Cost-Effectiveness of Multiplexed Predictive Biomarker Screening in Non-Small-Cell Lung Cancer

Dorothy Romanus, PhD, Stephanie Cardarella, MD,† David Cutler, PhD,‡ Mary Beth Landrum, PhD,§ Neal I. Lindeman, MD,‖ and G. Scott Gazelle, MD, PhD¶*

Introduction: Population-wide screening for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements to inform cancer therapy in non-small-cell lung cancer (NSCLC) is recommended by guidelines. We estimated cost-effectiveness of multiplexed predictive biomarker screening in metastatic NSCLC from a societal perspective in the United States.

Methods: We constructed a microsimulation model to compare the life expectancy and costs of multiplexed testing and molecularly guided therapy versus treatment with cisplatin-pemetrexed (CisPem). All testing interventions included a two-step algorithm of concurrent *EGFR* mutation and ALK overexpression testing with immunohistochemistry followed by *ALK* rearrangement confirmation with a fluorescence in situ hybridization assay for immunohistochemistry-positive results. Three strategies were included: "Test-treat" approach, where molecularly guided therapy was initiated after obtainment of test results; "Empiric switch therapy," with concurrent initiation of CisPem and testing and immediate switch to test-result conditional treatment after one cycle of CisPem; and "Empiric therapy" approach in which CisPem was continued for four cycles before start of a tyrosine kinase inhibitor.

Results: The incremental cost-effectiveness ratio for "Test-treat" compared with treatment with CisPem was $136,000 per quality-adjusted life year gained. Both empiric treatment approaches had less favorable incremental cost-effectiveness ratios. "Test-treat" and "Empiric switch therapy" yielded higher expected outcomes in terms of quality-adjusted life years and life-years than "Empiric therapy." These results were robust across plausible ranges of model inputs.

Conclusion: From a societal perspective, our cost-effectiveness results support the value of multiplexed genetic screening and molecularly guided therapy in metastatic NSCLC.

*Institute for Technology Assessment, Massachusetts General Hospital, Harvard University, Boston, Massachusetts; †Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; ‡Department of Economics, Harvard University, Cambridge, Massachusetts; §Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts; ‖Department of Pathology, Brigham and Women' Hospital, Harvard Medical School, Boston, Massachusetts; and ¶Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

This work was supported by the National Cancer Institute Program in Cancer Outcomes Research Training (R25CA092203).

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Dorothy Romanus, PhD, Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimack St., 10th floor, Boston, Massachusetts 02114. E-mail: dorothy.romanus@mail.harvard.edu

DOI: 10.1097/JTO.0000000000000474

ISSN: 1556-0864/15/1004-0586

Key Words: Multiplexed test, Non-small-cell, Lung cancer, Targeted therapy, Cost-effectiveness

(*J Thorac Oncol.* 2015;10: 586–594)

The expansion of targeted therapeutic options for metastatic non-small-cell lung cancer (NSCLC) is a welcome advance in a disease that historically has been resistant to treatment. Of the estimated 230,000 incident lung cancer cases annually, approximately 85% are diagnosed with NSCLC.[1,2] Most patients present with advanced disease, and adenocarcinoma is the most common histologic subtype.[2] Somatic mutations in *epidermal growth factor receptor* (*EGFR*) and *anaplastic lymphoma kinase* (*ALK*) gene rearrangements are found in 9.5% and 3.9% of unselected NSCLCs, respectively.[3] Patients whose tumors carry a sensitizing mutation of *EGFR* or *ALK* gene rearrangements experience higher response rates, longer progression-free survival (PFS), and improved quality of life when treated with a tyrosine kinase inhibitor (TKI) compared with platinum-based doublet chemotherapy. Guidelines recommend the ascertainment of *EGFR* and *ALK* mutational status to help guide first-line systemic therapy in all patients with nonsquamous, advanced NSCLC.[4] According to these recommendations, over 130,000 newly diagnosed NSCLC patients each year should undergo predictive biomarker screening.[5] But biomarker screening appears to be underutilized in routine care. Only 12% of acute care hospitals in the United States used the EGFR assay in 2010, which represented only 5.7% of guideline-directed patients.[4,5] In addition, recent evidence questions the cost-effectiveness of biomarker screening.[6]

Even among patients whose tumors are tested for predictive biomarkers, uncertainty surrounding the optimal timing of TKI therapy initiation adds to the complexity of treatment decision-making.[7] Turn-around-time (TAT), the time from tissue sample acquisition to reporting of test results, and inadequate tissue sample for analysis may tip the scale toward commencing empiric treatment with chemotherapy. Once test results reveal the presence of an actionable mutation after empiric therapy is begun, indirect evidence suggests that continuation of chemotherapy for four to six cycles before switching to a TKI may optimize outcomes.[7,8] In the present analysis, we compared a number of TKI initiation strategies.

