Cost Effectiveness of Evidence-Based Treatment Guidelines for the Treatment of Non–Small-Cell Lung Cancer in the Community Setting

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Abstract

Purpose: The goal of this study was to evaluate the cost-effectiveness of Level I Pathways, a program designed to ensure the delivery of evidence-based care, among patients with non–small-cell lung cancer (NSCLC) treated in the outpatient community setting.

Patients and Methods: We included patients with NSCLC initiating a chemotherapy regimen between July 1, 2006, and December 31, 2007, at eight practices in the US Oncology network. Patients were characterized with respect to age, sex, stage, performance status, and line of therapy and were classified by whether they were treated according to Level I Pathways guidelines. Twelve-month cost of care and overall survival were compared between patients treated on Pathway and off Pathway. A net monetary benefit approach and corresponding cost-effectiveness acceptability curves were used to evaluate the cost-effectiveness of Level I Pathways.

Results: Overall, outpatient costs were 35% lower for on-Pathway versus off-Pathway patients (average 12-month cost, $18,042 *v* $27,737, respectively). Costs remained significantly less for patients treated on Pathway versus off Pathway in the adjuvant and first-line settings, whereas no difference in overall cost was observed in patients in the second-line setting. No difference in overall survival was observed overall or by line of therapy. In the net monetary benefit analysis, after adjusting for potential confounders, we found that treating patients on Pathway was cost effective across a plausible range of willingness-to-pay thresholds.

Conclusions: Results of this study suggest that treating patients according to evidence-based guidelines is a cost-effective strategy for delivering care to those with NSCLC.

Introduction

Lung cancer is the second most common cancer diagnosed in the United States and is the leading cause of cancer-related deaths, with an estimated 219,440 new cases and 159,390 deaths in 2009.[1] The economic cost of lung cancer is high, with an estimated cost of $9 billion per year.[2] Non–small-cell lung cancer (NSCLC) makes up approximately 80% of lung cancer cases in the United States. More than 70% of patients are diagnosed with stage III to IV disease. Patients with stage III disease have an estimated 5-year survival of 9% to 24% versus only 2% for patients with stage IV disease.[3] Because of the incidence, severity, and rising costs, it is becoming increasingly important to deliver consistent, high-quality, cost-effective care for NSCLC.

From 2003 to 2008, the number of oncology-related Investigational New Drug (IND) applications increased from 935 to more than 1,400, with the US Food and Drug Administration Office of Oncology Drug Products approving 53 new indications in the last 3 years.[4] These advances are having a growing financial impact on patients and society. Cancer care costs are escalating at a rate of 15% per year, nearly three times the increase in overall health care spending.[5]

Various chemotherapeutic options are available for NSCLC. However, no single regimen has emerged as the superior choice for treatment of patients with advanced disease,[6-8] and there is limited evidence regarding the cost-effectiveness of newer treatment strategies.[9] The Level I Pathways program is a physician-led initiative that encourages the consistent delivery of value-driven, evidence-based treatment. The goal of this program is to delineate treatment options that meet the following criteria: maximize survival benefit, minimize toxicities, and provide cost-saving advantages. Level I Pathways are developed and regularly updated by a multidisciplinary task force in collaboration with a network of more than 1,200 practicing community oncologists. To promote standardized and predictable care that meet the abovementioned criteria, Level I Pathways recommendations have been incorporated into the iKnowMed (iKM) electronic medical record (EMR) system, which is currently used by 83% of practices in the US Oncology network. The purpose of this study was to evaluate the cost-effectiveness of treating patients with NSCLC according to Level I Pathways recommendations.

