Cost-Effectiveness of a 14-Gene Risk Score Assay to Target Adjuvant Chemotherapy in Early Stage Non-Squamous Non-Small Cell Lung Cancer

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Key Words. Gene-expression profiling • Non-small cell lung cancer • Cost effectiveness

ABSTRACT

Purpose. Life Technologies has developed a 14-gene molecular assay that provides information about the risk of death in early stage non-squamous non-small cell lung cancer patients after surgery. The assay can be used to identify patients at highest risk of mortality, informing subsequent treatments. The objective of this study was to evaluate the cost-effectiveness of this novel assay.

Patients and Methods. We developed a Markov model to estimate life expectancy, quality-adjusted life years (QALYs), and costs for testing versus standard care. Risk-group classification was based on assay-validation studies, and chemotherapy uptake was based on pre- and post-testing recommendations from a study of 58 physicians. We evaluated three chemotherapy-benefit scenarios: moderately predictive (base case), nonpredictive (i.e., the same benefit for each risk group), and strongly predictive. We calculated the incremental

cost-effectiveness ratio (ICER) and performed one-way and probabilistic sensitivity analyses.

Results. In the base case, testing and standard-care strategies resulted in 6.81 and 6.66 life years, 3.76 and 3.68 QALYs, and \$122,400 and \$118,800 in costs, respectively. The ICER was \$23,200 per QALY (stage I: \$29,200 per QALY; stage II: \$12,200 per QALY). The ICER ranged from “dominant” to \$92,100 per QALY in the strongly predictive and nonpredictive scenarios. The model was most sensitive to the proportion of high-risk patients receiving chemotherapy and the high-risk hazard ratio. The 14-gene risk score assay strategy was cost-effective in 68% of simulations.

Conclusion. Our results suggest that the 14-gene risk score assay may be a cost-effective alternative to standard guideline-based adjuvant chemotherapy decision making in early stage non-small cell lung cancer. *The Oncologist* 2014;19:466–476

Implications for Practice: Gene-expression profiles, like the 14-gene risk score assay, provide prognostic information that may improve adjuvant chemotherapy decision making in early stage non-small cell lung cancer relative to standard stage-based approaches. We evaluated the clinical and economic impacts of the 14-gene risk score assay and report a testing strategy that is likely to result in additional quality-adjusted survival at an additional cost that is generally considered to be cost-effective in the United States. Our findings can be used to inform decisions about clinical implementation and payer considerations.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is among the most commonly diagnosed malignancies in the U.S., with approximately 192,000 incident cases in 2012 [1]. Cases diagnosed in the early stages (i.e., stage I or II) have better survival prognosis relative to those diagnosed at more advanced stages, yet overall 5-year survival remains poor at 50% [2–4]. In stage I and II NSCLC, standard care typically begins with surgery to remove the malignant tissue [5, 6]. After surgery, patients and clinicians are faced with a decision about whether to use adjuvant chemotherapy to attempt to reduce the risk of disease recurrence. This decision is typically informed by a variety of

clinical and pathologic factors, with disease stage playing a prominent role [5, 6]. These prognostic factors are used to risk stratify patients so that the balance of benefits and risks of adjuvant chemotherapy can be weighed [7].

Large clinical trials have demonstrated that adjuvant chemotherapy does not provide a survival benefit on average in stage I NSCLC but shows moderate survival benefit in stage II NSCLC [8]. Accordingly, clinical guidelines from the American Society of Clinical Oncology and National Comprehensive Cancer Network generally recommend that stage I patients not receive adjuvant chemotherapy and that stage II patients

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receive chemotherapy [5, 6, 8]. However, even among stage I patients, the 5-year risk of recurrence remains high at 24%. In addition, adjuvant chemotherapy is often considered for high-risk subgroups, such as those with poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and/or incomplete lymph node sampling [7, 9].

