

# COST EFFECTIVENESS OF TARGETING CHEMOTHERAPY WITH THE 70-GENE PROGNOSTIC SIGNATURE IN EARLY STAGE BREAST CANCER PATIENTS

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KB Tong<sup>1</sup>, E Chen<sup>1</sup>, G Brink<sup>2</sup>, R Bender<sup>2</sup>, F de Snoo<sup>2</sup>, J Malin<sup>3</sup>

<sup>1</sup>Quorum Consulting, San Francisco, CA; <sup>2</sup>Agendia, Inc., Huntington Beach, CA; <sup>3</sup>David Geffen School of Medicine at UCLA, Los Angeles, CA

## BACKGROUND

- The 70-gene signature (MammaPrint™) is a Food and Drug Administration (FDA) cleared in vitro diagnostic test that uses gene expression profiling to enable a more accurate prognosis for each individual patient with early stage breast cancer (ESBC).
- A prospective clinical trial has shown less adjuvant chemotherapy would be given were the treatment decision based on the 70-gene signature instead of commonly used clinicopathological guidelines (i.e., St Gallen guidelines, Nottingham Prognostic Index, and Adjuvant! Online) (Bueno-de-Mesquita 2007).
- Discordances between the 70-gene prognosis profile and clinicopathological risk assessments indicate the 70-gene signature may improve the selection of patients benefiting from adjuvant systemic treatment (Buyse 2006; Bueno-de-Mesquita 2008).

## OBJECTIVE

The objective of this analysis was to evaluate the cost-effectiveness of the 70-gene signature guided treatment and Adjuvant Online! Software (Adjuvant!) guided treatment in the target population from the US payers perspective.

## STUDY DESIGN

- Type of Analysis:** Cost effectiveness (CE) and cost utility (CU) analysis
- Model Structure:** Markov model
- Comparator:** 70-gene signature guided treatment vs. Adjuvant! guided treatment
- Study Population:** Age <61 yrs, estrogen receptor (ER)-independent, T1/T2 (i.e., tumor size <5 cm), lymph node negative, human epidermal growth factor receptor 2 (HER-2) negative
- Perspective:** US payer
- Time Horizon:** Lifetime (one-year cycle length); costs and health benefits were discounted at 3% per annum.
- Outcome Measures:** Life years (LY) and quality-adjusted life years (QALY)
- Base-case Model:** Utilizing 70-gene validation population (Buyse 2006)
- Alternative Model:** Utilizing US SEER population

