Original Contribution

Cost Effectiveness of Personalized Therapy for First-Line Treatment of Stage IV and Recurrent Incurable Adenocarcinoma of the Lung

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Abstract

Purpose: Patients with epidermal growth factor receptor (*EGFR*) mutation–positive stage IV adenocarcinoma have improved survival with tyrosine kinase inhibitor (TKI) treatments, but the cost effectiveness of personalized first-line therapy using *EGFR* mutation testing is unknown.

Methods: We created a decision analytic model comparing the costs and effects of platinum combination chemotherapy with personalized therapy in which patients with *EGFR* mutation–positive tumors were treated with erlotinib. We used two testing strategies: testing only those with tissue available and performing a repeat biopsy if tissue was not available versus three nontargeted chemotherapy regimens (ie, carboplatin and paclitaxel; carboplatin and pemetrexed; and carboplatin, pemetrexed, and bevacizumab).

Results: Compared with a carboplatin plus paclitaxel regimen, targeted therapy based on testing available tissue yielded an incremental cost-effectiveness ratio (ICER) of $110,644 per quality-adjusted life year (QALY), and the rebiopsy strategy yielded an ICER of $122,219 per QALY. Probabilistic sensitivity analysis revealed substantial uncertainty around these point estimates. With a willingness to pay of $100,000 per QALY, the testing strategy was cost effective 58% of the time, and the rebiopsy strategy was cost effective 54% of the time. Personalized therapy with an EGFR TKI was more favorable when the nontargeted chemotherapy regimen was more expensive. Compared with carboplatin, pemetrexed, and bevacizumab, ICERs were $25,547 per QALY for the testing strategy and $44,036 per QALY for the rebiopsy strategy.

Conclusion: Although specific clinical circumstances should guide therapy, our cost-effectiveness analysis supports the strategy of testing for *EGFR* mutations in patients with stage IV or recurrent adenocarcinoma of the lung, rebiopsying patients if insufficient tissue is available for testing, and treating patients with *EGFR* mutations with erlotinib as first-line therapy.

Introduction

Lung cancer remains the leading cause of cancer-related death in North America and is the third most costly cancer.[1] Non–small-cell lung cancer (NSCLC) accounts for 85.3% of cases,[2] and approximately 50% of patients present with incurable metastatic disease (stage IV).[3] Standard chemotherapeutic treatments for stage IV NSCLC lengthen expected survival by a few months; however, recent studies have suggested that patients with advanced NSCLC whose tumors are positive for certain epidermal growth factor receptor (*EGFR*) gene mutations have substantially improved progression-free survival with tyrosine kinase inhibitors (TKIs) such as erlotinib, compared with conventional chemotherapy with a platinum combination regimen.[4-12] The National Comprehensive Cancer Network now recommends treating stage IV adenocarcinoma with first-line TKIs for patients with *EGFR*-activating mutations,[13] but debate continues over whether this is appropriate in the first-line setting[14,15] and, if so, whether the therapeutic gains are worth the increased cost.

Two analyses have examined the cost effectiveness of TKIs; however, one examined TKIs as second-line therapy, and the other was limited to an East Asian population. One study found that the incremental cost effectiveness of second-line treatment with erlotinib for patients with *EGFR*-activating mutations (*EGFR* positive) and docetaxel for patients without such mutations (*EGFR* negative) compared with docetaxel for all patients was $162,018 per quality adjusted life year (QALY) gained.[16] This figure is higher than commonly accepted cost-effective thresholds, and under most circumstances, it would be considered too expensive. However, this study focused on second-line treatment in an unselected population, for whom the survival and quality of life benefits were modest. There may be greater benefit in administering erlotinib as first-line treatment to *EGFR* mutation–positive patients. This study also evaluated gene copy and protein expression testing, which have mainly been replaced by more predictive mutation testing. The other study compared first-line treatment with the TKI gefitinib with platinum combination chemotherapy using costs and effects from Singapore.[17] They found that mutation testing was less costly and more effective than standard chemotherapy, but these results may not hold in a US population. *EGFR* mutations are much more common in Asian populations than in the general US population,[18] and costs may differ substantially between the two countries. In our study, we developed a decision analytic model to evaluate the incremental cost effectiveness (ICER) of *EGFR* mutation testing to inform first-line treatment

in patients with stage IV NSCLC in the United States from a payer's perspective.

