Utilization Patterns and Trends in Epidermal Growth Factor Receptor (EGFR) Mutation Testing Among Patients With Newly Diagnosed Metastatic Lung Cancer

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Abstract

Epidermal Growth Factor Receptor (EGFR)-targeted therapy significantly improves outcomes among non-small cell lung cancer patients with sensitizing mutations. However, the patterns of EGFR testing have not been well-documented. In this population-based study, we identified 5842 patients newly diagnosed with metastatic lung cancer 01/2013-06/2014 and observed an upward trend in testing. However, the testing rate is still lower than ideal.

Introduction: Epidermal growth factor receptor (EGFR)-targeted therapy significantly improves outcomes among patients with non–small-cell lung cancer (NSCLC) whose tumors harbor sensitizing mutations. Patterns of EGFR testing have not been well-documented. The objective of this population-based study is to assess the testing pattern on a national scale. **Patients and Methods:** Using MarketScan 2012 to 2014 data, we identified 5842 patients newly diagnosed with metastatic lung cancer from January 2013 to June 2014 and assessed their EGFR mutation testing pattern in the 6 months after diagnosis. We further examined the testing rate among patients who received the EGFR inhibitor erlotinib. Because histology information is not available in this database, we also conducted a subgroup analysis of EGFR testing among patients who were treated with bevacizumab or pemetrexed, who are likely to have non-squamous NSCLC. Multivariable logistic regression was performed to ascertain factors associated with EGFR testing. **Results:** Of 5842 patients with metastatic lung cancer, 1039 (18%) had claims for EGFR testing within 6 months of diagnosis, and 283 (5%) received erlotinib. The testing rate among patients who received erlotinib was 42%. Within a subgroup of 1685 patients treated with bevacizumab or pemetrexed, 616 (37%) underwent EGFR testing. Multivariable logistic regression showed that younger patients, female patients, patients with fewer comorbidities, and patients living in the West region were more likely to receive EGFR testing. **Conclusion:** This population-based study demonstrates low EGFR testing rates among advanced lung cancer patients in 2013 and 2014.

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Introduction

In the past decade, substantial advances in molecular and cellular biology have reshaped our understanding of non–small-cell lung cancer (NSCLC). In particular, genotype-based targeted therapies for patients with activating mutations in the epidermal growth factor receptor (EGFR) gene or rearrangements in the anaplastic lymphoma kinase (ALK) or ROS1 genes have improved outcomes significantly for patients with sensitizing mutations.[1-5]

In 2010, National Comprehensive Cancer Network (NCCN) guidelines included erlotinib as a first-line treatment option for patients with stage IV NSCLC harboring activating mutations in

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EGFR.[6] In 2011, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion[7] recommending EGFR mutation testing for patients with advanced NSCLC, suggesting consideration of EGFR inhibitor therapy as a first-line treatment for patients with EGFR mutations. In 2012, NCCN guidelines recommended that all patients with lung adenocarcinoma be tested for the EGFR mutation.[8] By early 2013, the standard of care for patients with advanced stage NSCLC was shifting towards treatment based on a patient's molecular profile.[9] In July 2013, the College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) issued a guideline on EGFR testing for patients with advanced lung adenocarcinoma, recommending that physicians use testing for EGFR mutations to guide patient selection for EGFR inhibitor treatment.[10] In October, 2014, ASCO endorsed this guideline.[11]

The EGFR inhibitors currently on the US market include erlotinib, afatinib, and gefitinib. Erlotinib initially received US Food and Drug Administration (FDA) approval in 2004 for second-line treatment of patients with advanced NSCLC. In 2013, erlotinib indications were expanded to include first-line treatment of patients with metastatic NSCLC with EGFR mutations.[12] Afatinib was also approved in July 2013 for the first-line treatment of patients with EGFR-mutated metastatic NSCLC.[13] Gefitinib received initial FDA approval in 2003 for the treatment of patients with locally advanced or metastatic NSCLC as a third-line therapy. However, the FDA withdrew that approval in 2005. In July 2015, gefitinib was re-approved as a first-line treatment for metastatic NSCLC patients with EGFR mutations.[14] In November 2015, the FDA granted accelerated approval to osimertinib for patients with T790M resistance mutations in EGFR who have progressed after prior EGFR-targeted therapy.[15-19]