## MODEL STRUCTURE

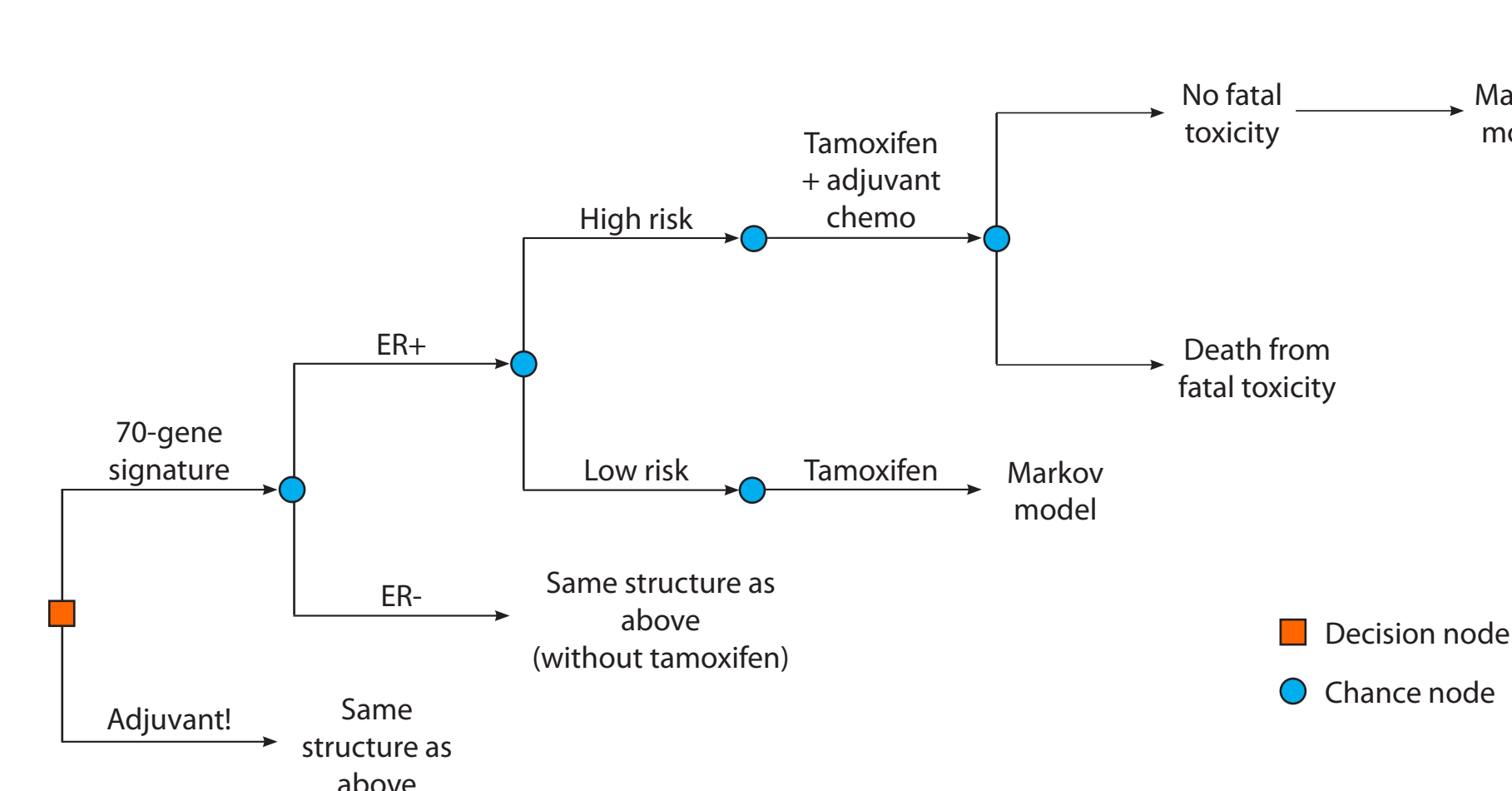
Patients were triaged to different adjuvant therapies depending on the risk classification results from the 70-gene signature or Adjuvant! (Figure 1):

- Chemotherapy + endocrine therapy
- Chemotherapy alone
- Endocrine therapy alone
- No adjuvant therapy

Clinical outcomes were modeled through Markov process (Figure 2)

