

Molecular Testing Patterns in Metastatic Non–Small Cell Lung Cancer

Elizabeth MacLean, PharmD; Anthony Louder, PhD, RPh; Kim Saverno, PhD, RPh; Gregory Smith, BA; Jack Mardekian, PhD; Cari Bruins, PharmD; Melea Ward, PharmD, PhD; Robert Sweetman, MD; and Margaret Pasquale, PhD

Significant progress has been made in the past decade in the use of molecular biomarkers to drive clinical decision making in oncology. This growth and recognition of the importance of identifying oncogene mutations and gene rearrangements have led to publication of guidelines by professional societies to guide the use and application of molecular tests.¹ The shift to a “personalized medicine” approach to treatment requires a multidisciplinary approach to diagnosis, management, and the adaptation of complex processes of healthcare delivery. Consequently, the potential exists for variable comprehension and implementation of guideline recommendations.

In the case of non–small cell lung cancer (NSCLC), the leading cause of cancer death in North America,^{2,3} several molecular biomarkers have been identified which predict patient survival or response to a particular treatment, specifically for advanced or metastatic NSCLC (mNSCLC).²⁻⁵ These include mutations in the epidermal growth factor receptor (EGFR) gene⁶⁻⁹ and mutations in genes that code for proteins in the EGFR signaling cascade. Mutations in Kirsten rat sarcoma viral oncogene homolog (KRAS) exemplify one of the genes that code for a protein in this cascade, alterations in which can predict poor survival in patients with NSCLC.¹⁰⁻¹³ With regard to treatment, mutations in the BRAF gene can predict response to tyrosine kinase inhibitor (TKI) therapy.^{14,15} In addition, the rearrangement of several genes—including anaplastic lymphoma kinase (ALK),¹⁶⁻¹⁸ ROS proto-oncogene 1, receptor tyrosine kinase (ROS1),¹⁹ and ret proto-oncogene (RET)²⁰—has been identified as a driver of tumor survival and proliferation. Similarly, gene amplification of MET proto-oncogene, receptor tyrosine kinase (MET), including exon 14 skipping,²¹ has been demonstrated to act as a predictive marker for mNSCLC.^{22,23}

Recommendations for the application of molecular tests in the management of mNSCLC have been introduced over time by different groups. In 2013, however, 3 professional

ABSTRACT

Objectives: Identification of oncogene mutations and gene rearrangements in individuals with non–small cell lung cancer (NSCLC) can help identify candidates for targeted therapy. This study examined whether clinicians are ordering molecular testing for patients with metastatic NSCLC (mNSCLC) prior to therapy initiation.

Study Design: Members from a national health plan with lung cancer and metastatic disease were followed retrospectively.

Methods: Members were identified in medical claims data from January 1, 2010, to December 31, 2012, if they had 2 or more claims for lung cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 162.xx*) and metastatic disease (≥ 1 claim with *ICD-9-CM code 196.xx-198.xx*) who were continuously enrolled in a fully insured plan 180 days prior to index date. Patients were excluded if they had a history of chemotherapy used primarily in small cell lung cancer, or a medical claim associated with an unrelated malignancy. The timing of molecular testing was compared with the start of chemotherapy and targeted therapy, if applicable.

Results: A total of 2623 patients presumed to have mNSCLC were included for analysis; of whom, 52.5% were male with a mean age of 72.5 years (SD = 8.2 years). A total of 1597 (60.9%) patients had a Current Procedural Terminology code associated with molecular testing at any time in their claims history. Of the 733 patients with molecular testing and chemotherapy or targeted therapy claims, testing occurred prior to systemic therapy initiation in 651 (88.8%; 95% CI, 86.1%-90.9%) patients. The median time between testing and therapy initiation was 38 days (interquartile range = 23-69 days).

Conclusions: Assessment of oncogene mutations and gene rearrangements in mNSCLC routinely occurs prior to treatment initiation as suggested by analyses of claims data from a large US health plan. Validation using patient medical records is needed.

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groups—the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology—jointly examined existing evidence and developed principal guidelines for molecular analysis for patients with mNSCLC.²⁴ Among other suggestions, these guidelines recommend testing for EGFR mutations and ALK mutations to determine if treatment with an EGFR-targeted TKI or ALK-targeted TKI is appropriate, respectively. The directive states that smoking history, sex, race, and other clinical factors should not be taken into account when deciding if a patient should receive these molecular tests.