Methods

Testing Strategies

Our decision analytic model estimated the incremental costs and benefits of a theoretic cohort of patients with stage IV adenocarcinoma under three different treatment pathways (Appendix Fig A1, online only). In the base case, all patients were treated with combination chemotherapy with a platinum agent, and none were tested for *EGFR* mutations. Because a substantial proportion of patients would not have tissue samples available for *EGFR* testing (44% and 55% in IPASS [Iressa Pan-Asia Study][17] and BR.21 [National Cancer Institute of Canada Clinical Trials Group Study][16] trials, respectively), we examined two *EGFR* mutation testing strategies: one in which testing was performed only on patients with sufficient tumor tissue (test strategy), and one in which patients without available tissue underwent a repeat biopsy to provide tissue for testing (rebiopsy strategy). In either testing strategy, patients who tested negative or had insufficient tissue for determination were treated with platinum combination chemotherapy. We assumed that 15% of repeat biopsies would yield insufficient tissue for mutation testing. Additionally, we assumed that 50% of rebiopsies would be performed bronchoscopically and 25% via transthoracic needle aspiration and the remaining 25% would be needle aspiration biopsies of metastatic sites. These percentages were based on clinical experience.

Comparator Chemotherapy Regimens

Many platinum combination chemotherapy regimens are available to treat adenocarcinoma. Because these regimens have widely varying costs,[19] we evaluated the testing strategies with three commonly used platinum combination regimens that span this variability: carboplatin plus paclitaxel, a relatively inexpensive and widely used treatment option considered standard by many clinicians; carboplatin plus pemetrexed, a more expensive and less toxic regimen; and carboplatin, pemetrexed, and bevacizumab, one of the most expensive and effective regimens available based on data from phase II trials.[20] Although a given chemotherapy regimen might not be appropriate for all patients, we framed the model as a choice between each regimen and *EGFR* testing in a population eligible for the regimen. The base results from each regimen were then compared against alternative treatment pathways whereby the patients underwent *EGFR* testing, for a total of nine possible treatment pathways.

Because of limited data about later clinical effects, we did not model second- or third-line treatments. We explicitly assumed that after failure of first-line treatment, subsequent treatments would have equal effects unrelated to treatment administered in the first-line setting. Furthermore, we assumed that the proportion of patients receiving additional treatments would be equal across all groups. The model was built in TREEAge Pro 2009 (TREEAge Software, Williamstown, MA).

Clinical Effects

We derived overall and progression-free survival on each medication from median survival times (Table 1) reported in randomized clinical trials conducted in US and European populations.[9,10,20-23,32] Although mean survival times would have been preferable, because they are consistent with the decision analytic model[39] and better describe average effects in the population, only median survival times were published in the literature.

We determined severe adverse event rates for the different clinical interventions from published results of randomized clinical trials (Table 1).[20-23,32] We considered only grades 3 and 4 adverse events, including those requiring hospitalization and those that were disabling, prevented self-care, or were life threatening.[40] We included only adverse events with a frequency of $\geq$ 5% and those requiring hospitalization, if frequency rates were lower.[16] We assumed adverse events were treated with one additional physician visit and other standard treatment as appropriate. For example, severe vomiting was treated with 2 hours of intravenous fluids and 24 mg intravenous ondansetron.

We adjusted our estimates for quality of life, because the value of a month of life varies according to severity of disease. We made adjustments using published utility estimates for patients with lung cancer.[16,24] The highest possible utility was the state of progression-free survival while receiving oral therapy (erlotinib), estimated at 0.67.[24] Disease progression reduced utility, as did adverse events resulting from treatment, with the size of reduction depending on severity of complication or disease state (Table 1). For an uncomplicated rebiopsy, we assumed the reduction in quality of life would be minimal. All treatment benefits were then calculated as QALYs.

Costs

We estimated costs for outpatient medications from retail charges collected from drugstore.com. We estimated inpatient medication costs from the 2010 Medicare Part B Average Selling Price file (Table 1). For carboplatin dosing, we used a standard area under the concentration curve of 6 mg/mL/min[41] and assumed male sex, 65 years of age, weight of 70 kg, height of 70 in, and serum creatinine of 1. For pemetrexed, we used 500 mg/m^2, assuming average body weight of 70 kg and height of 70 in.[42] Dosage of paclitaxel was 200 mg/m^3,[43,44] and dosage of bevacizumab was 15 mg/kg, each administered once every 3 weeks.[20] We assumed that all platinum combination regimens would be administered for six treatment cycles. The dosage for erlotinib was 150 mg daily for all patients, administered until progression. We derived medical resource costs for physician services and hospitalizations based on Medicare inpatient and outpatient reimbursement rates (Table 1).

We determined the cost of time spent in disease progression using the analysis by Yabroff et al,[37] which estimated the treatment costs of Medicare patients with lung cancer in the last 12 months of life using Surveillance, Epidemiology, and End Results–Medicare data. We derived a monthly cost from this analysis. We then updated the estimate to 2009 dollars using the