Multiplex detection of mutations has the advantage of tissue preservation and faster TAT. To date, economic analyses of screening for drug sensitivity biomarkers in lung cancer have

restricted their focus on single biomarkers.[6,9–17] We examined two molecular markers, *EGFR* mutations and *ALK* rearrangements, for which the evidence is sufficiently mature to support population-wide screening.[4] The goal of this article was to assess the cost-effectiveness of multiplexed predictive biomarker screening from a societal perspective in patients newly diagnosed with metastatic NSCLC living in the United States.

MATERIALS AND METHODS

Model and Treatment Strategies

We constructed a microsimulation, state-transition model to estimate the life expectancy and costs of four strategies: a "No Test" approach, treatment with cisplatin-pemetrexed (CisPem) chemotherapy and no biomarker testing, and two different empiric treatment strategies in which CisPem was initiated with concurrent biomarker testing. In one, the "Empiric therapy" strategy, chemotherapy was continued for four cycles followed by TKI maintenance treatment in mutation-positive patients. In the other, the "Empiric switch therapy," patients initiated first-line chemotherapy, and those with mutation-positive tumors switched to a TKI immediately upon return of test results; and finally, the "Test-treat" strategy, in which molecularly guided treatment was initiated only after results of testing became available. The simulated study population composed of newly diagnosed stage IV NSCLC patients with nonsquamous histology.

Figure 1 depicts the structure of the model. For all testing strategies, patients entered the model in the prescreen state on the day the test was ordered. If the sample was suitable for testing, the patient transitioned to the test sequence health states. With a daily cycle length, we were able to model wait times for test results before initiation of therapy. Patients with insufficient tumor samples from initial diagnostic samples transitioned to the rebiopsy prescreen state to account for elapsed time in determining appropriateness for a rebiopsy and for performing the procedure. Patients who did not undergo a rebiopsy, or whose rebiopsy samples were inadequate for testing, transitioned to the treatment states. Multiplexed molecular testing proceeded according to a two-step test sequence: concurrent *EGFR* mutation and ALK overexpression assays followed by ALK fluorescence in situ hybridization (FISH) confirmation for ALK immunohistochemistry (IHC)-positive results (1+, 2+, or 3+).[4] Mortality risk in the above health states was modeled based on the natural history of advanced NSCLC for the "Test-treat" approach and the first-line CisPem therapy for the empiric treatment strategies.

Patients in the "No test" strategy entered the model in the first-line CisPem treatment state (Fig. 1). Upon progression on each therapy, patients transitioned to the next line of therapy based on treatment conditional disease risk of progression. Treatment sequences for the other strategies (Table 1) followed the same model structure.

For the main analysis, we chose a time horizon of 2 years to capture the major health and economic consequences in metastatic NSCLC. This duration obviated the need for projecting survival outcomes beyond the primary clinical trial data.[18] Benefits and costs were discounted at 3% per annum. Analyses were performed in TreeAge Pro 2013 (TreeAge Software, Inc., Williamstown, MA).

Natural History

We used data from Surveillance, Epidemiology, and End Results-Medicare to model the natural history of untreated,

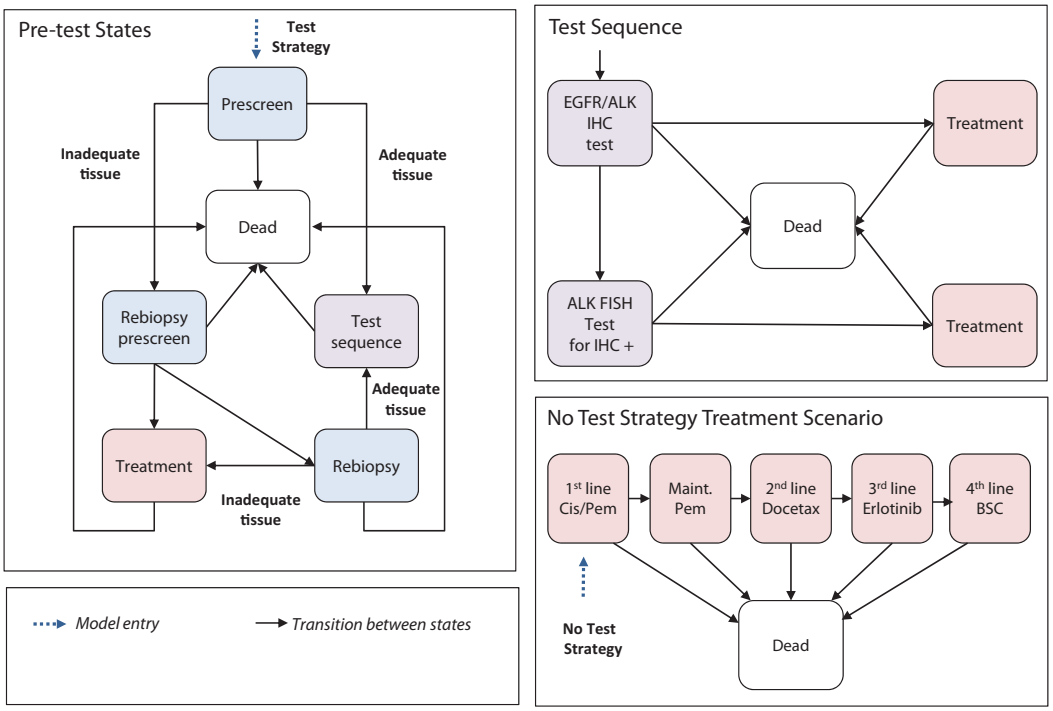

FIGURE 1. Model structure depicting health states and transitions.