At the forefront of the use of these emerging diagnostic tools, the responsibility of ensuring adequate and appropriate testing prior to treatment falls to clinicians, who play a vital role in these procedures.⁴ However, little is known about how frequently clinicians are assessing for oncogene mutations and gene rearrangements in patients with advanced or mNSCLC in a real-world setting. To address this knowledge gap, this study examined real-world clinical practice patterns, including rate and timing of molecular testing relative to the start of therapy for mNSCLC.

METHODS

Study Data

This study utilized data from Humana, Inc, a large national health insurance plan. The Humana Research Database (Louisville, KY) contains member enrollment and medical and pharmacy claims data for Humana's Medicare and commercial fully insured membership. Member enrollment data include information on member demographics and coverage start and end dates. Medical claims data include diagnoses, pharmacologic treatments administered in a clinical setting, and procedures, including biopsies and histologic and molecular testing. Pharmacy claims data include detailed information on each member's prescription utilization. Such information includes, but is not limited to, the specific medication filled, prescription fill date, quantity dispensed, and days' supply. All data sources were merged using de-identified patient data. The finalized protocol was approved by an independent institutional review board.

Study Design

This study was a retrospective cohort analysis of all Medicare Advantage and commercial fully insured patients in Humana's database identified as having mNSCLC dur-

Take-Away Points

The prevalence of histologic and molecular testing among patients with metastatic non–small cell lung cancer (mNSCLC), as well as the timing of testing relative to treatment initiation, were determined among subsamples initiating chemotherapy or targeted therapy.

- Among 2623 patients with mNSCLC, histologic testing was identified in 89.6% and molecular testing was identified in 60.9% of patients.
- Among a subset of 1015 patients with histologic testing who initiated therapy, 85% had a histological evaluation before therapy initiation.
- Of the 733 patients with evidence of molecular testing who initiated chemotherapy or targeted therapy, testing occurred prior to therapy initiation in 88.8% of patients.

ing the identification period between January 1, 2010, and December 31, 2012. The index date was the first medical claim with an *International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM)* code indicative of metastatic disease. Patients were followed from their index date until they were lost to follow-up due to death, loss of eligibility, or the end of the study period (June 30, 2013).

The clinical practice patterns evaluated included whether histologic testing was performed, the proximity of histologic testing to a metastatic diagnosis (within 45 days), and whether the histologic type of lung tumor was established prior to therapy initiation for patients with mNSCLC. In addition, we examined the degree to which clinicians tested patients with mNSCLC for oncogene mutations and gene rearrangements, and the timing of the molecular testing relative to the start of chemotherapy or targeted therapy.

Study Population

Study subjects were either Medicare Advantage with Prescription Drug (MAPD) or fully insured commercial patients aged 18 to 89 years who were continuously enrolled for 180 days before the index date. Due to differences in member demographics and insurance benefits, we considered the potential for differences in clinical practice patterns between the MAPD and commercial population. Therefore, the 2 populations were assessed separately. Patients were considered to have lung cancer by having at least 2 medical claims with *ICD-9-CM* codes of malignant neoplasm of trachea bronchus and lung (*ICD-9-CM* code 162.xx) in any position, occurring on separate days. Those patients identified with a malignant lung neoplasm also had to have at least 1 medical claim indicative of metastatic disease (*ICD-9-CM* codes of 196.xx, 197.xx, or 198.xx) in any position during the identification period.

Patients were excluded from analysis if they had a claim for a malignant neoplasm unrelated to lung cancer during the study period or had a claim for chemotherapy

used primarily for small cell lung cancer at any time during the study period, June 1, 2009, to June 30, 2013 (see eAppendix [available at www.ajmc.com]).

Statistical Analysis

Descriptive statistics were used to summarize the clinical and demographic characteristics of the study population. The following demographic characteristics were summarized for the target population: age, gender, race/ethnicity (MAPD only), low-income subsidy status (MAPD only), geographic location, and line of business (commercial or MAPD). Clinical characteristics of interest included the Deyo-Charlson comorbidity index (DCI), RxRisk-V Score, and physician specialty. The DCI score used in this study was modified to exclude cancer. The RxRisk-V score²⁵⁻²⁹ is a comorbidity index score derived from prescription claims data; it can be applied to data from a narrow window of claims rather than a broader window typically necessary for comorbidity scores based on medical claims, such as the DCI score.³⁰

To determine the extent to which histologic type was established for patients with mNSCLC, each patient was categorized dichotomously (yes/no) as to whether the medical claims indicated a history of histologic typing for NSCLC within ± 45 days of the index date using Current Procedural Terminology (CPT) codes (see eAppendix). The 45-day threshold was chosen by the investigators to approximate a short time period for temporally performing the histologic testing relative to metastatic diagnosis. In addition, each patient was categorized based on whether their medical claims indicated a history of histologic typing for NSCLC at any time in their claims history with Humana during the study period.