With such rapid developments in the standard of care, it is critical that oncologists remain up to date on new treatment standards. The literature is scarce on EGFR testing patterns among patients with advanced NSCLC. One study[20] investigated testing rates among patients with NSCLC treated in a community-based oncology network and found EGFR testing rates increasing substantially from 2.3% before 2010% to 32% in 2011. However, this study focused on patients receiving second-line treatment, and hence was not directly relevant to the more recent guidelines,[11] which recommend EGFR testing at the time of diagnosis. A more recent survey of oncologists conducted between December 2014 and January 2015[21] demonstrated a self-reported testing rate of 76% for patients with newly diagnosed advanced NSCLC in North America (including the US and Canada). However, studies based on surveys have the fundamental disadvantage of potential reporting bias. Therefore, we conducted a population-based study to assess biomarker testing patterns on a national scale. Our study aims to describe EGFR testing patterns and trends among patients with newly diagnosed advanced NSCLC. Further, we aim to identify factors associated with the uptake of EGFR testing.

Patients and Methods

Data Source

We used the Truven Health MarketScan database, which is a claims-based longitudinal database covering millions of unique patients in the US enrolled in commercial health insurance plans and Medicare supplemental plans. The MarketScan database includes health insurance claims for 50 million employees, spouses, retirees, and their dependents, enrolled in commercial health insurance plans sponsored by over 100 large or medium-sized United States-based employers. The beneficiaries had various types of health care coverage, such as privately insured fee-for-service, point-of-service (POS), or capitated health plans. The health plans include health maintenance organizations, preferred provider organizations, POS plans, and indemnity plans. The geographical distribution is approximately the same as the US population distribution. These data represent health care across a variety of settings (physician office visits, emergency room visits, inpatient hospital stays, outpatient visits, and outpatient pharmacy claims).[22] The MarketScan database is a well-trusted data source for studying treatment patterns. There are a large number of published studies based on MarketScan data in the literature.[23-26]

Study Cohort

We identified patients diagnosed with new lung cancer from January 2013 to June 2014 via International Classification of Disease 9th Revision (ICD-9) codes 162.0 through 162.9. Patients were considered to have newly diagnosed lung cancer if they had at least 1 inpatient claim or 2 outpatient claims between 30 and 180 days apart and did not have any other lung cancer claims within the 6 months prior to the first one during the time period between January 2013 and June 2014. We defined the first lung cancer claim in 2013 as the diagnosis date and excluded patients without continuous enrollment 6 months prior to and 6 months after the diagnosis date to ensure that we captured patients with data on all relevant claims around the time of diagnosis. To restrict the cohort to patients with recurrent or metastatic disease, we excluded patients with a claim for lung cancer surgery. The Current Procedural Terminology (CPT) codes used to identify surgical treatment included: 32440, 32442, 32445, 32480, 32482, 32484, 32486, 32488, 32500, 32503, 32504, 32520, 32522, 32525, 32657, and 32663. The list was established in a published study.[27] We did not include codes that indicate surgical biopsy (eg, 32405, 32096, 77012). It is unlikely that providers would downcode a lung surgery procedure as a surgical biopsy, because the reimbursement amount would depend on the coding. We further restricted the cohort to patients who had ICD-9 codes indicating secondary malignant neoplasms to specific other sites (197.4-198.7, 198.81, 198.82) within 6 months of diagnosis. These secondary malignancy codes were first proposed by Lamont and colleagues[28] for patients with breast cancer and further validated for determination of recurrent disease among several types of cancer, including lung cancer, by Hassett et al.[29] We modified the secondary malignancy codes list used in this study by further excluding secondary malignant neoplasm of mediastinum, pleura, and respiratory organs (197.1-197.3) and secondary malignant neoplasm of other specified sites (198.89), to create a specific cohort of patients with metastatic lung cancer. Our inclusion and exclusion criteria are detailed in Supplemental Figure 1 (in the online version).

