®) to guide chemotherapy use in T1-3N0-1M0 breast cancer was demonstrated in the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study. One thousand four ninety seven of 3356 (46.2%) enrolled patients with high clinical risk (in accordance with the modified Adjuvant! Online clinical-pathological assessment) had a low-risk 70-gene signature. Using patient-level data from the MINDACT trial, the cost-effectiveness of using the 70-gene signature to guide adjuvant chemotherapy selection for clinical high risk, estrogen receptor positive (ER+), human epidermal growth factor 2 negative (HER2-) patients was analysed.
Patients and methods: A hybrid decision tree-Markov model simulated treatment strategies in accordance with the 70-gene signature with clinical assessment versus clinical assessment alone, over a 10-year time horizon. Primary outcomes were quality-adjusted life years (QALYs), country-specific costs and incremental cost-effectiveness ratios (ICERs) for six countries: Belgium, France, Germany, Netherlands, UK and the US.
Results: Treatment strategies guided by the 70-gene signature result in more QALYs compared with clinical assessment alone. Costs of the 70-gene signature strategy were lower in five of six countries. This led to dominance of the 70-gene signature in Belgium, France, Germany, Netherlands and the US and to a cost-effective situation in the UK (ICER £22,910/QALY). Annual national cost savings were €4.2M (Belgium), €24.7M (France), €45.1M (Germany), €12.7M (Netherlands) and $244M (US). UK budget increase was £8.4M.
Conclusion: Using the 70-gene signature to safely guide chemotherapy de-escalation in clinical high risk patients with ER+/HER2- tumours is cost-effective compared with using clinical assessment alone. Long-term follow-up and outcomes from the MINDACT trial are necessary to address uncertainties in model inputs.

1. Introduction

Genomic profiling is a crucial tool to inform prognosis and support treatment decisions in the adjuvant setting. The recognition that patients with early breast cancer may be overtreated necessitated reliable prognostic tools to aid in therapy de-escalation. De-escalation simultaneously addresses the prioritisation of a patient's quality of life and reduces the strain on healthcare systems by avoiding high-cost treatments offering no additional or very limited benefit to a patient's survival.

The phase III EORTC 10041/BIG 3–04 Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial (NCT00433589) was an international, prospective, randomised study evaluating the clinical utility of the 70-gene expression signature (MammaPrint®) combined with clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer [1]. The trial enrolled patients with histologically-confirmed invasive breast cancer, with operable T1-3 disease and up to three positive lymph nodes. Five-year median results demonstrated that forgoing adjuvant chemotherapy in patients with high-risk clinical-pathological features, but whom are low-risk according to the 70-gene signature, does not compromise relapse and survival outcomes. The short- and long-term treatment-related adverse events of chemotherapy could be avoided, given the rate of distant metastasis free survival (DMFS) at five years that was 94·7% (95% confidence interval: 92·5%–96·2%), which remained above the pre-determined non-inferiority threshold of 92·0%.

This study reports a cost-effectiveness analysis of treatment strategies guided by the 70-gene signature versus treatment decisions based on clinical risk assessment for a target group of patients with ER+/HER2- breast cancer considered to be clinically high risk. The use of genomic signatures is recommended for this subset of patients by national and international clinical guidelines, such as those arising from the St. Gallen Consensus Conference, European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology [2–4]. Patient-level data were sourced from the MINDACT trial to model relapse and survival outcomes over a ten-year time horizon. This was the most clinically relevant horizon, given the availability of 5-year follow-up data from the MINDACT trial, and the large risk-reducing effect of adjuvant chemotherapy within the first five years [5]. As treatments, test adherence and costs vary widely across countries, analyses are conducted separately for five European countries participating in the MINDACT trial and the US.

2. Patients and methods

2.1. Model description

A hybrid decision tree-Markov cohort model was constructed. Three mutually exclusive health states were defined as follows: distant metastasis free survival (DMFS), distant metastasis and death (Fig. 1). Costs for six countries (Belgium, France, Germany, Netherlands, United Kingdom and the United States) were applied separately in the model. For all countries, a healthcare perspective was adopted. The model was constructed with a ten-year time horizon and six-month cycle length. Total costs and quality-adjusted life years (QALYs) were discounted at country-specific rates (Table S1). The model compared two strategies: (1) treatment strategies guided by the 70-gene signature in combination with clinical assessment and (2) treatment strategies guided by clinical assessment alone.

The primary outcome of interest, incremental cost-effectiveness ratios (ICERs), was calculated by dividing incremental costs by incremental QALYs. The ISPOR Guidelines for Good Modelling Practices and Cost-Effectiveness Alongside Clinical Trials were used for building the model [6]. The model was programmed in Microsoft Excel, version 2010 (Microsoft, Redmond, WA).