Of the patients with CPT codes associated with determination of histologic type (see eAppendix), the date of service for histologic typing was compared with the date of chemotherapy or targeted therapy initiation. Patients were classified according to whether the date of the histologic typing occurred before or after therapy initiation. In addition, the number of days between CPT codes associated with histologic typing and chemotherapy or targeted therapy initiation was established for the cohort.

Using a series of CPT codes corresponding to fluorescence in situ hybrid-

ization, polymerase chain reaction, and other molecular genetic tests (see eAppendix), the extent to which those likely to have mNSCLC that had been tested for oncogene mutations and gene rearrangements was determined by examining each patient’s medical claims for codes reflective of these laboratory procedures. The proportion of mNSCLC patients with a CPT code reflective of molecular testing at any time in their medical claims history with Humana was determined.

Of those likely to have mNSCLC, the timing and type of initial chemotherapy or targeted therapy was established. In those cases in which the patient received molecular testing, the date(s) of service for molecular testing was compared with the date of therapy initiation.

RESULTS

The study population was composed of 122 (4.7%) commercial patients and 2501 (95.3%) Medicare patients (Table 1). The mean age of the study population was 72.5 years (SD = 8.2 years), with males composing slightly more than half of the cohort (52.5%). The majority of the group was Caucasian/white (83.6%) and resided in the south or mid-west (57.2% and 31.4%, respectively) and/or in an urban setting (59.5%). The mean DCI score for the study popula-

■ **Table 1. Patient Characteristics**

	Medicare (n = 2501)	Commercial (n = 122)	Total ^a (N = 2623)
Age, years: mean (SD)	73.1 (± 7.6)	60.0 (± 8.7)	72.5 (± 8.2)
Age category, years: n (%)			
18-29	0 (0.0)	0 (0.0)	0 (0.0)
30-39	0 (0.0)	3 (2.5)	3 (0.1)
40-49	9 (0.4)	7 (5.7)	16 (0.6)
50-59	103 (4.1)	48 (39.3)	151 (5.8)
60-69	706 (28.2)	50 (41.0)	756 (28.8)
70-79	1139 (45.5)	11 (9.0)	1150 (43.8)
80-89	544 (21.8)	3 (2.5)	547 (20.9)
Gender, n (%)			
Male	1321 (52.8)	57 (46.7)	1378 (52.5)
Female	1180 (47.2)	65 (53.3)	1245 (47.5)
Race/ethnicity, ^b n (%)			
White	2192 (87.6)	0 (0.0)	2192 (83.6)
Black	251 (10.0)	0 (0.0)	251 (9.6)
Hispanic	21 (0.8)	0 (0.0)	21 (0.8)
Other	36 (1.4)	0 (0.0)	36 (1.4)
Unknown	1 (0.0)	122 (100.0)	123 (4.7)

(continued)

tion was 3.1 (SD = 2.4) with an RxRisk-V score of 5.8 (SD = 3.2). The geographic location of the clinicians associated with the diagnosis and treatment of mNSCLC paralleled the geographic location of the study population, with most clinicians located in the south and midwest.

The first lung cancer diagnosis was observed on a medical claim from an internal medicine clinician for 348 (13.3%) patients, while it was observed on a medical claim from an oncologist for 155 (5.9%) patients (Table 1). For the majority—2120 (80.8%) patients—however, the first observed diagnosis was from another source. The top 3 groups composing the “other” category were clinicians located at general acute care hospitals, pathologists, and diagnostic radiologists, respectively (data not shown). A similar pattern was observed for first observed metastatic diagnosis: 249 (9.5%) from an oncologist, 272 (10.4%) from an internal medicine clinician, and 2102 (80.1%) from an alternate source. The “other” category for specialties associated with first metastatic diagnosis was the same as described above for first lung cancer diagnosis.

