# Cost-Effectiveness of 70-Gene MammaPrint Signature in Node-Negative Breast Cancer

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**Objective:** To evaluate the cost-effectiveness of 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA) vs Adjuvant! Online software (AS) (http://www.adjuvantonline.com) in patients 60 years or younger with early-stage breast cancer.

**Study Design:** Cost-effectiveness and cost-utility analyses from a US payer perspective.

**Methods:** A Markov model with 3 health states was constructed. In the base case model, risk classification and patient outcomes were based on a 70-gene signature validation study. Efficacy of chemotherapy was derived from a published meta-analysis of clinical trials. An alternative model using data from AS and from the Surveillance, Epidemiology and End Results registry was built to examine the external validity of the base case model. The incremental benefits, costs, and cost-effectiveness of treatment guided by 70-gene signature were calculated.

**Results:** In the base case model, 70-gene signature reclassified 29% of patients and spared 10% of patients from chemotherapy. Compared with the AS strategy, the 70-gene signature strategy was associated with $1440 higher total cost per patient and with 0.14 additional life-year or 0.15 additional quality-adjusted life-year. Overall, the incremental cost-effectiveness ratios were approximately $10,000 per life-year or quality-adjusted life-year in the base case model and $700 in the alternative model. The model results were sensitive to estrogen receptor status, the proportion of patients classified as high risk vs low risk, and the overall survival in each risk group.

**Conclusion:** A 70-gene signature is likely to be a cost-effective strategy to guide adjuvant chemotherapy treatment in younger patients with early-stage breast cancer.

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For author information and disclosures, see end of text.

Breast cancer is a heterogeneous disease. Most routine clinical care for breast cancer depends on conventional clinicopathologic prognostic factors (eg, TNM, stage, and comorbidity), prognostic or predictive biomarkers (eg, estrogen receptor [ER], progesterone receptor, human epidermal growth factor receptor 2 [HER2], and grade), and clinical guidelines (eg, St Gallen International Expert Consensus, National Cancer Comprehensive Network (NCCN), and National Cancer Institute). Breast cancers with similar clinicopathologic characteristics may have strikingly different outcomes. The "one size fits all" approach may prompt ineffective use of therapy, causing unnecessary toxic effects, delaying alternative treatments, and wasting economic resources. Gene expression profiling using DNA microarray measures the expression levels of large numbers of genes simultaneously to study the effects of certain treatments, diseases, and developmental stages on gene expression. A DNA microarray test could influence clinical care based on the individual molecular profile.[1] A 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA) measures 70 risk profile mRNAs and 536 quality and reference mRNAs to predict the likelihood of distant metastases for early-stage breast cancer (ESBC).[2] It is the first assay to be cleared by the US Food and Drug Administration (FDA) using its new in vitro diagnostic multivariate index assay guidance.

A 70-gene signature was initially developed to predict the risk of developing distant metastases in 5 years for node-negative patients younger than 55 years.[3] Validation studies[2,4,5] demonstrated the prognostic value of 70-gene signature independent of clinical risk classification. In a prospective multicenter study[6] of 427 patients younger than 61 years, the use of 70-gene signature altered adjuvant treatment recommendations in 37% of patients, sparing 20% of patients from chemotherapy. In addition, 70-gene signature demonstrates clinical value in accurately selecting postmenopausal women for adjuvant chemotherapy and recently received FDA clearance for use among older women.[7,8]

Determining the extent to which 70-gene signature may influence clinical treatment decisions and ultimately outcomes may best be accomplished by prospective studies of prognosis and prediction of chemotherapy response; however, such studies take many years to complete.[9] In awaiting that information, decision

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A 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA) is commercially available and is being integrated into clinical practice.

- Results of this modeling analysis suggest that treatment guided by 70-gene signature may be associated with a decrease in chemotherapy use and an increase in life expectancy when applied appropriately.
- However, model predictions are highly sensitive to the range of uncertainty in the clinical variables.

makers need to evaluate the economic and clinical trade-offs of the test, as well as factors that would influence its appropriate use.

