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Total and Segmented Direct Cost-of-Care for Stage IV Non-Small Cell Lung Cancer in a Privately Insured Population

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Total and Segmented Direct Cost-of-Care for Stage IV Non-Small Cell Lung Cancer in a Privately Insured Population

by

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Thesis

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Dedication

This work is dedicated to my family – my parents, Karen and Rich, for providing support, encouragement, and for being there to listen to all my complaints; my brothers, Andy and Adam, and my sister-in-law Katie, for always being there when I needed them; my dog, Aussie, who has been my constant companion throughout pharmacy school and postgraduate education, and has adapted to a multitude of living situations and hectic schedules (thanks for being such a good dog); and to my cat, Kitty, who is just plain evil at times.

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Abstract

Total and Segmented Direct Cost-of-Care for Stage IV Non-Small Cell Lung Cancer in a Privately Insured Population

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The University of Texas at Austin, 2011

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Introduction: New treatments for stage IV (adv) NSCLC have emerged this past decade. Recent pharmacoeconomic research has focused on cost of treatment, comparative costs of therapies, and cost/cost effectiveness of adding a biologic to traditional therapy. Drug cost is thought to be a primary driver of cost change in NSCLC, yet to our knowledge, characterization of the direct cost of NSCLC has not been published since the new treatments have emerged in the guidelines. Our primary objective was to characterize the direct and segmented cost of adv NSCLC from 2000-9. We also want to determine cost impact of new therapies, and cost trend from 2000-9.

Methods: This PharMetrics claims database study includes diagnosed NSCLC patients ≥ 20 yo. Small cell lung cancer was excluded. Claims were divided into disease segments

and time periods representative of changes in therapy ("pre" [2000-2], "transition" [2003-5], and "current" [2006-9] periods). Descriptive statistics (median, interquartile range [IQR]), chi-square test (nominal data), and Wilcoxan rank sum tests were performed on the data. To adjust for baseline confounders, multivariate least squares regression models were created.

Results: Costs are reported as medians in terms of per patient per month (pppm). Overall monthly cost (n=969) was $10,281 pppm. Diagnosis cost $6,601 pppm, active treatment cost $9,287 pppm, and end-of life cost $12,215 pppm. There was no difference in cost between the "transition" (n=439) and "current" (n=503) periods overall or for any segment of disease. Comorbidities had no effect on cost. For patients receiving at least 5 months of active treatment medication (n=316) total median cost was $144,147 per patient ($9,371 pppm).

Discussion: There was no difference in cost between the transition and current periods, in regards to either overall cost or segmented cost. The most expensive segment was end-of-life, with a median cost exceeding $12,000 pppm. Surprisingly, comorbidities had no effect on cost. Newer agents (biologics, TKIs, and pemetrexed) represent only a modest portion of cost, with a majority of cost for stage IV NSCLC comprised of non-drug costs.

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Chapter 1: Introduction

Together, lung and bronchus cancer constituted the leading cause of cancer related deaths in 2010.[1] Non-small cell lung cancer (NSCLC) accounted for approximately 85% of these cases, while small cell lung cancer (SCLC) and other types comprised the remainder.[2,3] NSCLC is a disease of the elderly, with a median age of 71 years at diagnosis.[1] The median overall survival (OS) for a patient diagnosed with locally advanced (stage IIIb) or metastatic (stage IV) NSCLC is less than one year.[2,3]

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend platinum doublet (PD) chemotherapy over best supportive care for treatment of lung and bronchus cancer.[4] First-line therapy recommendations include combining PD chemotherapy with the biologic agents bevacizumab or cetuximab. Cetuximab has compendia listing for reimbursement but has yet to be FDA approved for advanced NSCLC. Pemetrexed, a newer anti-metabolite, is another option for use with PD chemotherapy. Other treatment options include the small molecule tyrosine kinase inhibitor (TKI) erlotinib. Second-line options are single agent docetaxel, pemetrexed, or erlotinib.[4] Erlotinib is also indicated in the compendia for third-line therapy.[4] Of note, some treatments are indicated for a specific cell histology, which narrows their use to a particular patient subset (bevacizumab and pemetrexed are only indicated for non-squamous cell NSCLC).

A common perception is newer treatment innovations contribute to a substantial increase in the cost of treating a NSCLC patient. The most recent literature describing

overall cost of treatment uses data from the turn of the decade.[5] To our knowledge, no studies evaluating the direct medical cost-of-care with the current treatment standards have been published.

Our primary objective was to characterize the total and segmented direct cost of care for stage IV NSCLC treatment. We also analyzed the cost of biologics, TKIs, PD, single agent chemotherapy, and other prescription medications during the active treatment phase of stage IV NSCLC. Additionally, we analyzed the cost of drugs in terms of overall NSCLC cost and the cost trend of stage IV NSCLC from 2003-2009.

Chapter 2: Background

EPIDEMIOLOGY

Non-small cell lung cancer carcinoma (NSCLC) accounts for approximately 85% of lung and bronchus cancers. The remaining lung and bronchus cancer diagnoses are comprised of small-cell lung cancer (SCLC) carcinoma (14%) and other (sarcoma/unspecified/other specified) (1%).[2,3] Regardless of the type, lung and bronchus cancers have poor prognoses; median overall survival for a patient diagnosed with locally advanced or metastatic NSCLC is currently less than one year. It is a disease primarily affecting the elderly. The median age at diagnosis is 71 years, and 68% of NSCLC patients are diagnosed at ≥ 65 years of age. Therapies for advanced (stage IIIb or IV) NSCLC have improved throughout the previous two decades to now include first, second, and even third-line therapies. However, no curative treatments have been identified.

CURRENT PRACTICE GUIDELINES

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend platinum doublet (PD) chemotherapy (to prolong survival, improve control of symptoms, and enhance quality of life) over best supportive care.[4] First-line therapy recommendations include combining PD chemotherapy with bevacizumab or cetuximab, both of which are biologic agents. Bevacizumab targets vascular endothelial growth factor (VEGF) while cetuximab targets epidermal growth factor receptor (EGFR). Of note, while cetuximab is listed in the NCCN compendia as a first-line option for advanced NSCLC, it is not currently approved by the FDA for

NSCLC. Pemetrexed, an anti-metabolite, is another option for use with PD chemotherapy. Other treatment options include the small molecule tyrosine kinase inhibitor (TKI) erlotinib for EGFR positive mutations.[4] Neither bevacizumab nor pemetrexed are recommended for advanced NSCLC with squamous cell histology.[4] Once the initial PD regimen is completed, continuation maintenance therapy may be utilized. Maintenance therapy is the continuation of at least one agent used during first-line therapy. This continuation of therapy is recommended after the first four to six cycle of chemotherapy until disease progression.[4] Pemetrexed has FDA approval for maintenance therapy. Another option is the use of switch maintenance therapy, where an agent not used during the PD chemotherapy regimen, such as docetaxel, is initiated for maintenance therapy.[4] Second-line options are single-agent docetaxel, pemetrexed, or erlotinib.[4]

EVOLUTION OF NSCLC TREATMENTS

Changes in pharmacotherapy for advanced NSCLC in the past decade can be grouped into three time periods. The time when newer therapies (biologics, TKIs, and pemetrexed) were first introduced can be considered the transition period (2003-2005). It bridges the time period between simple PD chemotherapy as the clear historical standard of care to the current recommended standard of care, which includes biologics, TKIs, and doublets including pemetrexed, in addition to the older PDs. The time period prior to the emergence of these new therapeutic classes (200-2002) provided only PD chemotherapy as a treatment option. After arrival of all new drug therapies on the market, the guidelines

set forth by the NCCN evolved; this was considered the current period (2006-2008), since available therapies are in line with the guidelines.[4]

PHARMACOECONOMIC CONSIDERATIONS

With all of the advances in lung cancer treatment, a common perception is that these innovations and newer treatment options have contributed to a substantial increase in the cost of treating an advanced NSCLC patient. In a 2005 publication, Kutikova et al described the cost of treatment at the turn of the decade; at this time PD was standard of care. Biologics, TKIs, and pemetrexed regimens were not available at that time. Based on claims data from 1999-2000, they estimated the per patient cost of lung cancer to be quite substantial at $6,181 per month, and $42,990 total per person (diagnosis until death or up to two years).[5] Nonetheless, cost analyses that have compared the cost of treatment to the cost of best supportive care have shown that advanced NSCLC treatment can be administered with satisfactory cost effectiveness in patients with acceptable ECOG performance status scores (bevacizumab PS 0-1; cetuximab PS 0-2; erlotinib PS 2).[3,4,6] One aspect associated with increased costs is the failure of initial treatment; an additional $19,149 monthly cost was associated with treatment failure.[5] The main driver of costs is an increase in hospitalizations.[5,7] Kutikova et al hypothesized that treatments that inhibit disease progression could decrease treatment failure, thereby lowering the overall cost of advanced NSCLC.[5] It has been noted that new treatment strategies that can help decrease hospitalizations could lower the economic burden of advanced NSCLC.[5-8]

NEWER NSCLC TREATMENTS

New treatments have emerged in the past several years and these show modest gains in progression free survival (PFS) and overall survival (OS) in various clinical trials. The ECOG 4599 phase III trial showed a statistically significant increase in PFS (6.2 vs. 4.5 months, respectively; $p<0.001$) and OS (12.3 vs. 10.3 months, respectively; $p=0.003$) when bevacizumab was combined with PD chemotherapy vs. PD chemotherapy alone. Subgroup analysis reported no statistically significant survival benefit for those ≥ 70 years of age.[9,10] It is important to note the use of bevacizumab was restricted to patients with non-squamous histology.