The number of patients with mNSCLC and evidence of procedural codes associated with the determination of NSCLC histologic type is reported in Table 2. Of the total study population, 1746 (66.6%) patients had at least 1 CPT code that could be associated with determination of histological type within 45 days of their index date. Nearly 90% (2351) of patients had at least 1 CPT code that could be associated with determination of a histological type at any time during their enrollment within the study period.

Of the 939 Medicare patients receiving systemic therapy, and in which histologic type was assumed to be performed, the data suggest the majority of patients (796; 84.8%) had histologic typing performed prior to systemic therapy initiation (Table 2). The median number of days between a CPT code associated with histologic testing and therapy initiation was 47 days (interquartile range [IQR] = 26-189 days). Similar results were observed in the commercial population with regard to the number of patients with a record of his-

tological typing prior to therapy initiation (76; 88.2%). Of the 1015 patients with CPT codes associated with histologic testing during the study period in their medical claims histories, 152 (15%) patients appeared to have initiated therapy prior to histologic testing.

The extent to which those with probable mNSCLC were tested for oncogene mutations and gene rearrangements is presented in Table 3. Slightly less than two-thirds of patients (1590; 60.6%) had 1 or more CPT code reflec-

■ **Table 1. Patient Characteristics** (continued)

	Medicare (n = 2501)	Commercial (n = 122)	Total ^a (N = 2623)
Member geographic region, n (%)			
Northeast	62 (2.5)	0 (0.0)	62 (2.4)
Midwest	780 (31.2)	44 (36.1)	824 (31.4)
South	1430 (57.2)	71 (58.2)	1501 (57.2)
West	207 (8.3)	7 (5.7)	214 (8.2)
Unknown	22 (0.9)	0 (0.0)	22 (0.8)
Population density (member), n (%)			
Rural	335 (13.4)	8 (6.6)	343 (13.1)
Suburban	674 (26.9)	23 (18.9)	697 (26.6)
Urban	1470 (58.8)	91 (74.6)	1561 (59.5)
Unknown	22 (0.9)	0 (0.0)	22 (0.8)
Medicare plan characteristics, ^e n (%)			
LIS only	135 (5.4)	N/A	135 (5.4)
Dual eligible only	128 (5.1)	N/A	128 (5.1)
LIS and dual eligible	230 (9.2)	N/A	230 (9.2)
DCI, mean (SD)	3.1 (± 2.4)	3.0 (± 2.5)	3.1 (± 2.4)
RxRisk-V Score, mean (SD)	5.8 (± 3.1)	4.9 (± 3.4)	5.8 (± 3.2)
Physician specialty: first lung cancer diagnosis, ^d n (%)			
Oncology	144 (5.8)	11 (9.0)	155 (5.9)
Internal medicine	329 (13.2)	19 (15.6)	348 (13.3)
Other	2028 (81.1)	92 (75.4)	2120 (80.8)
Physician specialty: first metastatic diagnosis, ^d n (%)			
Oncology	229 (9.2)	20 (16.4)	249 (9.5)
Internal medicine	261 (10.4)	11 (9.0)	272 (10.4)
Other	2011 (80.4)	91 (74.6)	2102 (80.1)
Time to chemotherapy initiation (days), ^e mean (SD)	135.7 (± 317.2)	115.7 (± 296.6)	134.2 (± 315.6)

CPT indicates Current Procedural Terminology; DCI, Deyo-Charlson comorbidity index; LIS, low-income subsidy; N/A, not applicable; NSCLC, non–small cell lung cancer.

^aCommercial + Medicare.

^bRace/ethnicity not available for commercial members.

^cPercentages based on Medicare population as denominator.

^dTop 3 clinician specialties composing the “other” category for clinicians associated with initial lung cancer and metastatic diagnosis were general acute care hospitals, pathologists, and diagnostic radiologists, respectively.

^eTime to chemotherapy initiation (days) calculated as index date minus date of first NSCLC chemotherapy treatment.