Adjuvant! Online software (http://www.adjuvantonline.com) (AS), a Web-based tool that calculates individualized 10-year survival probabilities and predicts benefit of adjuvant systemic therapy, is the most widely used prognostic tool to help inform clinicians and patients in decision making about therapeutic options. Risk estimates in AS were based on 10-year observed overall survival for women with ESBC in the Surveillance, Epidemiology and End Results (SEER) registry in the United States and were independently validated with the British Columbia Breast Cancer Outcomes Unit database and a large cohort of Dutch patient series.[10,11] The objectives of our study were (1) to estimate the incremental benefits, costs, and cost-effectiveness of 70-gene signature–guided treatments vs AS-guided treatments using a decision analytic model, (2) to identify factors that contribute to the cost-effectiveness of 70-gene signature, and (3) to determine patient groups in which the use of 70-gene signature is optimal.

## METHODS

### Model Structure

A decision analytic model from a US payer perspective was developed. Prognosis of a hypothetical cohort of women with ESBC was provided via 70-gene signature or AS to determine whether they were at high risk or low risk for distant metastases, on which the treatment was based. Because this evaluation critically depends on the quality of evidence related to the performance of 70-gene signature, the population assessed in this study was consistent with the FDA-cleared indication at the time of the analysis, namely, patients 60 years or younger with ER-independent, T1 or T2, lymph node–negative tumors. Because most US patients with HER2-positive tumors receive trastuzumab-containing chemotherapy, these patients were excluded from our evaluation.

After surgery, patients were triaged to different therapies depending on risk profile indicated by 70-gene signature or AS. The following 4 treatment scenarios were included: (1) chemotherapy plus endocrine therapy for ER-positive and high-risk patients, (2) chemotherapy alone for ER-negative and high-risk patients, (3) endocrine therapy alone for ER-positive and low-risk patients, and (4) no adjuvant therapy for ER-negative and low-risk patients (**Figure 1**). After risk evaluation and adjuvant treatment, patients were evaluated through a Markov process.

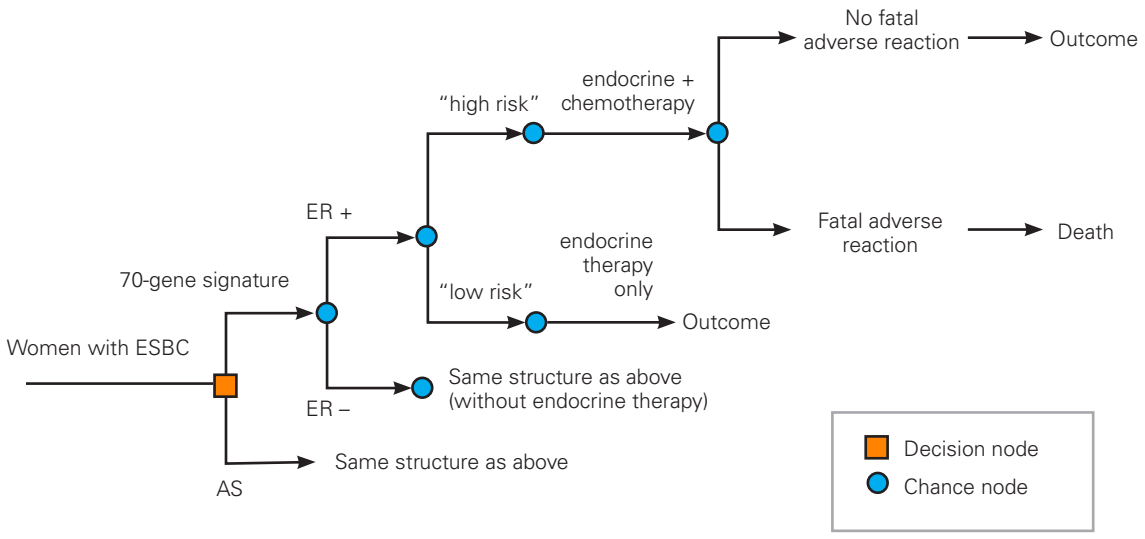
The Markov model contained the following 3 mutually exclusive health states designed to simulate the transition of patients with ESBC after adjuvant treatment: (1) no recurrence, (2) death from cancer, and (3) death from other causes. All patients started in the no recurrence state. Patients might experience local, contralateral, distant recurrence, or metastatic progression before dying of cancer. Patients who did not die of cancer had a constant probability of dying of other causes based on the risk for similar patients with breast cancer. Events of interest were modeled according to patients' transitions from one state to another in 1-year intervals. The Markov process was stopped when more than 99% of patients were in the state of death (**Figure 2**).