An application to extend the approved uses of cetuximab to include first-line treatment of advanced NSCLC is currently under consideration at the FDA. The pivotal trial for this use was the FLEX phase III trial. It included 1125 patients with all histological types of advanced NSCLC, demonstrated statistically significant increases in OS for patients treated with cetuximab in conjunction with PD chemotherapy versus chemotherapy alone (11.3 vs. 10.1 months, respectively; $p=0.044$).[11] A second phase III trial, BMS099, compared cetuximab in conjunction with PD chemotherapy versus chemotherapy alone. BMS099 failed to show the same statistically significant results as the FLEX trial, though it showed a trend to improve survival with the addition of cetuximab; an underpowered study design may have contributed to the lack of statistical significance.[12] Erlotinib has also demonstrated statistically significant OS improvement in clinical trials when used as second-line monotherapy vs. placebo (6.7 vs. 4.7 months, respectively; $p<0.001$).[13] In addition to use as a second-line agent, erlotinib is also used

first-line in patients with poor performance scores, who cannot tolerate PD chemotherapies.[4] Erlotinib is also an approved third-line agent for treating advanced NSCLC.[4]

Though these new treatments for advanced NSCLC have shown modest gains in PFS and/or OS, when compared to the traditional PDs (now mostly generic), they are significantly more costly. Criticism of the cost of new therapies has been editorialized, [14,15] yet direct cost-of-care evaluations for NSCLC since introduction of new therapies has yet to be published to our knowledge.

Research analyzing the economic outcomes associated with advanced NSCLC has focused on cost of treatment, cost-benefit of adhering to pathways based on guidelines set forth from the NCCN,[18] comparative costs of different PD therapies,[19] and the cost effectiveness of adding bevacizumab to PD therapy.[20] Studies examining cost of illness associated with advanced NSCLC have not included the time period since the introduction of bevacizumab and pemetrexed as first-line treatments. In addition, the overall cost of advanced lung cancer has not been studied in regards to segments of disease (diagnosis, active treatment, and end-of-life care).[21-23]

SEGMENTING COST-OF-CARE

Song et al studied the cost of medical care in metastatic colorectal cancer (mCRC) based on the three segments: diagnosis, active treatment, and end-of-life care.[24] When monthly costs for each segment were calculated, active treatment proved to be the least costly segment, with a mean monthly cost of $8,599, even though biologics therapies

such as bevacizumab, cetuximab, and panitumumab were commonly used as part of metastatic colorectal cancer (mCRC) treatment during the period of observation (2004-2009). Diagnosis was a defined as a time period of 90 days after diagnosis of mCRC and end-of-life was defined as a time period of 90 days prior to death. Active treatment fell between diagnosis and end-of-life care and varied based on treatment length. Mean monthly cost during the diagnostic segment was $16,340 and $26,649 for end-of-life care. Set against these substantial diagnostic and end-of-life costs, the cost of anti-cancer therapy treatment was $8,599 pppm. A study analyzing the cost of medical care throughout distinct disease segments in advanced (stage IV) NSCLC will help determine the true economic impact of newer biological agents when utilized as active treatment, as set against the overall cost of treatment. Additionally, characterizing the changes in overall cost of treating stage IV NSCLC will enhance our perspective on the magnitude of increases in direct healthcare costs associated with stage IV NSCLC in the past decade.

Chapter 3: Methods

This retrospective database study used private claims data spanning the period of 01/01/00 through 06/30/09 ("study period"). All newly diagnosed stage IV NSCLC cases between 07/01/00 and 06/30/08 ("enrollment period") were identified by an algorithm developed for use with healthcare claims data and ICD-9-CM coding (Figure 1).[25-27]

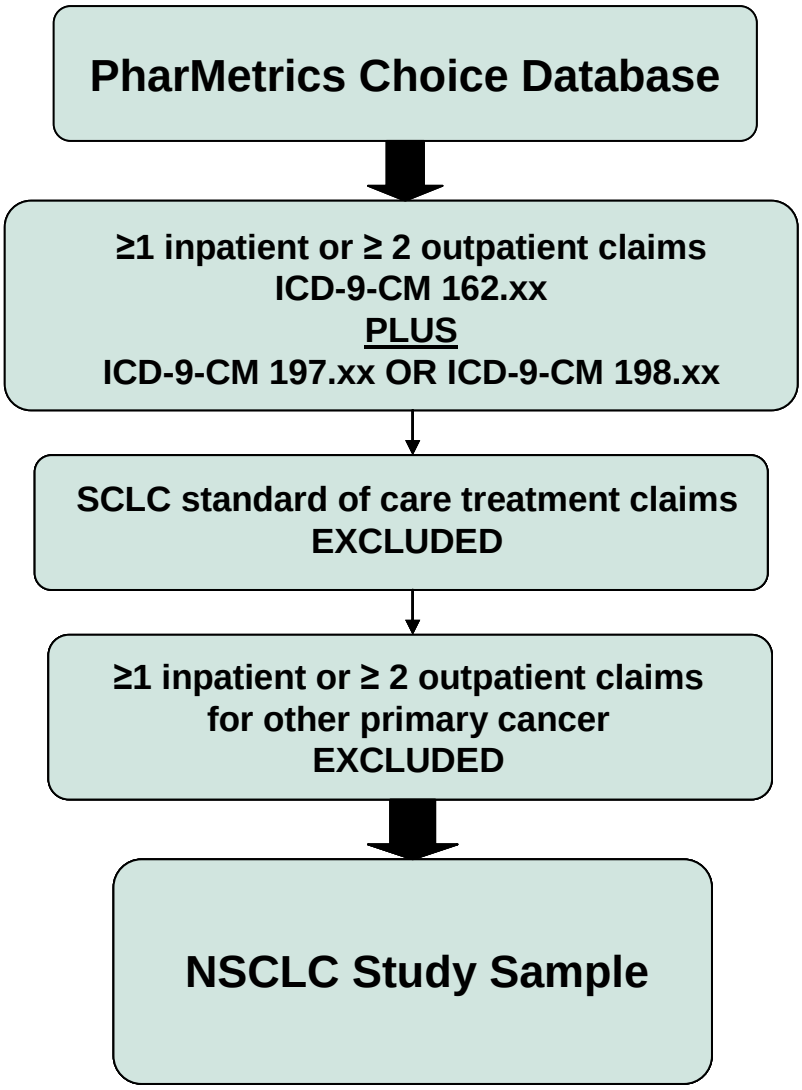

Figure 1: Algorithm for Study Sample Selection

Inclusion criteria were patients ≥ 20 years of age diagnosed with primary lung cancer (ICD-9-CM 162.xx) on ≥ 1 inpatient claim or ≥ 2 outpatient claims. Patients must have had a diagnosis code of secondary malignancy (ICD-9-CM 197.xx or 198.xx) on ≥ 1 inpatient claim or ≥ 2 outpatient claims. The claim for primary lung cancer fell within the 6 months prior to or 30 days following the index date (date of first metastatic disease). Patients who had SCLC standard of care treatment (Table 1)[28,29] or substantial evidence of another primary cancer (≥ 1 inpatient or ≥ 2 outpatient claims) were excluded.

Table 1: SCLC Standard of Care Treatment

SCLC treatments
•Etoposide
•Irinotecan
•Topotecan
•Cyclophosphamide
•Doxorubicin
•Vincristine

SEGMENTS OF DISEASE

Disease progression was divided into 3 segments: diagnosis, active treatment, and end-of-life care (Figure 2). Diagnosis was defined as 90 days prior to index date until initiation of active treatment. Active treatment was defined as claims for biologics, TKIs, PD, single agent chemotherapy, and other agents used in NSCLC. It spanned the time between the end of diagnosis and beginning of the end-of-life segment. End-of-life segment was defined as 30 days prior to death.[31] A previously published proxy for death

with ICD-9-CM claims was used to define death.[32-34] Patients must have had claims for all three disease segments for inclusion into the study analysis. Those who received active treatment prior to index date were excluded. Diagnosis and active treatment segments had variable lengths; end-of-life care was a set length of 30 days (1 month).

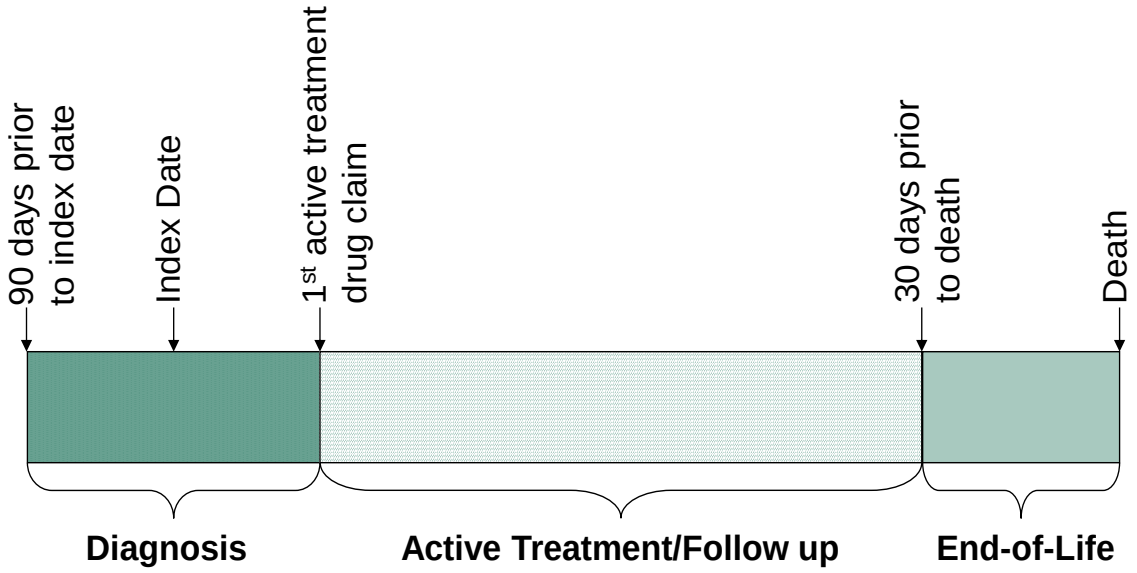

Figure 2: Segments of Disease

TIME PERIODS

Emergence of new treatments allowed us to split the study period into 3 separate time periods (Figure 3). This allowed us to track changes in cost which may be related to active treatment over time. We based patient classification into a time period strictly by index date. Patients who had an index date from 07/01/00-12/31/02 were in the "pre" period (time before newer NSCLC treatments were available for purchase). Those who

had an index date from 01/01/03-12/31/05 fell into the "transition" period. The "transition" signified the time when biologics, TKIs, and pemetrexed first entered as treatment options. Finally, patients in the "current" period had an index date from 01/01/06-06/30/08. These patients were diagnosed with metastatic NSCLC when all classes of active treatment currently listed in the NCCN compendium were available treatment options. All costs an individual patient incurred fell into the time period of their index date. Costs noted are reimbursements, not billed amounts.