Table 2. Number of Metastatic NSCLC Patients With Evidence of Histological Typing and Timing of Histologic Subtyping Relative to Chemotherapy Initiation

	Medicare (n = 2501)	Commercial (n = 122)	Total ^a (N = 2623)
Population with procedural codes			
Number of patients <u>with</u> CPT codes associated with histologic typing within ± 45 days of index date, n (%)	1662 (66.5)	84 (68.9)	1746 (66.6)
Number of patients <u>without</u> CPT codes associated with histologic typing within ± 45 days of index date, n (%)	839 (33.5)	38 (31.1)	877 (33.4)
Number of patients <u>with</u> CPT codes associated with histologic typing at any point during their enrollment with Humana, n (%)	2236 (89.4)	115 (94.3)	2351 (89.6)
Number of patients <u>without</u> CPT codes associated with histologic typing at any point during their enrollment with Humana, n (%)	265 (10.6)	7 (5.7)	272 (10.4)
Population receiving systemic therapy, with histological typing, N	939	76	1015
Number of patients in which histologic typing was completed before therapy initiation, n (%)	796 (84.8)	67 (88.2)	863 (85.0)
Number of days between histologic typing and therapy initiation for those in which histologic typing occurred before therapy initiation, mean (SD)	217.3 (± 370.3)	135.6 (± 286.6)	210.9 (± 365.0)
Median (IQR)	47 (26-189)	43 (22-71)	47 (25-180)
Number of patients in which histologic typing was completed after therapy initiation, n (%)	143 (15.2)	9 (11.8)	152 (15.0)
Number of days between histologic typing and therapy initiation for those in which histologic typing occurred after therapy initiation: mean (SD)	393.3 (± 386.8)	224.4 (± 201.5)	383.3 (± 380.0)
Median (IQR)	254 (136-554)	120 (104-326)	248 (126-535)
CPT indicates Current Procedural Terminology; IQR, interquartile range; NSCLC, non-small cell lung cancer. ^a Commercial + Medicare.			

tive of molecular testing and histologic typing at any time in their medical claims history. The median time between histologic and molecular testing was 2 days (IQR = 0-78 days). A much smaller percentage of patients had at least 1 CPT code associated with molecular testing without histologic typing in their claims history (7; 0.3%). Nearly 30% of patients (761) had evidence of CPT codes associated with histologic testing, but not molecular testing. Approximately 10% of probable mNSCLC patients (265) had no evidence of CPT codes associated with either molecular or histologic testing.

Of the 1597 patients with evidence of CPT codes associated with molecular testing, less than half (46%; 733) received treatment (Table 3). Of these, the majority (89%; 651) had testing performed before systemic therapy initiation. For those patients for which molecular testing occurred prior to systemic therapy initiation, the median time between testing and therapy initiation was 38 days (IQR = 23-69 days). When testing occurred after systemic therapy initiation, the median number of days that elapsed between therapy initiation and testing was 352 days (IQR = 183-589 days).

DISCUSSION

Great progress has been made in a relatively short period of time in identifying a number of oncogenic mutations that both drive and maintain lung cancer. This has led to the development of targeted therapies for patients with mNSCLC and has shifted emphasis to treatment based on the results of not only tumor histology, but also molecular testing. Since use of targeted therapies informed through predictive biomarker testing is generally associated with higher response rates and longer progression-free survival compared with chemotherapy, understanding histologic and molecular subtype is crucial for clinicians to deliver appropriate therapy. A number of organizations have put forth recommendations to guide physicians to routinely use this information in clinical practice, including the National Comprehensive Cancer Network, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology; however, whether clinicians adhere to these published guidelines is not known.^{24,31}

Table 3. Number of Metastatic NSCLC Patients With Evidence of Procedural Codes Associated With Molecular Testing and/or Histologic Testing, and Timing of Molecular Testing Relative to Therapy Initiation