2.2. Population

The MINDACT trial used the modified version of Adjuvant! Online as a clinical-pathological assessment for all patients enrolled in the study. Based on this assessment, all patients were assigned a binary 'high' or 'low' clinical risk score [1]. For our studied patient population and base-case cost-effectiveness analysis, we used data on all patients identified as 'high risk' with ER+/HER2 tumours (n = 2297) (Table 3). Therefore we compared two simulated populations and their associated treatment strategies: (1) patients assessed as clinically 'high risk' with ER+/HER2 tumours who do not undergo genomic profiling, with adjuvant treatment decisions based solely on clinical-pathological characteristics; (2) patients assessed as clinically 'high risk' with ER+/HER2 tumours who undergo genomic profiling with the 70-gene signature, with adjuvant treatment decisions based on their clinical and genomic risk.

2.3. Probabilities

2.3.1. Survival probabilities and extrapolations

Using patient-level data on clinically 'high' risk individuals with ER+/HER2 tumours from the MINDACT study, two event end points were evaluated in the model: DMFS, defined as time until the first distant metastatic recurrence or death from any cause, and overall survival (OS), defined as time until death from any cause. Patients were censored at last examination date, if no event was experienced. Survival and hazard rates for each risk and treatment allocation group, based upon the intention-to-treat population, were modelled with three different parametric survival distributions (Weibull, Gompertz, exponential) to estimate rates for the observed five-year follow-up period and for extrapolation to ten years. These survival distributions were fitted to 1000 bootstrapped samples to obtain standard errors of the survival and hazard rates. The Weibull survival distribution was selected for the full

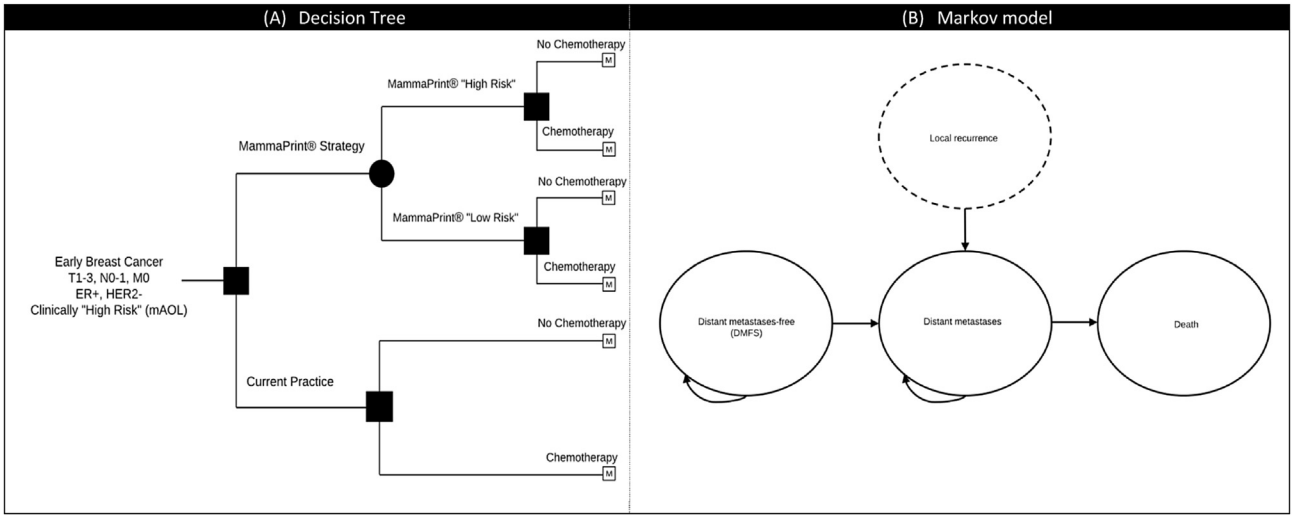

Fig. 1. Hybrid decision tree-Markov model. The hybrid (A) decision tree/(B) Markov model structure used to estimate costs, clinical outcomes and quality-adusted life years of using MammaPrint® compared with current practice (clinical risk assessment using the modified Adjuvant! Online [mAOL]) in patients with ER+, HER2- early breast cancer. In the decision tree, a square node represents the decision node at entry, the filled circles are chance nodes, and the squares with the letter M represent Markov nodes.

extrapolated model based upon the known treatment effect of chemotherapy beyond five years [5]. Interval-specific conditional survival probabilities and associated standard errors were used as the transition probabilities for each cycle of the model. Analyses were conducted with Stata, version 13. A detailed description and visualisation of the parametric modelling approach, including conditional survival probabilities are shown in Supplementary Methods 1, Tables S2–S3, and Fig. S1.

2.4. Other probabilities

In accordance with the ESMO guidelines, the parameters in the base-case model reflect the standard treatment pathway of patients with early breast cancer [3]. If current national treatment guidelines deviate from the ESMO guidelines, these were captured as country-specific treatment assumptions (Table 1, and Supplementary Methods 2–3). Adherence to chemotherapy recommendations guided by the 70-gene signature was based upon real-world values for a patient cohort with predominantly ER+/HER2- tumours reported by Kuijer et al. [7]. These patients demonstrated 95% adherence towards the 70-gene signature test results. Adherence following the clinical risk assessment alone was based on expert opinion used by the National Institute for Health and Care Excellence diagnostics assessment program (in 77% of clinical high-risk patients, chemotherapy is recommended) [8].