The limited success of the traditional TNM staging system for predicting outcomes after primary therapy has led to efforts to identify biomarkers of disease risk and treatment response [10–14]. One example is a novel 14-gene risk score (RS) assay (Pervenio Lung RS; Life Technologies, Rockville, MD, <http://www.lifetech.com>) developed by Kratz and colleagues [12]. In a study of this assay, patients with completely resected non-squamous non-small cell lung tumors were shown to have a continuum of overall survival prognosis based on the assay's risk score classification. Stage I patients classified as low, intermediate, and high risk had median overall survival times of 113 months, 91 months, and 59 months, respectively [12]. Stage II patients classified as low, intermediate, and high risk had median overall survival times of 62 months, 49 months, and 33 months, respectively [12]. Although currently established as a prognostic test, the 14-gene RS may also provide information in early stage NSCLC to improve targeting of adjuvant chemotherapy, as has been seen with similar assays in early stage breast cancer [15].

Prospective research is under way to further investigate the ability of the 14-gene RS to inform adjuvant chemotherapy treatment decisions (i.e., as a predictive test), but endpoints will not be reached for several years [16]. In the interim, thousands of patients with early stage NSCLC, in consultation with their physicians, will face adjuvant chemotherapy treatment decisions [10, 17]. In this study, we inform these decisions by using simulation modeling to evaluate the potential health outcomes and cost-effectiveness of the 14-gene RS relative to standard guideline-based care. Our findings could be used to inform decisions about clinical implementation and payer considerations.

MATERIALS AND METHODS

Overview

We developed an integrated decision tree and Markov state-transition model to simulate health outcomes for a cohort of 67-year-old patients with completely resected stage I/II non-squamous NSCLC from the time of adjuvant chemotherapy decision making until death (Fig. 1) [12]. The model compares health outcomes for the cohort in two clinical strategies: a 14-gene RS strategy and a standard guideline-based strategy. In the 14-gene RS strategy, patients undergo gene-expression profiling and are classified as having low-, intermediate-, or high-risk overall survival prognosis, and subsequent treatments are affected by patients' risk status (i.e., high-risk patients are recommended to receive adjuvant chemotherapy). In the standard-care strategy, adjuvant chemotherapy decisions are informed solely by standard clinical-pathological factors (e.g., stage, tumor size, histology). The cohort is then tracked for disease recurrence and mortality over a lifetime horizon. Model outcomes include life years, quality-adjusted life years (QALYs), and direct medical expenditure (referred to

Figure 1. Simplified decision model (A) and Markov model schematics (B).

Abbreviations: NSCLC, non-small cell lung cancer; RS, risk score.

as “costs”). Our analysis took a payer perspective, and cost and QALY outcomes were discounted at 3% per year.

The decision model was implemented in Microsoft Excel (Microsoft Inc., Redmond, WA, <http://www.microsoft.com>).

Model Structure

The model was developed as a Markov cohort, tracking long-term outcomes in 1-month cycles for each patient cohort strata defined by stage (I or II), 14-gene RS risk group (low, intermediate, or high), and adjuvant chemotherapy use or nonuse. The model consists of five health states following diagnosis and primary treatment (nodule resection): observation, chemotherapy, postchemotherapy, recurrence, and death (Fig. 1). In addition, we tracked adverse event rates related to chemotherapy use (anemia, neutropenia, febrile neutropenia, fatigue, anorexia, and nausea or vomiting) [18]. We calculated outcomes for the 14-gene RS and standard-care strategies using weighted averages of outcomes from stage and risk subgroups.

Model Inputs

Model inputs were derived from the 14-gene RS validation studies; a physician decision-making survey; the U.S. Surveillance, Epidemiology, and End Results (SEER) database; published literature; and government sources [4, 11, 19–22].