	Medicare (n = 2501)	Commercial (n = 122)	Total* (N = 2623)
Population with procedural codes for testing			
Number of patients with CPT codes associated with mutation and histologic testing, n (%)	1506 (60.2)	84 (68.9)	1590 (60.6)
Number of days between histologic testing and molecular testing, mean (SD)	146.5 (± 326.3)	103.6 (± 278.8)	144.2 (± 324.0)
Median (IQR)	2 (0-79)	1 (0-48)	2 (0-78)
Number of patients with CPT codes associated with mutation and no histologic testing, n (%)	7 (0.3)	0 (0.0)	7 (0.3)
Total number of patients with CPT codes associated with molecular testing, n (%)	1513 (60.5)	84 (68.9)	1597 (60.9)
Number of patients with CPT codes associated with histologic and no molecular testing, n (%)	730 (29.2)	31 (25.4)	761 (29.0)
Number of patients CPT codes associated with no mutation or histologic testing, n (%)	258 (10.3)	7 (5.7)	265 (10.1)
Population with evidence of timing related to testing, N			
Patients in which molecular testing was completed <u>before</u> systemic therapy initiation, n (%)	595 (88.3)	56 (94.9)	651 (88.8)
Number of days between molecular testing and therapy initiation for those in which molecular testing occurred <u>before</u> systemic therapy initiation, mean (SD)	109.4 (± 216.3)	91.8 (± 243.9)	107.9 (± 218.6)
Median (IQR)	39 (23-71)	35 (21-52)	38 (23-69)
Patients in which molecular testing was completed <u>after</u> systemic therapy initiation, n (%)	79 (11.7)	3 (5.1)	82 (11.2)
Number of days between molecular testing and therapy initiation for those in which molecular testing occurred <u>after</u> therapy initiation, mean (SD)	454.4 (± 387.1)	517.7 (± 669.4)	456.8 (± 394.3)
Median (IQR)	366 (185-589)	159 (104-1290)	352 (183-589)
CPT indicates Current Procedural Terminology; IQR, interquartile range; NSCLC, non–small cell lung cancer. *Commercial + Medicare.			

In examining healthcare claims data from a large national health insurance plan, we found evidence suggesting clinicians generally follow recommended guidelines for genetic testing prior to determination of treatment for patients with mNSCLC. The data imply that the majority of patients in the study, both Medicare and commercial, had the histological type of their tumors evaluated before the start of therapy, while a small proportion (15%) had therapy initiated prior to histologic typing. Interestingly, almost a third of patients who received histological testing were not screened for mNSCLC-related mutations or gene rearrangements, while only a small proportion (10%) had no evidence of either mutation or histological testing in their claims history.

Guidelines state that patients with nonsquamous mNSCLC benefit from molecular testing to inform treatment decisions, and that those with squamous mNSCLC may

benefit as well.^{31,32} We observed adherence to these guidelines in the majority of mNSCLC cases examined in our study, in that approximately two-thirds of the study population was tested for oncogenes and gene rearrangements. Interestingly, when molecular analysis occurred after chemotherapy or targeted therapy had begun, the elapsed time between the start of any therapy and gene-specific therapy was surprisingly large (median = 352 days [82 patients; 11.2%]). This could be due to a number of reasons, including desire by the patient or clinician to try older, more established therapies, or a lack of understanding or knowledge of the existence or specifics of available treatments. However, a similar timespan was observed when histology determination was postponed until after treatment initiation (383 days [152 patients; 15%]), which suggests that evaluating the tumor's characteristics was not a priority when

a treatment plan was established. Also, it may be that the 352 and 383 days between initial therapy and molecular and histologic testing, respectively, could represent a time period for preparation for second-line therapy. However, chemotherapy may be appropriate to initiate while waiting for test results due to symptomatic disease or other clinical concerns. Although the reasons behind these issues are intriguing, defining them is beyond the scope of this study.

Limitations

Limitations for this study include that NSCLC does not have a unique *ICD-9-CM* code; therefore, this analysis may be prone to misclassification errors despite attempts to derive an algorithm for identifying those with probable NSCLC based on lung cancer *ICD-9-CM* codes and medication claims data, which has not been validated. In addition, the database used for this study lacks information on the results of tumor histology testing, which can guide treatment decisions in mNSCLC. The CPT codes used to identify the occurrence of histologic typing can also be used by clinicians to indicate the confirmation of cancer. Because of the nonspecific nature of CPT codes, there may be some misclassification of the frequency of histologic typing. Similarly, many of the older CPT codes used to identify molecular diagnostic testing are nonspecific, precluding definitive confirmation that specific genetic testing had been undertaken.

Furthermore, we are limited by physician specialty coding, such as the fact that an oncologist may be board-certified in internal medicine and not appear as an oncologist in the claims data, or the fact that a facility may be listed rather than a specific provider. These limitations underscore challenges payers face when using administrative claims data to determine whether patients with mNSCLC are receiving care in accordance with treatment guidelines, and whether targeted therapies are being appropriately prescribed. All of these limitations highlight the need for validation of these findings in an alternative but complementary data source, such as medical records.

CONCLUSIONS

Although this study revealed that, in most cases, histological typing and molecular testing occur prior to treatment decisions, further analysis should include chart reviews to confirm which tests were ordered and from where they originated. Further work should also validate that algorithms used in this study correctly identified NSCLC patients with metastatic disease. As patient treatment continues to become individualized, these studies

will enhance the understanding of the application of new treatment paradigms in real-world practice.