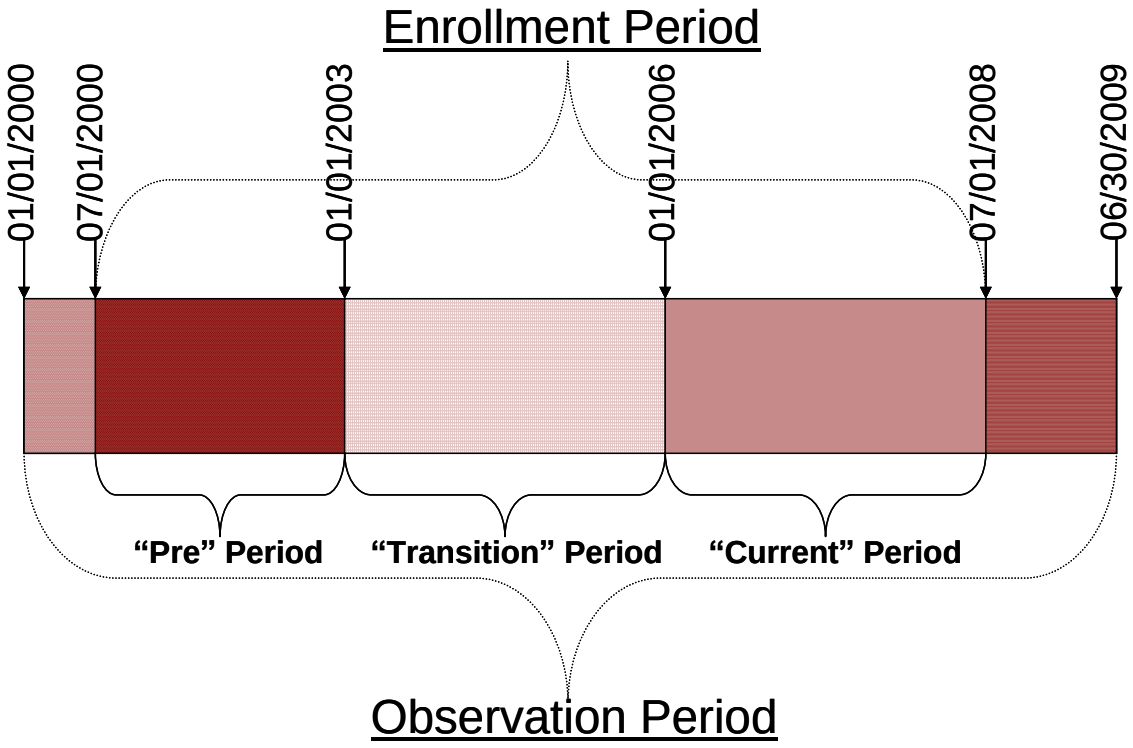

Figure 3: Time periods throughout study

STUDY VARIABLES

The primary dependent variable was total direct cost-of-care per patient per month (pppm). Secondary dependent variables were cost per disease segment pppm, effect of comorbidities on cost, and current total and pppm cost for patients who had an active treatment length of at least 5 months ("gold standard" patient). Percentage of each segment in relation to overall cost, percentage of each active treatment class in regards to the active treatment segment cost and overall cost were also dependent variables. Independent variables included gender, age at index, comorbidity score (NCI Combined Index),[36] and region.

STATISTICAL ANALYSIS

Nominal data were compared using the chi square method. All continuous data were compared using the Wilcoxan Rank Sum test. To adjust for possible confounding variables in baseline characteristics, multivariate least squares regression models were used. Nominal data was reported in percent. Continuous data was reported in median and interquartile range (IQR). All costs were reported in United States dollars cost discounted to the year 2009 using published inflation rates to account for change in dollar value over time.

Chapter 4: Results

BASELINE CHARACTERISTICS

A total of 969 patients with newly diagnosed stage IV NSCLC met study criteria. The "pre" period had 27 patients, while the "transition" period had 439 patients, and the "current" period had 503 patients. Due to the low number of patients in the "pre" period, statistical analyses were limited to "transition" and "current" periods when comparing time frames. Baseline characteristics can be found in Table 2. Age at index (61 years in "transition" and 63 years in "current"), comorbidity score, region, length from index until death (9.9 months in "transition" and 8.8 months in "current"), and active treatment length (4.8 months in "transition" and 4.2 months in "current") were all significantly different between the "transition" and "current" groups at baseline.

Table 2: Baseline Characteristics

	Overall observation period	**Pre Period 2000-2002**	**Transition period 2003-2005**	**Current period 2006-2009**	**p value Transition vs Current**
Number of patients (n)	969	27	439	503	
Sex (n, %)					0.7
• Male	546, 56%	19, 70%	249, 57%	278, 55%	
• Female	423, 44%	8, 30%	190, 43%	225, 45%	
Age at index (yrs)					0.05
• Median	62	62	61	63	
• IQR	56-70	58-67	55-69	57-71	
NCI Combined Index Comorbidity score (n, %)					0.008
• 0	359, 37%	10, 37%	182, 41%	167, 33%	
• > 0 but < 2	381, 39%	13, 48%	165, 38%	203, 40%	
• ≥ 2	229, 24%	4, 15%	92, 21%	133, 27%	
Region (n, %)					<0.0001
• East	260, 27%	5, 19%	116, 26%	139, 28%	
• Midwest	371, 38%	22, 81%	183, 42%	166, 33%	
• South	177, 18%	0, 0%	52, 12%	125, 25%	
• West	161, 17%	0, 0%	88, 20%	73, 14%	
Length from index date to date of last claim (months)					0.007
• Median	9.1	9.1	9.9	8.8	
• IQR	6.1-14.2	5.7-15.7	6.3-15.8	6-13.5	
Diagnosis length (months)					0.2
• Median	3.3	3.3	3.3	3.2	
• IQR	2.7-3.9	3.1-4.2	2.7-4	2.7-3.8	
Active treatment length (months)					0.04
• Median	4.6	3.9	4.8	4.2	
• IQR	2-8.8	1.1-6.6	2.1-9.8	1.9-8.2	

*End-of-life was a fixed length segment of 1 month

PRIMARY OBJECTIVE

Overall total monthly cost for the entire observation period was $10,281 pppm (IQR $6,613-15,359). There was no statistically significant difference in total monthly cost between the "transition" and "current" period (Table 3). The multivariate regression model showed baseline confounders had no effect on total cost between the two groups. Age, region, and length are significant independent predictors of difference in cost.

Table 3: Total Costs and Costs per Segment of Disease

	Overall observation period	**Transition period 2003-2005**	**Current period 2006-2009**	**p value Transition vs Current**
Number of patients (n)	969	439	503	
Overall cost				
Monthly cost (PPPM) • Median • IQR	 $10,281 $6,613-15,359	 $10,525 $6,168-15,910	 $10,226 $6,808-$15,162	0.6
Diagnosis segment				
Monthly cost (PPPM) • Median • IQR	 $6,601 $3,376-11,881	 $6,884 $3,350-12,186	 $6,644 $3,424-11,872	1
Active treatment segment				
Monthly cost (PPPM) • Median • IQR	 $9,287 $5,221-16,463	 $10,113 $5,333-16,594	 $8,984 $5,116-13,991	0.1
End-of-life segment				
Monthly cost (PPPM) • Median • IQR	 $12,215 $4,958-24,703	 $12,150 $5,270-25,938	 $12,364 $4,696-23,609	0.6

Cost per segment of disease overall and by time period is listed in Table 3. Patients in the "pre" period were included in analysis of overall cost, but due to small sample size, were not included in statistical analyses. Overall diagnosis cost was $6,601

pppm (IQR $3,376-11,881); median length for diagnosis was 3.3 months. Active treatment cost was $9,287 pppm (IQR $5,221-16,463); median length for active treatment was 4.6 months. End-of-life cost was $12,215 pppm (IQR $4,958-24,703); length was set at one month. Figure 4 shows a breakdown of overall cost by disease segment in terms of percentage of cost; 28% of cost was incurred during diagnosis, 57% during active treatment, and the remaining 15% in end-of-life. This figure is not calculated in pppm, rather it is the breakdown of the total cost for the entire sample (n=969). There were no statistically significant differences between the "transition" period and the "current" period for any segment of disease. When baseline confounders were applied, there was no effect on cost between the groups. Age was an independent predictor in difference in cost for all three disease segments in a multivariate least squares regression model. Region was an independent predictor in diagnosis and end-of-life segments. Figure 5 shows a breakdown of the monthly cost per patient by disease segment and time period.