### Data Sources

***Risk Classification and Survival for the Base Case Model and the Alternative Model.*** Evaluated were 2 distinct patient populations, namely, a 70-gene signature validation population (the base case model) and patients with ESBC in the SEER registry (alternative model). In the base case model, risk classification and 10-year overall survival were estimated from the results of a 70-gene signature validation study described by Buyse and colleagues.[4] In that study, tumor samples were collected from 302 ESBC patients 60 years or younger with T1 or T2 lymph node–negative tumors who did not receive any adjuvant chemotherapy. Patients were assigned to high-risk and low-risk groups based on 70-gene signature and AS classifications. Patients were followed up for a median of 13.6 years to evaluate the risk of distant metastases, disease-free survival, and overall survival in each risk group.[4]

The study by Buyse et al[4] may not be representative of the US ESBC population. For example, it did not include any ER-negative patients who were clinically classified as low risk, implying a "high risk" population. Recognizing this potential limitation, an alternative model was built using data from patients with breast cancer who were included in the

**Figure 1.** Risk Classification and Treatment Decision



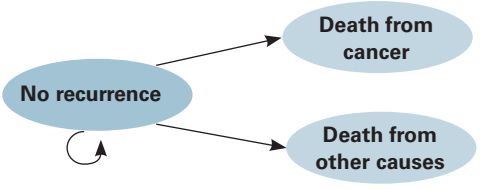

AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ER, estrogen receptor; ESBC, early-stage breast cancer; and 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).

SEER registry, were aged between 20 and 60 years, had T1 or T2 lymph node–negative tumors, and underwent primary surgery. The SEER registry data were used to model risk classification among clinically classified patients. Based on the median age at diagnosis,[12] to be conservative, the overall survival was estimated by AS in the alternative model based on a 50-year-old woman with comorbidities that were average for her age. As specific data were unavailable for 70-gene signature, its risk classification result was extrapolated from the study by Buyse et al, assuming the same rate of cross-classification between low-risk and high-risk groups relative to AS. While a full validation is possible only with prospective studies for both prognosis and prediction of chemotherapy response, application of the test results among the SEER population provides an opportunity to evaluate the likely cost-effectiveness of 70-gene signature in a real-world population if ongoing studies confirm early findings of the utility of the test.

***Risk Reduction Associated With Chemotherapy.*** The effect of adjuvant chemotherapy on overall survival was based on a meta-analysis[13] of randomized trials. The proportional risk reductions for all-cause death associated with adjuvant chemotherapy were 26% among patients with ER-positive cancer (compared with those receiving tamoxifen citrate only) and 32% among patients with ER-negative cancer.

The clinical variables used in the base case model are given in Table 1. A comparison of clinical variables used in the base case model vs the alternative model is given in Table 2.

**Figure 2.** Markov Process for Outcome Evolution




## Resource Use and Costs

Values for resource use and cost were obtained from the literature. Evaluated were the cost of risk classification, adjuvant endocrine therapy, adjuvant chemotherapy, administration, treatment-related toxic effects, and breast cancer surveillance. For patients who died of cancer, a 1-time cost of treating local recurrence or distant recurrence, as well as the cost of terminal care for cancer-related death, was included. For patients whose death was unrelated to cancer, the cost of terminal care for patients without cancer was added.

The price of 70-gene signature was obtained from Agendia Inc. The cost of caring for patients receiving adjuvant chemotherapy was estimated from a population-based study[17] of women younger than 63 years with newly diagnosed breast cancer. Using insurance claims, Hassett et al[18] estimated an