TABLE 1 Strategies

Strategy	Test	Treatment
No test	None	CisPem[a] ► Pem ► DTX ► Erlot ►BSC
Empiric therapy[b]	EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+	Empiric CisPem × 4 cycles ► test result conditional treatment:
		EGFR +: Erlot ► DTX ► BSC
		ALK +: Criz ► DTX ► BSC
		Other: CisPem[a] ► Pem ► DTX ► Erlot ►BSC
Empiric- switch therapy[c]	EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+	Empiric CisPem × 1 cycle ► test result ► test result conditional treatment:
		EGFR +: Erlot ► CisPem[a] ► DTX ► BSC
		ALK +: Criz ► CisPem[a] ► DTX ► BSC
		Other: CisPem[a] ► Pem ► DTX ► Erlot ►BSC
Test-treat	EGFR/ALK IHC ► ALK FISH for ALK IHC 1–3+	EGFR +: Erlot ► CisPem[a] ► DTX ►BSC
		ALK +: Criz ► CisPem[a] ► DTX ►BSC
		Other: CisPem[a] ► Pem ► DTX ►Erlot ► BSC

[a]CisPem therapy was administered for up to four cycles; upon progression on CisPem, patients transitioned to the next line of therapy.
[b]TKI maintenance treatment was initiated in presence of drug-sensitizing mutations upon completion of four cycles of CisPem.
[c]Patients with drug-sensitizing mutations switched to a TKI at time of test results after receiving one cycle of empiric CisPem therapy.
CisPem, cisplatin and pemetrexed doublet; Pem, pemetrexed; DTX, docetaxel; Erlot, erlotinib; BSC, best-supportive care; Criz, crizotinib; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

metastatic NSCLC for simulated patients who were awaiting molecular test results. Predicted probabilities from a Cox proportional hazards model for incident Surveillance, Epidemiology, and End Results' (SEER) cases with Stage IV NSCLC and a pathologic diagnosis of nonsquamous histology, aged 66–69 years with diagnoses between 2007 and 2009, who were managed with best supportive care were generated. The model was weighted using the inverse conditional probability of exposure to chemotherapy to balance observable covariates between treatment naive and chemotherapy-treated patients. Time dependent transitional probabilities for the simulation model were calibrated to the predicted survival probabilities from the Cox proportional hazard model using a piecewise-exponential approach.

Clinical Outcomes

Randomized clinical trials (RCTs) for initiation and maintenance therapy with erlotinib and crizotinib in *EGFR* mutation and *ALK* rearrangement-positive patients, respectively, were identified for calculating treatment-conditional progression and survival estimates. Efficacy data for other therapies were pulled from RCTs that enrolled molecularly unselected patients. The trial-based median estimates for treatment-specific overall survival and PFS were used as calibration targets. Transition probabilities were calculated using a constant hazard assumption.

Quality of Life

We estimated utilities based on a mixed model, which included parameters for best tumor response and toxicities usually encountered with chemotherapy treatments in NSCLC (neutropenia, febrile neutropenia, fatigue, diarrhea, nausea and vomiting, rash, and hair loss).[19] We used rates for best tumor response and grades 3 and 4 adverse drug events (ADEs) from RCTs to calculate treatment-specific utilities based on the mixed model (Table 2).[19] Disutilities for ADEs were incorporated in the first month of therapy.[11,20]

Genomic Markers

Prevalence rates of biomarkers were drawn from a population-based registry (Table 2) of 10,000 NSCLC patients who were enrolled for routine screening of predictive biomarkers.[3] The cumulative TAT for test results is congruent with guidelines, which recommend that EGFR and ALK testings both be completed within 10 working days of receiving the specimen in the laboratory.[4]

We estimated that 30% of patients would undergo a rebiopsy, and 85% of repeat biopsies would yield adequate samples for molecular testing.[10] The distribution of repeat biopsy techniques (bronchoscopic, or transthoracic needle aspiration of primary cancer, and metastatic site needle aspirations) and pneumothorax complication rates were based on a prior analysis.[10]

We used ALK FISH positivity as the reference standard for presence of *ALK* rearrangements.[4,25] Estimates for IHC test performance were taken from the largest published case series evaluating a novel 5A4 monoclonal antibody (Table 1).[28]

Costs

Cancer-related medical costs, costs of travel, and patient time spent seeking medical care were included in the model (Table 2). We used the Centers for Medicare and Medicaid Services reimbursement rates for each biomarker assay in our base-case analysis and for other direct medical costs, including drug administration, imaging, and ADEs. Costs for treatment specific ADEs were assumed to accrue in the first month of therapy.[11,20] The average sale price and average wholesale price were used to value injectable and orally administered drugs, respectively. With the exception of CisPem chemotherapy, which was administered up to four cycles, patients were assumed to accrue drug-related costs up to the time of progression. Costs for rebiopsy and related complications were derived from the analysis by Handorf et al.[10] The cost for treating progressive disease was based on lung cancer attributable