Table 1. Model input values, distributions, and data sources

Input	Point estimate	Low	High	Distribution	Data source
14-gene risk score strategy					
Stage I: low risk					
Baseline 5-year recurrence risk	6.5%			N/A	Imputed
Base case recurrence hazard ratio	1.09	0.86	1.37	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.95	0.76	1.19	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	3.84			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	3.8%	2.7%	5.0%	Beta	[23]
Proportion of all stage I patients	27.7%	26.3%	29.1%	Beta	[12]
Stage I: intermediate risk					
Baseline 5-year recurrence risk	37.0%			N/A	Imputed
Base case recurrence hazard ratio	0.99	0.79	1.23	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.95	0.76	1.19	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	3.84			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	26.3%	18.4%	34.2%	Beta	[23]
Proportion of all stage I patients	20.1%	19.1%	21.1%	Beta	[12]
Stage I: high risk					
Baseline 5-year recurrence risk	69.0%			N/A	Imputed
Base case recurrence hazard ratio	0.87	0.76	1.09	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.95	0.76	1.19	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	0.44			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	70.6%	49.4%	91.8%	Beta	[23]
Proportion of all stage I patients	52.2%	49.6%	54.8%	Beta	[12]
Stage II: low risk					
Baseline 5-year recurrence risk	34.3%			N/A	Imputed
Base case recurrence hazard ratio	0.82	0.59	0.90	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.69	0.57	0.83	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	2.93			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	1.0%	0.1%	5.0%	Beta	[23]
Proportion of all stage II patients	15.4%	14.6%	16.2%	Beta	[12]
Stage II: intermediate risk					
Baseline 5-year recurrence risk	100%			N/A	Imputed
Base case recurrence hazard ratio	0.75	0.54	0.83	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.69	0.57	0.83	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	2.93			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	57.1%	40.0%	74.3%	Beta	[23]
Proportion of all stage II patients	14.3%	13.6%	15.0%	Beta	[12]

(continued)

Table 1. (continued)

Input	Point estimate	Low	High	Distribution	Data source
Stage II: high risk					
Baseline 5-year recurrence risk	100%			N/A	Imputed
Base case recurrence hazard ratio	0.66	0.48	0.72	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.69	0.57	0.83	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	0.24			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	95.2%	66.7%	100.0%	Beta	[23]
Proportion of all stage II patients	70.3%	66.8%	73.8%	Beta	[12]
Standard care strategy					
Stage I					
Baseline 5-year recurrence risk	45.3%			N/A	Imputed
Base case recurrence hazard ratio	0.95	0.76	1.19	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.95	0.76	1.19	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	0.8			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	14.3%	10.0%	18.6%	Beta	[23]
Stage II					
Baseline 5-year recurrence risk	89.9%			N/A	Imputed
Base case recurrence hazard ratio	0.69	0.57	0.83	Log-normal	[8]
Nonpredictive scenario recurrence hazard ratio	0.69	0.57	0.83	Log-normal	[8]
JBR.10 scenario recurrence hazard ratio	0.8			Log-normal	[26]
Proportion receiving adjuvant chemotherapy	68.8%	48.1%	89.4%	Beta	[23]
Chemotherapy grade 3/4 adverse events					
Neutropenia	73.0%	58.4%	87.6%	Beta	[27]
Febrile neutropenia	7.0%	5.6%	8.4%	Beta	[27]
Fatigue	15.0%	12.0%	18.0%	Beta	[27]
Anorexia	10.0%	8.0%	12.0%	Beta	[27]
Nausea	10.0%	8.0%	12.0%	Beta	[27]
Vomiting	7.0%	5.6%	8.4%	Beta	[27]
Anemia	7.0%	5.6%	8.4%	Beta	[27]
Mortality					
Postrecurrence mortality rate (1 year)	0.52	0.494	0.546	Beta	[30]
Background mortality	Life table				[29]
Health state utility values					
Observation utility	0.67	0.54	0.80	Beta	[47]
On chemotherapy utility	0.55	0.44	0.66	Beta	[47]
Postchemotherapy utility	0.67	0.54	0.80	Beta	[47]
Recurrence utility	0.49	0.39	0.59	Beta	[48]
Cost (2013 U.S. dollars)					
Cost of 14-gene risk score assay	\$3,995	\$3,795	\$4,195	Normal	Life Technologies
Cisplatin (10 mg)	\$2	\$2	\$2	Normal	[49]
Vinorelbine (10 mg)	\$10	\$8	\$12	Normal	[50]
Cost of chemotherapy infusion (first hour)	\$143	\$115	\$172	Normal	[51]

(continued)