**Table 1.** Clinical Variables Used in the Base Case Model

| Variable | Value (95% Confidence Interval) | Source |
|---|---|---|
| **Probability of ER-positive** | 0.78 ±20% | Li et al[14] |
| **Probability of high risk** | | |
| By 70-gene signature if ER positive | 0.52 (0.46-0.59) | Buyse et al[4] |
| By 70-gene signature if ER negative | 0.94 (0.88-0.98) | Buyse et al[4] |
| By AS if ER positive | 0.62 (0.56-0.69) | Buyse et al[4] |
| By AS if ER negative | 1.00 (0.96-1.00) | Buyse et al[4] |
| **Probability of death from fatal adverse effects of chemotherapy** | 0.005 ±50% | Hillner and Smith[15] |
| **10-y Overall survival** | | |
| For high risk by 70-gene signature if ER positive | 0.78 (0.72-0.85) | Buyse et al[4] |
| For low risk by 70-gene signature if ER positive | 0.90 (0.85-0.95) | Buyse et al[4] |
| For high risk by AS if ER positive | 0.83 (0.78-0.89) | Buyse et al[4] |
| For low risk by AS if ER positive | 0.85 (0.78-0.92) | Buyse et al[4] |
| For high risk by 70-gene signature if ER negative | 0.64 (0.55-0.72) | Buyse et al[4] |
| For low risk by 70-gene signature if ER negative | 0.80 (0.51-1.09) | Buyse et al[4] |
| For high risk by AS if ER negative | 0.64 (0.56-0.73) | Buyse et al[4] |
| For low risk by AS if ER negative | NA | Buyse et al[4] |
| **Probability of death from other causes** | 0.0085 ±50% | Karrison et al[16] |
| **Relative risk reduction for all-cause death with chemotherapy** | | |
| ER positive | 0.26 ±50% | Early Breast Cancer Trialists' Collaborative Group[13] |
| ER negative | 0.32 ±50% | |

AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ER, estrogen receptor; 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA); NA, not applicable.

incremental expenditure of $35,964 ($31,134 in 2006 US dollars) attributable to chemotherapy use, which included payments for chemotherapy medications, hospitalizations or emergency department visits for chemotherapy-related serious adverse events, hospitalization and emergency department visits for all causes, and ambulatory encounters and prescriptions. The study included patients receiving alkylating agents (58%), anthracyclines (51%), taxanes (25%), and antimetabolites (18%). Annual tamoxifen cost was used as the cost of endocrine therapy. The costs of caring for patients who did not develop recurrence and for patients who died of cancer were derived from a retrospective analysis of patients with ESBC identified from a large integrated tumor registry.[19]

All costs were calculated in 2007 US dollars. Costs incurred beyond the first year were discounted at 3% in the base case model and varied from 0% to 6% in the sensitivity analyses.[20]

## Quality of Life and Utility

Utility refers to the preference that an individual or society places on health outcomes. Utility may range from 0 (equivalent to death) to 1 (equivalent to perfect health). A utility weight of 0.70 was assigned for patients undergoing chemotherapy (6 months), and a utility weight of 0.98 was assigned for patients not undergoing chemotherapy or after completion of chemotherapy (Table 3).[21,22] Clinical outcomes were expressed as life-years (LYs) and as quality-adjusted life-years (QALYs) gained, calculated as the total number of cycles spent in each health state multiplied by the utility associated with that health state. Patient outcomes were discounted at the same rate as costs. Detailed cost and utility variables are presented in Table 3.

## Analysis

The costs and outcomes for patients with ESBC were

forecasted over patients' lifetimes. The incremental cost-effectiveness ratio (ICER) was calculated, comparing the difference in the mean total costs and the difference in the mean LYs or QALYs gained between 70-gene signature–guided and AS-guided treatment strategies. Results are presented for the overall population and separately for ER-positive and ER-negative patients. One-way sensitivity analyses were conducted on all model variables. The effect of uncertainties in each variable on the ICER was determined. In most cases, the values for these variables were varied by 50% of their base case, unless otherwise noted in Table 1 and Table 3. Models were constructed using TreeAge Pro 2006 software (Williamstown, Massachusetts).

**Table 2**. Comparison of Clinical Variables Used in the Base Case Model Versus the Alternative Model

| Variable | Base Case Model | Alternative Model |
|---|---|---|
| **Probability of high risk** | | |
| By 70-gene signature if ER positive | 0.524 | 0.524 |
| By 70-gene signature if ER negative | 0.944 | 0.944 |
| By AS if ER positive | 0.623 | 0.710 |
| By AS if ER negative | 1.000 | 1.000 |
| **10-y Overall survival** | | |
| For high risk by 70-gene signature if ER positive | 0.784 | 0.784 |
| For low risk by 70-gene signature if ER positive | 0.901 | 0.901 |
| For high risk by AS if ER positive | 0.833 | 0.761[a] |
| For low risk by AS if ER positive | 0.850 | 0.924[a] |
| For high risk by 70-gene signature if ER negative | 0.635 | 0.635 |
| For low risk by 70-gene signature if ER negative | 0.800 | 0.800 |
| For high risk by AS if ER negative | 0.644 | 0.675[a] |
| For low risk by AS if ER negative | NA | 0.895[a] |

AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ER, estrogen receptor; 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA); NA, not applicable.
[a]Based on 10-year overall survival estimate by AS (version 8.0) for an untreated 50-year-old patient with average-for-age comorbidity by tumor size and ER status.