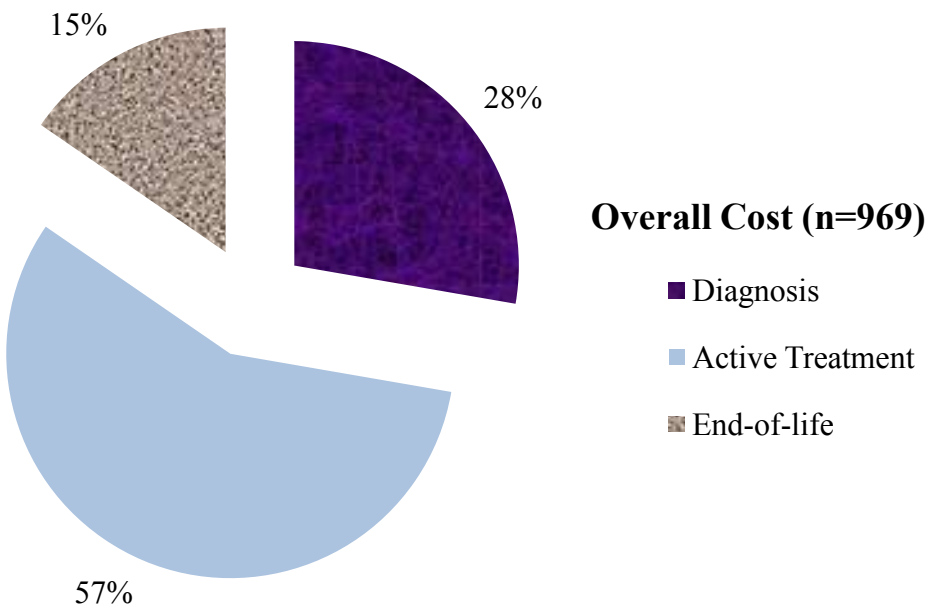

Figure 4: Breakdown of Overall Cost (total, not per patient per month)

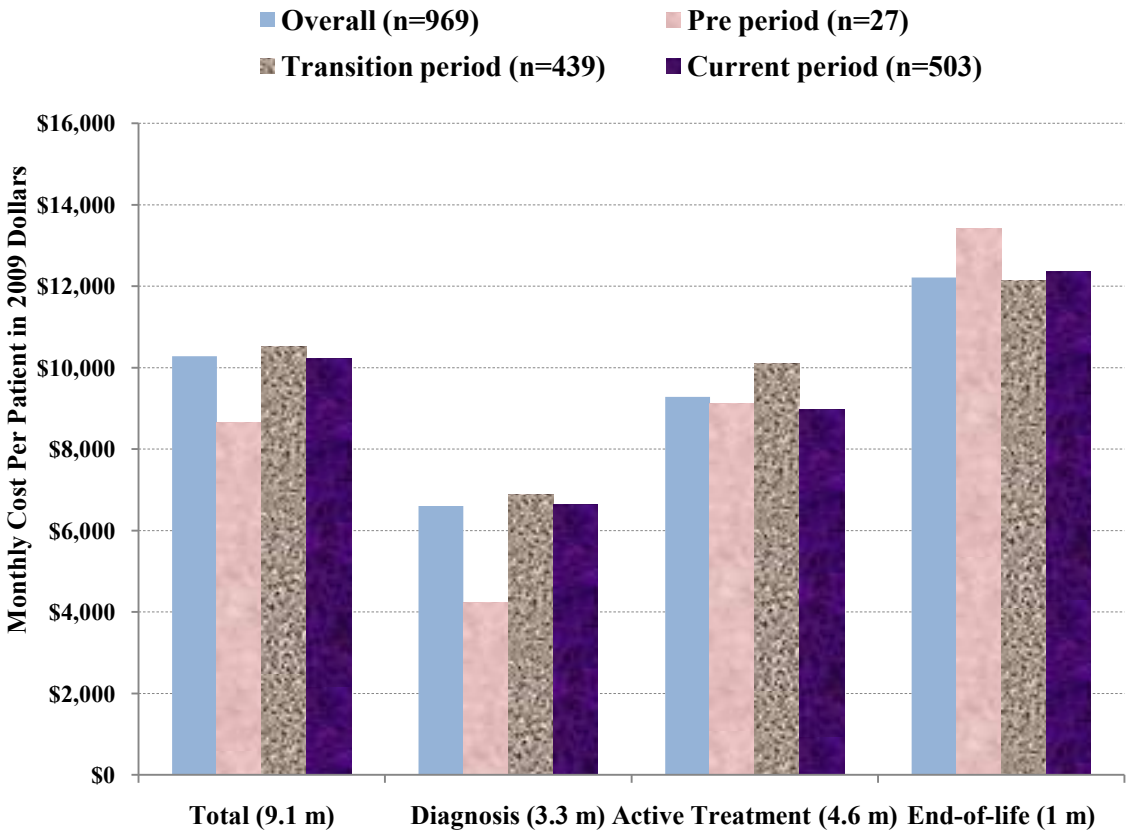

Figure 5: Monthly Cost Per Patient by Disease Segment

SECONDARY OBJECTIVES

Figure 6 shows the percentage of cost each class of active treatment drugs comprised when examining the costs encompassed in the active treatment segment, displaying the differences between the "transition" and "current" periods. PD chemotherapy represented the greatest cost of active treatment classes at 19% of cost in the "transition" and 11% in the "current". Biologics represented 4% of active treatment costs in the "transition" period and 9% in the "current" period. TKIs were 6% of active

treatment costs in the "transition" period and 3% in the "current" period. Pemetrexed comprised 3% of costs in the "transition" period, while in the "current" period it represented 6% of active treatment costs. All other prescription drugs accounted for 6% of cost in the active treatment segment for both "transition" and "current" periods. Non-drug costs were the greatest active treatment costs, making up 62% of costs in the "transition" period, and 65% of costs in the "current" period. Non-drug costs included hospitalizations, nursing costs, radiation, outpatient visits, and other costs that are not drug-related.

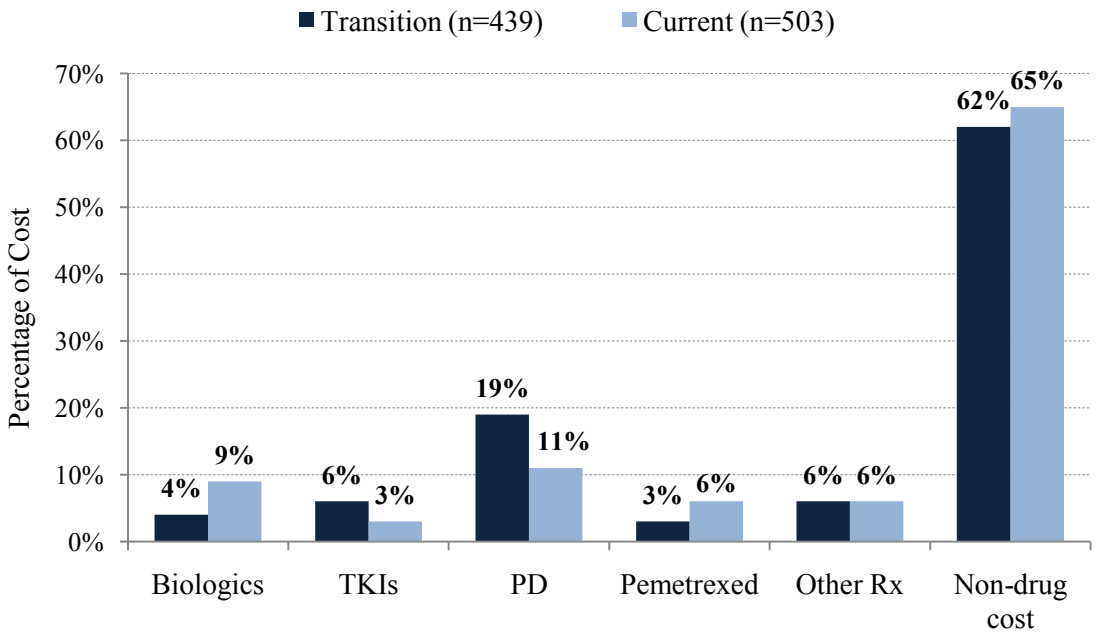

Figure 6: Drug Cost in Active Treatment Segment

Figure 7 represents drug cost in regards to overall cost of NSCLC, with differences between "transition" and "current" periods highlighted. In the "transition" period, drug cost was 23% of overall cost for NSCLC, while in the "current" period, drug cost was 21% of overall cost. New drug classes represented 2% (biologics), 4% (TKIs), and 2% (pemetrexed) of overall cost during the "transition" period. In the current period, 5% of overall cost was attributed to biologics, 2% to TKIs, and 4% to pemetrexed. Again, non-drug costs were the highest component of overall cost for both the "transition" (77%) and "current" (79%) periods. Drugs given in the end-of-life care segment are included in the drug classes in Figure 7 to prevent biasing cost results. Due to length of time required for efficacy of active NSCLC treatments, these drugs should not be administered in the month prior to death.