Table 1. (continued)

Input	Point estimate	Low	High	Distribution	Data source
Cost of chemotherapy infusion (subsequent hours)	\$31	\$24	\$37	Normal	[52]
Outpatient visit	\$69	\$55	\$83	Normal	[53]
Computed tomography scan	\$308	\$246	\$369	Normal	[54]
Cost per month monitoring	\$125	\$100	\$150	Normal	Assumption
Cost per month after recurrence	\$9,999	\$7,999	\$11,999	Normal	[55]
Cost per month no recurrence at 5 years to death	\$272	\$217	\$326	Normal	[56]
Erythropoietin (40,000 units)	\$489	\$391	\$587	Normal	[57]
Subcutaneous erythropoietin injection (per injection)	\$51	\$41	\$62	Normal	[58]
Hospitalization, febrile neutropenia (per episode)	\$5,530	\$4,424	\$6,635	Normal	[59]

Abbreviation: N/A, not available.

All model parameters and data sources are provided in Table 1. Mean input values and uncertainty ranges were derived directly from source studies when possible.

Risk-Group Distribution Inputs

The proportions of patients with early stage NSCLC classified by the 14-gene RS as low, intermediate, and high risk were derived from the test-validation results reported by Kratz and colleagues [12]. Specifically, we based the risk-group distribution of stage I patients on that of 433 patients in the Kaiser Permanente validation cohort (28% low, 20% intermediate, 52% high) and the risk-group distribution of stage II patients on that of 222 patients in the China Clinical Trials Consortium cohort (16% low, 14% intermediate, 70% high) [12].

Chemotherapy Use and Effectiveness Inputs

Chemotherapy utilization rates in the 14-gene RS and usual-care strategies were based on the findings of a physician survey that evaluated pre- and post-testing adjuvant chemotherapy recommendations [23]. Updated results from that study tracked 58 physicians in community-practice settings who provided adjuvant chemotherapy recommendations for 120 patients based on clinical-pathological factors and then made another recommendation after receiving the 14-gene RS risk-group classification. We assumed that the proportion of patients receiving chemotherapy in the standard-care strategy was equal to that recommended to receive chemotherapy before 14-gene RS testing (i.e., 14.3% of stage I and 68.8% of stage II) and that the proportion of patients receiving chemotherapy in the 14-gene RS strategy was equal to that recommended to receive chemotherapy after testing (i.e., 3.8% of low-risk, 26.3% of intermediate-risk, and 70.6% of high-risk patients among stage I and 1.0% of low-risk, 57.1% of intermediate risk, and 95.2% of high-risk patients among stage II). Our standard-care chemotherapy-utilization rates were consistent with prior reports in the peer-reviewed literature [24].

Patients that received chemotherapy were assumed to get the cisplatin and vinorelbine regimen used in the International Adjuvant Lung Cancer Trial (IALT) and recommended by

Figure 2. HR distributions for stage I patients (A) and stage II patients (B) by risk group. To derive mean HRs by risk group, we assumed that the HRs had a log-normal distribution, generated the cumulative HR distribution, scaled the distribution with the increasing risk of death in the underlying population as calculated by the 14-gene risk score assay, used the risk category cutoffs to segment the population, and calculated the mean HR by risk group.

Abbreviation: HR, hazard ratio.

National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines [5, 7, 25].

We modeled the impact of adjuvant chemotherapy through its effect on the rate of disease recurrence (local and distant). To estimate the effects of chemotherapy in the 14-gene RS risk groups, we evaluated health outcomes across