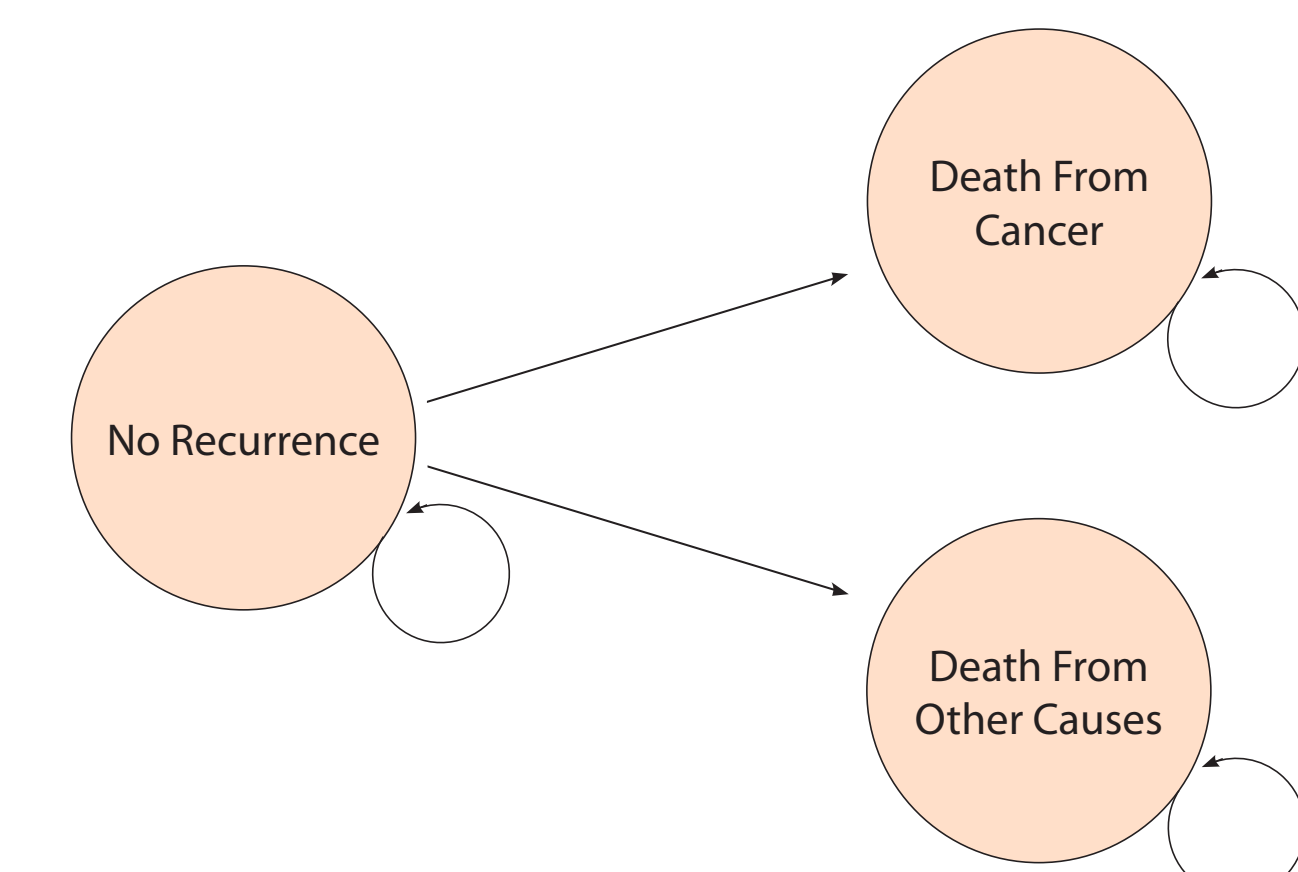
- Benefit of adjuvant chemotherapy was modeled based on data from meta-analyses.
- Markov process consisted of three health states: No Recurrence, Death from Cancer and Death from Other Causes.
- All patients started with No Recurrence.
- Patients may experience local, contralateral or distant recurrence, metastatic progression before dying from cancer; for simplicity, these clinical states were combined to Death from Cancer.
- Patients who did not die from cancer had a constant probability of dying from other causes.

Figure 1: Risk Classification and Treatment Decision



## MODEL STRUCTURE (Continued)

Figure 2: Markov Model



Patients in the No Recurrence state in the first year could, in the next year, remain No Recurrence; transition to Death due to breast cancer; or transition to Death due to other causes. The Markov process stopped when there were >99% of patients in the Death state. The model was developed with TreeAge Pro 2006.

## BASE-CASE MODEL

- In the base-case model, risk classification and clinical outcomes data were estimated from the results of a 70-gene validation study in which no patients received any systemic adjuvant therapy (Buyse 2006).
- Efficacy of chemotherapy was derived from published meta-analysis of clinical trials.
- Costs and utility values were obtained from the published literature.

Table 1: Clinical Parameters

Probability	Value	Range	Data Source
Proportion of ER+ patients	0.78	± 20%	Li 2003
Prob. of HR by 70-gene signature – ER +	0.52	0.46 - 0.59 <sup>1</sup>	Buyse 2006
Prob. of HR by 70-gene signature – ER -	0.94	0.88 - 0.98 <sup>1</sup>	Buyse 2006
Prob. of HR by Adjuvant! – ER +	0.62	0.56 - 0.69 <sup>1</sup>	Buyse 2006
Prob. of HR by Adjuvant! – ER -	1	0.96 - 1 <sup>1</sup>	Buyse 2006
Prob. of death from fatal toxicity of chemotherapy	0.005	± 50%	Hillner 1991
10-yr OS for HR by 70-gene signature – ER+	0.784	0.720 - 0.848 <sup>1</sup>	Buyse 2006
10-yr OS for LR by 70-gene signature – ER+	0.901	0.852 - 0.950 <sup>1</sup>	Buyse 2006
10-yr OS for HR by Adjuvant! – ER+	0.833	0.780 - 0.887 <sup>1</sup>	Buyse 2006
10-yr OS for LR Adjuvant! – ER+	0.85	0.784 - 0.916 <sup>1</sup>	Buyse 2006
10-yr OS for HR by 70-gene signature – ER-	0.635	0.549 - 0.721 <sup>1</sup>	Buyse 2006
10-yr OS for LR by 70-gene signature – ER-	0.80	0.506 - 1.094 <sup>1</sup>	Buyse 2006
10-yr OS for HR by Adjuvant! – ER-	0.644	0.561 - 0.727 <sup>1</sup>	Buyse 2006
Annual RRR of OS with chemotherapy – ER+	0.26	± 50%	EBGTCG 1998
Annual RRR of OS with chemotherapy – ER-	0.32	± 50%	EBGTCG 1998
Annual prob. of death from other causes	0.0085	± 50%	Karrison 1999