2.5. Health effects

Health-related quality of life (HRQol) was modelled by assigning utilities to the different health states. Baseline

Table 1
Model input parameters.

Probabilities	Mean	SE	Distribution	Source		
Survival probabilities: See Supplementary Table S2 (DMFS), Supplementary Table S3 (OS)						
Probabilities long-term treatment-related adverse events						
Acute myeloid leukaemia	0.00025	0.0001	Beta	Wolff *et al.*, 2015 [12]		
Congestive heart failure	0.037	0.001	Beta	Boekel *et al.*, 2018 [39]		
Utilities	Mean	SE	Distribution	Source		
C-high/G-low/chemotherapy	0.828	0.036	Beta	MINDACT trial, Retel *et al.*, 2013 [9]		
C-high/G-low/no chemotherapy	0.838	0.039	Beta	MINDACT trial, Retel *et al.*, 2013 [9]		
C-high/G-high	0.832	0.021	Beta	MINDACT trial, Retel *et al.*, 2013 [9]		
Distant metastasis free survival state[a]	0.824	0.002	Beta	Lidgren *et al.*, 2007 [10]		
Distant metastasis state	0.685	0.004	Beta	Lidgren *et al.*, 2007 [10]		
Disutility chemotherapy (first 6 months)	−0.067	0.004	Beta	Campbell *et al.*, 2011 [11]		
Disutility chemotherapy (6–18 months)	−0.019	0.004	Beta	Campbell *et al.*, 2011 [11]		
Acute myeloid leukaemia	0.260	0.040	Beta	Younis ea 2011 [13]		
Costs[b]	BE (€)	FR (€)	DE (€)	NL (€)	UK (£)[f]	US ($)
MammaPrint®[c]	2675	1850	2675	2675	2375	4200
Endocrine therapy total[d]	1150	550	1440	1194	284	459
Tamoxifen, AI, GnRH analogues	337	–	546	381	21	351
PB, calcium, vitamin D, DEXA scan	813	–	893	813	263	108
Chemotherapy total[c]	11,627	9821	14,314	16,600	5440	43,307
Chemotherapy	3064	–	8579	10,226	4265	–
Chemotherapy administration	2367	–	1039	3094	–	–
Anti-emetics	459	–	935	108	20	–
Prophylactic G-CSF	2742	–	3123	2535	834	–
Short-term treatment-related AE	2995	426	637	637	321	–
Monitoring/follow-up first year[e]	151	441	107	151	214	733
Monitoring/follow-up years 2–10[e]	87	441	53	87	120	733
Local/regional recurrence	18,359	18,359	18,359	18,359	15,164	21,659
Distant metastasis[e]	26,992	26,992	26,992	26,992	4949	125,152
Acute myeloid leukaemia[c]	31,259	31,259	31,259	31,259	28,468	35,644
Congestive heart failure[c]	3710	3710	3710	3710	3378	7458

AE, adverse events; G-CSF, granulocyte-colony stimulating factor; DEXA scan, dual energy X-ray absorptiometry scan; AI, aromatase inhibitors, PB, prophylactic bisphosphonates, DMFS, distant metastasis free survival; OS, overall survival; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy.

[a] Country-specific population utility norms are applied in a sensitivity analysis (Supplementary Appendix Table S8).

[b] A Gamma distribution was used for costs in the probabilistic sensitivity analysis; details on country-specific treatment utilisation assumptions and references are listed in Supplementary Methods 2–3 and Supplementary Table 4.

[c] One-off costs.

[d] Per 6-month cycle, for 5 years. Extended tamoxifen up to 7 years use applied for 25% of patients in the DMFS state.

[e] Per 6-month cycle.

[f] Between 2017–2018, the British pound sterling (£) had an average annual exchange rate of 1.1359 to the Euro (€) in accordance with the European Central Bank.

clinical-genomic subgroup-specific health state utility values were drawn from a study which captured patient well-being specific to receiving the results of their clinical and gene expression profile. These were measured with the three-level EuroQoL (EQ-5D-3L) amongst 800 enrolled patients in the MINDACT trial (Supplementary Methods 4) [9]. This baseline utility value was used for the first six-month cycle for all patients in the DMFS state. In the second cycle, patients remaining in the DMFS state revert to the utility value reported by Lidgren et al. [10]. For patients receiving adjuvant chemotherapy, HRQoL decrements drawn from Campbell et al. [11] were applied for the first three cycles in the DMFS state to reflect the negative impacts of chemotherapy (i.e. chemotherapy-related adverse events) on underlying HRQoL during and immediately following chemotherapy. The utility value for the experience of acute myeloid leukaemia as a rare late-effect chemotherapy-related adverse event (cumulative ten-year probability of 0·0049 [12]) was also applied to patients in the DMFS state and drawn from Younis et al. [13]. Utility values for the distant metastasis state were also drawn from Lidgren et al. [10].