Table 1. Model Inputs

Variable	Base Patient Case	Low	High	Source
Overall survival, months				
Carboplatin plus paclitaxel (EGFR negative or unknown)	8.1	7	9.5	Schiller et al[21]
Carboplatin plus pemetrexed (EGFR negative or unknown)	12.0	7.6	17.1	Zinner et al,[22] Scagliotti et al[23]
Carboplatin, pemetrexed, and bevacizumab (EGFR negative or unknown)	14.1	10.6	19.6	Patel et al[20]
Erlotinib (EGFR positive)	24.0	17.5	27.0	Rosell et al,[9] Sequist et al[10]
Progression-free survival, months				
Carboplatin plus paclitaxel (EGFR negative or unknown)	3.1	2.8	3.9	Schiller et al[21]
Carboplatin plus pemetrexed (EGFR negative or unknown)	5.5	3.4	8.3	Zinner et al,[22] Scagliotti et al[23]
Carboplatin, pemetrexed, and bevacizumab (EGFR negative or unknown)	7.8	5.2	11.5	Patel et al[20]
Erlotinib (EGFR positive)	12.0	6.2	16.7	Rosell et al,[9] Sequist et al[10]
Health state utilities				
Stable disease while receiving oral therapy	0.670	0.335	0.080	Carlson et al[16]
Stable disease while receiving IV chemotherapy	0.653	0.327	0.670	Carlson et al,[16] Nafees et al[24]
Progressive disease	0.473	0.237	0.670	Carlson et al,[16] Nafees et al[24]
Stable disease plus				
Rash	0.640	0.320	0.670	Carlson et al,[16] Nafees et al[24]
Neutropenia	0.670	0.335	0.670	Expert opinion
Febrile neutropenia	0.563	0.282	0.670	Carlson et al,[16] Nafees et al[24]
Pneumothorax	0.630	0.315	0.670	Expert opinion
Hemorrhage	0.630	0.315	0.670	Expert opinion
Nausea/vomiting	0.605	0.303	0.670	Nafees et al[24]
Neuropathy	0.620	0.310	0.670	Carlson et al[16]
Thrombocytopenia	0.650	0.325	0.670	Expert opinion
Thrombosis	0.563	0.281	0.670	Expert opinion
Probabilities				
EGFR positive	0.15	NA	NA	Rosell et al,[9] Shigematsu et al,[18] Johnson et al[25]
Not enough tissue for EGFR testing	0.50	0.30	0.70	Mok et al,[7] Tsao et al[26]
Noninformative rebiopsy	0.15	0.10	0.25	Expert opinion
Pneumothorax (bronchoscopic biopsy)	0.01	0.01	0.05	Eberhardt et al,[27] Facciolongo et al,[28] Geraghty et al,[29] Hergott et al[30]
Pneumothorax (transthoracic needle aspiration biopsy)	0.09	0.05	0.15	Geraghty et al,[29] Hergott et al[30]
Hemorrhage resulting from biopsy	0.01	NA	NA	Facciolongo et al[28]
Carboplatin plus pemetrexed AE				
Neutropenia	0.197	0.080	0.310	Zinner et al,[22] Scagliotti et al[23]
Febrile neutropenia	0.014	0.000	0.050	Zinner et al,[22] Scagliotti et al[23]
Thrombocytopenia	0.085	0.000	0.160	Zinner et al,[22] Scagliotti et al[23]
Erlotinib AE				
Rash	0.060	0.038	0.082	Genentech[31]
Carboplatin plus paclitaxel AE				
Neutropenia	0.630	0.574	0.633	Schiller et al[21]
Febrile neutropenia	0.040	0.017	0.063	Schiller et al[21]
Nausea/vomiting	0.080	0.049	0.111	Schiller et al[21]
Neuropathy	0.100	0.065	0.135	Schiller et al[21]
Anemia	0.100	0.065	0.135	Schiller et al[21]
Carboplatin, pemetrexed, and bevacizumab AE				
Anemia	0.091	0.027	0.155	Patel et al,[20] Malhotra et al[32]
Thrombocytopenia	0.039	0.000	0.082	Patel et al,[20] Malhotra et al[32]
Thrombosis	0.052	0.002	0.102	Patel et al,[20] Malhotra et al[32]
Febrile neutropenia	0.091	0.027	0.155	Patel et al,[20] Malhotra et al[32]

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Table 1. (Continued)