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Author Affiliations: Pfizer, Inc (EM, GS, JM, RS), New York, NY; Comprehensive Health Insights, Inc (AL, KS, MP), Louisville, KY; Humana, Inc (CB, MW), Louisville, KY.

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Address correspondence to: Margaret K. Pasquale, PhD, Comprehensive Health Insights, Inc, 515 W Market St, Louisville, KY 40202. E-mail: mpasquale@humana.com.

REFERENCES

- Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 2013;8(7):823-859. doi:10.5858/arpa.2012-0720-OA
- Cheng H, Xu X, Costa DB, Powell CA, Halmos B. Molecular testing in lung cancer: the time is now. *Curr Oncol Reports*. 2010;12(5):335-348. doi:10.1007/s11912-010-0118-z
- Cancer facts & figures 2015. American Cancer Society website. <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf>. Published 2015. Accessed January 11, 2016.
- Tanner NT, Pastis NJ, Sherman C, Simon GR, Lewin D, Silvestri GA. The role of molecular analyses in the era of personalized therapy for advanced NSCLC. *Lung Cancer*. 2012;76(2):131-137. doi:10.1016/j.lungcan.2011.11.013
- Berge EM, Doebele RC. Targeted therapies in non-small cell lung cancer: emerging oncogene targets following the success of epidermal growth factor receptor. *Semin Oncol*. 2014;41(1):110-125. doi:110.1053/j.seminoncol.2013.1012.1006.
- Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139.
- Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500.
- Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A*. 2004;101(36):13306-13311.
- Yoshida K, Yatabe Y, Park JY, et al. Prospective validation for prediction of gefitinib sensitivity by epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer. *J Thorac Oncol*.

- 2007;2(1):22-28.
10. Santos E, Martin-Zanca D, Reddy EP, Pierotti MA, Della Porta G, Barbacid M. Malignant activation of a K-ras oncogene in lung carcinoma but not in normal tissue of the same patient. *Science*. 1984;223(4637):661-664.
 11. van Zandwijk N, Mathy A, Boerrigter L, et al. EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. *Ann Oncol*. 2007;18(1):99-103.
 12. Wong DW, Leung EL, So KK, et al; University of Hong Kong Lung Cancer Study Group. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer*. 2009;115(8):1723-1733. doi:1710.1002/cncr.24181., 2009
 13. Langer CJ. Roles of EGFR and KRAS mutations in the treatment of patients with non-small-cell lung cancer. *PT*. 2011;36(5):263-279.
 14. Kobayashi M, Sonobe M, Takahashi T, et al. Clinical significance of BRAF gene mutations in patients with non-small cell lung cancer. *Anticancer Res*. 2011;31(12):4619-4623.
 15. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol*. 2011;29(15):2046-2051. doi:10.1200/JCO.2010.33.1280.
 16. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007;448(7153):561-566.
 17. Mano H. Non-solid oncogenes in solid tumors: EML4-ALK fusion genes in lung cancer. *Cancer Sci*. 2008;99(12):2349-2355. doi:10.1111/j.1349-7006.2008.00972.x.
 18. Casaluce F, Sgambato A, Maione P, et al. ALK inhibitors: a new targeted therapy in the treatment of advanced NSCLC. *Targeted Oncol*. 2013;8(1):55-67. doi:10.1007/s11523-012-0250-9.
 19. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30(8):863-870. doi:10.1200/JCO.2011.35.6345.
 20. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. *Nat Med*. 2012;18(3):375-377. doi:10.1038/nm.2644.
 21. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov*. 2015;5(8):842-849. doi:10.1158/2159-8290.CD-14-1467
 22. Robinson KW, Sandler AB. The role of MET receptor tyrosine kinase in non-small cell lung cancer and clinical development of targeted anti-MET agents. *Oncologist*. 2013;18(2):115-122. doi:10.1634/theoncologist.2012-0262.
 23. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol*. 2003;4(12):915-925.
 24. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *Arch Pathol Lab Med*. 2013;137(6):828-860. doi:10.1016/j.jmoldx.2013.03.001.
 25. Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DJ, O'Keeffe Rosetti MC. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care*. 2003;41(1):84-99.
 26. Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care*. 2003;41(6):761-774.
 27. Sales AE, Liu C-F, Sloan KL, et al. Predicting costs of care using a pharmacy-based measure risk adjustment in a veteran population. *Med Care*. 2003;41(6):753-760.
 28. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992;45(2):197-203.
 29. Farley JF, Harley CR, Devine JW. A comparison of comorbidity measurements to predict healthcare expenditures. *Am J Manag Care*. 2006;12(2):110-119.
 30. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
 31. Lindeman NI, Cagle PT, Beasley MB, et al; College of American Pathologists International Association for the Study of Lung Cancer and Association for Molecular Pathology. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Mol Diagn*. 2013;15(4):415-453. doi:10.1016/j.jmoldx.2013.03.001.
 32. Fiala O, Pesek M, Finek J, et al. Erlotinib in the treatment of advanced squamous cell NSCLC. *Neoplasma*. 2013;60(6):676-682. doi:10.4149/neo_2013_086 ■