TABLE 2. Model Parameters and Ranges for Sensitivity Analyses

Variable	Base Case	Low	High	Source
Overall survival (months)				
Cisplatin plus pemetrexed	11.8	10.4	13.2	(21)
Pemetrexed	13.9	12.8	16.0	(22)
Docetaxel	8.0	6.4	9.6	(13)
Erlotinib (1st line)	19.3	14.7	26.8	(23)
Erlotinib (maintenance)[a]	24.0	19.2	28.8	(24)
Crizotinib	20.3	18.1	26.8	(25)
Erlotinib (third line)	6.7	5.5	7.8	(26)
Best supportive care	4.5	4.3	4.9	SEER-Medicare
Progression-free survival (months)				
Cisplatin plus pemetrexed	5.3	4.8	5.7	(21)
Pemetrexed	4.1	3.2	4.6	(22)
Docetaxel	3.3	2.6	4.0	(13)
Erlotinib (first line)	9.7	8.4	12.3	(23)
Erlotinib (maintenance)	10.3	8.2	12.4	(24)
Crizotinib	7.7	6.0	8.8	(25)
Erlotinib (third line)	2.2	1.9	2.8	(26)
Health state utilities				
With best response and adverse events				
Cisplatin plus pemetrexed	0.59	0.51	0.66	(19,21)
Pemetrexed	0.60	0.54	0.65	(19,22)
Docetaxel	0.48	0.37	0.59	(13,19)
Erlotinib (first line)	0.64	0.58	0.70	(19,23)
Erlotinib (maintenance)	0.66	0.61	0.71	(19,24)
Crizotinib	0.64	0.58	0.70	(19,25)
Erlotinib (third line)	0.56	0.49	0.64	(19,26)
No treatment	0.46	0.36	0.55	(19)
With best response and no adverse events				
Cisplatin plus pemetrexed	0.62	0.56	0.67	(19,21)
Pemetrexed	0.60	0.55	0.66	(19,22)
Docetaxel	0.57	0.51	0.64	(13,19)
Erlotinib (first line)	0.65	0.60	0.71	(19,23)
Erlotinib (maintenance)	0.66	0.61	0.71	(19,24)
Crizotinib	0.66	0.60	0.71	(19,25)
Erlotinib (third line)	0.59	0.53	0.65	(19,26)
Probabilities (%)				
EGFR mutation positive	9.5	8.9	10.7	(3)
ALK rearrangement positive	3.9	3.5	4.3	(3)
Inadequate tissue—initial biopsy	37.7	26	49	(27)
Re-biopsy	30	15	45	Expert opinion
Inadequate tissue—rebiopsy	15	10	25	(10)
ALK IHC specificity	96	95	100	(28)
ALK IHC sensitivity	100	100	100	(28)
Proportion of patients tested	100	5.7	100	(5)
TAT (days)[b]				
With no re-biopsy	12	7	16	(4), expert opinion
With re-biopsy	24	13	34	(4), expert opinion
Costs, 2013 US$				
EGFR mutation assay	$201	$201	$718	(29,30)
ALK IHC assay	$136	$136	$217	(29,30)
ALK FISH assay	$489	$489	$598	(29,30)

(*Continued*)

TABLE 2. (*Continued*)

Variable	Base Case	Low	High	Source
Cisplatin and pemetrexed				
Drug acquisition (per 21 day cycle)	$5721	$4577	$6865	(31)
Premedication	$254	$203	$305	(31,32)
Administration, monitoring	$446	$357	$535	(29,30)
Adverse drug event treatment	$760	$608	$912	(29–33)
Pemetrexed maintenance				
Drug acquisition (per 21 day cycle)	$5689	$4551	$6827	(31)
Premedication	$6	$5	$7	(31,32)
Administration, monitoring	$276	$221	$331	(29,30)
Adverse drug event treatment	$304	$243	$365	(29–33)
Docetaxel				
Drug acquisition (per 21 day cycle)	$937	$750	$1124	(31)
Premedication	$8	$6	$10	(31,32)
Administration, monitoring	$329	$263	$395	(29,30)
Adverse drug event treatment	$2525	$2020	$3030	(29–33)
Erlotinib				
Drug acquisition (per 21 day cycle)	$3982	$3186	$4778	(32)
Premedication	$0	$0	$0	(31,32)
Administration, monitoring	$165	$132	$198	(29,30)
Adverse drug event treatment				
First line	$358	$286	$430	(29–33)
Third line	$727	$582	$872	(29–33)
Maintenance	$358	$286	$430	(29–33)
Crizotinib				
Drug acquisition (per 21 day cycle)	$8041	$6433	$9649	(32)
Premedication	$0	$0	$0	(31,32)
Administration, monitoring	$165	$132	$198	(29,30)
Adverse drug event treatment	$550	$440	$660	(29–33)
Disease progression, per month	$5457	$5,283	$5605	(34)
Patient time, per hour	$19	$10	$29	(35)
Travel, per 30 mile round trip	$15	$8	$23	(36)