Variable	Base Patient Case	Low	High	Source
Cost				
Erlotinib (150 mg per day for 30 days)	$4,336	$2,168	$6,505	Drugstore.com[33]
Pemetrexed (per cycle)	$4,709	$2,354	$7,063	Centers for Medicare & Medicaid Services[34]
Carboplatin (per cycle)	$83	$41	$124	Centers for Medicare & Medicaid Services[34]
Paclitaxel (per cycle)	$86	$43	$129	Drugstore.com[33]
Bevacizumab (per cycle)	$6,538	$3,269	$9,807	Drugstore.com[33]
Cleocin-T gel	$105	$52	$157	Drugstore.com[33]
Neupogen	$3,866	$1,933	$5,799	Drugstore.com[33]
EGFR gene copy test (CPT-88368)	$243	$122	$365	Centers for Medicare & Medicaid Services[35]
IV chemotherapy infusion per cycle (CPT-96413)	$335	$168	$503	Centers for Medicare & Medicaid Services[35]
Transthoracic needle biopsy (CPT-32405)	$733	$366	$1,099	Centers for Medicare & Medicaid Services[35]
Broncoscopic rebiopsy (CPT-31625)	$840	$420	$1,261	Centers for Medicare & Medicaid Services[35]
Other biopsy (CPT-47000)	$732	$366	$1,098	Centers for Medicare & Medicaid Services[35]
Chest tube (CPT-32551)	$527	$286	$791	Centers for Medicare & Medicaid Services[35]
Outpatient visit (CPT-99233)	$96	$48	$143	Centers for Medicare & Medicaid Services[35]
Inpatient visit (CPT-99255)	$202	$101	$303	Centers for Medicare & Medicaid Services[35]
Febrile neutropenia (MS-DRG 814)	$7,057	$3,528	$10,585	Centers for Medicare & Medicaid Services[36]
RBC transfusion per unit (CPT-36430)	$515	$258	$773	Centers for Medicare & Medicaid Services[35]
Pyridoxine (per month)	$16	$8	$23	Drugstore.com[33]
Oral ondansetron (treating one episode of vomiting)	$12	$6	$18	Drugstore.com[33]
IV ondansetron (treating one episode of vomiting)	$100	$50	$150	Drugstore.com[33]
Administering IV fluids	$172	$86	$258	Centers for Medicare & Medicaid Services[35]
Gabapentin	$586	$243	$729	Drugstore.com[33]
US/dopplers (for diagnosis of DVT CPT-93970)	$254	$127	$381	Centers for Medicare & Medicaid Services[35]
Enoxaparin (per day)	$100	$50	$150	Drugstore.com[33]
Rebiopsy pathology (CPT-88305 and -88342)	$271	$136	$407	Centers for Medicare & Medicaid Services[35]
Disease progression per month	$5,219	$2,610	$7,829	Yabroff et al,[37] Bureau of Labor and Statistics[38]

Abbreviations: AE, adverse event; CPT, current procedural terminology; DVT, deep vein thrombosis; EGFR, epidermal growth factor receptor; IV, intravenous; MS-DRG, Medicare severity–diagnosis-related group; NA, not applicable.

consumer price index for medical care services.[38] Because of the short survival times, we did not discount costs.

Sensitivity Analysis

We performed univariate and multivariate sensitivity analyses to test the robustness of the model and to determine which parameters most influenced the model findings. We set upper and lower limits for the model inputs based on the literature or expert opinion. Limits for survival times and adverse event probabilities were based on the 95% CIs reported in the literature,[9,10,20-23,31,32] and costs were set at ± 50% of their mean point estimates. We also investigated the effect of increasing all survival times by a constant rate, because the median survival would likely underestimate the mean survival.

We were particularly interested in the effects of the pretest probability of *EGFR*-positive tumors on the cost effectiveness of the treatments. In the US population, approximately 15% of lung adenocarcinomas are *EGFR* mutation positive.[9,25] That figure is higher in women (22%), never smokers (27%), and patients of East Asian origin (30%).[18] We hypothesized that alternative strategies including *EGFR* mutation testing would be more cost effective in patients who were more likely to have an *EGFR* mutation.

We performed multivariate sensitivity analysis by simultaneously varying the most influential parameters in a Monte Carlo simulation. We defined distributions for the parameters of interest, took repeated random draws from those distributions, and recalculating the model results based on those draws. This process was repeated 10,000 times to provide a distribution of the model results. Costs were assumed to be gamma distributed with the standard deviation set equal to the mean estimate because of the long tails typically associated with health care costs. Survival times were modeled using exponential distribution, and probabilities and utilities were modeled using beta distribution assuming a standard deviation of 0.1.

Results

Our first set of analyses compared the three strategies (ie, base, test, and rebiopsy) within each of the three platinum chemotherapy regimens: carboplatin plus paclitaxel; carboplatin plus pemetrexed; and carboplatin, pemetrexed, and bevacizumab. The model estimated the benefits for the three testing strategies as 0.361 (base), 0.420 (test), and 0.454 (rebiopsy) QALYs, with carboplatin plus paclitaxel as the standard regimen (Table 2). Total costs, including direct medication costs as well as ancillary costs, for the three testing strategies with carboplatin plus paclitaxel were $29,987 (base), $36,460 (test), and $40,689 (rebiopsy). As expected, drug acquisition and delivery costs accounted for a substantial proportion of total cost; these varied considerably across regimens. For the duration of first-line treatment, the mean medication costs were $1,995 (carboplatin plus paclitaxel), $30,611 (carboplatin plus pemetrexed), and $69,837 (carboplatin, pemetrexed, and bevacizumab). In all cases, starting patients on first-line erlotinib under the test or rebiopsy strategy increased both QALYs and costs compared with the base strategy (Table 2). Therefore, the ICER comparing carboplatin plus paclitaxel under the test strategy with the same regimen under the base strategy was $110,658 per QALY; comparing carboplatin plus paclitaxel under the rebiopsy strategy with same regimen under the test strategy, it was $122,234 per QALY. For the more expensive chemotherapy regimens (ie, carboplatin plus pemetrexed and carboplatin, pemetrexed, and bevacizumab), the test and rebiopsy strategies had more favorable ICERs than when carboplatin plus paclitaxel was the baseline regimen (Table 2; Fig 1).