Key Variables

Our first key outcome variable was whether or not EGFR testing was performed for a given patient. We identified EGFR testing

using CPT code 81235 (EGFR gene analysis, common variants, nonspecific to methodology of testing). This specific code for EGFR testing was new in 2013; before January 2013, there was no specific code for EGFR testing, and claims for EGFR testing usually included several non-specific CPT codes. We focused on patients with lung cancer identified from January 2013 to June 2014 to ensure a 6-month follow-up window. Although it is possible that patients may have received multiplex testing, there was no CPT code for multiplex testing during the time frame of our study cohort. As providers are reimbursed based on the medical claims, we expect that most providers would use the EGFR testing billing code to ensure proper reimbursement.

Our second key outcome variable was filled prescriptions for erlotinib, which was the only FDA-approved EGFR inhibitor covering the whole study period. We captured the use of erlotinib by National Drug Codes (NDCs): 50242-0062-01, 50242-0063-01, 50242-0064-01, 54868-5290-00, 54868-5447-00, and 54868-5474-00.

Explanatory Variables

We conducted multivariable analyses to examine the factors associated with the uptake of EGFR testing. We included patient demographics, comorbidity scores, a binary variable (yes/no) indicating radiation therapy, and type of insurance. The demographic information included age (18-54, 55-64, 65-74, and $\geq$ 75 years), gender (male vs. female), and region (Northeast, North Central, West, South). We used the Deyo-Romano modified Charlson comorbidity score, which is a commonly adopted measure for ascertainment of comorbidity in studies using claims data.[30-33] The comorbidity score was derived from Medicare Provider Analysis and Review, Outpatient, and Carriers claims files during the 6 months preceding diagnosis and categorized into 3 groups: 0, 1, or at least 2. We captured whether a patient received radiation within 6 months of diagnosis based on CPT codes (77371-77373, 77401-77525, 77761-77799, G0174, G0251, G0339, G0340). We categorized type of insurance into 4 groups: Preferred Provider Organization, Health Maintenance Organization, POS, and other. To examine the time trend, we also included a categorical variable for time of diagnosis: first half of year 2013, second half of year 2013, and first half of year 2014.

Analyses

We described the percentage of patients receiving EGFR mutation testing by quarter in order to evaluate for a trend in testing rates. Group differences in the use of EGFR testing were tested with χ^2 statistics. We also used multivariate logistic regression to explore factors associated with EGFR testing, and we present findings as adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs).

One limitation of the MarketScan database is that it does not provide histology information. Therefore, a cohort defined by billing claims may include patients with lung cancer histologies that would not merit EGFR testing (including squamous cell and small cell carcinoma). We therefore conducted a subgroup analysis to address this issue. In the subgroup analysis, we focused on the patients who were treated with bevacizumab, pemetrexed, or both within the 6 months after diagnosis. This group should be highly enriched for patients with non-squamous NSCLC, because these 2 drugs are almost exclusively used for patients with non-squamous histology, and they would not be indicated for small cell lung cancer.[34-37]

It is possible that some patients received EGFR testing more than 6 months after diagnosis. For sensitivity analyses, we therefore released the 6-month time window restriction and included all EGFR testing captured at any time point in 2013 through 2014. We then examined the timing of EGFR testing relative to diagnosis. In case some claims for EGFR mutation testing were submitted using the nonspecific 2012 CPT codes instead of the new 2013 codes, we conducted another sensitivity analysis considering a 2012 molecular pathology CPT code (83912: interpretation and report) adopted by the Mayo Clinic and 2 insurance companies.[38-40]

All statistical analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC). The Institutional Review Board at The University of Texas MD Anderson Cancer Center exempted this study from review because all patients in the database had been de-identified.

Results

Characteristics of the study cohort are provided in Table 1. Of 5842 metastatic lung cancer patients, 1039 (18%) had a claim for EGFR testing within 6 months of diagnosis. We found that 283 (5%) received erlotinib treatment. Notably, 163 (58%) of the patients who received erlotinib did not have EGFR testing.

Of the 5842 patients, 1685 (29%) were treated with bevacizumab or pemetrexed within 6 months of diagnosis. Within this group of patients likely to have non-squamous NSCLC, 616 (37%) had EGFR testing; among patients treated with erlotinib, 43% did not have EGFR testing.