[a]Probability of survival = 0.6; median survival probability not reported.
[b]Includes time for delivery of tissue sample to the laboratory.
ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; EGFR, epidermal growth factor receptor; TAT, turnaround time from receipt of specimen to report of test results; SEER, Surveillance, Epidemiology, and End Results.

costs in the last year of life.[34] All costs in the model were adjusted to 2013 values using the gross domestic product deflator series.[37]

Cost-Effectiveness Analysis

We calculated the incremental cost-effectiveness by ranking the strategies in order of increasing effectiveness. Strongly dominated strategies, those that had a lower or equal effectiveness and higher costs, were eliminated. Incremental cost-effectiveness ratios (ICERs) were calculated for each strategy in relation to the next best strategy. The ICER is a ratio of the difference in mean costs divided by the difference in mean quality-adjusted life years (QALYs). Strategies with a higher ICER that were less effective than another strategy were eliminated by extended dominance. The ICERs were recalculated for the remaining nondominated strategies.[38]

Sensitivity Analyses

We conducted sensitivity analyses to evaluate which parameters were most influential on model results. Where available, the ranges used for the parameters corresponded to the 95% confidence intervals (Table 2). Costs were varied ±20%, and plausible ranges for TATs were used based on expert opinion. We also simulated the lifetime (5 year) costs and effectiveness where prognosis beyond trial observation period was modeled using exponential distributions. In addition, model outputs were generated based on commercial prices for molecular assays and proportion of patients tested. We also ran a sensitivity analysis for the transition probability of dying while awaiting test results based on treatment naive patients who were randomized to best supportive care in a RCT.[39] Finally, we conducted a threshold sensitivity analysis by varying the TAT for testing and results to determine the break-even point at which the expected benefits of

the "Empiric therapy" approach would be equivalent to the "Test-treat" strategy.

RESULTS

Multiplexed testing approaches of "Test-treat" and "Empiric switch" were most effective (Table 3). Both yielded an average life expectancy of 0.97 life years (LYs) and 0.56 QALYs, which represents 0.04 and 0.03 increases in LYs and QALYs, respectively, compared with no test and treatment with standard chemotherapy. The "Empiric therapy" approach, in which chemotherapy was continued for four cycles before initiation of molecularly guided therapy, was less effective (0.95 LYs and 0.55 QALYs). Because the "Empiric switch" approach was more expensive than the "Test-treat" strategy (but equally effective), it was ruled out by strong dominance. The "Empiric therapy" approach was eliminated by extended dominance because it was associated with a higher ICER than the "Test-treat" approach. Compared with the "No test" strategy, the "Test-treat" approach of concurrent *EGFR* mutation and ALK IHC testing followed by ALK FISH confirmation before initiation of any therapy yielded an ICER of $136,000 per additional QALY (0.03 additional QALYs and $4082 extra spending). Without adjustment for quality of life, the "Test-treat" approach had an ICER of $102,000 per LY gained compared with the "No test" strategy.

Sensitivity Analyses

Changing the parameters values over ranges listed in Table 2 did not impact the rank order of the strategies. Also, both empiric treatment strategies remained dominated. A comparison of the nondominated strategies revealed that the most influential parameters were utilities and acquisition costs for TKIs (Fig. 2). We found that the ICER for the "Test-treat" approach compared with the "No test" strategy ranged from $124,000 to $157,000 per additional QALY, with high and low utility values, respectively; and from $83,000 to $190,000 per QALY gained when costs of TKI therapy were varied by minus and plus 20%, respectively. In all other scenarios, the ICER for "Test-treat" compared with "No test" ranged from $130,000 to $150,000 per QALY.

Commercial prices for assays had a small effect on the ICER ($148,000 per QALY for the "Test-treat" vs. "No test" strategy). Extrapolation of long-term survival increased the ICER for "Test-treat" to $148,000 per QALY compared with "No Test." With a trial-based mortality risk in the pretreatment health states (using a piecewise exponential model with survival probabilities of 97% and 90% at 1 and 2 months after diagnosis, respectively), the same dominance pattern was observed and the ICER remained stable for the "Test-treat" strategy compared with "No Test" ($153,000/QALY).[39]

Varying the proportion of patients for whom multiplexed molecular testing is ordered showed that decreasing this proportion to 5.7%, from 100% in the base-case analysis, would lower the outcomes in terms of expected QALYs to 0.54 for all testing strategies.[5] Finally, our threshold analysis of TATs revealed that increasing the wait times for testing and results by 1.5-fold of the base-case estimates would render the "Empiric therapy" approach equivalent in terms of expected benefits to the "Test-treat" strategy, at 0.55 QALYs each.