Our second set of analyses compared the rebiopsy approach across the three platinum chemotherapy strategies. The ICER for carboplatin plus pemetrexed under the rebiopsy strategy versus carboplatin plus paclitaxel under the same strategy was $180,665, and the ICER of carboplatin, pemetrexed, and bevacizumab under rebiopsy versus carboplatin plus pemetrexed under the same strategy was $359,619. Comparing across chemotherapy regimens, the rebiopsy strategy had a more favorable ICER than the base or test strategy for both carboplatin plus pemetrexed and carboplatin, pemetrexed, and bevacizumab (Table 2; Fig 1).

Results of the univariate and multivariate sensitivity analyses are available in Appendix Tables A1 and A2 (online only). We found the results to be largely insensitive to varying the probability that a patient was *EGFR* positive. Although our results were based on median survival, results were not sensitive to analyses based on alternative approaches designed to provide a proxy for mean survival.

The multivariate sensitivity analysis revealed that for carboplatin plus paclitaxel under test versus the same regimen under base, carboplatin plus paclitaxel under test was more expensive and more effective for 44.3% of the draws. For carboplatin plus paclitaxel under rebiopsy versus the same regimen under test, carboplatin plus paclitaxel under rebiopsy was more expensive and more effective for 39.5% of the draws (Appendix Figs A2 and A3, online only). Using cost-effectiveness acceptability curves, we found that the test and rebiopsy strategies with any of the baseline chemotherapy regimens were cost effective slightly more than 50% of the time for a wide range of commonly used cost-effectiveness thresholds (Appendix Fig A4, online only).

Discussion

Our study has two main findings. First, our analysis showed that targeted first-line treatment with erlotinib for mutation-positive patients with stage IV adenocarcinoma is marginally cost effective when compared within any of the three standard platinum combination chemotherapy regimens. A cutoff of $100,000 per QALY is widely cited in the literature, but somewhat larger ratios are often accepted for treatment of advanced cancer.[45,46] Therefore, with an ICER of $110,658 per QALY for the test strategy and $122,234 per QALY for the rebiopsy strategy, *EGFR* mutation testing with targeted use of erlotinib may be considered cost effective when compared with carboplatin plus paclitaxel as a baseline regimen. However, the results of the probabilistic sensitivity analysis showed that there is uncertainty surrounding this conclusion. Furthermore, others may have higher or lower thresholds for cost effectiveness, which could lead to different conclusions.

Second, our analysis showed that the more expensive platinum combination regimens do not necessarily meet conventional cost-effectiveness acceptability thresholds when compared with carboplatin plus paclitaxel. It should be noted that the choice of chemotherapy platform regimen is not molecularly driven but instead based on toxicity, convenience, and historic efficacy. The carboplatin, pemetrexed, and bevacizumab regimen had a particularly unfavorable incremental cost-effectiveness ratio of $359,619 per QALY for the rebiopsy strategy. Although these regimens generate suboptimal cost effectiveness, they are commonly used in current clinical practice. Hence, one might question the use of these more expensive platinum combination regimens because of their relatively poor cost effectiveness, but if a clinician were to choose to use these regimens, cost effectiveness would be enhanced by following the rebiopsy strategy.

Our analysis has several limitations. First, we were unable to model the full course of therapy across a patient's lifetime, which often includes second- and even third-line treatments. Ideally, we would want to fully account for both the costs and effects of these treatments, but inputs for such a model are not readily available in the existing literature, particularly in pa-

Table 2. Base Patient Case Results

Strategy	Cost	Incremental Cost	Effect	Incremental Effect	C/E	Incremental Ratio	Final ICER
Carboplatin plus paclitaxel							
1. Base	$29,987		0.361		$83,046		
2. Test	$36,460	$6,474	0.420	0.058	$86,892	$110,658	$110,658
3. Rebiopsy	$40,689	$4,229	0.454	0.035	$89,583	$122,234	$122,234
Carboplatin plus pemetrexed							
4. Base	$64,962	$24,273	0.555	0.101	$117,067	$241,303	Extended dominance*
5. Test	$68,812	$3,850	0.599	0.044	$114,901	$87,561	Extended dominance*
6. Rebiopsy	$71,480	$2,668	0.625	0.026	$114,413	$103,132	$180,665
Carboplatin, pemetrexed, and bevacizumab							
7. Base	$104,104	$32,624	0.664	0.039	$156,817	$834,334	Extended dominance*
8. Test	$105,019	$915	0.700	0.036	$150,100	$25,547	Extended dominance*
9. Rebiopsy	$105,940	$921	0.721	0.021	$147,021	$44,036	$359,619

Abbreviations: C/E, cost/effect; ICER, incremental cost effectiveness ratio.
* Strategy had a less favorable ICER than a more effective and expensive strategy.