2.6. Costs

Costs of the 70-gene signature were provided by Agendia NV. This included transport, local specimen processing and value-added tax. Treatment costs were obtained from multiple sources: national drug databases, literature and from governmental white papers on coverage decisions for the 70-gene signature. All direct medical costs relevant to the treatment and disease pathway (from initial treatment to death) for ER+ patients are considered, including costs of endocrine treatment and local/regional recurrence which are not expected to differ between strategies; all are listed in detail in Table S4. European country costs are expressed in 2017/18 Euros, UK costs are expressed in 2017/18 pound sterling and US costs are expressed in 2017/18 dollars.

2.7. Probabilistic analyses

Cost and utility parameter values were randomly drawn from assigned distributions. Five thousand Monte Carlo simulation iterations were used. The results of the simulation are illustrated in an Incremental Cost-Effectiveness plane. To show decision uncertainty, cost-effectiveness acceptability curves (CEACs) are presented [14]. CEACs show the probability that a strategy has the highest net monetary benefit, given a range of willingness-to-pay (WTP) thresholds. A strategy is deemed cost-effective depending on how much society is willing to pay for a gain in effect (i.e. per QALY gained). The World Health Organization has previously proposed a WTP threshold of one to three times annual gross domestic product per capita, although some countries follow other approaches to determining an appropriate threshold which may be more conservative [15]. We assumed an average WTP threshold of €30,000 for Europe, £20,000-£30,000 for the UK and $50,000-$100,000 for the US.

2.8. Sensitivity and scenario analyses

To test the robustness of model outcomes, a series of sensitivity analyses were performed. Cost and utility parameters were individually assessed at the 2·5 and 97·5th percentile of their assigned distribution to identify those most influential on incremental costs and incremental QALYs. Two alternative parametric distributions (exponential and Gompertz) were used in the modelling and extrapolation of DMFS and OS. To model the possibility that patients return to the same quality of life as the general population, we apply country-specific population utility norms for the distant metastasis free state, based off the values reported by Janssen et al. [16].

Finally, because adherence to guidelines can vary widely (e.g. from 40 to 99% in the Netherlands) [17], a two-way table was constructed varying the chemotherapy adherence proportions under both treatment strategies to demonstrate how this impacts costs, QALYs and ICERs. In a scenario analysis, disease-free survival was used as an alternative health state to DMFS to capture locoregional recurrences (Supplementary Methods 6).

2.9. Budget impact based on costs per population

In the countries examined in this study, early-stage breast cancer (stage I and II) comprises approximately 90% of breast cancers diagnosed, with ~70–75% of these cases being ER+/HER2 by clinical-pathological assessment [18–23]. Total costs for the 70-gene signature strategy were therefore multiplied by the current country-specific annual incidence of eligible patients in the target group. For Belgium this amounted to an incidence of 4000/year [21], for France 20,000/year [22], for Germany 24,000/year [20], for the NL 5000/year [23], for the UK 19,000 patients/year [18], and for the US 85,000/year [19].

2.10. Model validation

The cost-effectiveness model was validated using the Assessment of the Validation Status of Health-Economic decision models [24] tool (described in Supplementary Methods 5) and evaluated by two external experts.

3. Results

3.1. Mean results of the base-case analysis

The 70-gene signature-guided strategies gained 0·02 QALYs for all countries, compared with strategies guided by clinical assessment alone (Table 2). The total trajectory costs per patient amounted to the following: €39,571 vs. €40,626 in Belgium; €36,002 vs. €37,237 in France; €43,483 vs. €45,361 in Germany; €41,582 vs. €44,130 in the Netherlands; £13,711 vs. £13,268 in the UK; and $104,400 vs. $107,269 in the US (Table 2).

3.2. Probabilistic analyses

The 70-gene signature-guided strategies were cost-effective compared with clinical assessment–guided strategies in all countries, given the WTP thresholds of €30,000/£30,000/$30,000 (Table 2). The probability that the 70-gene signature produced higher net benefit than clinical assessment alone using this threshold was 72% for Belgium, 75% for France, 79% for Germany, 85% for the Netherlands, 54% for the UK and 64% for the US (Fig. 2, Fig. S2).

3.3. Sensitivity analyses

One-way sensitivity analyses did not affect the cost-effectiveness of the 70-gene signature-guided treatment strategies. Fig. 3 and S3 show the value of the test utilities, chemotherapy costs and 70-gene signature costs to be the biggest drivers of cost-effectiveness. The different parametric distributions used to extrapolate outcomes to 10 years did not change the cost-effectiveness result. Application of country-specific population utility norms led to a lower incremental QALY for all countries, except for the UK and US which saw a higher incremental QALY (Table S8). Finally, the two-way adherence analysis which was tested on the German model revealed that when 99% of clinical high-risk cases receive chemotherapy, adherence to treatment strategies guided by the 70-gene signature among clinical high/genomic low cases should be at least 70% to remain cost-effective. If the proportion of chemotherapy given in clinical high-risk cases drops to 50%, then the adherence towards the 70-gene signature low-risk result should be at least 90% (Table S5).