Patients and Methods

Patient Identification and Characterization

Using a retrospective cohort design, we identified all patients with NSCLC initiating a chemotherapy regimen between July 1, 2006, and December 31, 2007, at eight practices in the US Oncology network. Using clinical data from the US Oncology iKM EMR system and online Pathways reporting system, we characterized patients by age, sex, stage at diagnosis, perfor-

mance status, line of therapy, and vital status. Age, performance status, and line of therapy were measured at initiation of first chemotherapy regimen in the study period. Patients were assigned a Pathway status depending on whether they were treated according to Level I Pathways for NSCLC (Appendix Table A1, online only). Patients were classified as treated: on Pathway, if they received care according to Level I Pathways recommendations for the entire study period; off Pathway, if they were treated with regimens not included in Level I Pathways; or both on and off Pathway, if they were switched from being treated on to off Pathway or vice versa during the study period. Because the group of patients treated both on and off Pathway was small (n = 109; 6%), and because of the difficulty in attributing costs and outcome to Pathway status among these patients, they were excluded. To avoid likely confounding of costs and survival estimates, we also excluded patients enrolled onto clinical trials (n = 128; 7%) or patients who had a diagnosis of a cancer other than NSCLC (n = 130; 7%).

Cost Analysis

We compared 12-month cost of care for patients on Pathway versus off Pathway using the Kaplan-Meier Sample Average (KMSA) approach, a robust method for estimating costs over time when complete follow-up is not available and when costs are likely to vary over time.[10] Variances and 95% CIs were calculated by applying the percentile method to 10,000 bootstrap samples.[11] The cost analysis was conducted from a payer's perspective and considered only direct costs. Discounting was not applied because of the short duration of the cost period. Outpatient charges were extracted from the US Oncology Claims Data Warehouse (CDW), a repository of all claims for services provided in the network. Data included Healthcare Common Procedure Coding System (HCPCS) and Common Procedural Terminology (CPT) codes, date of services, quantities, amounts billed, and primary payers. All charges (except diagnostic services and surgery costs) from the initiation of chemotherapy regimen through 12 months of follow-up were included. We excluded costs related to radiologic services (including radiation therapy) because these services were not provided uniformly across all practices. To normalize cost estimates, unadjusted 2007 Medicare reimbursement rates (Geographic Practice Cost Index 93) were applied. Costs for oral chemotherapy agents were estimated using 2007 average wholesale prices. In addition to directly measuring costs incurred in the US Oncology network, we conducted a sensitivity analysis to estimate the impact of hospitalizations on total cost for patients treated on versus off Pathway. Because claims data captured in the CDW do not capture total hospitalization costs, we calculated an average total cost for an inpatient stay for patients with lung cancer using national claims and reimbursement data from Aetna. This average total hospitalization cost was then applied to the total cost (as calculated using CDW data) for patients who were identified as having been hospitalized to determine if and to what extent inpatient costs might have affected observed cost differences. Hospitalization events were identified by searching for evaluation and management

charges in the CDW data corresponding to inpatient admissions and consultations.

To identify underlying cost drivers, cost was broken into several categories (eg, outpatient visits, chemotherapy/nonchemotherapy medications, laboratory services, and ancillary services/therapies) using HCPCS and CPT codes. To address likely confounding that may be associated with Pathway status and cost, stratified analyses were conducted by line of therapy.

Survival Analysis

Twelve-month overall survival was compared between patients treated on Pathway and patients treated off Pathway using the Kaplan-Meier method and corresponding log-rank test. Vital status was supplemented for patients who were lost to follow-up by querying the Social Security Death Master File. Cox proportional hazards regression analysis was used to explore the impact of Pathway status on risk of mortality after adjusting for other relevant clinical and demographic characteristics. The proportionality assumption was confirmed visually.