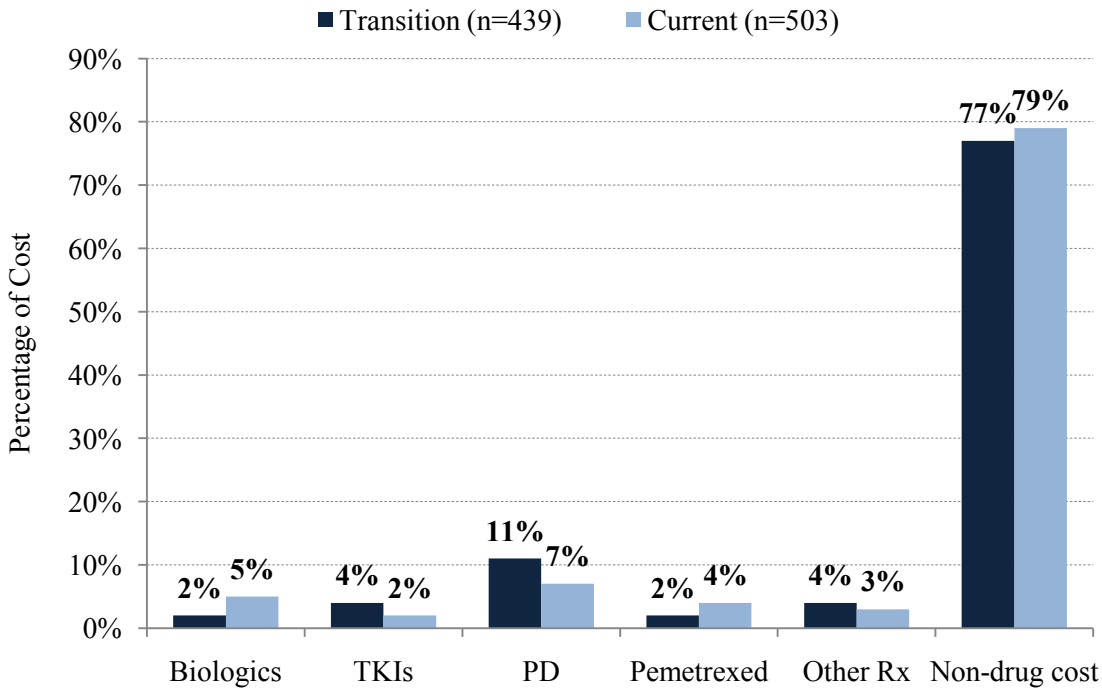

Figure 7: Drug Cost in Regards to Overall Cost

PD chemotherapy was the most common regimen used, and a majority of patients in both the "transition" (87%) and "current" (89%) periods received it. (Figure 8) Use of biologics increased three-fold, from 6% in the "transition" period to 18% in the "current" period. TKI use decrease from 28% in the "transition" period to 17% in the "current" period. Pemetrexed use increased from 13% in the "transition" period to 25% in the "current" period. PD chemotherapy was the most common initial treatment in both time periods (Figure 9).

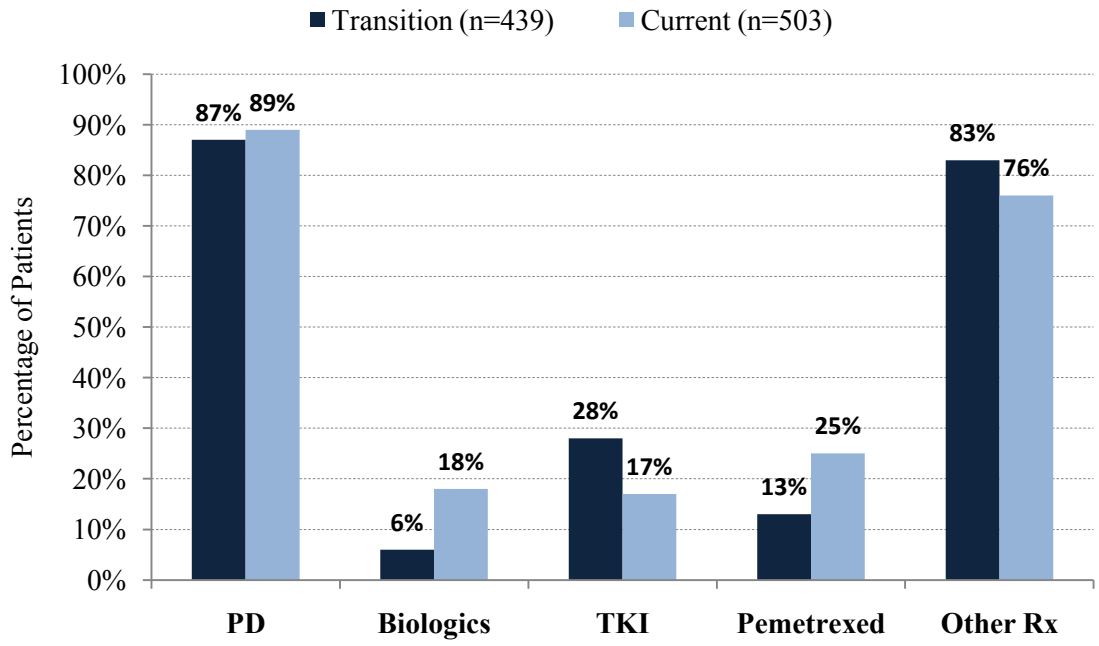

Figure 8: Percent of Patients Receiving Each Active Drug Treatment

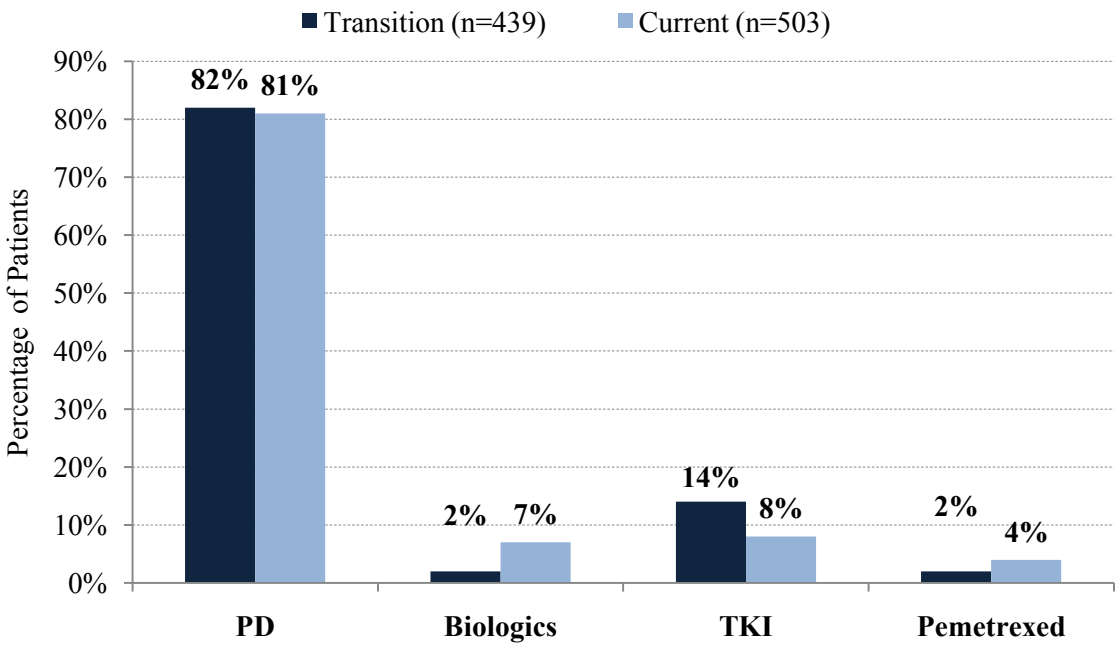

Figure 9: Initial Treatment Choice

EFFECT OF COMORBIDITIES

Effect of comorbidities on cost can be found in Table 4. There was no statistically significant difference in cost between those with comorbidities and those without. There was a statistically significant difference in diagnosis length and active treatment length when comparing patients with comorbidities to those without. There was no significant difference in overall length between the two groups. Diagnosis length for those without comorbidities was 3.1 months, while those with 2+ comorbidities had a longer diagnosis of 3.4 months. Patients without comorbidities had a median treatment length of 4.9

months while those with 2+ comorbidities had a median active treatment length of 3.6 months.

Table 4: Effect of Comorbidities on Cost

	No comorbidities	**>0 but <2 comorbidities**	**2+ comorbidities**	**p-value No comorbidities vs 2+ comorbidities**
Number of patients (n)	359	381	229	
Overall				
Length (months)				0.1
• Median	9.8	8.9	8.8	
• IQR	6.2-15.2	6.2-13.9	6-13.3	
Monthly cost (PPPM)				0.2
• Median	$10,666	$10,075	$9,988	
• IQR	$6,982-15,820	$6,295-15,105	$5,757-15,894	
Diagnosis				
Length (months)				<0.0001
• Median	3.1	3.3	3.4	
• IQR	2.5-3.8	2.6-4	3-4	
Monthly cost (PPPM)				0.6
• Median	$6,393	$7,000	$6,400	
• IQR	$3,372-11,368	$3,419-12,312	$3,281-12,031	
Active treatment				
Length (months)				0.003
• Median	4.9	4.7	3.6	
• IQR	2.3-9.8	2.1-8.4	1.5-7.9	
Monthly cost (PPPM)				0.4
• Median	$9,815	$8,818	$9,525	
• IQR	$6,215-16,182	$4,676-13,940	$4,993-16,225	
End-of-life				
Monthly cost (PPPM)				0.4
• Median, IQR	$12,632	$11,777	$13,085	
• IQR	$5,270-26,675	$4,973-23,115	$4,504-24,277	

Table 5: NCI Combined Index for Comorbidity Assessment

Comorbidity	Weight
Acute myocardial infarction	**1.13**
Old myocardial infarction	**0.91**
Congestive heart failure	**2.16**
Peripheral vasculature disease	**1.26**
Cerebrovascular disease	**1.41**
Chronic obstructive pulmonary disorder	**1.40**
Dementia	**1.92**
Paralysis	**1.65**
Diabetes	**0.99**
Diabetes with sequelae	**1.50**
Moderate/severe renal disease	**2.23**
Ulcers	**0.95**
Rheumatologic disease	**1.09**

GOLD STANDARD TREATMENT

Three hundred and sixteen patients in the study (33% of overall sample) received five or more months of active treatment therapy. One hundred and fifty three of these patients were in the "transition" period while one hundred and fifty six were in the "current" period (Table 6). 7 patients were in the "pre" period; due to this low number, the "pre" period was excluded from statistical analysis. Median overall total cost per patient with five months or more of active treatment length was $144,147 (IQR $93,576-206,940). Monthly total cost was $9,371 pppm (IQR $6,634-12,898). There was no significant difference in either total cost or total monthly cost between patients in the "transition" group and "current" group. Drug cost in these patients comprised a higher percentage of active treatment (42% in "transition, 40% in "current" periods) and overall cost (32% in "transition", 33% in "current" periods) when compared to all patients (Figures 10 and 11).