<sup>1</sup>95% confidence interval; ER=estrogen receptor; HR=high risk; LR=low risk; OS= overall survival; prob.=probability; RRR=relative risk reduction; yrs=year

Table 2: Cost Parameters

Cost <sup>1</sup>	Value	Range	Data Source
Adjuvant! classification	\$0	0	Free online tool
70-gene signature	\$4,200	± 50%	Agendia
Tamoxifen (per year)	\$1,383	± 50%	2007 RedBook
Caring pts receiving adjuvant chemotherapy <sup>2</sup>	\$35,964	± 50%	Hassett 2006
Caring pts without recurrence (per year)	\$5,928	± 50%	Lamerato 2006
Treatment of recurrence (including contralateral, locoregional, distant)	\$57,424	± 50%	Lamerato 2006
Terminal care for death from cancer	\$76,557	± 50%	Lamerato 2006
Terminal care for death from other causes	\$65,016	± 50%	Lamerato 2006

<sup>1</sup>Costs were based on charges/payments reported in the literature

<sup>2</sup>Included payments for chemotherapy medications, administration costs and hospitalizations, ER visits or ambulatory encounters for chemotherapy-related SAEs; the study population included 58% receiving alkylating agents, 51% anthracyclines, 25% taxanes, 18% antimetabolites. Pt=patients

Table 3: Utility Parameters

Utility	Value	Range	Data Source
Utility for recurrence-free survival	0.98	0.96 - 1	Earle 2000
Utility of receiving chemotherapy (for 6 months)	0.7	0.5 - 1	Hornberger 2005

## BASE-CASE MODEL: RESULTS

- Compared to Adjuvant!, the 70-gene signature resulted in 29% of patients being reassigned to a different risk group, and spared 10% of patients from receiving adjuvant chemotherapy (Table 4).
- The lifetime costs of the 70-gene signature guided treatment was \$1,140 higher than Adjuvant! guided treatment.
- The overall LY and QALY gains associated with the use of the 70-gene signature were 0.14 and 0.15 year, respectively.
- The ICER was \$10,059 per LY and \$9,428 per QALY (Table 5).

Table 4: Risk Classification and Change of Treatment Regimen

Probability	Adjuvant!					
	ER+		ER-		All	
<b>70-gene signature</b>	Low risk	High risk	Low risk	High risk	Low risk	High risk
Low risk	24.5%	25.5%	0%	5.6%	17.2%	19.5%
High risk	13.2%	36.8%	0%	94.4%	9.3%	54.0%
Change in adjuvant chemotherapy	38.7%		5.6%		29%	
Adjuvant chemotherapy avoided	12.3%		5.6%		10%	

ER=estrogen receptor

Table 5: Cost-Effectiveness of the 70-gene Signature Guided Treatment vs. Adjuvant! Guided Treatment