Net Monetary Benefit Analysis

To estimate the overall cost effectiveness of treating patients with NSCLC according to Level I Pathways, we calculated the net monetary benefit (NMB) of Pathways. This metric overcomes the limitations of estimating cost effectiveness using cost-effectiveness ratios in the presence of small differences in effectiveness and also provides a less biased estimate of cost effectiveness in the presence of differences in baseline measures between treatment groups often seen in observational studies.[12-14] The basic model for deriving the NMB is presented:

$$NMB(\lambda Bij) - Cij = \beta_0 + \beta_1(\text{on Pathway}) + \beta_j X_j + \varepsilon j$$

In this equation, Bij = survival time for patient i; Cij = cost of treatment for patient i; X = demographic and clinical characteristics; and λ = specified ceiling ratio (willingness to pay). The uncertainty of the estimated NMB was illustrated using cost-effectiveness acceptability curves.[15-16]

Results

A total of 1,409 patients with NSCLC were identified who met the eligibility criteria for this study. Of these, 1,095 (78%) were treated on Pathway, and 314 (22%) were treated off Pathway. During the 12-month follow-up period, 735 patients (52%) died. Of those who lived, 494 (73%) had a full 12 months of follow-up time. Median follow-up time was similar for patients on pathway (median, 8.8 months) and off Pathway (median, 9.0 months).

Table 1 shows the patient characteristics overall and by Pathway status. The overall median age of patients was 67 years (range, 30 to 94 years), and 54% (n = 766) were male. A majority of patients (n = 931; 72%) were diagnosed with advanced disease (stage IIIB to IV). Approximately two thirds of patients were initially treated with first-line regimens, 14% (n = 200) were treated in the adjuvant/neoadjuvant setting, 13% (n = 184) were treated with second-line care, and 7%

Table 1. Patient Demographic and Clinical Characteristics

Factor	Total (N = 1,409)		Pathway Status			
			On (n = 1,095)		Off (n = 314)	
	No.	%	No.	%	No.	%
Age, years						
Median	67		67		66	
Range	30-94		30-94		35-90	
<60	360	26	274	25	86	27
60-69	468	33	362	33	106	34
70-79	454	32	366	33	88	28
≥80	127	9	93	9	34	11
Sex						
Female	643	46	492	45	151	48
Male	766	54	603	55	163	52
Stage IIIB to IV at diagnosis						
No	368	28	278	28	90	31
Yes	931	72	731	72	200	69
Unknown	110		86		24	
ECOG performance status						
0	574	49	465	50	109	45
1	523	44	409	44	114	47
2-3	83	7	64	7	19	8
Unknown	229		157		72	
Initial line of therapy						
Adjuvant/neoadjuvant	200	14	166	15	34	11
First	920	65	785	72	135	43
Second	184	13	138	13	46	15
Third	58	4	6	1	52	17
Fourth to sixth	47	3	—	—	47	15
No. of involved clinics	126		122		105	
Distribution of patients by state						
Colorado	69	5	44	4	25	8
Missouri	417	30	388	35	29	9
New York	152	11	122	11	30	10
Ohio	59	4	45	4	14	4
Texas	385	27	273	25	112	36
Virginia	282	20	185	17	97	31
Washington	45	3	38	3	7	2

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

(n = 105) were treated with third-line care or greater. Patients treated on versus off Pathway were similar with respect to age, sex, stage at diagnosis, and Eastern Cooperative Oncology Group performance status; however, they differed by line of therapy. Of patients treated on Pathway, 87% (n = 951) received adjuvant/neoadjuvant or first-line care, compared with 54% (n = 169) of off Pathway patients. By definition, patients treated with chemotherapy beyond third line were considered off Pathway (n = 47).

Cost Analysis

Figure 1 presents the 12-month cumulative costs of patients treated on Pathway versus patients treated off Pathway. Outpa-tient costs were 35% lower for on-Pathway (average 12-month cost, $18,041.62) versus off-Pathway patients (average 12-month cost, $27,736.51; on/off cost ratio, 0.65; 95% CI, 0.58 to 0.76). Applying estimated total hospitalization costs (on/off cost ratio for hospitalizations, 0.98; 95% CI, 0.83 to 1.17) to patients identified as having inpatient admissions did not have a significant effect on the observed difference in total cost by Pathway status (on/off cost ratio, 0.71; 95% CI, 0.64 to 80).