Table 6: Gold Standard Treatment Cost

	Overall with ≥ 5 months active treatment	**Transition period with ≥ 5 months active treatment**	**Current period with ≥ 5 months active treatment**	**p-value Transition vs Current**
Number of patients (n)	316	153	156	
Overall				
Total cost (per patient) • Median • IQR	 $144,147 $93,576-206,940	 $149,534 $101,746-211,343	 $135,912 $86,532-204,381	0.3
Monthly cost (PPPM) • Median • IQR	 $9,371 $6,634-12,898	 $9,229 $6,107-12,338	 $9,522 $7,218-13,493	0.1
Length (months)				
Overall • Median • IQR	 15 11.5-20	 16.6 12-22.8	 13.9 11-17.6	0.0001
Diagnosis • Median • IQR	 3.3 2.7-3.8	 3.3 2.8-4.1	 3.2 2.5-3.8	0.01
Active Treatment • Median • IQR	 10.3 7.5-15.6	 11.8 7.7-19.1	 9.4 7.3-13	0.004

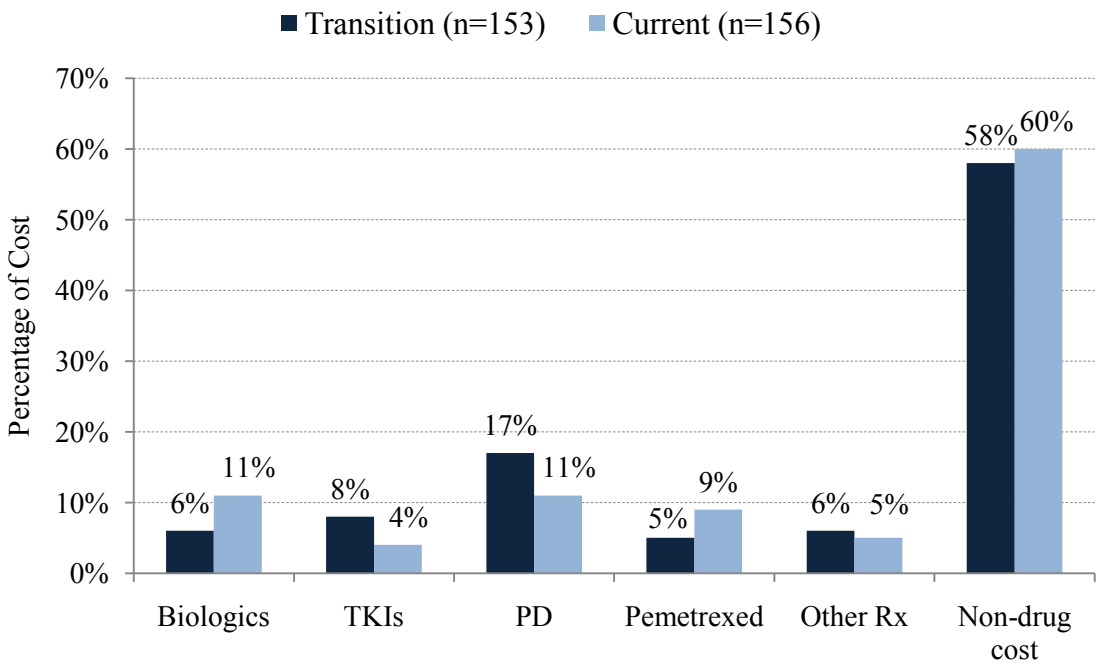

Figure 10: Active Treatment Segment Drug Cost for Gold Standard Treatment

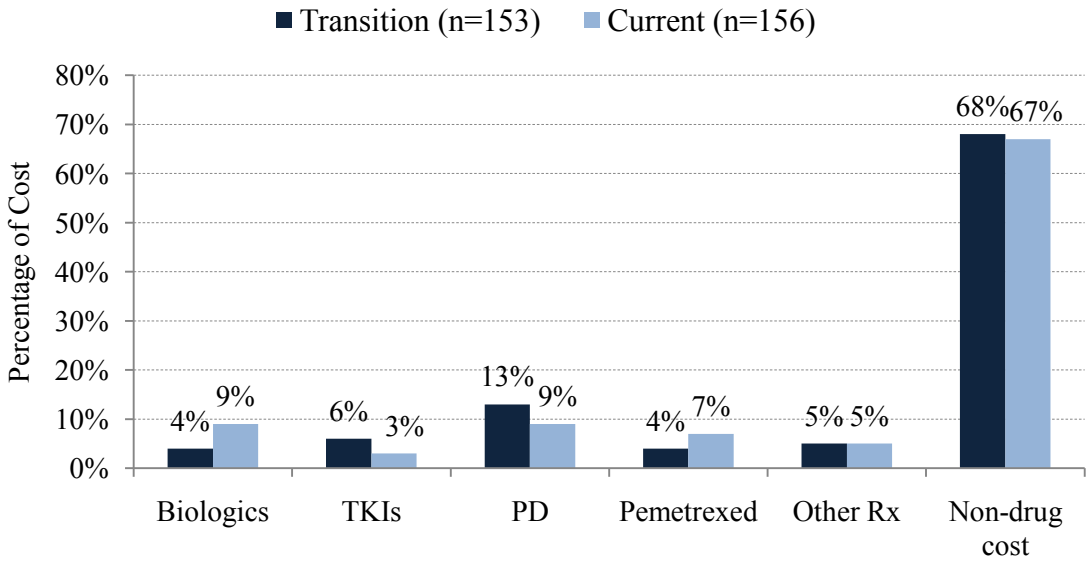

Figure 11: Overall Cost for Gold Standard Treatment

Chapter 5: Discussion

PRIMARY OUTCOME

Overall Total Monthly Cost

Overall total monthly cost for the study period was $10,281 pppm. There was no difference in monthly cost between the "transition" and "current" periods; this is an interesting finding in regards to reports noting ever growing cost of cancer treatment and criticisms for the cost of newer therapies, such as biologics, TKIs, and pemetrexed. The "current" period should represent the full impact of all classes of newer agents. It also represented the rapid uptake of new agents. If the new drugs were phased in quickly while generic use of agents for traditional PD chemotherapy increased rapidly, our results reflecting no change in cost between "transition" and "current" periods were reasonable. The most recent cost data available for comparison was the study of all stage NSCLC performed by Kutikova et al,[5] with data from the turn of the decade.

Baseline Confounders of Cost

Age, region, and length from index date until last claim were identified as independent predictors for difference in cost using a multivariate regression analysis. Increased age correlates with decreased cost, most likely due to less aggressive overall management of elderly cancer patients (more single agent treatment, fewer cycles, and decreased length of treatment). Recently, it has been shown that some elderly patients can tolerate aggressive chemotherapies as well as their younger counterparts.[38] The

correlation between older age and lower cost may be diminished as elderly patients are treated more aggressively or for a longer period of time in the future. Though region was a significant independent predictor in cost according to regression analysis, the PharMetrics database was being built throughout the study period. Insurance plans have been continually added, allowing for more homogeneity in terms of region for later study periods. Due to the incorporations of different regions during different time periods, we cannot determine the significance of region in terms of cost. Length of time from index until last claim was also an independent predictor of cost, with a greater length correlating with greater monthly cost. Our overall length correlates with expected life expectancy from diagnosis of advanced NSCLC until death.[2,3] Overall, more than half of the cost in stage IV NSCLC occurred during the active treatment segment (median 4.6 months), which is not surprising given that the active treatment length is greater than either diagnosis (median 3.3 months) or end-of-life (1 month). Greater length overall and in the active treatment segments for the "transition" period may be due to a limited follow-up period of 1 year for those patients enrolled into the "current" period near the end of the enrollment period. Though the 1 year follow-up allowed in the study design exceeds the median life expectancy of a patient diagnosed with stage IV NSCLC, it can be expected that patients who exceeded the median expectancy would not be captured due to lack of a death proxy prior to cessation of the study period. This situation was a limitation to working with a claims database.

Segmented Cost

End-of-life is the most costly segment of disease by month, with median cost slightly over $12,000 for the overall observation period. This correlates with the finding by Song et al that end-of-life was the costliest segment when metastatic colorectal cancer was studied.[24] Unlike the findings by Song et al, active treatment had greater monthly cost during active treatment than during diagnosis in stage IV NSCLC. This difference may have to do with a difference in study designs, since Song et al set diagnosis at 90 days past index, regardless of initiation of active treatment drug. Our study sought to capture costs related to diagnostic test and inpatient/outpatient visits in the 90 days prior to index. Diagnosis segment ceased in our study as soon as a patient received any active treatment drug. When comparing end-of-life segments between our study and Song et al, we chose a 30 day time period to represent end-of-life based on previously published literature concerning end-of-life in advanced NSCLC.[31] The median life expectancy for advanced NSCLC is 10 months shorter than the life expectancy for mCRC; therefore, a 90 day end-of-life segment as used by Song et al would be inappropriate for studying segments of disease in advanced NSCLC. End-of-life costs included some active treatment costs, if those treatments were administered during the last 30 days of life. It was not just supportive care, hospice, or hospital costs.