In unadjusted analyses of the whole cohort, the EGFR testing rate was lower among older patients, patients living in the North Central region, patients with higher comorbidity scores, and patients who did not receive radiation therapy (Table 1). Within the smaller subgroup of patients treated with bevacizumab or pemetrexed, the result was similar except that males had a significantly lower EGFR testing rate, and there were no statistically significant differences by region. In both the whole cohort and the subgroup, we observed an upward trend in the uptake of EGFR testing. In the whole cohort, the testing rate increased from 16% in the first half of 2013 to 20% in the first half of 2014. In the subgroup with bevacizumab or pemetrexed, the testing rate increased from 32% to 41%.

In multivariable logistic regression models conducted on the whole cohort, age was strongly associated with EGFR testing. Younger patients (18-54 years old) were more likely to receive EGFR testing compared with those aged 65 to 74 years with an OR of 1.79 (95% CI, 1.45-2.22). We also found significant associations between comorbidity scores, region and testing rate; however, in the subgroup analysis restricted to patients treated with bevacizumab or pemetrexed, region and comobidity score were no longer significant predictors. In this subgroup, we found that female patients were significantly more likely to have testing (OR, 1.23; 95% CI, 1.01-1.51). In both the whole cohort and the subgroup analysis, testing rates were significantly higher in the first half of 2014 compared with the first half of 2013. Detailed results are provided in Table 2.

Table 1 Patient Characteristics and EGFR Mutation Testing Rates

Covariates	Whole Cohort N (%)			Subgroup Treated With Bev or Pem N (%)		
	EGFR Testing Performed	No EGFR Testing Performed	*P*	EGFR Testing Performed	No EGFR Testing Performed	*P*
All	1039 (17.79)	4803 (82.21)		616 (36.56)	1069 (63.44)	
Treated with erlotinib			<.001			<.001
No	919 (16.53)	4640 (83.47)		562 (35.32)	1029 (64.68)	
Yes	120 (42.40)	163 (57.60)		54 (57.45)	40 (42.55)	
Age			<.001			<.001
18-54	252 (25.02)	755 (74.98)		148 (41.93)	205 (58.07)	
55-64	457 (21.27)	1692 (78.73)		285 (40.89)	412 (59.11)	
65-74	208 (14.15)	1262 (85.85)		120 (30.46)	274 (69.54)	
75+	122 (10.03)	1094 (89.97)		63 (26.14)	178 (73.86)	
Gender			.126			.024
Female	539 (18.55)	2366 (81.45)		332 (39.20)	515 (60.80)	
Male	500 (17.02)	2437 (82.98)		284 (33.89)	554 (66.11)	
Region			.009			.618
North Central	291 (15.99)	1529 (84.01)		193 (36.83)	331 (63.17)	
Northeast	248 (18.86)	1067 (81.14)		137 (39.26)	212 (60.74)	
South	305 (17.20)	1468 (82.80)		187 (34.95)	348 (65.05)	
West	195 (20.88)	739 (79.12)		99 (35.74)	178 (64.26)	
Comorbidity score			<.001			.015
0	491 (21.16)	1829 (78.84)		306 (39.90)	461 (60.10)	
1	338 (17.41)	1603 (82.59)		199 (35.41)	363 (64.59)	
2+	210 (13.28)	1371 (86.72)		111 (31.18)	245 (68.82)	
Radiation therapy			<.001			.009
No	316 (13.49)	2026 (86.51)		207 (32.60)	428 (67.40)	
Yes	723 (20.66)	2777 (79.34)		409 (38.95)	641 (61.05)	
Insurance			<.001			.037
HMO	97 (17.29)	464 (82.71)		58 (36.48)	101 (63.52)	
POS	69 (20.72)	264 (79.28)		35 (40.23)	52 (59.77)	
PPO	600 (19.69)	2448 (80.31)		363 (38.99)	568 (61.01)	
Other	273 (14.37)	1627 (85.63)		160 (31.50)	348 (68.50)	
Time of diagnosis			.013			.008
2013 first half	316 (15.99)	1660 (84.01)		186 (32.46)	387 (67.54)	
2013 second half	359 (17.83)	1654 (82.17)		211 (36.13)	373 (63.87)	
2014 first half	364 (19.64)	1489 (80.36)		219 (41.48)	309 (58.52)	

Abbreviations: bev = Bevacizumab; HMO = Health Maintenance Organization plan; pem = pemetrexed; POS = Point of Service plan; PPO = Preferred Provider Organization plan.