## RESULTS

### Baseline

In the base case model, 70-gene signature identified 63% of the cohort (50% of ER-positive patients and 94% of ER-negative patients) as high risk. AS identified 73% of the cohort (62% of ER-positive patients and 100% of ER-negative patients) as high risk. Therefore, 70-gene signature reclassified 29% of patients to a different risk group and spared 10% of patients from adjuvant chemotherapy (Table 4). Applying 26% and 32% risk reduction to the overall survival for ER-positive and ER-negative patients who received chemotherapy, the use of 70-gene signature increased the total cost by $1440 per patient compared with AS-guided treatment. In addition, 70-gene signature was expected to increase life expectancy by 0.14 year or QALYs by 0.15 year. Therefore, the ICER was approximately $10,000 per LY or QALY, suggesting that approximately $10,000 would have to be spent to gain an additional LY or QALY using 70-gene signature to guide treatment compared with AS (Table 5).

When patients with differing ER status were analyzed separately, 70-gene signature–guided treatment was shown to be more cost-effective in ER-positive patients. Specifically, it increased the mean life expectancy by 0.22 year and increased total cost by $1332. In ER-negative patients, 70-gene signature classified fewer patients as high risk than AS. Therefore, fewer patients were candidates for chemotherapy, and the overall life expectancy was reduced by approximately 0.1 year. Because the use of 70-gene signature also increased the total cost by $1811, the use of 70-gene signature was not cost-effective in ER-negative patients (Table 6).

We validated the base case model by applying risk reclassification and outcomes results from the study by Buyse et al[4] to the SEER registry. A 70-gene signature was still shown to be cost-effective by sparing 14% of patients from receiving chemotherapy. The ICER was approximately $700 for an additional LY and QALY gained if 70-gene signature was used among patients in the SEER registry (Table 6).

### Sensitivity Analysis

The ICER was more sensitive to clinical variables than to cost or utility variables (Figure 3). The results were highly

**Table 3.** Cost and Utility Variables

| Variable | Value | Range | Source |
|---|---|---|---|
| **Cost, $[a]** | | | |
| 70-Gene signature | 4200 | ±50% | Agendia Inc |
| Tamoxifen citrate per year | 1383 | ±50% | Red Book[18] |
| Caring for patients with adjuvant chemotherapy[b] | 35,964 | ±50% | Hassett et al[17] |
| Caring for patients without recurrence per year | 5928 | ±50% | Lamerato et al[19] |
| Treatment of recurrence[c] | 57,424 | ±50% | Lamerato et al[19] |
| Terminal care for death from cancer | 76,557 | ±50% | Lamerato et al[19] |
| Terminal care for death from other causes | 65,016 | ±50% | Lamerato et al[19] |
| **Utility** | | | |
| Recurrence-free survival | 0.98 | 0.96-1.00 | Earle et al[22] |
| Receiving chemotherapy for 6 mo | 0.7 | 0.5-1.0 | Hornberger et al[21] |

70-Gene signature indicates 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).
[a]Costs are in 2007 US dollars, based on charges or payments reported in the literature.
[b]Payments included chemotherapy medications, administration costs and hospitalizations, emergency department visits, or ambulatory encounters for chemotherapy-related serious adverse events; 58% of the study population received alkylating agents, 51% received anthracyclines, 25% received taxanes, and 18% received antimetabolites.
[c]Recurrence may include contralateral, locoregional, or distant recurrence.