3.4. Budget impact based on costs per population

The 70-gene signature led to annual cost savings ranging from €4.2M in Belgium, €24.7M in France, €45.1M in Germany, €12.7M in the Netherlands and $244M in the US. A budget impact of £8.4M was seen for the UK. The variation in costs and cost savings can be attributed to the size of the target population in each

Table 2
Base-case results (Clinical high-risk ER+/HER2- patients).

Country	Strategy	Costs (CI)	LYs (CI)	QALYs (CI)	Δ Costs	Δ QALYs[a]	ICER	Budget Impact[b]	Incremental net monetary benefit
Belgium (€)	70-g	39,571 (30,984–51,049)	8.83 (8.77–8.88)	7.17 (7.11–7.23)	−1055	0.018	70-G dominates	−4.2 M	2458
	CA	40,626 (34,350–47,585)	8.85 (8.80–8.90)	7.15 (7.10–7.21)					
France (€)	70-g	36,353 (23,410–45,869)	7.83 (7.78–7.88)	6.36 (6.31–6.41)	−1234	0.020	70-G dominates	−24.7 M	2810
	CA	36,611 (31,758–43,245)	7.85 (7.80–7.89)	6.34 (6.29–6.38)					
Germany (€)	70-g	43,483 (34,659–55,191)	8.21 (8.16–8.26)	6.67 (6.61–6.71)	−1878	0.019	70-G dominates	−45.1 M	3390
	CA	45,361 (37,989–53,217)	8.23 (8.18–8.27)	6.65 (6.60–6.69)					
Netherlands (€)	70-g	41,582 (33,402–52,276)	8.83 (8.77–8.88)	7.17 (7.11–7.23)	−2548	0.019	70-G dominates	−12.7 M	3951
	CA	44,130 (37,269–51,512)	8.85 (8.80–8.90)	7.15 (7.10–7.20)					
UK (£)	70-g	13,711 (11,830–15,981)	8.02 (7.97–8.06)	6.51 (6.46–6.56)	+442	0.019	22,910	+8.4 M	1102
	CA	13,268 (11,441–15,113)	8.03 (7.98–8.08)	6.49 (6.44–6.54)			70-G more effective, more costly		
US ($)	70-g	104,400 (69,754–154,475)	8.21 (8.16–8.26)	6.67 (6.61–6.71)	−2869	0.019	70-G dominates	−244 M	4381
	CA	107,269 (84,515–136,119)	8.23 (8.18–8.27)	6.65 (6.60–6.69)					

CA, clinical assessment strategy (based on the modified Adjuvant! Online); CI, confidence intervals, representing the 2.5th and 97.5th percentiles of the 5000 Monte Carlo simulation iterations of the probabilistic analysis; ICER, incremental cost-effectiveness ratio; 70-g, 70-gene signature strategy; LYs, life years; M, million; QALYs, quality-adjusted life years; Δ, difference. "70-g dominates" meaning 70-g is more effective and less costly compared with CA.

[a] QALYs rounded to two decimal places.

[b] Total costs for the 70-gene signature strategy were multiplied by the current country-specific annual incidence of eligible patients in the target group. For Belgium, this amounted to 4000/year [21], for France 20,000/year [22], for Germany 24,000/year [20], for the NL 5000/year [23], for the UK 19,000 patients/year [18] and for the US 85,000/year [19].

Table 3
Patient characteristics. Summary of clinical-pathological characteristics of the clinical high-risk, ER+, HER2- MINDACT patients (N = 2297). Chemotherapy assignment according to randomisation.

Characteristic		Clinical high/genomic low, ER+, HER2-, no chemotherapy (n = 693) n (%)	Clinical high/genomic low, ER+, HER2-, chemotherapy (n = 709) n (%)	Clinical high/genomic high, ER+, HER2- (n = 895) n (%)	All clinical high, ER+, HER2- (N = 2297) N (%)
Age (years)	<35 years	10 (1.4)	5 (0.7)	29 (3.2)	44 (1.9)
	35 to <50 years	222 (32.0)	239 (33.7)	310 (34.6)	771 (33.6)
	50–70 years	455 (65.6)	455 (64.2)	550 (61.5)	1460 (65.6)
	>70 years	6 (0.9)	10 (1.4)	6 (0.7)	22 (1.0)
Tumour size (cm)	≤1	18 (2.6)	18 (2.5)	13 (1.5)	49 (2.1)
	>1 to 2	265 (38.2)	274 (38.6)	401 (44.8)	940 (40.9)
	>2 to 5	381 (55.0)	390 (55.0)	468 (52.3)	1239 (53.9)
	>5	29 (4.2)	27 (3.8)	13 (1.5)	69 (3.0)
Lymph node status	Negative	352 (50.8)	364 (51.3)	593 (66.3)	1309 (57.0)
	Positive				
	N1	228 (32.9)	239 (33.7)	189 (21.1)	656 (28.6)
	N2	76 (11.0)	73 (10.3)	72 (8.0)	221 (9.6)
	N3	35 (5.0)	30 (4.2)	40 (4.5)	105 (4.6)
	N4+	2 (0.3)	2 (0.3)	1 (0.1)	5 (0.2)
	n.a.	–	1 (0.1)	–	1 (0.04)
Tumour grade	Grade 1	49 (7.0)	41 (5.8)	11 (1.2)	101 (4.3)
	Grade 2	454 (65.5)	461 (65.0)	292 (32.6)	1207 (52.5)
	Grade 3	184 (26.6)	200 (28.2)	589 (65.8)	973 (42.4)
	Undefined	6 (0.9)	7 (1.0)	3 (0.3)	16 (0.7)
Adjuvant treatment received[a]	ET only	597 (86.1)	96 (13.5)	41 (4.6)	734 (32.0)
	ET + ChT	75 (10.8)	576 (81.2)	810 (90.5)	1461 (63.6)
	ChT only	0 (0.0)	7 (1.0)	21 (2.3)	28 (1.2)
	No adjuvant treatment	10 (1.4)	8 (1.1)	4 (0.4)	22 (1.0)
	Missing	1 (0.1)	8 (1.1)	11 (1.2)	19 (0.8)
Country[b]	Belgium	91 (13.1)	91 (12.8)	99 (11.1)	281 (12.2)
	France	241 (34.8)	236 (33.3)	286 (32.0)	763 (33.2)
	Germany	106 (15.3)	109 (15.4)	111 (12.4)	326 (14.2)
	Netherlands	174 (25.1)	163 (23.0)	246 (27.5)	583 (25.4)
	United Kingdom	9 (1.3)	13 (1.8)	19 (2.1)	41 (1.8)
	Other[c]	72 (3.1)	97 (4.2)	134 (5.8)	303 (13.2)

MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy.
ChT, chemotherapy; ET, endocrine therapy; ER+, estrogen receptor positive; HER2-, human epidermal growth factor 2 negative; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; N1-N4+, refers to the number of nearby lymphnodes have cancer based on the TNM staging system.
[a] Actual adjuvant treatment received; n = 21 patients have missing ChT treatment information; n = 50 patients have missing ET treatment information.
[b] It is assumed that the distribution of clinical pathological characteristics are balanced within the country populations as a result of the randomisation procedure.
[c] Other countries included Italy, Spain, Switzerland and Slovenia.

country and differences in country-specific treatment guidelines and costs.

4. Discussion

Based on MINDACT data, for patients with ER+/HER2 tumours deemed to be clinically high risk in accordance with Adjuvant! Online, treatment strategies guided by the 70-gene signature saved costs in five of six countries, gained QALYs and were cost-effective in all six countries, given country-specific WTP thresholds. Several considerations should be made in interpreting the results of our analyses. The real-world use of and adherence to the 70-gene signature can differ widely from recommendations outlined in clinical guidelines. This has been highlighted in a range of publications [7,25,26]. Provided that a country closely follows guidelines for adjuvant chemotherapy use in clinical 'high' and 'intermediate'-risk patients, adopting the 70-gene signature and adhering to its recommendation to avoid chemotherapy in 'genomic-low' patients, this will prove to be cost-effective. To demonstrate this in a sensitivity analysis, we varied chemotherapy prescription rates (which may vary according to patient and provider preferences) and analysed the impact on cost-effectiveness. Another important consideration is chemotherapy-specific costs, which were found to be the biggest driver of incremental costs. In countries where chemotherapy costs are low (such as the UK), the 70-gene signature strategy might be cost-effective up to a WTP threshold of £30,000 but no longer dominates. The UK was the only country in our study where the 70-gene