There was no significant difference between "transition" and "current" periods for diagnosis, active treatment, or end-of-life segments of disease. This correlates with our findings of no difference in overall monthly cost between these periods. As with the overall cost, multivariate regression models indicated age to be an independent predictor

of cost in all 3 disease segments. Neither length from index until last claim nor length of active treatment was an independent indicator of monthly cost during active treatment.

SECONDARY OUTCOMES

Drug Cost in Active Treatment and Overall

When analyzing the breakdown of drug cost in the active treatment segment, we found a vast majority of costs in both the "transition" and "current" periods were non-drug costs (i.e. inpatient, outpatient, and others). Almost two-thirds of costs in each period were non-drug. PD chemotherapies had the greatest cost associated with them in both "transition" and "current" periods, seeing that almost all patients received PD chemotherapy. Biologic use tripled from "transition" to "current" periods, though percentage of cost for biologics only doubled. The use of pemetrexed almost doubled as did the percentage of cost attributed to pemetrexed. The increased safety profile of pemetrexed over traditional PD chemotherapy agents along with it's increased tolerability, equivalent efficacy, and expanded indications may account for the increased use of this drug in the "current" period. TKI use dropped by 40%, possibly due to the withdrawal of gefitinib and drop in percentage of cost for TKIs correlated with decreased use. The drop in cost of PD chemotherapy is more than likely due to the increased availability of generic versions in this class since use remained the same; use also remained the same between the periods. FDA applications for abbreviated new drug applications from various generic drug manufacturers for carboplatin, paclitaxel, and vinorelbine had been approved throughout the study period. Individually, the newer

active treatment agents do not appear to drive costs greatly; they may be replacing costs previously held by brand name PD chemotherapies. However, the new agents are generally not given as monotherapy, instead they are often used in combination with traditional PD chemotherapy. As mentioned previously, generic PD chemotherapy availability increased throughout the past decade, resulting in decreased cost of drug. Drug cost comprising approximately 20% of the overall cost for treating stage IV NSCLC corresponds with expected percentage of cost when treating cancers.[39] This is higher than the typical 13% cost of drug when treating many non-cancerous diseases,[40] but falls in line with treatment for patients with metastatic disease.

Effect of Comorbidities on Cost

We were surprised to find that comorbidities had little effect on monthly cost, either overall or in the individual segments of disease. Comorbidites were screened for in the 6 months prior to index, using ICD-9-CM codes. Comorbidity score was calculated using the NCI Combined Comorbidity Index, derived and validated for use in lung cancer.[36] We compared those with a score of 0 to those with a score of 2 or more in an effort to distinguish the cost impact of comorbidities. While there was little effect on cost, patients without comorbidities had a shorter time in diagnosis and longer time in the active treatment segment. It is possible that those without comorbidities have a better performance score, leading to better outcomes and increased tolerance of treatment. This accounts for a median treatment length of 4.9 months in those without comorbidities

verses those with 2+ comorbidities having a median active treatment length of 3.6 months.

"Gold Standard" Treatment Cost

Lastly, we wanted to determine the total cost of a patient who received at least five months of active cancer treatment medications (actually received medications for this long, not just an active treatment length of five months). We considered these patients "gold standard" patients, as their treatment course follows what would be considered optimal treatment per recommendations from the NCCN guidelines. These patients more than likely would have received first, second, and possibly third-line therapies. Overall monthly cost for these patients was similar to overall monthly cost for the entire study sample. There was no significant difference in cost between the "transition" and "current" periods. The closest published data to compare the overall cost to was that of Kutikova et al.[5] They showed the cost of all stage NSCLC to be $42,000 in 1999-2000. Since our study requires patients receive active treatment, includes sicker patients than the Kutikova study, and overall cost is calculated for those receiving at least five months of active treatment, the two cannot legitimately be compared. In the Kutikova study, more than half of NSCLC patients do not receive active treatment, due to poor performance scores or intolerability of treatment.[5]

STRENGTHS AND LIMITATIONS

Study Strengths

Study strengths include the use of a large claims database. The PharMetrics Choice database collected data from patients throughout the nation, allowing for a diverse population in the study sample representing the entire United States. From the 5,625 patients diagnosed with stage IV NSCLC, we were able to include 969 patients who had claims for all 3 segments of disease. The 4,626 patients not included in this study did not have claims for active treatment drug, were receiving active treatment for NSCLC prior to index date, or did not have a death proxy. For these reasons, we were unable to segment disease for those 4,626 patients and they were not included in our study. Claims data from a private insurer has been shown to be 99.4% sensitive.[27] Other studies have validated using administrative claims data for observational cohort studies.[25,37] Additionally, to strengthen our study, we included the 90 days immediately prior to index date into the diagnosis segment to help capture the true cost of diagnosing advanced NSCLC. Many diagnostic tests are likely to be performed before the index date. We captured diagnostic test costs listed in the NCCN guidelines. To our knowledge, our study is the first to capture the costs of advanced NSCLC since the newer agents including biologics have been incorporated into the current guidelines. This information, and the lack of cost change between "transition" and "current" periods gives perspective on the true cost of NSCLC and the impact that newer treatments have had on this cost.

Study Limitations

One limitation to our study was the few patients in the "pre" period. The PharMetrics database had few patients in the early years when it was just starting, resulting in only 27 patients qualifying for the "pre" period of our study. This time period was excluded from statistical analysis as low sample size could provide erroneous results. Instead, we ran analysis between "transition" and "current" groups, both having greater numbers of patients. The information for patients in the "pre" period was included for descriptional purposes.

Our patient population had a younger median age (62 years) than the national median age (71 years) of diagnosis for NSCLC. This was likely due to the lack of Medicare patients in this database. Eligibility age for Medicare being 65, resulting in our private claims sample focusing on a younger age group. We showed age to be an independent predictor of cost; costs may have possibly been lower had the median age in our study correlated with the median age for diagnosis in the US.

Another limitation of this study was reliance on ICD-9-CM coding. We were unable to distinguish stage IIIa from IIIb, thus had to limit our study to stage IV patients instead of including all patients with advanced disease (IIIb/IV by NCCN definition). Claims data does not provide information in regard to cancer cell histology, which can have a profound influence on treatment selection. Bevacizumab is only indicated for non-squamous NSCLC.[4] Due to the inability to link patients to a death registry, we had to use a validated proxy to determine death.[32-34]

Patients may have had secondary insurance, which is not distinguishable when analyzing claims the PharMetrics database. Reimbursements from these patients may be artificially low if their claims were from secondary insurance rather than from a primary source.

Our final limitation was only having database access to the first two quarters of 2009. Our study was designed to allow at least 12 months of follow up after index; this is longer than the median life expectancy of a patient diagnosed with metastatic NSCLC. It was possible that patients enrolled at the end of the "current" period who survived longer than a year were excluded from the study if they did not expire before 06/30/09, when data availability terminated. This could account for the statistically significant baseline difference in length from index until last claim between the "transition" and "current" periods and the difference in active treatment lengths between the two periods. To help account for this issue, all costs were normalized to monthly cost per patient. The normalization to a monthly cost per patient allows comparison between the different periods. The monthly cost can be used to calculate total cost overall based on expected length from index until death per patient.

AUTHOR'S CONCLUSIONS

We have analyzed the direct total and segmented cost-of-care for stage IV NSCLC in a privately insured population. Surprisingly, the per patient per month costs of treating NSCLC had not changed significantly when comparing the time periods of 2003-2005 to 2006-2009. Individual newer agent costs did not appear to be the primary drivers

of treatment cost. However, overall drug cost still represented roughly 35% of overall treatment cost, and roughly 20% of overall cost for stage IV NSCLC. When looking at the overall cost of stage IV NSCLC in the "current" period, none of the newer agents exceeded 5% of overall cost. This countered the common belief that newer cancer treatments were driving an increase in costs. Non-drug costs (hospitalizations, outpatient visits, radiation, nursing care, etc) accounted for a majority of expense in all segments of disease (65% in active treatment), with end-of-life being the costliest segment of disease per month. Some patients did receive active drug treatment in the last 30 days of life, when they should not be receiving active treatments. Non-drug costs also comprised about 80% of costs in the "current" period. Overall, costs during active treatment still represent over half of all costs regarding stage IV NSCLC.

Glossary

Active treatment – Treatment with an agent in the NCCN guidelines for advanced NSCLC; begins with initiation of NSCLC drug therapy and terminates when the end-of-life segment begins

Biologics – Class of drug consisting of monoclonal antibodies used to target cancer cells; includes bevacizumab and cetuximab

BMS099 – Cetuximab plus chemotherapy phase III trial conducted in USA

Current period – Time when all drug classes recommended in the current NCCN guidelines were on the market; patients indexed between 01/01/06 and 06/30/08

Death proxy – Claim for an event that would likely indicate death if no further claims are made; hospitalization, hospice, emergency department visit, ambulance usage, resuscitation, defibrillation, cardiac arrest/failure, and injections used to stimulate the heart were used as death proxy claims

Disease segment – Division of disease into diagnosis, active treatment, and end-of-life

ECOG – Eastern Cooperative Oncology Group

EGFR – Epidermal growth factor receptor; target of cetuximab

End-of-life – 30 days prior to last claim for a patient; a death proxy must be present within the 30 days prior to last claim

FLEX – Cetuximab plus chemotherapy phase III trial conducted in Europe

Locally advanced – Invasion of tumor into supraclavicular/contralateral lymph nodes, heart, great vessels, chest wall, pleural effusion, diaphragm, trachea, carina, esophagus, or vertebral bodies; also known as stage IIIb NSCLC