Figure 1A describes the percentage of patients with metastatic lung cancer that received EGFR testing by quarter of diagnosis. We observed a gradual increasing time trend in the rates of EGFR testing throughout our study period, though rates remained below 25% (ranging from 16% to 21%) in every quarter that we studied. The testing rate was consistently much higher among patients who received erlotinib treatment, but it was still never above 50% in the overall cohort. Among patients who received bevacizumab or pemetrexed, rates of EGFR testing were consistently higher, but remained under 45% across quarters of diagnosis (Figure 1B). The increase in the rate of testing with time was more pronounced within this subgroup, growing from 31% to 43%.

In sensitivity analyses, we included EGFR testing captured after 6 months following diagnosis. By releasing the 6-month restriction, we added 85 patients with testing, which was 7.3% of all patients who received EGFR testing at any time point of the year. We also examined the time from diagnosis to EGFR testing. The mean time until testing was 40 days (standard deviation, 90 days); median time was 9 days (interquartile range, 36 days). Therefore, a 6-month window from diagnosis was likely to be sufficient to capture most EGFR testing.

We found that only 4 patients in our cohort had the discontinued nonspecific 2012 molecular pathology CPT code in 2013 to 2014. It is not clear whether these codes represented EGFR testing or some other molecular test. However, the low rate implies that most practices adopted the new CPT codes promptly, such that the new CPT codes should not have failed to identify many patients who had EGFR testing.

Table 2 Multivariable Logistic Model for EGFR Mutation Testing

Covariates	Whole Cohort			Subgroup Treated With Bev or Pem		
	OR	CI	*P*	OR	CI	*P*
Age						
18-54	1.79	1.45-2.22	<.001	1.45	1.06-1.99	.019
55-64	1.50	1.25-1.81	<.001	1.44	1.10-1.90	.008
65-74	Reference			Reference		
75+	0.74	0.58-0.94	.015	0.86	0.60-1.24	.431
Gender						
Male	Reference			Reference		
Female	1.07	0.93-1.23	.33	1.23	1.01-1.51	.045
Region						
North Central	Reference			Reference		
Northeast	1.13	0.93-1.37	.226	1.06	0.79-1.41	.697
South	0.97	0.81-1.16	.727	0.83	0.64-1.08	.171
West	1.36	1.10-1.67	.004	0.93	0.68-1.27	.636
Comorbidity score						
0	Reference			Reference		
1	0.86	0.73-1.00	.052	0.86	0.68-1.08	.187
2+	0.73	0.60-0.87	<.001	0.82	0.62-1.09	.179
Radiation therapy						
No	Reference			Reference		
Yes	1.58	1.36-1.83	<.001	1.23	1.00-1.53	.054
Insurance						
HMO	0.90	0.71-1.15	.411	0.97	0.68-1.38	.846
POS	1.10	0.82-1.46	.534	1.02	0.65-1.62	.917
PPO	Reference			Reference		
Other	0.85	0.72-1.00	.055	0.79	0.62-1.01	.056
Time of diagnosis						
2013 first half	Reference			Reference		
2013 second half	1.11	0.93-1.31	.246	1.13	0.88-1.44	.348
2014 first half	1.25	1.05-1.48	.01	1.47	1.14-1.89	.003

Abbreviations: bev = Bevacizumab; HMO = Health Maintenance Organization plan; pem = pemetrexed; POS = Point of Service plan; PPO = Preferred Provider Organization plan.