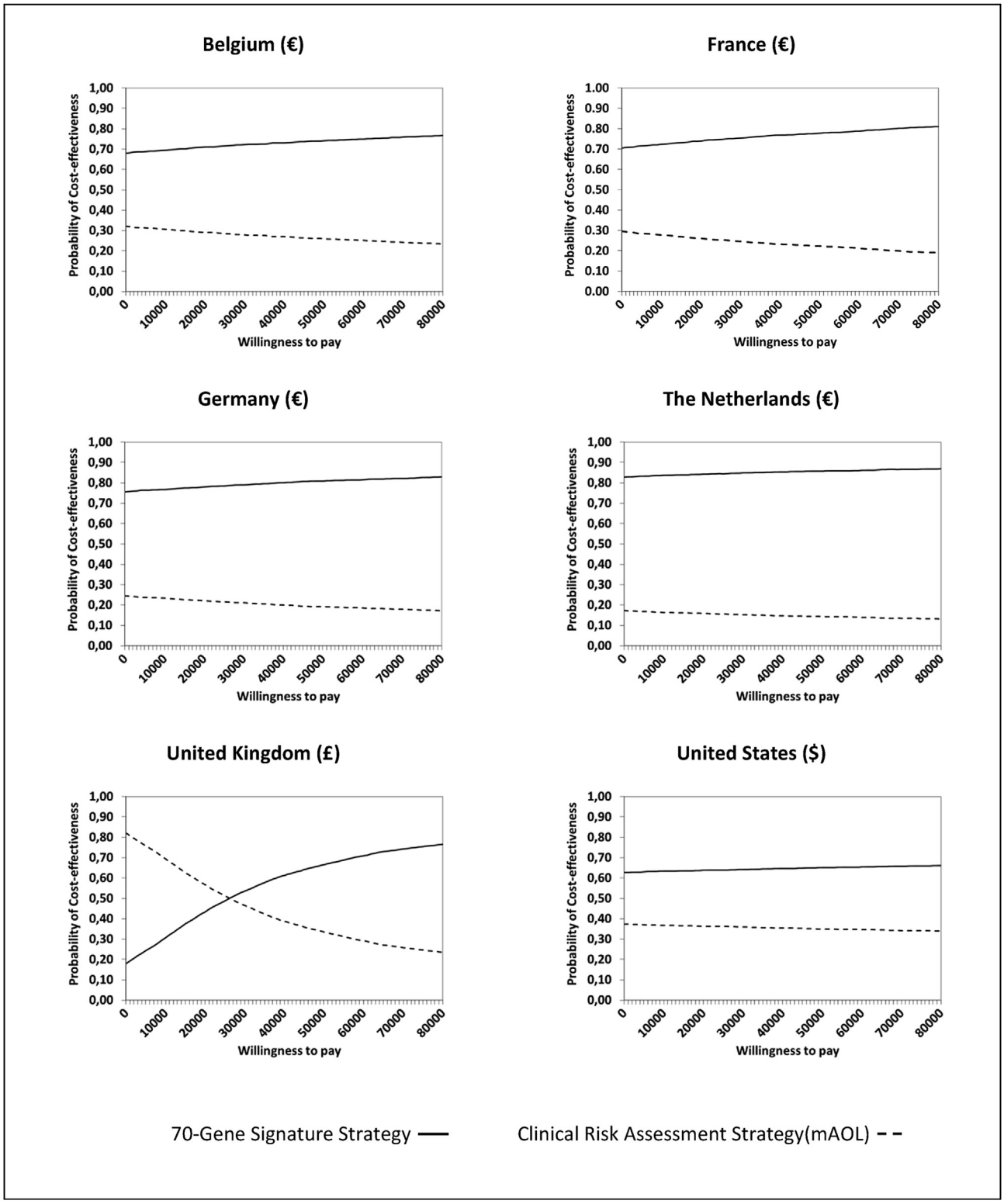

Fig. 2. Cost-effectiveness acceptability curves. The solid line represents the probability of a treatment strategy guided by the 70-gene signature to be cost-effective (Y-axis), given a series of within-country willingness-to-pay thresholds as displayed on the X-axis. The dashed line represents the same but for a treatment strategy guided by clinical risk assessment only.

signature strategy was cost-effective but not cost-saving. In a study of the performance of the UK National Health Service compared with other high-income countries (including France, Germany, the Netherlands and the US), the UK demonstrated the lowest per capita healthcare spending [27]. This is

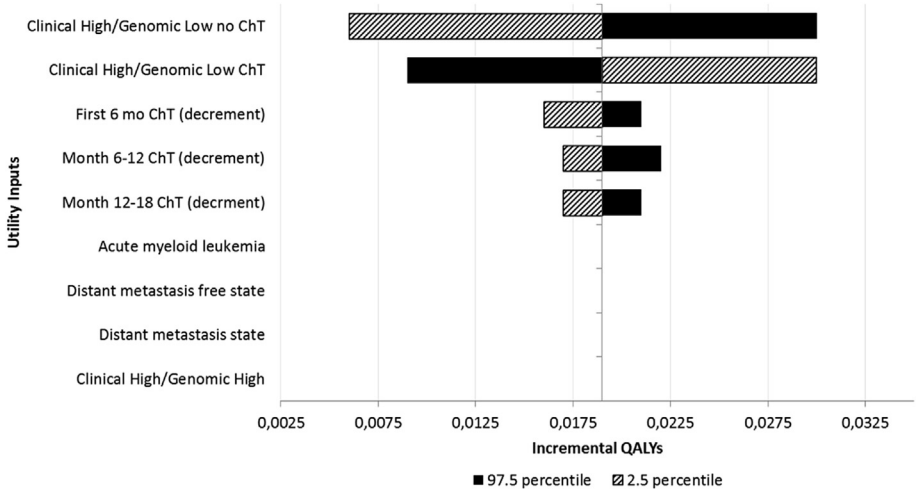

Fig. 3. One-way sensitivity analysis of utility input effect on incremental quality-adjusted life years. The model for Germany is used as an example. The sensitivity of the incremental quality-adjusted life years gained under the treatment strategy guided by the 70-gene signature (X-axis) is tested by varying the utility inputs (displayed on the Y-axis) by their respective values in the 2.5th and 97.5th percentiles. ChT, chemotherapy; QALYs, quality-adjusted life years.

certainly reflected in the comparatively lower cost inputs used in our UK model (Table 1). Although reliable and up-to-date inputs from published literature were difficult to obtain, subsequently introducing uncertainty into our model parameters and outcomes, it is obvious that in a health system with overall lower costs, potential gains will be accordingly lower.