We categorized costs to identify possible drivers of the observed cost differences and found that the majority of cost differences could be attributed to lower costs of chemotherapy and other infused medications among the on-Pathway cohort (Table 2). Chemotherapy costs were 37% lower (cost ratio, 0.63;
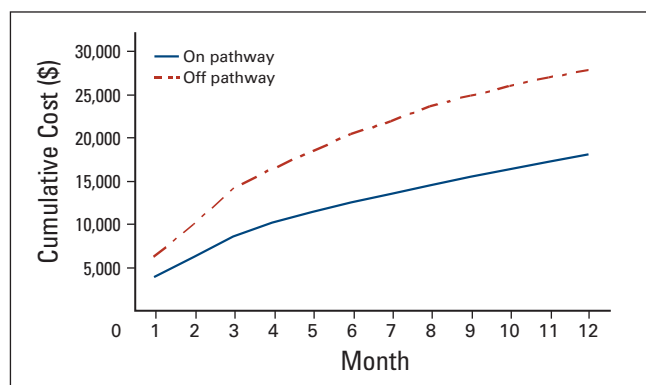
Figure 1. 12-month cumulative cost by Pathway status.

95% CI 0.55 to 0.76) for on-Pathway patients versus off-Pathway patients, and nonchemotherapy medications were 39% lower (cost ratio, 0.61; 95% CI, 0.52 to 0.74). For nonchemotherapy medications, we found that use of both erythropoietin stimulating agents (ESAs; cost ratio, 0.54; 95% CI, 0.42 to 0.69) and WBC growth factors (CSFs; cost ratio, 0.42; 95% CI, 0.32 to 0.63) was significantly lower in the on-Pathway cohort than in the off-Pathway cohort.

Because of the significant difference in line of therapy for patients on Pathway versus off Pathway, we stratified the cost analysis by line of therapy. Figure 2 shows 12-month total costs by Pathway status for patients receiving adjuvant, first-line, and second-line care. We found that costs remained significantly lower for patients treated on Pathway versus off Pathway in the adjuvant and first-line settings, whereas no difference in overall cost was observed in patients receiving second-line care. Among patients in the adjuvant setting, we found that those treated on Pathway had a reduced cost of 39% compared with patients treated off Pathway (cost ratio, 0.61; 95% CI, 0.44 to 0.88); a 29% decreased overall cost was associated with on-Pathway

patients receiving first-line care compared with off-Pathway patients receiving first-line care (cost ratio, 0.71; 95% CI, 0.59 to 0.87). Use of ESAs and CSFs was significantly less frequent among on-Pathway patients in adjuvant, first-line, and second-line settings. Because of the insufficient number of on-Pathway patients, we were unable to evaluate differences in cost by Pathway status among patients receiving third-line care.

Overall Survival

No difference in 12-month overall survival was observed by Pathway status (Fig 3; 12-month survival probability, 0.45 *v* 0.46 for on *v* off Pathway; log-rank *P* = .867). In a multivariable Cox regression model (Table 3), we found that Pathway status was not associated with 12-month risk of mortality after adjusting for age, sex, stage, performance status, and line of therapy (multivariable hazard ratio [HR], 0.95; 95% CI, 0.77 to 1.16). Significant independent predictors of overall survival included stage at diagnosis (HR, 1.41; 95% CI, 1.10 to 1.80), lower performance status (HR, 1.78; 95% CI, 1.50 to 2.11 for performance status of 1; HR, 3.46; 95% CI, 2.63 to 4.57 for performance status of 2 to 3; *P* trend < .0001), and current treatment for metastatic disease (HR, 2.78; 95% CI, 1.83 to 4.23).

Again, because of differences in line of therapy by Pathway status, we evaluated the association between overall survival and Pathway status by line of therapy. No significant differences were observed in survival for patients on and off Pathway in adjuvant, first-line, and second-line settings. Furthermore, because patients receiving therapy beyond third line were considered to be off Pathway, and because there were few patients treated on Pathway in the third-line setting, we compared survival among patients receiving adjuvant and second line care combined and found no difference in survival by Pathway status (data not shown).