Gold standard patient – A patient who received at least 5 months of active treatment drug (actually had claims throughout the 5 months, not just length of active treatment segment); represents a patient who likely received 1st, 2nd, and 3rd line therapies; used to denote cost of a patient treated to the guideline standards

mCRC – Metastatic colorectal cancer

Metastatic – Invasion of tumor to distant sites such as brain, bone, liver, distant lymph nodes, or contralateral lung; also known as stage IV NSCLC

NCCN – National Comprehensive Cancer Network; publishes guidelines for cancer treatment

NCI Combined Index – Comorbidity scoring system based on the Charlson comorbidity score; adapted and validated for use in cancers such as NSCLC

NSCLC – Non-small cell lung cancer; accounts for approximately 85% of lung and bronchus cancers

OS – Overall survival; how long a patient survives after diagnosis

PD – Platinum doublet chemotherapy; includes carboplatin/paclitaxel, cisplatin/vinorelbine for treating NSCLC

PFS – Progression free survival; how long a patient goes without disease progression

PPPM – Per patient per month

Pre period – Time period before new treatments for advanced NSCLC were available; patients indexed from 07/01/00-12/31/02

PS – Performance score; a method of rating how poorly a cancer patient is doing; PS 0 is the best score a patient can have, the higher the score the more poorly a patient is

SCLC – Small cell lung cancer; accounts for approximately 14% of lung and bronchus cancers

Time period – Division of the first decade of this century into periods that correspond with emerging NSCLC treatments

TKIs- Tyrosine kinase inhibitors; class of drug consisting of small molecules that target tyrosine kinase in cancer cells; includes gefitinib and erlotinib

Transition period – Time when new advanced NSCLC treatments were emerging onto the market; patients indexed between 01/01/03 and 12/31/05

VEGF – Vascular endothelial growth factor; target of bevacizumab

References

1. Jemal A, Siegel R, XU J, and Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; 60(5):1-24. Epub ahead of print July 2010.

2. Surveillance Epidemiology and End Result (SEER). Table 15.28. National Cancer Institute. Available at: http://seer.cancer.gov/statfacts/html/lungb.html. Accessed August 17, 2010.

3. Navaratnam S, Kliewer E, Butler J, et al. Population-based patterns and cost of management of metastatic non-small cell lung cancer after completion of chemotherapy until death. *Lung Cancer* 2010; 70(1):110-5. Epub 2010 Feb 13.

4. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: non-small cell lung cancer. Version 2.2010. http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf Accessed August 9, 2010.

5. Kutikova L, Bowman L, Chang S, et al. The economic burden of lung cancer and the associated costs of treatment failure in the United States. *Lung Cancer* 2005; 50(2):143-54.

6. Chouaid C, Atsou K, Hejblum, and Vergnenegre A. Economics of treatments for non-small cell lung cancer. *Pharmacoeconomics* 2009; 27(2):113-25.

7. Fox KM, Brooks JM, and Kim J. Metastatic non-small cell lung cancer: costs associated with disease progression. *Am J Manag Care* 2008; 14(9):565-71.

8. Carlson JJ, Veenstra DL, and Ramsey SD. Pharmacoeconomic evaluations in the treatment of non-small cell lung cancer. *Drugs* 2008; 68(8):1105-13.

9. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355(24):2542-50.

10. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group trial 4599. *J Clin Oncol* 2008; 26(1):60-5.

11. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. *Lancet* 2009; 373(9674):1525-31.

12. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. *J Clin Oncol* 2010; 28(6):911-7.

13. Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353(2):123-32.

14. Fojo T, and Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question. *J Natl Cancer Inst* 2009; 101(15):1044-8.

15. Ramsey SD. Economics and the new generation of targeted therapies for non-small cell lung cancer. *J Natl Cancer Inst* 2010; 102(5):287-8.

16. Ramsey SD, and Schickedanz A. How should we define value in cancer care? *Oncologist* 2010; 15(S1):1-4.

17. Mason A, Drummond M, Ramsey S, et al. Comparison of anticancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric? *J Clin Oncol* 2010; 28(20):3234-8.

18. Neubauer MA, Hoverman JR, Kolodziej M, et al. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Pract* 2010; 6(1):12-8.

19. Lang K, Marciniak MD, Faries D, et al. Costs of first-line doublet chemotherapy and lifetime medical care in advanced non-small-cell lung cancer in the United States. *Value Health* 2009; 12(4):481-8.

20. Grusenmeyer PA, and Gralla RJ. Examining the cost and cost-effectiveness of adding bevacizumab to carboplatin and paclitaxel in advanced non-small cell lung cancer. J Clin Oncol 2006; 24(18s)(suppl; abstr 6057). ASCO meeting presentation.

21. Newcomer LN. Cost and duration of illness for lung cancer in national payer database. J Clin Oncol 2010; 28 (suppl; abstr e16563).

22. Bischoff H, Hermes A, Gatzemeier U, et al. The cost-effectiveness of bevacizumab plus cisplatin and gemcitabine (BCG) compared with pemetrexed plus cisplatin (PC)

induction treatment of advanced non-squamous non-small cell lung cancer (NSCLC) in Germany. J Clin Oncol 2010; 28 (suppl; abstr e18054).

23. Goulart BL, and Ramsey SD. Initial use of newer agents for advanced non-small cell lung cancer: evidence from the National Cancer Institute patterns of care study. J Clin Oncol 2010; 28(15s) (suppl; abstr 6043).

24. Song X, Zhao Z, Barber B, et al. Cost of illness in patients with metastatic colorectal cancer. *J Med Econ* 2011; 14(1):1-9.

25. Eichler AF, and Lamont EB. Utility of administrative claims data for the study of brain metastases: a validation study. *J Neurooncol* 2009; 95(3):427-31.

26. Phillips-Wren G, Sharkey P, and Dy S. Mining lung cancer patient data to assess healthcare resource utilization. *Expert Syst Appl* 2008; 35(4):1611-9.

27. Ramsey SD, Scoggins JF, Blough DK, et al. Sensitivity of administrative claims to identify incident cases of lung cancer: a comparison of 3 health plans. *J Manag Care Pharm* 2009; 15(8):659-68.

28. Duh MS, Reynolds Weiner J, Lefebvre P, et al. Costs associated with intravenous chemotherapy administration in patients with small cell lung cancer: a retrospective claims database analysis. *Curr Med Res Opin* 2008; 24(4):967-74.

29. CancerMPact®. Kantar Health. Available from www.cancermpact.com. Accessed 08/23-09/17/2010.

30. Thomas SK, Brooks SE, Mullins CD, et al. Use of ICD-9 coding as a proxy for stage of disease in lung cancer. *Pharmacoepidemiol Drug Saf* 2002; 11(8):709-13.

31. Murillo JR, and Koeller J. Chemotherapy given near end of life by community oncologists for advanced non-small cell lung cancer. *Oncologist* 2006; 11(10):1095-99.

32. Joyce AT, Iacoveillo JM, Nag S, et al. End-stage renal disease-associated managed care costs among patients with and without diabetes. *Diabetes Care* 2004; 27(12):2829-35.

33. Rao S, Kubisiak J, and Gilden D. Cost of illness associated with metastatic breast cancer. *Breast Cancer Res Treat* 2004; 83(1):25-32.

34. Paramore LC, Thomas SK, Knopf KB, et al. Estimating costs of care for patients with newly diagnosed metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; 6(1):52-8.

35. Hoverman JR, Gruschkus SK, Muehlenbein CE, et al. Impact of comorbidities on clinical and economic outcomes among patients with advanced non-small cell lung cancer (NSCLC) receiving care in the community-based outpatient setting. J Clin Oncol 2010; 28(15s) (suppl; abstr 6137)

36. Klabunde CN, Legler JM, Warren JL, et al. A refined comorbidity measurement algorithm for claims-based studies in breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol* 2007; 17(8):584-90.

37. Riley GF. Administrative and claims records as sources of health care cost data. *Med Care* 2009; 47(S7):S51-5.

38. Pallis AG, Karampeazis A, Vamvakas L, et al. Efficacy and treatment tolerance in older patients with NSCLC: a meta-analysis of five phase III randomized trials conducted by the Hellenic Oncology Research Group. *Ann Oncol* 2011. Epub ahead of print.

39. Meropol NJ, Schulman KA. Cost of Cancer Care: Issues and Implications. *J Clin Oncol* 2007; 25(2):180-6.

40. Pearson M. Disparities in health expenditure across OECD countries: Why does the United States spend so much more than other countries? *Written statement to Senate Special Committee on Aging: Health Division, OECD.* Sept 2009. Available at http://www.oecd.org/dataoecd/5/34/43800977.pdf. Accessed 4/27/11.

Vita

Allison Bell was born and raised in Milford, Ohio. After graduating from Milford High School, she attended Randolph-Macon Woman's College in Lynchburg, Virginia where she earned a Bachelor of Science in Biology. Immediately after graduating college, Allison put her biology degree to good use by working as a horse groom for a dressage barn and as a show groom for a hunter/jumper trainer. A year later, Allison started work as an analytical chemist, analyzing soil, water, and air samples for semi-volatile organic compounds and polynuclear aromatic hydrocarbons. In 2005, she entered into the dual Pharm.D./Ph.D. program at Mercer University College of Pharmacy and Health Sciences in Atlanta, Georgia. While completing course work for both programs and performing bench research concerning cell cycle regulatory proteins, apoptosis, and gap junctions in H2009 and WB-ras1 cells, Allison realized she really loved the clinical pharmacy more than bench research. Switching to a Pharm.D. from the dual degree, Allison graduated from Mercer University in 2009 and enrolled in the two year dual program, Master of Science in Pharmacy at The University of Texas at Austin College of Pharmacy in combination with a two year Pharmacotherapy Residency at The University of Texas Health Science Center San Antonio. Finally, she is done with school and will not be pursuing a higher degree at the time of this publication.

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