three plausible scenarios representing the likely range of outcomes in clinical practice. In our base case, we used stage I and II distant recurrence-free survival hazard ratios reported in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis conducted by Douillard and colleagues and distributed the overall recurrence rate benefit in each stage to the risk groups based on baseline recurrence risk (Fig. 2) [8]. Specifically, we assumed that chemotherapy-benefit scales, from least benefit to greatest benefit, within its uncertainty range (i.e., 95% confidence interval for the hazard ratio), according to underlying prognosis for the stage I and II cohort (Fig. 2). This assumption is supported by evidence in the peer-reviewed literature demonstrating increased benefit from adjuvant chemotherapy in patient subgroups with increased baseline risk of disease recurrence and death [8]. We also evaluated a scenario with a nonpredictive chemotherapy effect (i.e., equal chemotherapy benefit across all risk groups), in which the 14-gene RS strategy improved health outcomes solely through its impact on treatment decisions (with more patients receiving chemotherapy because of classification as high-risk). These patients then were assumed to receive the average stage-specific chemotherapy benefit. Last, we evaluated a strongly predictive chemotherapy scenario based on the findings of an analogous molecular marker study conducted by Zhu and colleagues with patients from the JBR.10 trial (a phase III randomized controlled trial that evaluated cisplatin and vinorelbine versus observation alone in stage I/II NSCLC) [25, 26]. The chemotherapy effects from this study are not directly applicable, given differing gene panels and risk-group cutoffs, but nonetheless, it can be used to represent the upper end of the spectrum of predictive impact that could be achieved. Collectively, these scenarios represent the plausible range of chemotherapy impacts in clinical practice and facilitate evaluation of the plausible range of cost-effectiveness of the 14-gene RS assay strategy.

Adjuvant Chemotherapy Adverse Event Rates and Resource Utilization

We considered grade 3/4 chemotherapy adverse events occurring in $\geq 5\%$ of patients in the JBR.10 trial (Table 1) [27]. Neutropenia was assumed to require two office visits, treatment with 500 mg of clindamycin three times daily for 1 month, and 500 mg of amoxicillin three times daily for 1 month. We assumed that 70% of febrile neutropenia cases required inpatient treatment, and the remaining 30% was treated in an outpatient setting with two office visits and 2 g of cefepime three times daily for 2 days. Anemia was assumed to be treated with one vial of erythropoietin injected per week until disease recurrence. Fatigue, anorexia, nausea, and vomiting were assumed to require two office visits.

Recurrence Inputs

We estimated lung cancer recurrence using the relationship between lung cancer-specific mortality and recurrence (local and distant), as reported in the IALT study [20]. Specifically, we applied the observed IALT ratio of recurrence to lung cancer-specific mortality to the 14-gene RS validation cohort to obtain recurrence rates for the initial 5 years of follow-up. In years 5–10 of follow-up, we applied recurrence rates derived from a study of long-term outcomes in early stage NSCLC from

Maeda and colleagues [28]. We assumed that no recurrences occurred beyond 10 years of follow-up [28].

Mortality Inputs

We implemented separate overall mortality rates by disease stage and risk-group classification, in accordance with the findings of the 14-gene RS validation study [12]. Overall mortality rates were divided into lung cancer-specific mortality and other-cause mortality by subtracting other-cause mortality from overall mortality. Other-cause mortality rates were derived from life tables for former smokers reported as part of the National Cancer Institute CISNET project [29].

Cost Inputs

We utilized adjuvant chemotherapy, adverse event treatment, and procedure costs based on the 2013 U.S. Centers for Medicare and Medicaid Services reimbursement schedule (Table 1). The cost of the 14-gene RS assay (\$3,995) was provided by Life Technologies.

Model Validation and Calibration

We calibrated our model in each stage and risk-group strata by fixing postrecurrence mortality (in accordance with current evidence) and adjusting the annual recurrence rate to align simulated 5-year overall survival with overall survival rates from the 14-gene RS clinical studies [12, 30].

We validated our long-term survival outcomes by comparing mean overall survival with mean survival in similar patients in the JBR.10 clinical trial [31]. We also calculated 5-year overall survival hazard ratios for stage I and II patients receiving chemotherapy (vs. observation only) and evaluated whether they were within the stage-specific 95% confidence intervals reported in the LACE meta-analysis [8].