**Table 4.** Results of Risk Classification and Treatment Decision

| | ER Positive | | ER Negative | | Overall | |
|---|---|---|---|---|---|---|
| | AS,% | | AS,% | | AS,% | |
| 70-Gene signature | Low Risk | High Risk | Low Risk | High Risk | Low Risk | High Risk |
| Low risk | 24.5 | 25.5 | 0.0 | 5.6 | 17.2 | 19.5 |
| High risk | 13.2 | 36.8 | 0.0 | 94.4 | 9.3 | 54.0 |
| Change in adjuvant chemotherapy | 38.7 | | 5.6 | | 28.8 | |
| Adjuvant chemotherapy avoided | 12.3 | | 5.6 | | 10.2 | |

AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ER, estrogen receptor; 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).

sensitive to the proportion of ER-positive patients classified as high risk by 70-gene signature, as well as estimates for overall survival in both ER-positive and ER-negative patients in the high-risk and low-risk groups. Within the range of uncertainty for the clinical variables, model predictions ranged from 70-gene signature being dominant (ie, less costly and more effective) to being less costly and less effective, as well as more costly and less effective, compared with AS. Among the cost variables, 70-gene signature price and cost associated with adjuvant chemotherapy were the 2 strongest factors, although neither had a significant effect on the results. When costs were assumed to be 50% more than the base case, the ICER did not exceed $25,000 per QALY, and when they were 50% less than the base case, 70-gene signature dominated the AS strategy.

## DISCUSSION

This study compared the potential clinical and economic benefits of 70-gene signature vs AS as a tool to identify women 60 years or younger with ESBC for receipt of adjuvant chemotherapy. The model results suggest that treatment guided by 70-gene signature may be associated with an increase in the mean life expectancy and a slight increase in cost. The ICER of approximately $10,000 per LY or QALY for the base case is well within the range of value generally considered cost-effective for a diagnostic or therapeutic intervention[7] and is substantially lower than ICERs reported in the literature for other oncology therapies.[23-29] When extended to the SEER population, the test was potentially more cost-effective. Of note, the benefits did not extend

**Table 5.** Cost-Effectiveness of 70-Gene Signature–Guided Treatment vs AS-Guided Treatment in the Base Case Model

| | Overall | | | ER Positive | | | ER Negative | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **AS** | **70-Gene Signature** | **Difference** | **AS** | **70-Gene Signature** | **Difference** | **AS** | **70-Gene Signature** | **Difference** |
| **Total cost, $** | 162,140 | 163,580 | 1440 | 163,814 | 165,146 | 1332 | 163,814 | 165,146 | 1811[ |
| **Life-years** | 21.596 | 21.739 | 0.143 | 22.859 | 23.075 | 0.216 | 17.246 | 17.139 | −0.108 |
| **Quality-adjusted life-years** | 21.065 | 21.218 | 0.153 | 22.315 | 22.540 | 0.225 | 16.762 | 16.664 | −0.098 |
| **ICER, $** | | | | | | | | | |
| Per life-year | | 10,059 | | | 6167 | | | Dominated | |
| Per quality-adjusted life-year | | 9428 | | | 5908 | | | Dominated | |

AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ICER, incremental cost-effectiveness ratio; 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).

**Table 6.** Cost-Effectiveness of 70-Gene Signature–Guided Treatment vs AS-Guided Treatment in the Alternative Model

| **Variable** | **AS** | **70-Gene Signature** | **Difference** |
|---|---|---|---|
| **Total Cost, $** | 163,108 | 163,509 | 401 |
| **Life-years** | 21.191 | 21.751 | 0.560 |
| **Quality-adjusted life-years** | 20.659 | 21.230 | 0.571 |
| **ICER, $** | | | |
| Per life-year | | 716 | |
| Per quality-adjusted life-years | | 702 | |