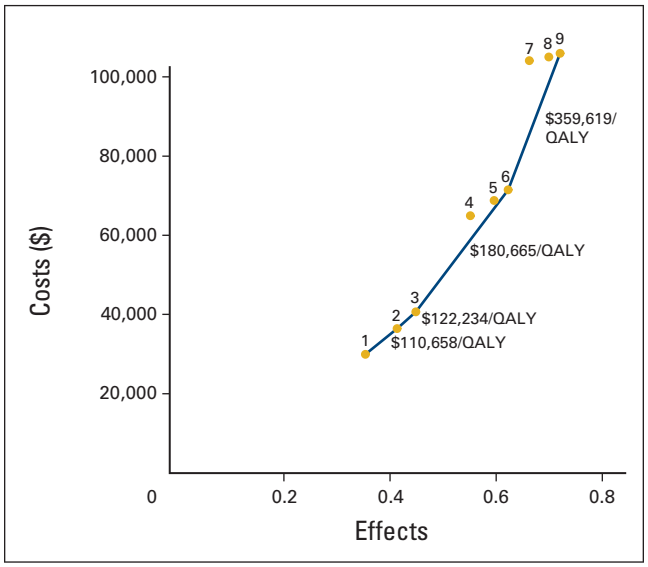

Figure 1. Cost-effectiveness frontier. Costs and effects of each of the nine potential treatment strategies are plotted. Strategies 4, 5, 7, and 8 lie inside of the cost-effectiveness frontier, because alternative strategies are preferred to them. QALY, quality-adjusted life year.

tients who receive a TKI first line. Virtually no randomized trial assigns both first- and second-line treatments, and the distinctions among second- and third-line therapies are relatively small with respect to survival. A study of European patients with *EGFR* mutations showed no difference in survival when TKIs were administered in the first or second line,[9] but this study was observational and potentially subject to selection bias for patients treated in the second line.

This analysis is also limited by our use of a model-based approach rather than a randomized trial. As such, our conclusions are dependent on the validity of the assumptions used to develop the model. For example, we used estimates of costs and effects from available sources, such as clinical trial results and Medicare reimbursement rates, which may not be reflective of costs and effects in the entire treatment population. To assess the effects of any violations of our assumptions, we used sensitivity analyses, in which we showed that our conclusions were fairly robust over plausible ranges. Because *EGFR* mutation testing and first-line use of erlotinib have only recently been adopted, we were not able to gather costs and effects from claims and registry data. Ideally, our results should be validated with such data as they become available. Finally, the current analyses are subject to modifications in cost. Drug costs, in particular, are typically reduced with time, and those reductions will make all strategies more favorable.

Despite these limitations, our model reveals that personalized therapy with TKIs for advanced adenocarcinoma is cost effective using thresholds acceptable in current US practice. This was especially true when we compared the personalized strategy with newer, more expensive chemotherapy regimens. When comparing treatment strategies with different chemotherapy regimens, the strategy including a repeat biopsy for patients without tissue available for *EGFR* testing was favorable, indicating that the additional biopsy adds value. This analysis supports the current clinical recommendation to test for *EGFR* mutations early in the course of treatment for advanced adenocarcinoma.

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Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

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Appendix

Table A1. One-Way Sensitivity Analysis* of the Most Influential Inputs (cost per QALY)

	Least Favorable		Most Favorable	
Variable	**Test *v* Base**	**Rebiopsy *v* Test**	**Test *v* Base**	**Rebiopsy *v* Test**
Carboplatin plus paclitaxel as reference regimen				
Utility of stable disease during oral therapy	$221,316	$244,656	$74,136	$81,852
Cost of erlotinib	$144,012	$155,784	$77,304	$88,680
Cost of progression per month	$121,884	$133,524	$83,184	$94,596
PFS with erlotinib	$133,344	$146,568	$95,940	$106,452
Utility of disease progression	$134,436	$148,644	$96,444	$106,476
Carboplatin plus pemetrexed as reference regimen				
Utility of stable disease during oral therapy	$175,122	$206,396	$73,332	$86,351
Cost of erlotinib	$131,938	$148,014	$43,184	$58,249
PFS with carboplatin plus pemetrexed	$121,097	$138,907	$65,380	$79,679
Cost of pemetrexed	$111,659	$127,504	$63,468	$78,764
PFS with erlotinib	$114,756	$133,572	$71,202	$84,852
Carboplatin, pemetrexed, and bevacizumab as reference regimen				
OS with erlotinib	$46,764	$61,848	Base dominated†	Test dominated†
OS with carboplatin, pemetrexed, and bevacizumab	$48,432	$63,228	Base dominated†	Test dominated†
Cost of erlotinib	$80,052	$99,540	Base dominated†	Test dominated†
Cost of bevacizumab	$66,636	$85,872	Base dominated†	$2199
PFS with carboplatin, pemetrexed, and bevacizumab	$73,944	$96,432	Base dominated†	$13,967

Abbreviations: OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.
* In the one-way sensitivity analysis, the value of a single input is set to the end of its hypothesized range, and the ICER is recalculated.
† A strategy is dominated if it is more costly and less effective than the alternative.