Model Outcomes

We used our model to calculate overall life expectancy, quality-adjusted life years (QALYs), and direct medical expenditures for the 14-gene RS and standard-care strategies. The QALY is a standard metric from comparative effectiveness research that incorporates a quality of life “utility score” adjustment applied to life expectancy [32–34]. A utility score of 0 represents the value for death, and 1 represents the value for “full” health. Thus, 10 years of life at a utility of 0.5 is equivalent to 5 years of life with full health [33]. The QALY allows consideration of morbidity and mortality in a single measure, allows for comparability between studies, and is considered the gold standard metric in cost-effectiveness studies [35, 36]. These outcomes enable calculation of the incremental cost-effectiveness ratio (ICER), the ratio of the difference in costs between strategies and the difference in effects (e.g., QALYs) between strategies. We also conducted similar analyses stratified by disease stage (I or II) to evaluate whether there were differential health outcome impacts and ICERs.

Sensitivity Analyses

We evaluated outcome uncertainty using one-way and probabilistic sensitivity analyses. In our one-way sensitivity analysis, we propagated low- and high-input-value estimates through the model and obtained the resulting range of

Table 2. Health outcomes by scenario

Treatment	14-gene RS assay cost, \$	Chemotherapy cost, \$	Monitoring cost, \$	Recurrence cost, \$	Adverse event cost, \$	Total cost, \$	LYs	QALYs
Base case scenario: moderately predictive chemotherapy benefit by risk group								
14-gene RS strategy	3,995	1,995	7,254	104,001	727	117,972	6.81	3.76
Standard care strategy	0	1,182	7,134	107,415	432	116,163	6.66	3.68
Difference	3,995	813	120	−3,414	296	1,810	0.15	0.08
ICER							\$11,952	\$23,154
Alternative scenario 1: strongly predictive chemotherapy benefit by risk group								
14-gene RS strategy	3,995	2,025	8,387	83,165	727	98,300	7.57	4.18
Standard care strategy	0	1,193	7,394	102,527	432	111,546	6.83	3.78
Difference	3,995	833	993	−19,362	296	−13,246	0.15	0.40
ICER							Dominant	Dominant
Alternative scenario 2: nonpredictive chemotherapy benefit by risk group								
14-gene RS strategy	3,995	1,992	7,137	106,073	727	119,924	6.73	3.72
Standard care strategy	0	1,181	7,122	107,588	432	116,323	6.65	3.68
Difference	3,995	811	16	−1,516	296	3,601	0.08	0.04
ICER							\$44,305	\$92,074

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; RS, risk score.

incremental QALYs and costs for each individual input. We present our one-way sensitivity analysis results in tornado diagrams displaying the 10 most influential model inputs. We also conducted a probabilistic sensitivity analysis using Monte Carlo simulation [37–39]. This approach involved specifying the distribution of model inputs, simultaneously sampling parameter sets from the distributions, and propagating the values through the model framework to calculate the joint distribution of model outcomes [37, 38]. We used the probabilistic sensitivity analysis results to calculate 95% credible intervals (95% CI) around model outcomes, and we display these results in the form of cost-effectiveness acceptability curves.

Willingness-to-Pay (per QALY) Threshold

We evaluated the cost-effectiveness of the 14-gene RS at willingness-to-pay thresholds ranging from \$50,000 to \$200,000 per QALY [40–43]. This range reflects the implied willingness to pay for cancer treatments in the U.S. and is consistent with values used in prior analyses [40, 44, 45].

RESULTS

Base Case Results

In our base case analysis, the 14-gene RS strategy and the standard-care strategy respectively resulted in 54% and 32% of patients receiving adjuvant chemotherapy, in 6.81 and 6.66 life years, in 3.76 and 3.68 QALYs, and in lifetime costs of \$118,000 and \$116,200 (Table 2). Accordingly, the 14-gene RS strategy resulted in greater life expectancy and QALYs compared with the standard-care strategy at a greater overall cost. The resulting incremental cost-effectiveness ratio for the

combined analysis of stage I and II patients was \$23,200 per QALY gained.

Stage-Stratified Results

When we restricted our analysis to stage I patients, the 14-gene RS strategy and the standard-care strategy respectively resulted in 43% and 14% of patients receiving adjuvant chemotherapy, in 7.56 and 7.41 life years, in 4.18 and 4.11 QALYs, and in lifetime costs of \$98,200 and \$96,100 (Table 2). The resulting incremental cost-effectiveness ratio for only stage I patients was \$29,200 per QALY gained.