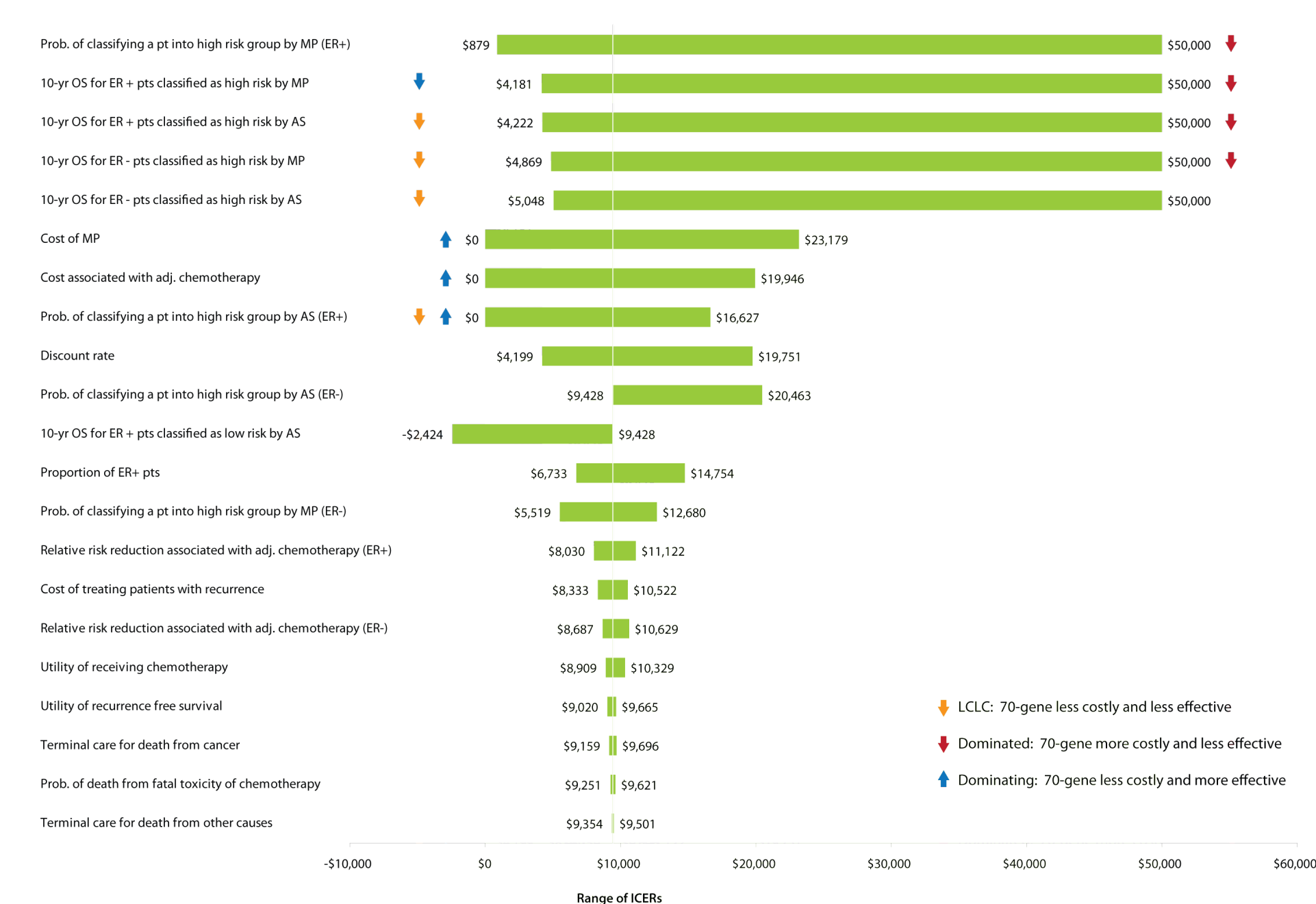
	Total Cost (\$)	Effect	Incremental Cost (\$)	Incremental Effect	ICER (\$)
<b>Life Years (LY)</b>					
Adjuvant!	\$162,140	21.596	-	-	-
70-gene signature	\$163,580	21.739	\$1,440	0.143	\$10,059
<b>Quality-Adjusted Life Years (QALY)</b>					
Adjuvant!	\$162,140	21.065	-	-	-
70-gene signature	\$163,580	21.218	\$1,440	0.153	\$9,428

ICER=incremental cost effectiveness ratio

Table 6: Cost-Effectiveness of the 70-gene Signature Guided Treatment vs. Adjuvant! Guided Treatment by ER Status

	Total Cost (\$)	Effect	Incremental Cost (\$)	Incremental Effect	ICER (\$)
<b>ER+ Patients</b>					
<b>Life Years (LY)</b>					
Adjuvant!	\$163,814	22.859	-	-	-
70-gene signature	\$165,146	23.075	\$1,332	0.216	\$6,167
<b>Quality-Adjusted Life Years (QALY)</b>					
Adjuvant!	\$163,814	21.065	-	-	-
70-gene signature	\$165,146	21.218	\$1,332	0.225	\$5,908
<b>ER- Patients</b>					
<b>Life Years (LY)</b>					
Adjuvant!	\$163,814	17.246	-	-	-
70-gene signature	\$165,146	17.139	\$1,811	-0.108	dominated
<b>Quality-Adjusted Life Years (QALY)</b>					
Adjuvant!	\$156,373	16.762	-	-	-
70-gene signature	\$158,184	16.664	\$1,811	-0.098	dominated