Table 2. 12-Month Average Cost by Pathway Status

Charge Category	12-Month Average Cost ($)		Comparison of Cost		
	On Pathway (n = 1,095)	Off Pathway (n = 314)	Cost Difference ($; on − off)	Cost Ratio (on/off)	95% CI* for Cost Ratio
Outpatient visits	1,124	1,060	64	1.06	0.99 to 1.11
Acute care visits	437	364	73	1.20	0.95 to 1.46
Chemotherapy	11,839	18,762	−6,923	0.63	0.55 to 0.76
Other medication	4,374	7,198	−2,824	0.61	0.52 to 0.74
ESAs	1,011	1,867	−856	0.54	0.42 to 0.69
CSFs	1,867	2,951	−1,083	0.63	0.52 to 0.83
Laboratory procedures	223	295	−73	0.75	0.67 to 0.84
Minor procedures	33	43	−10	0.78	0.66 to 0.92
Nursing care/hospice	2.68	2.16	0.52	1.24	0.14 to 15.20
Other	1.25	0.99	0.25	1.25	0.39 to 9.04
G codes	7.86	11.94	−4.08	0.66	0.40 to 1.27
Total cost	18,042	27,737	−9,695	0.65	0.58 to 0.76

Abbreviations: ESA, erythropoietin stimulating agent; CSF, WBC growth factor.
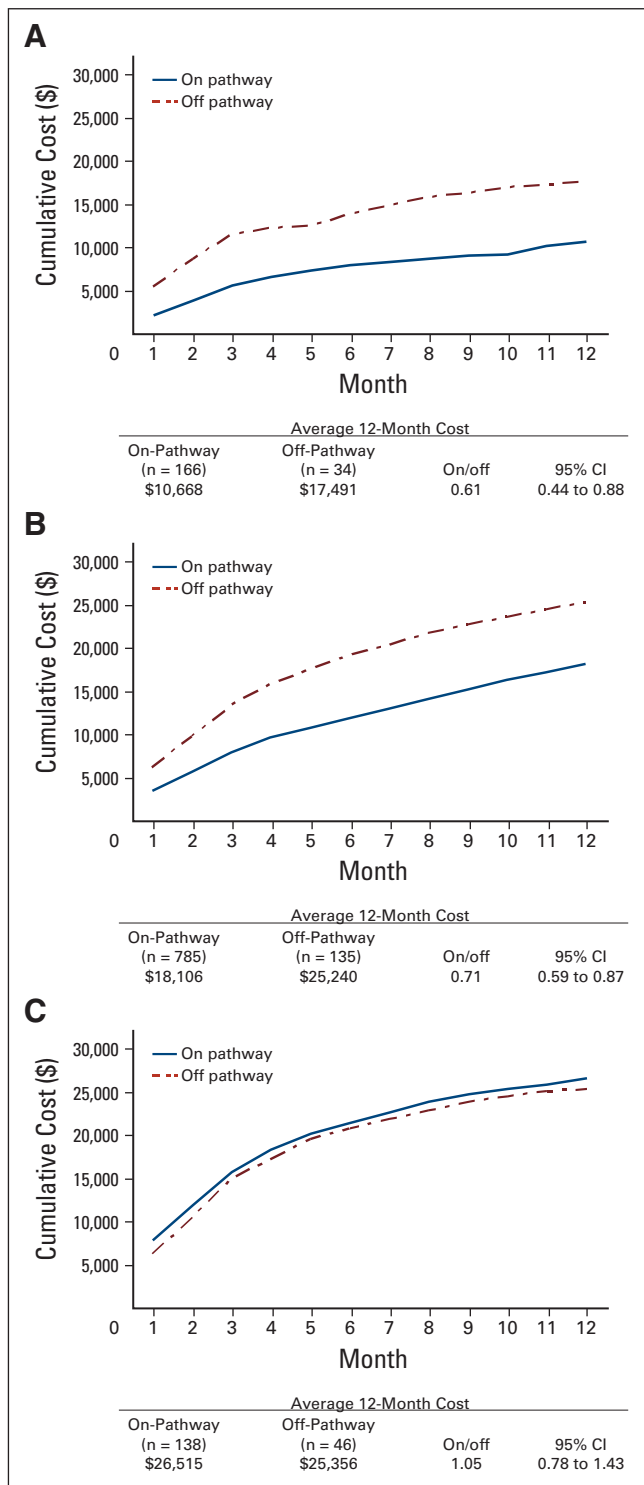*95% CIs calculated using percentile method using 10,000 bootstrap samples.