When we restricted our analysis to stage II patients, the 14-gene RS strategy and the standard-care strategy respectively resulted in 75% and 69% of patients receiving adjuvant chemotherapy, in 5.22 and 5.07 life years, in 2.86 and 2.78 QALYs, and in lifetime costs of \$159,900 and \$158,800 (Table 2). The resulting incremental cost-effectiveness ratio for only stage II patients was \$12,200 per QALY gained.

Calibration and Validation Results

In our validation analysis comparing mean expected survival, the results estimated by the model were well aligned with those from the JBR.10 trial in patients undergoing observation only (5.97 years vs. 5.65 years; 95% CI: 4.98–6.32 years) and those receiving adjuvant chemotherapy (6.61 years vs. 7.00 years; 95% CI: 6.27–7.73 years) [31]. In addition, our simulated stage I and II 5-year overall survival hazard ratios were aligned with those reported in the LACE database meta-analysis (stage I overall survival, HR: 1.10 vs. 1.01; 95% CI: 0.78–1.30; stage II overall survival HR: 0.88 vs. 0.74; 95% CI: 0.60–0.91) [8].

Figure 3. One-way sensitivity analysis tornado diagrams for incremental quality-adjusted life years (A) and lifetime costs (B). Abbreviation: QALYs, quality-adjusted life years.

Sensitivity Analysis Results

Our one-way sensitivity analysis demonstrated that the base case QALY and cost results were most sensitive to the proportion of high-risk patients receiving chemotherapy, the high-risk recurrence hazard ratios, and the proportion of stage II patients receiving chemotherapy in the standard-care strategy (Fig. 3). Lifetime costs and the ICERs were modestly sensitive to the cost of the 14-gene RS.

Our probabilistic sensitivity analysis results demonstrate that the 14-gene RS strategy is likely to be cost effective at willingness-to-pay thresholds greater than \$40,000 per QALY (Fig. 4).

Alternative Chemotherapy-Benefit Scenario Results

In our scenario analysis evaluating a strongly predictive chemotherapy benefit by risk group, the 14-gene RS strategy and the standard-care strategy respectively resulted in 7.57 and 6.83 life years, in 4.18 and 3.78 QALYs, and in \$98,300 and \$111,546 of cost (Table 2). The 14-gene RS testing was a dominant strategy because it led to decreased lifetime cost of care and increased QALYs.

In our scenario analysis evaluating a nonpredictive chemotherapy-benefit scenario by risk group, the 14-gene RS assay strategy and the standard-care strategy respectively resulted in 6.73 and 6.65 life years, in 3.72 and 3.68 QALYs, and

Figure 4. Cost-effectiveness acceptability curves for the base case predictive chemotherapy benefit, nonpredictive chemotherapy benefit, and strongly predictive chemotherapy benefit scenarios.

Abbreviation: QALY, quality-adjusted life year.

in \$119,900 and \$116,300 of cost (Table 2). The resulting incremental cost-effectiveness ratio was \$92,100 per QALY gained. The results of these alternative scenarios are shown in Table 2.

DISCUSSION

Newly diagnosed early stage NSCLC patients continue to have suboptimal outcomes compared with many other types of cancer, as demonstrated by their poor disease-free and overall survival [46]. There are two primary mechanisms through which these health outcomes can be improved: the development of more effective and less toxic treatment regimens and the use of existing treatments to optimize risk-benefit tradeoffs for individual patients. The 14-gene RS is a prime example of the latter, providing information about mortality risk and potentially enabling physicians to limit the use of standard cytotoxic agents to those patients who stand to gain the greatest treatment benefit. We created a decision-analytic model to systematically evaluate the plausible range of clinical and economic impacts of the 14-gene RS strategy and to assess the potential cost-effectiveness of a 14-gene RS testing strategy relative to a standard-care strategy informed by clinical-pathological factors. We found that the 14-gene RS strategy has the potential to improve clinical outcomes and to be cost-effective under a wide variety of plausible assumptions. These projected benefits could potentially become more pronounced with the continued development of more effective treatments for early stage NSCLC patients.