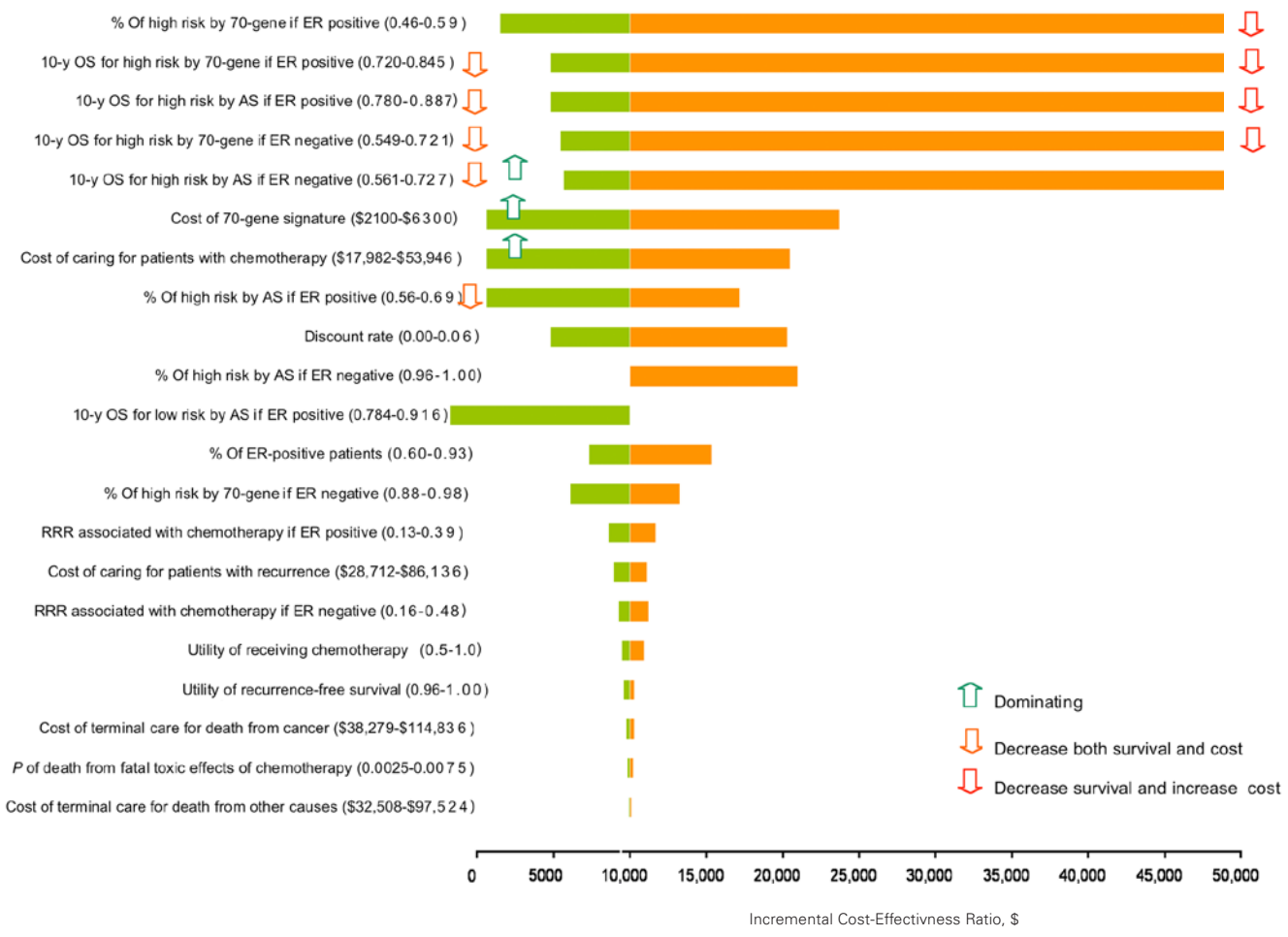
AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ICER, incremental cost-effectiveness ratio; 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).

equally to all subgroups, and based on available data, the test was associated with worse outcomes when used in patients with ER-negative tumors. Because we used data from the literature on the benefits of chemotherapy and did not assume any differential effect of chemotherapy based on the results of 70-gene signature, our base case estimates may be conservative. Given the range of uncertainty for many of the clinical variables, these results are not definitive; however, they provide evidence that, as data mature to support the clinical utility, 70-gene signature is likely to be a cost-effective strategy to improve clinical outcomes in younger women with ESBC.

The present study is similar in structure to a cost-utility study[21] to compare treatment decisions in patients with ER-positive disease based on a 21-gene recurrence score vs those based on NCCN guidelines. The NCCN guidelines classify 92% of patients as high risk for distant recurrence. For patients evaluated as high risk by NCCN guidelines, the 21-gene recurrence score increases QALYs and decreases costs. However, the results are sensitive to the mix of high-risk and low-risk patients. For patients classified by NCCN guidelines as low risk, the 21-gene recurrence score is associated with an ICER of $31,529 per QALY gained. Results of both studies suggest that there is great uncertainty around the underlying patient population in whom these tests will be applied.