DISCUSSION

Concurrent *EGFR* mutation and ALK IHC testing with ALK FISH confirmation for tumors that overexpress the ALK protein before initiation of therapy yielded an ICER of $136,000 per QALY gained compared with no testing and treatment with chemotherapy alone. Whether or not an ICER of $136,000 provides good value is contingent upon the willingness-to-pay threshold, which serves as a guide of how much society is willing to pay for an additional QALY. The World Health Organization (WHO) defines interventions with ICERs within three times the gross domestic product per capita as being cost-effective (approximately $155,000 in the United States in 2014).[40] Others posit that a threshold of $200,000 per QALY may be more appropriate based on empirical data of ICERs for often used interventions.[41,42] Using these benchmarks, our results suggest that multiplexed testing followed by molecularly guided therapy in metastatic NSCLC provides good value from a societal perspective.

Our simulation study confirms that waiting for test results before initiation of treatment optimizes outcomes in newly diagnosed patients with metastatic NSCLC.[7] Although empiric therapy in which chemotherapy is initiated concurrently with testing for mutations, followed by an immediate switch to molecularly guided therapy at the time test results become available yielded the same life expectancy as the test then treat approach, the former strategy was dominated

TABLE 3. Cost-Effectiveness Results[a]

Strategy	LYs	Incremental LYs[b]	QALYs	Incremental QALYs[b]	Cost[c]	Incremental Cost[b]	ICER ($/LY)	ICER ($/QALY)
Standard care: No test, CisPem	0.93	—	0.53	—	$79,331	—	—	—
Empiric therapy	0.95	0.02	0.55	0.02	$82,762	$3431	Extended dominance	Extended dominance
Test-treat	0.97	0.02	0.56	0.01	$83,413	$651	102,000	136,000
Empiric switch therapy	0.97	0.00	0.56	0.00	$86,645	$3232	Dominated	Dominated

[a]Costs and life expectancy outcomes were discounted at a 3% annual rate. The "Empiric therapy" approach composed of CisPem continuation for four cycles before start of molecularly guided therapy. In the "Test-treat" approach, molecularly guided therapy was initiated after ascertainment of test results. In the "Empiric switch therapy," concurrent initiation of CisPem and testing was modeled followed by an immediate switch to test-result conditional treatment after one cycle of CisPem.

[b]Compared with the next-best strategy in terms of effectiveness.

[c]2013 $US.

LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; CisPem, cisplatin and pemetrexed doublet.

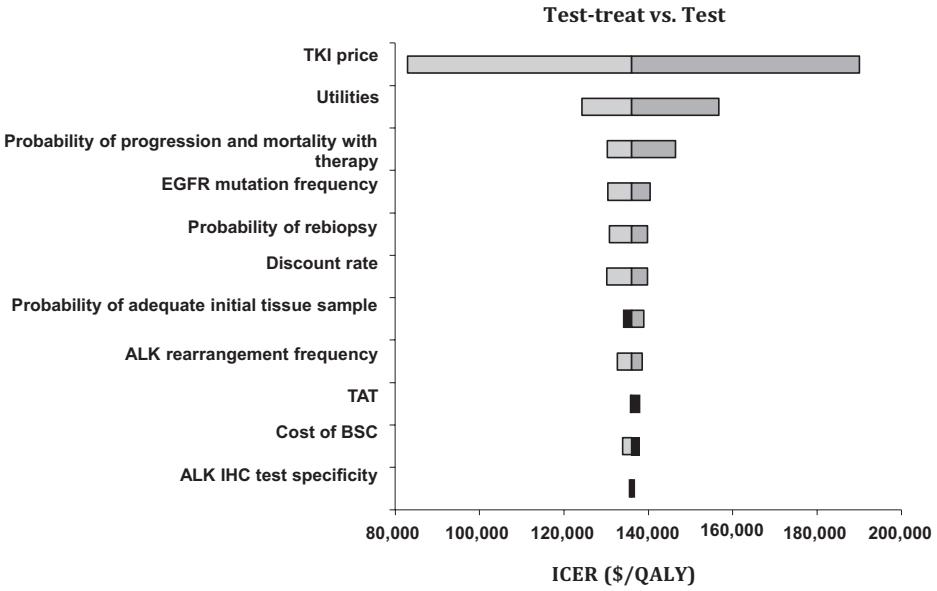

FIGURE 2. Sensitivity analyses. Tornado diagram of influential parameters on the incremental cost-effectiveness ratio (ICER) of "Test-treat" versus "No Test" strategies. TKI, tyrosine kinase inhibitor; *EGFR*, epidermal growth factor drug sensitizing mutation; *ALK*, anaplastic lymphoma kinase rearrangement; TAT, turn-around time; BSC, best-supportive care; IHC, immunohistochemistry; QALY, quality-adjusted life year.

because it was more expensive. Continuation of empiric chemotherapy for four cycles before switching to test-result conditional treatment yielded less favorable outcomes than the above two approaches, both in terms of QALYs and LYs. This strategy was eliminated by extended dominance. These results were robust to variations over plausible ranges of model parameters.