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eAppendix. Medical and Pharmacy Codes associated with Diagnosis, Testing, and Treatment

		Medical Codes (ICD-9-CM diagnosis, ICD-9-CM procedure, CPT, HCPCS)	Pharmacy Codes (Generic Product Identifier 8)
Malignant neoplasm other than lung		140.xx-239.xx excluding 162.xx, 196.xx, 197.xx, 198.xx, and 210.xx-229.xx	
Chemotherapy used primarily for small cell lung cancer	Cyclophosphamide	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097	21.50.10.20
	Irinotecan	J9206	21.55.00.40
	Ifosfamide	J9208	21.10.10.25
	Ifosfamide/Mesna	J9209	21.99.00.02
	Temozolomide	J8700	21.10.40.70
	Doxorubicin	J9000	21.20.00.40
	Etoposide	J8560	21.50.00.10
	Vincristine Topotecan	J9370, J9375, J9380 J8705	21.50.00.20 21.55.00.80
Histology testing		33.20, 33.24, 33.25, 33.26, 33.27, 33.28	
		81479, 88104, 88108, 88112, 88173, 88305, 88307, 88309, 88342, 88360, 31623, 31624, 31625, 31628, 31629, 31632, 31633, 32095, 32100, 32400, 32402, 32405, 32420, 32421, 32422, 32554, 32555, 32556, 32557, 32602, 32604, 32606, 76942, 77002, 77012, 77021	
Mutation testing		83890, 83891, 83892, 83896, 83898, 83900, 83901, 83902, 83903, 83904, 83905, 83906, 83907, 83908, 83909, 83912, 83913, 83914, 88271, 88272, 88274, 88291, 88342, 88365, 88367, 88368	

CPT indicates Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*

eAppendix. Medical and Pharmacy Codes associated with Diagnosis, Testing, and Treatment

		Medical Codes (ICD-9-CM diagnosis, ICD-9-CM procedure, CPT, HCPCS)	Pharmacy Codes (Generic Product Identifier 8)
Malignant neoplasm other than lung		140.xx-239.xx excluding 162.xx, 196.xx, 197.xx, 198.xx, and 210.xx-229.xx	
Chemotherapy used primarily for small cell lung cancer	Cyclophosphamide	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097	21.50.10.20
	Irinotecan	J9206	21.55.00.40
	Ifosfamide	J9208	21.10.10.25
	Ifosfamide/Mesna	J9209	21.99.00.02
	Temozolomide	J8700	21.10.40.70
	Doxorubicin	J9000	21.20.00.40
	Etoposide	J8560	21.50.00.10
	Vincristine Topotecan	J9370, J9375, J9380 J8705	21.50.00.20 21.55.00.80
Histology testing		33.20, 33.24, 33.25, 33.26, 33.27, 33.28	
		81479, 88104, 88108, 88112, 88173, 88305, 88307, 88309, 88342, 88360, 31623, 31624, 31625, 31628, 31629, 31632, 31633, 32095, 32100, 32400, 32402, 32405, 32420, 32421, 32422, 32554, 32555, 32556, 32557, 32602, 32604, 32606, 76942, 77002, 77012, 77021	
Mutation testing		83890, 83891, 83892, 83896, 83898, 83900, 83901, 83902, 83903, 83904, 83905, 83906, 83907, 83908, 83909, 83912, 83913, 83914, 88271, 88272, 88274, 88291, 88342, 88365, 88367, 88368	

CPT indicates Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*