Figure 3: Sensitivity Analyses



## ALTERNATIVE MODEL

- In the alternative model, prognostic projections for Adjuvant! were based on tumor size and ER status for a 50-year-old ESBC patient. The overall survival cut-offs for the high- and low- risk groups were consistent with the Buyse study (i.e., low risk, if predicted 10-year overall survival  $\geq 0.88$  for ER+ patients and  $\geq 0.92$  for ER- patients) (Table 7).
- Risk classification for the 70-gene signature strategy was extrapolated from the Buyse study, assuming the same rate of cross-classification between low- and high-risk groups (Table 7).
- Efficacy of chemotherapy, cost and utility data remained the same as the base-case model.

Table 7: Comparison of Clinical Parameters in Different Populations

Probability	Buyse Population	US SEER Population <sup>1</sup>
Prob. of HR by 70-gene signature – ER+	0.524	0.52
Prob. of HR by 70-gene signature – ER -	0.944	0.944
Prob. of HR by Adjuvant! – ER +	0.623	0.71
Prob. of HR by Adjuvant! – ER -	1	1
10-yr OS for HR by 70-gene signature – ER +	0.784	0.784
10-yr OS for LR by 70-gene signature – ER +	0.901	0.901
10-yr OS for HR by Adjuvant! – ER +	0.833	0.761
10-yr OS for LR by Adjuvant! – ER +	0.85	0.924
10-yr OS for HR by 70-gene signature – ER -	0.635	0.635
10-yr OS for LR by 70-gene signature – ER -	0.80	0.80
10-yr OS for HR by Adjuvant! – ER -	0.644	0.675
10-yr OS for LR by Adjuvant! – ER -	NA	0.895

<sup>1</sup> Average age=50 year. Comorbidity=average for age; ER=estrogen receptor; HR=high risk; LR=low risk; OS=overall survival; prob.=probability; RRR=relative risk reduction; yrs=year

- Extrapolating the risk classification and outcomes results from the Buyse study to the US SEER database, the 70-gene signature was still shown to be cost-effective. It resulted in incremental costs of approximately \$700 for an additional LY and QALY gained (Table 8).

Table 8: Cost-Effectiveness of the 70-gene Signature Guided Treatment vs. Adjuvant! Guided Treatment in the Treatment Model

	Total Cost (\$)	Effect	Incremental Cost (\$)	Incremental Effect	ICER (\$)
<b>Life Years (LY)</b>					
Adjuvant!	\$163,108	21.191	-	-	-
70-gene signature	\$163,509	21.751	\$401	0.560	\$716
<b>Quality-Adjusted Life Years (QALY)</b>					
Adjuvant!	\$163,108	20.659	-	-	-
70-gene signature	\$163,509	21.230	\$401	0.571	\$702

## LIMITATIONS

- Models presented charges not paid amounts or actual costs; however, the results were not sensitive to most cost parameters.
- Due to the small patient sample include in the Buyse study, we extrapolated the risk classification and outcome results to the US SEER population.
- The Buyse study included both HER-2 positive and negative patients. As HER-2 status was not assessed in the Buyse study, all patients were evaluated as HER-2 negative in the Markov model. Thus, the model outcomes could have been different, if HER-2 status were known.
- Patients in Buyse study did not receive adjuvant chemotherapy, so we used data from meta-analyses and modeled the effectiveness of adjuvant therapy. This may over- or underestimate the actual effectiveness of chemotherapy in patients who are classified as high risk by the 70-gene signature.

## CONCLUSION

- The 70-gene signature strategy was associated with a reduction in chemotherapy use and an increase in life expectancy.
- The 70-gene signature appears to be a cost-effective strategy for obtaining additional information to guide the decision to use adjuvant chemotherapy in patients with lymph node negative ESBC.
- The model was sensitive to ER status, proportion of ER positive patients classified as high risk and long-term outcomes data.
- The base-case model utilized the Buyse study as the primary source for clinical parameters. However, the population included in the Buyse study may not fully represent ESBC population in the US.
- An alternative model was built employing data from Adjuvant! regarding risk classification and population-based data (i.e., US SEER database) for estimates of survival.