In sensitivity analyses, the ICER was highly sensitive to drug acquisition costs. At lower TKI prices (80% of brand name product price), the ICER for the "Test-treat" strategy decreased to $83,000 per QALY compared with standard treatment with chemotherapy. Over time, once generic versions of TKIs become available, these innovations will confer even better value. The optimal price point that maximizes social welfare, while minimizing the impact on technological innovation, is outside the scope of this analysis. However, growing concerns over the increasing cost burden of these innovations on patients deserve scrutiny.[43–45] Patient access to these drugs may be impeded by onerous out of pocket costs. One way to attenuate the impact of cost sharing may be through value-based benefit design. Arguably, breakthrough therapies that offer substantial improvement in outcomes and are placed into lower cost sharing tiers would benefit society as a whole from healthier patients who remain productive, as they are able to access these beneficial treatments.

We were unable to identify published economic analyses that examined multiplexed testing in advanced NSCLC. Handorf et al. evaluated the cost-effectiveness of molecularly guided first-line therapy using *EGFR* mutation testing in the United States from a payer perspective. The ICERs for testing with and without rebiopsy and *EGFR* mutation guided treatment ranged from $110,644 to $122,219 per QALY gained compared with treatment with a carboplatin-paclitaxel doublet.[10] Similar to our analysis, the cost-effectiveness results from that study support the value of molecularly guided therapy. Another recently published study examined the cost-effectiveness of *ALK* rearrangement testing alone before first-line crizotinib treatment in *ALK*-positive tumors or cisplatin-gemcitabine combination chemotherapy in wild-type tumors.[6] From a Canadian public health perspective, that analysis generated an ICER of $255,970 per additional QALY for molecularly guided therapy compared with chemotherapy. The authors concluded that genetic testing and treatment with molecularly guided therapy was not cost-effective. Unlike the Canadian study, we combined multiplexed testing in our analysis of the two molecular markers that are guideline-recommended for population-wide screening in advanced NSCLC, which de facto produced better outcomes for the molecular testing strategy because more patients benefit from testing.

Our results are subject to modeling assumptions and need to be interpreted in this context. For example, due to treatment crossover after progression and lack of direct comparisons in RCTs, we relied on single-arm data for our parameters. Furthermore, we used data from PROFILE 1007, a phase 3 RCT of second-line crizotinib, to inform hazard rates in our model for overall survival and PFS.[25] These estimates apply to a small subset of patients in our model, those with *ALK* rearrangement-positive status. Any bias introduced into the model would thus be marginal given the size of this subgroup.[46] Overall, varying the hazard rates for treatment effects in sensitivity analyses revealed that the base-case results were robust to these assumptions. Also, we used Medicare reimbursements as a proxy for the societal costs of test assays. However, the true costs of the tests may vary across providers. But even with commercial test prices, the ICER for the "Test-treat" compared with the "No test" strategy increased to $148,000 per additional QALY, which is still below commonly acceptable willingness-to-pay thresholds.[41]

In summary, our analysis suggests that multiplexed testing for *EGFR* mutations and ALK overexpression with an IHC assay followed by *ALK* rearrangement confirmation with FISH for IHC-positive results and biomarker conditional treatment is a cost-effective strategy compared with treatment with chemotherapy and no testing in metastatic NSCLC. Empiric

CisPem therapy for four cycles with concurrent molecular testing before initiation of TKI maintenance therapy generated inferior outcomes compared with waiting for test results before treatment and compared with "Empiric switch therapy" in which chemotherapy initiated treatment was immediately switched to molecularly guided therapy when test results became available.