Figure 3. Overall survival by Pathway status.

pay ceiling ratios (Fig 4, online only). We found that treating patients on Pathway remained cost effective across the plausible range of society's (or payers') willingness to pay, even after adjusting for potential confounders (age, stage, line of therapy, and performance status).

Conclusion

The findings of this study reinforce the concepts introduced in the landmark studies of Fisher et al[17-19] and Wennberg et al,[20] which convincingly demonstrated that high quality was not necessarily associated with high cost. Assuming that value is directly proportional to outcomes and inversely proportional to costs, quality would be improved by either improved outcomes and/or lower costs. These studies left oncologists with the task of determining the behaviors that lead to cost-effective oncology care.[21,22]

To our knowledge, this is the first study to empirically measure the cost effectiveness of evidence-based treatment guidelines for cancer therapy. Results suggest that treating patients according to evidence-based guidelines is a cost-effective strategy for delivering care to patients with NSCLC, especially in the adjuvant and first-line settings. Over 12 months, average cost of care for patients on Pathway was 35% less compared with patients treated off Pathway. This cost difference was driven predominately by significantly lower costs for chemotherapy and other medications. It is worth pointing out that Pathways includes costly cancer chemotherapeutics like bevacizumab and erlotinib, albeit restricted to lines of therapy in which evidence is sound, so this is not simply a cost comparison between one group receiving expensive drugs and another receiving cheaper ones. Patients treated on Pathway also did not receive chemotherapy beyond third line, which may be another reason why costs were lower in this cohort. We also found that there were no observed differences in 12-month overall survival by Pathway status, suggesting that the added cost associated with treat-

Figure 2. 12-month cumulative cost by Pathway status and line of therapy for patients receiving (A) adjuvant, (B) first-line, and (C) second-line care.

Cost Effectiveness

Finally, to estimate the overall cost effectiveness of Level I Pathways, we modeled the joint density of cost and effect (as measured by overall survival) by calculating the net monetary benefit approach of Pathways across a range of willingness to
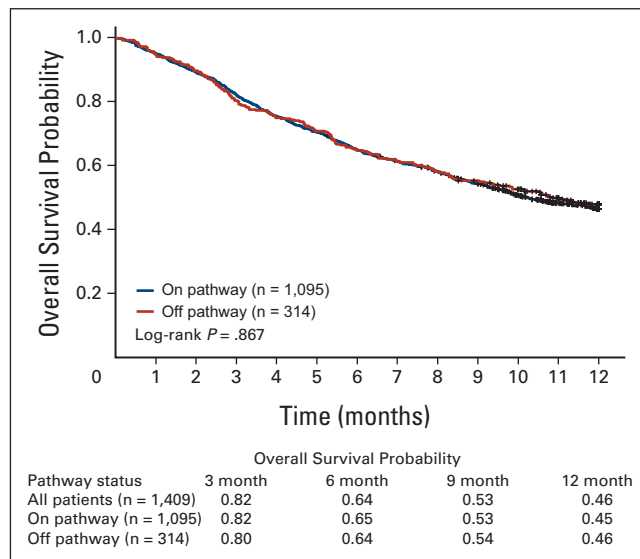
Table 3. Cox Regression Analysis: Overall Survival