Five-year median follow-up data was available from the MINDACT trial. Using a parametric modelling approach, we extrapolated this over a ten-year time horizon. This was important for two reasons: (1) to address regulator decision-making requirements and (2) to predict a more complete recurrence impact of the 70-gene signature-guided strategy. Although the 70-gene signature was designed to predict the chance of breast cancer recurrence within five years after surgery, our modelled population of clinical 'high-risk' patients typically experiences recurrence events within ten years. Furthermore, the risk-reducing effect of adjuvant chemotherapy occurs within the first five years. At 10 years and beyond, the absolute risk of breast cancer mortality for ER+ patients previously treated with endocrine therapy remains low. Therefore, there is low absolute benefit from chemotherapy in this population, despite the continued response after 10 years. For ER+ patients, this effect cannot easily be parsed out from the patient's receipt of endocrine therapy [5]. It is for these reasons that a ten-year time horizon was used in our analysis, instead of the typical guideline-prescribed lifetime horizon, while also avoiding unnecessary introduction of uncertainty into the model. The standard errors applied in the later cycles of our model are larger, an indication of the uncertainty for the extrapolated period after 5 years.

The strength of this article lies in the use of patient-level data from the MINDACT RCT. This is the best available evidence to model recurrence and survival outcomes and their impact on cost-effectiveness with a high level of accuracy [6,28]. Test utilities directly measured from a sample of MINDACT patients were also integrated into our model [9]. This information reflects differences between subgroups immediately following receipt of personalised recurrence risk information.

Previous cost-effectiveness analyses found the same trend of the cost-effectiveness of the 70-gene signature compared with clinical risk assessments. Despite small differences in recurrence rates between strategies, HRQoL gains and cost savings were apparent [29,30]. This however is contested by other studies which found that the 70-gene signature was not cost-effective or that uncertainty was too high to draw a conclusion [31–33].

The current analysis confirms findings of cost-effectiveness from earlier analyses but is set apart as the first cost-effectiveness modelling study of the 70-gene signature incorporating data stemming from a prospective RCT. With this data, we demonstrate how minimal expected survival differences in life years are offset by HRQoL gains, with patient outcomes proving to be similar in both strategies. Cost differences vary across countries; some countries see considerable cost savings per patient when using the 70-gene signature in guiding treatment decisions. In a patient-centred simulation, Caruana et al. [34] similarly demonstrate the significant deterioration of HRQoL due to chemotherapy side-effects for MINDACT patients. In both analyses, patients forgoing chemotherapy gain more QALYs. The minimal clinically important difference (MCID), i.e. the smallest benefit of value to patients, was not investigated and defined for the EQ-5D index-derived utilities used this study. It is possible that the observed gain in QALYs (an average of 0.02) may be smaller than a pre-defined MCID [35,36].

Interpreting the results of the MINDACT trial calls for personalised decisions tailored to the individual patient. For women with ER+/HER2- tumours, the rate of breast cancer–specific survival without distant metastasis remains favourable. However, observed recurrence differences within MINDACT may mean more to one patient than to another in the real-world, and Cardoso et al. [1] note that risk-benefit considerations must involve shared decision-making between physician and patient. Despite the seemingly small loss in life years which is counterbalanced by gains in quality of life, it is possible that QALYs do not capture the heterogeneity of preferences for patients regarding a chance of a loss in survival time. From a health systems perspective, our model provides information for country-wide policy decision-making. In this perspective, risk-benefit decisions must be weighed against 'average' (sub)groups of patients to decide if the 70-gene signature is suitable to bring into practice.

At the time of writing, the national health authorities of a number of the European countries studied in this analysis have not extended coverage over the 70-gene signature. These authorities have argued that, following the publication of 5-year median results of the MINDACT trial [1], uncertainty remains over the evidence of clinical utility using the 70-gene signature to de-escalate adjuvant chemotherapy [8,37,38]. Furthermore, cost and quality of life inputs required for cost-effectiveness modelling stem from outdated publications. Aside from the recurrence and survival outcomes drawn directly from the MINDACT trial, modelling the full impact of the 70-gene signature on quality of life and country-specific costs will continue to be riddled with uncertainty. These conclusions will likely remain until longer-term follow-up from the MINDACT trial is provided, accompanied by robust utility and cost evidence for this patient population. Future research into uniform cost data collection would be of value, for this study in particular related to chemotherapy costs, treatment-related adverse events and distant metastasis.

5. Conclusion

With the available evidence, these country-specific models demonstrated that adjuvant chemotherapy strategies guided by the 70-gene signature can save healthcare expenditures over ten years and offer a modest gain in quality-adjusted long-term survival. This information provides clinicians and policy makers with additional evidence of the clinical and economic value of the 70-gene signature for clinical high-risk patients with ER+/HER2- breast cancer in Europe and the US.

Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. W.H.v.H, V.P.R. and DB received an unrestricted 60,000 EUR grant from Agendia BV for the cost-effectiveness analysis. Agendia BV was not involved in the design, collection, analysis and interpretation of the data within this study. L.J.v.V is a cofounder, stockholder and part-time employee of Agendia BV. The other authors declare no relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.07.002.

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