Table A2. Expected Cost Per QALY for Population Subgroups

		Carboplatin Plus Paclitaxel As Reference		Carboplatin Plus Pemetrexed As Reference		Carboplatin, Pemetrexed, and Bevacizumab As Reference	
Probability EGFR Positive (%)	**Population**	**Test *v* Base**	**Rebiopsy *v* Test**	**Test *v* Base**	**Rebiopsy *v* Test**	**Test *v* Base**	**Rebiopsy *v* Test**
6	Men, smokers (low estimate)	$113,784	$142,620	$91,712	$131,028	$30,645	$78,184
10	Men, smokers	$111,696	$129,000	$88,945	$112,343	$27,246	$55,231
15	General population	$110,664	$122,232	$87,561	$103,132	$25,547	$44,036
20	Women (low estimate)	$110,136	$118,860	$86,869	$98,558	$24,697	$38,508
26	Eastern Asian (low estimate)	$109,776	$116,532	$86,225	$94,319	$24,109	$34,707
32	Eastern Asian, nonsmoker	$109,548	$115,068	$86,091	$93,438	$23,741	$32,342
38	Women	$109,404	$114,084	$85,886	$92,096	$23,489	$30,728
59	Women (high estimate)	$109,104	$112,188	$85,497	$89,552	$23,012	$27,676
69	Nonsmokers (high estimate)	$109,032	$111,696	$85,395	$88,885	$22,887	$26,878

Abbreviations: EGFR, epidermal growth factor receptor; QALY, quality-adjusted life year.