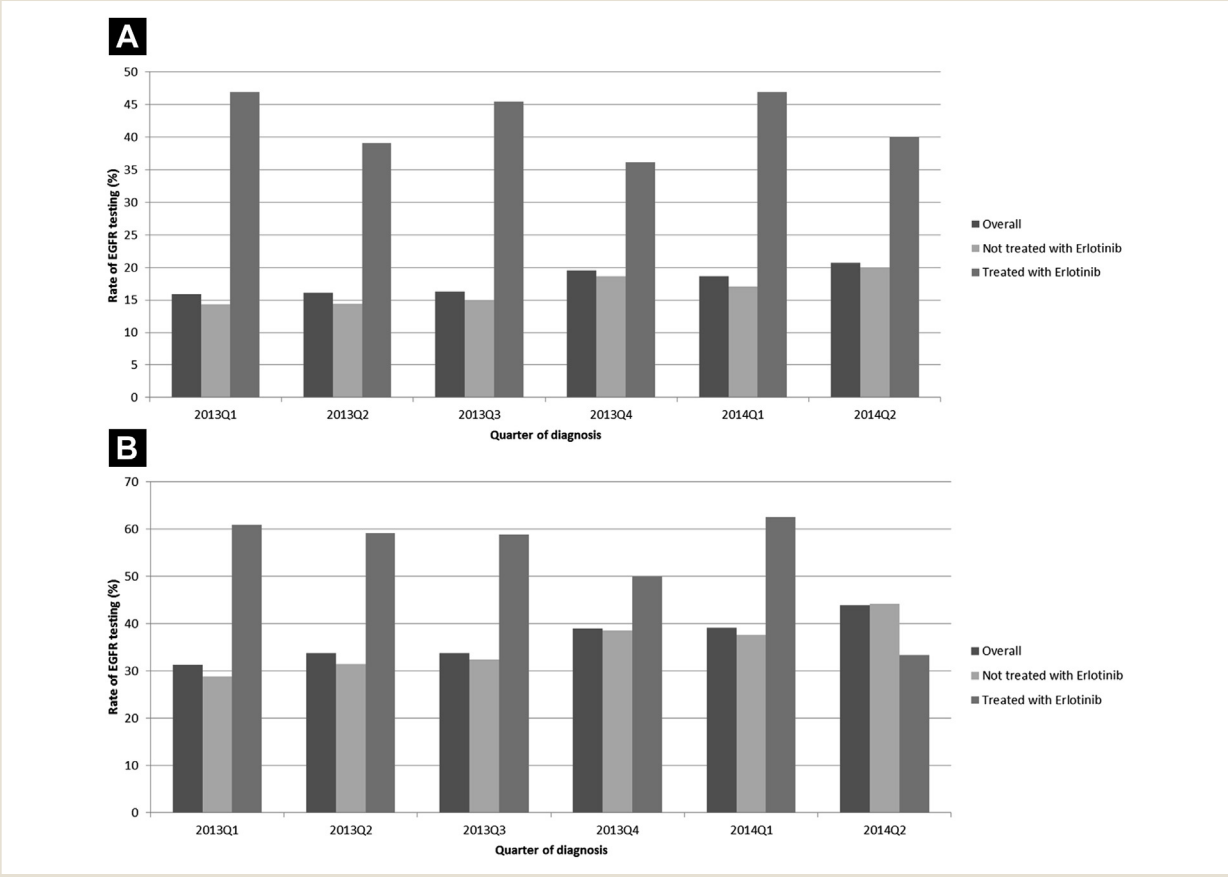
Discussion

Our study provides a population-based view of the rates of EGFR testing among patients with newly diagnosed advanced lung cancer from January 2013 to June 2014. We found that less than 25% of patients with newly diagnosed metastatic NSCLC received EGFR testing within 6 months of diagnosis. We additionally assessed rates of EGFR testing among the subgroup of patients who received erlotinib and found that only 42% of patients who were prescribed erlotinib within 6 months of diagnosis had testing for an EGFR mutation. Although erlotinib is FDA-approved both as first-line therapy for patients with EGFR mutation-positive NSCLC and as maintenance therapy and second-line therapy without regard to EGFR mutation status,[41] the efficacy of EGFR inhibitors is greater among patients who harbor EGFR mutations.[42,43] When we restricted the sample to patients treated with bevacizumab or pemetrexed, the vast majority of whom likely had non-squamous NSCLC, we observed a higher testing rate of 37%. Nevertheless, this testing rate is low, considering the clinical benefits of erlotinib among patients with EGFR-mutated NSCLC.