Despite the growing number of prognostic assays in early stage NSCLC, little has been published in the peer-reviewed literature about their potential cost-effectiveness. Consequently, this is the first peer-reviewed publication evaluating the potential clinical and economic outcomes of a practical

prognostic assay in early stage NSCLC. Our study highlights several key drivers of the cost-effectiveness in this setting. Most important, assays must be able to classify patients into subgroups with clinically meaningful differences in disease prognosis and/or treatment effectiveness. In the case of the 14-gene RS assay, testing can identify subgroups of stage I disease with relatively poor overall survival prognosis and in which adjuvant chemotherapy may be beneficial and subgroups of stage II disease with relatively favorable prognosis and in which adjuvant chemotherapy may not be beneficial. Both represent a departure from current standard care, and it is through this mechanism that value can be realized in the form of improved survival, health-related quality of life, and/or reduced treatment costs. Beyond the direct value created as a function of the magnitude of the clinical benefits or cost savings, the total value created by a testing strategy is also substantially dictated by the degree to which patients and physicians are willing to follow its recommended treatment pathway. For this reason, post-testing patient and physician chemotherapy preferences are also important determinants of cost-effectiveness. Finally, because of the relatively moderate cost of testing and adjuvant chemotherapy (with standard platinum-doublet regimens) compared with the high cost of postrecurrence care, a key driver of cost-effectiveness is the impact of testing on recurrence rates.

This study has several key limitations that should be noted. First and foremost, there is no direct evidence of a predictive effect for chemotherapy by 14-gene RS status. Clinical trials are currently under way to address this evidence gap; however, given the current understanding of the relationship between baseline prognosis and chemotherapy benefit, it is plausible that there is some differential chemotherapy impact by prognostic status. We addressed this issue by evaluating

a scenario with current best evidence about the range of chemotherapy impact within and by stage and a scenario based on an analogous biomarker study using a retrospective trial-based analysis. In these scenarios, the ICER ranged from dominant to \$92,100 per QALY, demonstrating that the 14-gene RS is expected to be a cost-effective intervention for a wide range of chemotherapy impacts in the U.S.

The published data on the 14-gene RS assay does not include sufficient information about recurrence rates to derive direct estimates of disease-free survival by risk status. In the absence of such data, we estimated the recurrence rates for each risk group and stage combination using the observed relationship between lung cancer-specific mortality and recurrence (local and distant), as reported in the International Adjuvant Lung Cancer Trial [20]. Actual recurrence rates may differ from these estimates, but there is a strong correlation between disease recurrence and lung cancer-specific survival, as demonstrated in prior studies in this disease setting [8]. An additional limitation is that the data that were used to estimate the change in physician treatment selection after use of the 14-gene RS was obtained from a study that included known users of the assay [23]. These early adopters may be different from other physicians in ways that would affect our study results. Specifically, if fewer physicians changed their recommendations, the results would be attenuated. However, this is the best available evidence as to how the assay is used in current practice and its likely impact on actual treatment decisions because these data reflect the actual pre- and post-testing adjuvant chemotherapy recommendations made in clinical practice as opposed to hypothesized use or idealized guidelines-based use. Future studies will further inform this specific aspect of clinical utility (i.e., the impact of physician behavior). Last, it should be noted that cost impacts and efficiencies beyond those considered in this analysis might arise when the 14-gene RS is applied in clinical settings, and health economic impact should be reassessed accordingly.

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CONCLUSION

The results of our analysis suggest that at implied willingness-to-pay levels in the U.S., the 14-gene RS assay is a cost-effective alternative to a standard guideline-based adjuvant chemotherapy decision-making strategy in early stage NSCLC. However, the predictive ability of the assay has great influence on cost-effectiveness, with a predictive assay being highly cost-effective and a nonpredictive assay being only marginally cost-effective. Future studies should address this question of differential chemotherapy benefit by risk group and should further examine post-testing chemotherapy preferences in community-practice settings.

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DISCLOSURES

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