REFERENCES

1. American Cancer Society. Key statistics about lung cancer. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics. Accessed June 4, 2013.
2. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol* 2007;25:5570–5577.
3. Barlesi F, Blons H, Beau-Faller M, et al. Biomarkers France: Preliminary results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 non-small cell lung cancer (NSCLC) patients. Presented at 2013 ASCO Annual Meeting, Chicago, Illinois; 2013. Available at: http://meetinglibrary.asco.org/content/114562-132. Accessed September 15, 2013.
4. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823–859.
5. Lynch JA, Khoury MJ, Borzecki A, et al. Utilization of epidermal growth factor receptor (EGFR) testing in the United States: a case study of T3 translational research. *Genet Med* 2013;15:630–638.
6. Djalalov S, Beca J, Hoch JS, et al. Cost effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non-small-cell lung cancer. *J Clin Oncol* 2014;32:1012–1019.
7. Moran T, Sequist LV. Timing of epidermal growth factor receptor tyrosine kinase inhibitor therapy in patients with lung cancer with EGFR mutations. *J Clin Oncol* 2012;30:3330–3336.
8. Cappuzzo F, Ciuleanu T, Stelmakh L, et al.; SATURN Investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
9. Atherly AJ, Camidge DR. The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers. *Br J Cancer* 2012;106:1100–1106.
10. Handorf EA, McElligott S, Vachani A, et al. Cost effectiveness of personalized therapy for first-line treatment of stage IV and recurrent incurable adenocarcinoma of the lung. *J Oncol Pract* 2012;8:267–274.
11. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health* 2009;12:20–27.
12. Arrieta O, Anaya P, Lopez RJ, Polanco AC. Cost-effectiveness analysis of EGFR mutation testing in patients with advanced non small-cell lung cancer (ANSCLC) treated with gefitinib or carboplatin-paclitaxel. *Value Health* 2010;13:A37–38.
13. Chen W, Ellis P, Levin L, Krahn M. Cost-effectiveness of epidermal growth factor receptor gene mutation testing in the selection of first-line therapy for patients with advanced non-small cell lung cancer in Ontario. *Value Health* 2011;14:A82.
14. Jacob J, Henriksson M, Brattstrbm D. Cost-effectiveness of gefitinib versus doublet chemotherapy in first-line treatment of non-small cell lung cancer (NSCLC) in Sweden. *Value Health* 2010;13:A270.
15. Lopes GD, Segal J, Tan D, Do Y, Mok T, Finkelstein E. Cost-effectiveness of epidermal growth-factor receptor mutation testing and first-line treatment with gefitinib for advanced non-small-cell lung cancer. *EJC Suppl* 2011;9:2.
16. Shiroiwa T, Miyoshi Y, Tsutani K. Cost-effectiveness analysis of EGFR testing and gefitinib for nonsmall-cell lung cancer (NSCLC) in Japan. *Value Health* 2012;15:A67.
17. Borget I, Cadranel J, Pignon JP, et al.; ERMETIC Collaborative Group. Cost-effectiveness of three strategies for second-line erlotinib initiation in nonsmall-cell lung cancer: the ERMETIC study part 3. *Eur Respir J* 2012;39:172–179.
18. Gold MR, Siegal J, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
19. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84.
20. Westwood ME, Joore M, Whiting P, van Asselt T, Ramaekers B, Armstrong N, Misso K, Severens J, Kleijnen J. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2014;18:1–166.
21. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
22. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247–255.
23. Rosell R, Carcereny E, Gervais R, et al.; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–246.
24. Brugger W, Triller N, Blasinska-Morawiec M, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2011;29:4113–4120.
25. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368:2385–2394.
26. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
27. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol* 2007;25:760–766.
28. Paik JH, Choe G, Kim H, et al. Screening of anaplastic lymphoma kinase rearrangement by immunohistochemistry in non-small cell lung cancer: correlation with fluorescence in situ hybridization. *J Thorac Oncol* 2011;6:466–472.
29. Clinical Laboratory Fee Schedule. Available at: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Gapfill-Pricing-Inquiries.html. Accessed May 12, 2013.
30. Physician Fee Schedule. Available at: http://www.cms.gov/apps/physician-fee-schedule/search/search-results.aspx?Y=1&T=0&HT=0&CT=3&H1=88381&M=5. Accessed May 15, 2013.
31. BDIPharma. HCPCS codes & medicare payment. Available at: http://www.bdipharma.com/services-hcpcs-codes-medicare-payment.aspx. Accessed June 2, 2013.
32. Price Rx Pro. Available at: https://pricerx.medispan.com. Accessed May 15, 2013.
33. Veterans Affairs. MS-Diagnosis-Related Group (MS-DRG) weights (2008–2013). Available at: http://www.herc.research.va.gov/resources/faq_f03.asp. Accessed May 19, 2013.
34. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst* 2008;100:630–641.
35. Bureau of Labor Statistics. Usual weekly earnings of wage and salary workers. Available at: http://www.bls.gov/news.release/wkyeng.toc.htm. Accessed May 17, 2013.
36. US General Services Administration. Privately owned vehicle (POV) mileage reimbursement rates. Available at: http://www.gsa.gov/. Accessed May 21, 2013.
37. US Government GPO. Chain-type price indexes for gross domestic product, *1964–2012*. Available at: http://www.gpo.gov/fdsys/granule/ERP-2013/ERP-2013-table7/content-detail.html. Accessed June 2, 2013.
38. Hunink M, Glasziou P, Siegel J, et al. Decision-Making in Health and Medicine: Integrating Evidence and Values. New York, NY: Cambridge University Press; 2001.

39. Roszkowski K, Pluzanska A, Krzakowski M, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* 2000;27:145–157.
40. Worldbank. GDP per capita (current US$). Available at: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed April 10, 2014
41. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med* 2003;163:1637–1641.
42. Mullins CD, Hsiao FY, Onukwugha E, Pandya NB, Hanna N. Comparative and cost-effectiveness of oxaliplatin-based or irinotecan-based regimens compared with 5-fluorouracil/leucovorin alone among US elderly stage IV colon cancer patients. *Cancer* 2012;118:3173–3181.
43. Experts in CML. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood* 2013;121:4439–4442.
44. Hall S. The cost of living. Available at: http://nymag.com/news/features/cancer-drugs-2013-10/. Accessed July 3, 2014.
45. Bach P SL, Wittes R. Cancer care, cost matters. Available at: http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html?_r=0. Accessed July 3, 2014.
46. Mok T, Yang JJ, Lam KC. Treating patients with EGFR-sensitizing mutations: first line or second line–is there a difference? *J Clin Oncol* 2013;31:1081–1088.