We also found that older patients were less likely to receive testing in both the whole study cohort and the subgroup treated with bevacizumab and pemetrexed. It is possible that older patients were more likely to have extensive smoking histories, and therefore to have squamous or small cell lung cancer that did not warrant EGFR testing. Additionally, elderly or very ill patients may have been less likely to pursue cancer-directed therapy at all, and in those cases, EGFR mutation testing might not have been performed.

On the other hand, the association between female gender and EGFR testing was stronger in the subgroup of patients treated with bevacizumab or pemetrexed. Female patients with lung adenocarcinoma are more likely to harbor sensitizing EGFR mutations.[44-46] It is possible that physicians were aware of the higher prevalence of EGFR mutations among women and therefore performed EGFR testing more often for female patients. However, because these patients largely had non-squamous NSCLC, for which EGFR testing is now recommended, this disparity was likely not clinically appropriate.

Figure 1 (A) Rate of EGFR Testing Among Patients by Quarter of Diagnosis in 2013 and 2014. (B) Rate of EGFR Testing by Quarter of Diagnosis in 2013 and 2014 Among Patients Treated With Bevacizumab and/or Pemetrexed



Abbreviation: EGFR = Epidermal growth factor receptor.

Our results emphasize the need to promote rapid dissemination of medical advances among physicians. Indeed, our study analyzed patients diagnosed with metastatic lung cancer from January 2013 to June 2014. By the beginning of that time period, erlotinib had been listed as an option for first-line treatment in NCCN guidelines for 3 years,[6] ASCO's provisional clinical opinion recommending EGFR mutation analysis for patients considering first-line EGFR-targeted therapy had been available for 2 years,[7] and NCCN guidelines had recommended EGFR mutation testing for all patients with lung adenocarcinoma in the previous year. Results of the Iressa Pan-Asia Study trial, demonstrating a significant progression-free survival advantage for gefitinib over chemotherapy in the first-line setting, were published 4 years prior.[1] Our study showed a modest pace of increase in testing rate with time; however, it is still possible that uptake of EGFR testing in the community has further increased at a faster pace since our study period, and further research should assess subsequent testing rates.

This study has several limitations. First, the ICD-9 codes we used to determine our cohort were able to define cancer site, but did not directly contain information regarding cancer histology. Therefore, the rate of EGFR testing may be higher among a more selected group of patients with advanced non-squamous NSCLC. It has been estimated that approximately 40% of lung cancers are adenocarcinomas.[47] We also used SEER*Stat software (version 8.3.2; Surveillance Research Program, National Cancer Institute, Bethesda, MD) and found that approximately 36% of patients with metastatic lung/bronchus cancer had adenocarcinoma histology. If we assumed that 35% to 40% of our cohort had adenocarcinomas, and that EGFR testing occurred only within that subgroup, our EGFR testing rate would have been 44% to 51%, still indicating that a large proportion of potentially eligible patients did not receive EGFR testing. Indeed, our analysis of the subgroup treated with bevacizumab and/or pemetrexed was in line with the above observation; we found a 37% testing rate among this subgroup. It is important to note that not all patients with metastatic adenocarcinomas would receive bevacizumab and/or pemetrexed. Our sample showed that only 29% of the patients with metastatic lung cancer received bevacizumab and/or pemetrexed, which is lower than our expected percentage with adenocarcinoma histology (35%-40%). The literature shows that the rate of guideline adherence of first-line therapy for advanced and metastatic disease in patients with NSCLC is relatively good at 75% (compared with 61% for adjuvant therapy among early-stage disease) in US community oncology practices.[48] Another study found the rate among medically fit

patients with stages II to IV NSCLC was 71%.[49] Further, it is possible that patients received erlotinib as first-line treatment and were not included in the subgroup. We conducted both whole group analysis including all patients with newly diagnosed metastatic lung cancer and a subgroup analysis for patients treated with bevacizumab and/or pemetrexed. We expect that the whole group is probably sensitive but not specific, the subgroup is probably specific but not sensitive, in terms of capturing NSCLC patients with adenocarcinoma histology.

Additionally, it is possible that some patients did not receive EGFR mutation testing owing to lack of tissue to submit for molecular analyses. Our observational study based on claims data does not provide information on the availability of tissue for testing. Additionally, patients who participated in clinical trials and had EGFR testing performed according to a study protocol, rather than billed to insurance, would not have been captured using claims data. However, because 5% or less of adults with cancer in the US participate in clinical trials,[50-54] underestimation of testing for this reason was likely not substantial.