Characteristic	Univariable			Multivariable		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Pathway status						
On	1.00			1.00		
Off	0.99	0.83 to 1.17	.87	0.95	0.77 to 1.16	.58
Sex						
Male	1.00			—	—	
Female	0.91	0.79 to 1.05	.20	—	—	—
Age (continuous)	1.01	1.002 to 1.02	.01	1.01	1.001 to 1.02	.03
Stage IIIB to IV at diagnosis						
No	1.00			1.00		
Yes	2.13	1.75 to 2.58	<.001	1.41	1.10 to 1.80	.002
ECOG performance status						
0	1.00			1.00		
1	1.94	1.64 to 2.30	<.001	1.78	1.50 to 2.11	<.001
2-3	3.95	2.99 to 5.21	<.001	3.46	2.61 to 4.57	<.001
Line of therapy						
Adjuvant	1.00			1.00		
Metastatic	3.79	2.77 to 5.20	<.001	2.78	1.83 to 4.23	<.001

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

ing patients off Pathways (including therapy beyond third line) did not translate to improved outcomes.

One question that arises is the extent to which differences in cost by Pathway status are driven simply by use of less expensive drugs or a decrease in use of therapy overall. We found that it is likely a combination of both. Although costs were demonstrably lower among patients treated on Pathway, we also found that patients treated on Pathway had a 22% lower frequency ($P < .001$) of chemotherapy infusion visits and 23% lower frequency ($P < .001$) of administrations of nonchemotherapy agents, including supportive care agents (data not shown). One specific difference is that on-Pathway regimens have standard order sets that define dosing strengths and number of cycles. Off-Pathway regimens have much more likelihood of being administered for additional cycles by the treating physician.

Possible explanations for the observed difference in cost of nonchemotherapy medications by Pathway status is that by definition, on-Pathway regimens are typically lower in toxicity, so fewer antiemetics and growth factors are required, and doctors who choose to adhere to Pathways tend to be less likely to prescribe more expensive supportive care drugs unless there is to strong evidence to validate use.

The limitations of this study include the fact that costs were estimated using outpatient claims, and we were therefore unable to directly calculate total cost related to hospitalizations. To address this limitation, we identified events using evaluation and management charges in the CDW data related to inpatient admissions/consultations and applied a total hospitalization cost estimate to our overall outpatient cost. Results of the cost analyses were robust to the application of these quasi-theoretical inpatient cost estimates. Furthermore, although there is always the possibility of misclassification as a result of missing hospi-

talization events in the CDW claims data, the probability of this occurring would likely be balanced across comparison groups, in which case any bias introduced would be toward the null hypothesis leading to an underestimation of the true differences in cost.

The strength of this study lies in the clinically rich EMR data used in conjunction with claims data to evaluate the impact of Level I Pathways on costs and survival of patients with NSCLC receiving care in a large, geographically dispersed network of community-based oncology practices. Given the extensive use and range of chemotherapy use for NSCLC without strong evidence regarding therapeutic superiority of any given regimen, it is important to consider the economic impact treatment may have on patients and society.

Given an absence of difference in survival by treatment strategy, as demonstrated in this article, it becomes increasingly important to focus on delivering consistent, high-value care that maximizes patient quality of life while at the same time minimizing the economic burden of care. Results of this study indicate that Level I Pathways is a cost-effective treatment strategy for NSCLC in the community setting, and future studies should evaluate these evidence-based guidelines for other cancer sites.

It is important to ask whether there are attributes to the Level I Pathways program that contributed to the enhanced value realized. Grilli et al[23] suggested critical components to guidelines: types of professionals involved in guideline development are specified, strategy used to identify primary evidence is specified, and recommendations are clearly graded. To these we add the following characteristics to the Pathways process used in this study: ready access and mandatory participation in the Pathways program and a prospective review process, in which

Pathways exceptions are reviewed before the administration of treatment. Satisfying these five criteria has been critical to the success of the program.

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