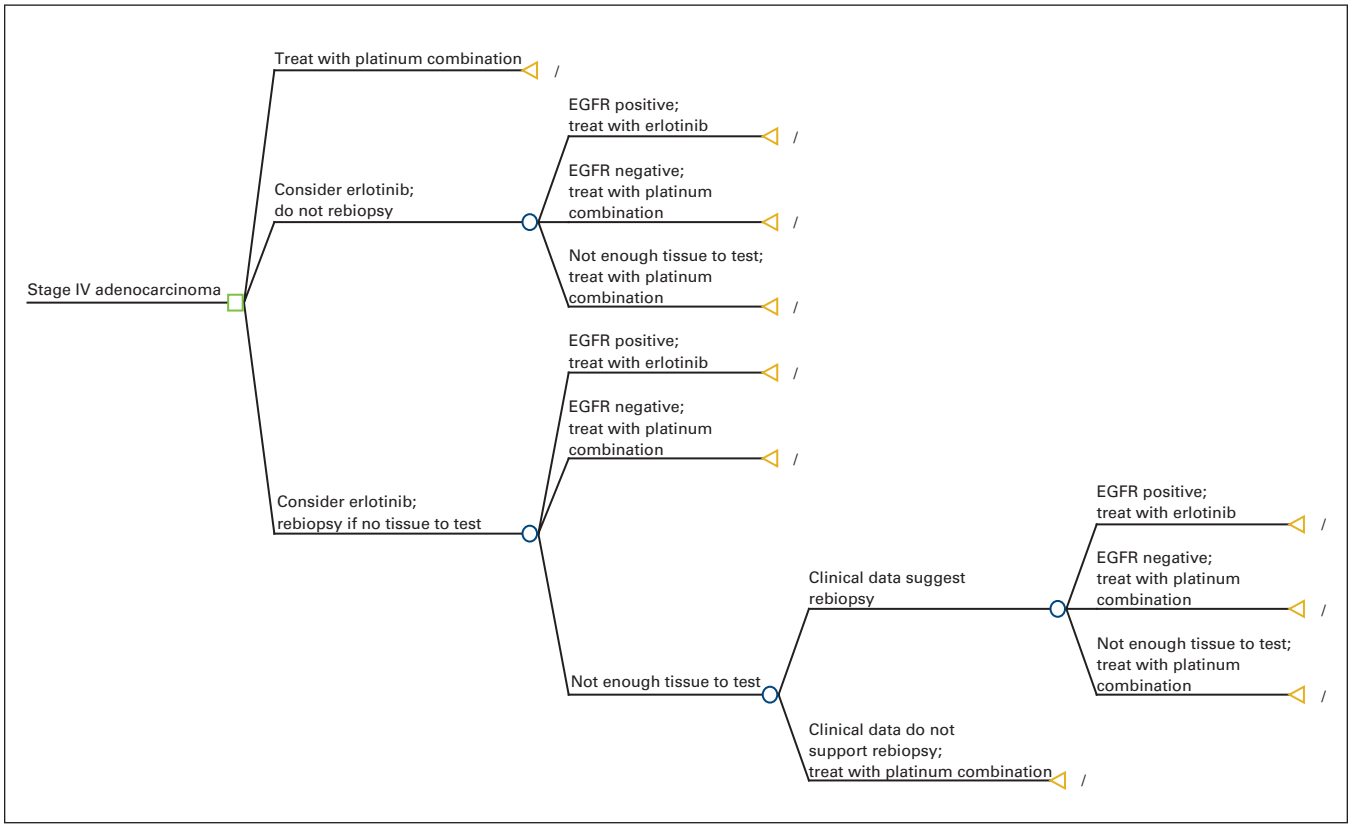

Figure A1. Baseline decision tree reflecting three testing strategies. Each path contained possible adverse events, which are not shown here. EGFR, epidermal growth factor receptor.

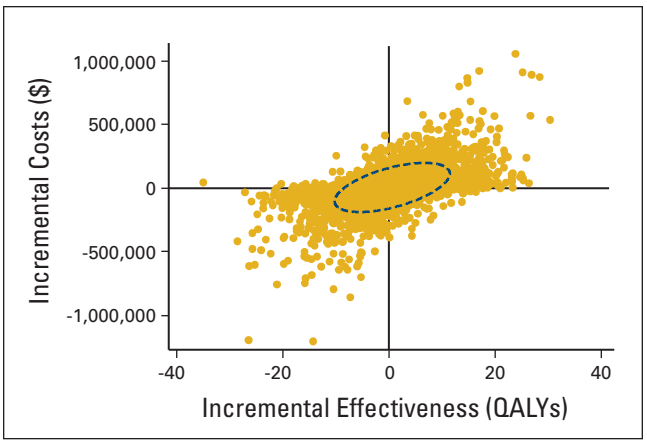

Figure A2. Probabilistic sensitivity analysis of carboplatin plus paclitaxel under the test strategy versus the same regimen under the base strategy. The ellipse represents the 95% CI, and it spans all four quadrants of the cost-effectiveness plane. QALY, quality-adjusted life year.

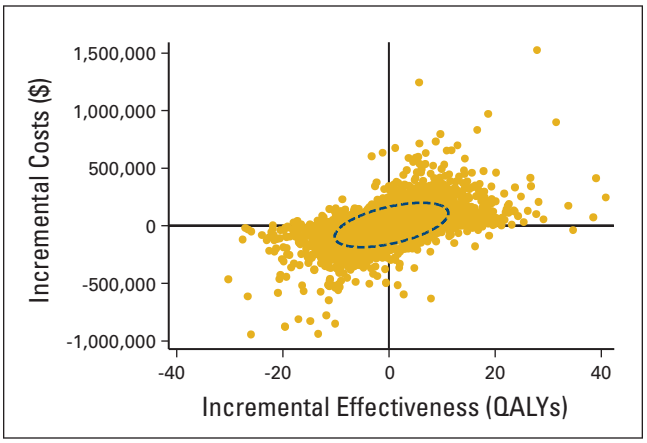

Figure A3. Probabilistic sensitivity analysis of carboplatin plus paclitaxel under the rebiopsy strategy versus the same regimen under the test strategy. The ellipse represents the 95% CI, and it spans all four quadrants of the cost-effectiveness plane. QALY, quality-adjusted life year.

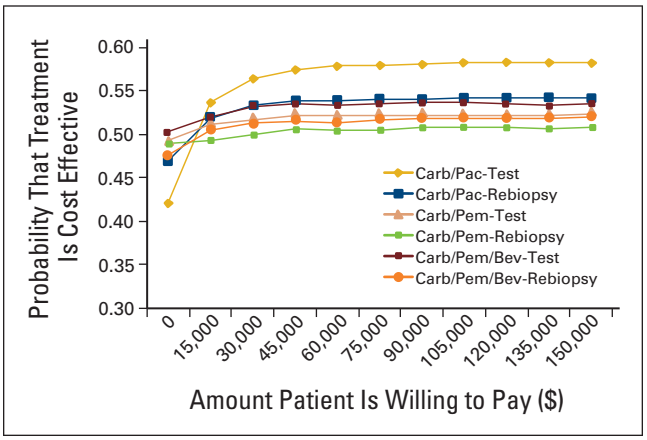

Figure A4. Cost-effectiveness acceptability curve. On the basis of the probabilistic sensitivity analysis, all strategies are cost effective slightly more than 50% of the time over a wide range of cost-effectiveness thresholds. Bev, bevacizumab; Carb, carboplatin; Pac, paclitaxel; Pem, pemetrexed.