Our data do not include information on whether patients were treated at community-based hospitals and academic medical centers. It is possible that the testing rate at community-based hospitals and academic medical centers are different. However, we do not have information on the proportion of community-based hospitals and academic medical centers included in the database. It would also be interesting to study the first-, second-, and third-line treatments of patients with metastatic lung cancer. However, it is challenging to use claims data to identify the line of therapy. One important paper in the literature developed an algorithm to identify first-, second-, and third-line chemotherapy among patients with lung cancer.[55] The algorithm requires that patients have at least 3 chemotherapy claims to ascertain the first-line therapy and then at least 28 days following the last delivery date of a different first-line chemotherapy to ascertain the second-line therapy. They found that the mean interval between the last date of administration of the first-line agent and the initiation of the second-line treatment was 114 days for injectable agents. In our study, the follow-up time is only 6 months, which hinders the study of first-, second-, and third-line therapies for the patients.

Our study is one of the few papers in the literature to report the uptake of EGFR testing among patients with advanced lung cancer from a population perspective. Another study examined 1358 patients diagnosed in 2010 with histologically-confirmed NSCLC from the Surveillance, Epidemiology, and End Results (SEER) data and found that the rate of EGFR testing was 17% overall and 23% for stage IV patients.[56] Our study identified 5842 patients newly diagnosed with metastatic lung cancer from January 2013 to June 2014 from MarketScan data and found that the rate of EGFR testing was 18% overall and 37% among a subgroup treated with bevacizumab and/or pemetrexed who are likely to have non-squamous NSCLC. Although the results from the 2 studies cannot be compared directly, they are reasonably in line with each other. The overall rate in our study would include patients with small cell lung cancer, who would be less likely to receive EGFR testing; therefore, we expect the testing rate among patients with metastatic NSCLC overall to be higher than 18%. If we assume that 80% of the patients with lung cancer have NSCLC[47] and none of the SCLC patients received EGFR testing, then this calculation implies a 23% testing rate in metastatic NSCLC, which is the same as in the study based on SEER data.

Further research should examine the uptake of testing for other molecular biomarkers such as the ALK and ROS1 rearrangements, as well as identify specific barriers to the dissemination of novel evidence-based testing and therapy. Some other interesting future research directions include studying the adoption of first-, second-, and third-line treatments and examining the potential disparities in the adoption of EGFR testing by community-based and academic medical centers.

Clinical Practice Points

- What is already known about this subject? EGFR-targeted therapy significantly improves outcomes among patients with NSCLC whose tumors harbor sensitizing mutations. Several guidelines recommend EGFR mutation testing for patients with advanced NSCLC, and suggesting consideration of EGFR inhibitor therapy as a first-line treatment for patients with EGFR mutations. However, the literature is scarce on EGFR testing patterns among patients with advanced NSCLC.
- What are the new findings? This is the first population-based study to assess EGFR testing patterns on a national scale. We identified 5842 patients newly diagnosed with metastatic lung cancer from January 2013 to June 2014 from MarketScan data.Of these 5842 patients with metastatic lung cancer, 1039 (18%) had claims for EGFR testing within 6 months of diagnosis, and 283 (5%) received erlotinib. The testing rate among patients who received erlotinib was 42%. Within a subgroup of 1685 patients treated with bevacizumab or pemetrexed, 616 (37%) underwent EGFR testing, and 94 (6%) also received erlotinib; the testing rate among the patients treated with erlotinib was 57%. Multivariable logistic regression showed that younger patients, female patients, patients with fewer comorbidities and patients living in the West region were more likely to receive EGFR testing.
- How might it impact on clinical practice in the foreseeable future? The relatively low testing rate and the disparities in testing rate by age, sex and region emphasizes the need to promote rapid dissemination of medical advances among physicians. Our study did show a modest pace of increase in testing rate with time; however, it is still possible that uptake of EGFR testing in the community has further increased at a faster pace since our study period.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.cllc.2016.11.002.

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Supplemental Figure 1 Derivation of the Study Cohort