In addition to AS, other clinical guidelines are used to guide treatment, including NCCN, National Institutes of Health (NIH), and St Gallen International Expert Consensus guidelines. The use of these guidelines instead of AS may yield a higher proportion of high-risk patients and may increase the treatment cost in clinically classified patients. In another cost-

**Figure 3**. One-Way Sensitivity Analyses of the Effect of Variable Uncertainty on the Incremental Cost-Effectiveness Ratio




AS indicates Adjuvant! Online software (http://www.adjuvantonline.com); ER, estrogen receptor; ESBC, early-stage breast cancer; OS, overall survival; RRR, relative risk reduction; and 70-gene signature, 70-gene MammaPrint signature (Agendia Inc, Huntington Beach, CA).

effectiveness study[30] that compared 70-gene signature with NIH guidelines to identify premenopausal women as candidates for adjuvant chemotherapy, the authors concluded that 70-gene signature–guided treatment led to lower overall cost and a decrease in life expectancy. The NIH guidelines classified 96% of patients as high risk (compared with 61% for 70-gene signature), prompting widespread use of chemotherapy if these guidelines were followed. Therefore, applying the same benefit for chemotherapy, patients treated according to NIH guidelines incurred higher costs and longer survival. Our findings suggest the opposite. Such a discrepancy may be explained in part by the choice of comparator. The ability of AS to accurately predict overall survival, breast cancer–specific survival, and event-free survival has been externally validated.[10,11] We believe that the use of AS as the comparator for 70-gene signature has the most relevance to current clinical practice.

Our study has several limitations. The prognostic value of 70-gene signature has been assessed in various populations, however, the validation studies are limited largely to Agendia Inc sources; independent validation is unavailable to date. In addition, none of these studies were performed in a randomized fashion. Because the base case model in this study used retrospective data from patients who had not received systemic treatment, the number of its predictions that would result in different therapeutic decisions was unavailable.

Furthermore, the approach used in this study may underestimate the clinical benefits associated with 70-gene signature.

Because of limited evidence available regarding the predictive value of 70-gene signature (ie, the degree of benefit from adjuvant chemotherapy for the low-risk and high-risk patients) at the time of our evaluation,[31] the analysis applied the same chemotherapy benefit to all chemotherapy recipients. Emerging evidence suggests that patients with a high-risk score on 70-gene signature are more likely to benefit from chemotherapy than patients with a low-risk score.[32] If these results had been included in this present study, 70-gene signature would have resulted in longer survival and, therefore, a better cost-effective profile than predicted herein.

Outcome predicted by AS was presented as a continuous variable, whereas clinical decision making in our model assumes dichotomization into low-risk and high-risk groups.[4] Although the prognostic value of 70-gene signature was almost entirely independent of the definition of clinical risk, the use of different cutoff points for high-risk and low-risk dichotomization may affect the proportion of high-risk patients, the percentage of patients receiving chemotherapy, and the outcomes in the clinically classified patients.

The present study focused only on patients 60 years or younger. At the time of this analysis, FDA clearance for 70-gene signature was available only for younger patients; thus, we limited our analysis to this group, and we applied the model to patients with comparable ages in the SEER registry. Meta-analysis[13] has shown less benefit from chemotherapy in older patients compared with younger patients. Because 70-gene signature for older patients has recently been cleared by the FDA and is covered by Medicare, there may be additional clinical value for selecting postmenopausal patients from adjuvant chemotherapy. The present findings will need to be verified using a validation study for 70-gene signature among postmenopausal patients.

A 70-gene signature is being integrated into clinical practice.[33] The test has been shown to be prognostic and predictive of outcomes.[31,32] A dichotomous result at an individual level provides clinicians with invaluable information that is unavailable using other methods. Our study findings suggest that the use of this test is highly cost-effective among ER-positive patients but is less so among ER-negative patients. In addition, the clinical and economic trade-offs of using the test in postmenopausal women need further evaluation. The Microarray in Node-Negative Disease May Avoid Chemotherapy trial[9,34] prospectively compares patients in the adjuvant treatment setting by the standard clinicopathologic prognostic factors included in AS and by 70-gene signature. While data from this trial, once available, can be used to refine our model, results of the modeling-based analysis herein suggest that the 70-gene signature strategy is associated with a decrease in chemotherapy use and may increase life expectancy when applied appropriately.

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