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Biomarker Testing Rates in Patients with Advanced Non-Small Cell Lung Cancer Treated in the Community

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Abstract

Introduction: Over the past few years, molecular targeted therapies have been emerging for the treatment of metastatic non-small cell lung cancer (NSCLC). Targeted therapy is associated with improved outcomes in patients with identified gene alterations, and national guidelines recommend routine biomarker testing. This study evaluated real-world rates of documented epidermal growth factor receptor (EGFR) mutation and other biomarker testing in patients with advanced NSCLC over time. Methods: Adult patients with Stage IV NSCLC were identified between January 1, 2012 and May 31, 2017 from the US Oncology Network iKnowMed™ electronic health records. Patients were examined overall and by histology. Rates of documented EGFR mutation and other biomarker testing were calculated. Multivariable regression analyses were conducted to identify characteristics associated with documented biomarker testing. Results: A total of 14,461 patients were identified: median age was 69.3 years, 52.3% were male, 14.6% were nonsmokers, and 64.7% had non-squamous histology. EGFR mutation testing rates were 35.5% overall, with an increase in rates seen over time: 30.0% in 2012 to 44.0% in 2016 ($p < 0.001$). Anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and programmed death-ligand 1 (PD-L1) mutation testing rates were 32.9%, 5.7%, and 5.7%, respectively. More recent diagnosis year, non-squamous histology, larger practice size, and nonsmoking status were strongly associated with higher documented EGFR and ALK mutation testing rates. Conclusions: EGFR mutation testing rates steadily increased over time, but remained less than 50%, with lower mutation testing rates reported for ALK, ROS1, and PD-L1, suggesting that opportunities exist to improve education on testing

for biomarkers in NSCLC.

Keywords

Non-Small-Cell Lung Cancer, NSCLC, Biomarkers, EGFR, Testing

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in the USA. It is estimated that there will be 228,150 new cases and 142,670 deaths due to lung cancer in 2019 [1]. Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC), and non-squamous histologies are the most common. The most common non-squamous histologies are adenocarcinoma (approximately 40%) and large cell (approximately 10% - 15%) [2]. Over the past few years, molecular targeted therapies have been emerging for the treatment of metastatic NSCLC with identified gene alterations. Actionable targets that can impact treatment selection include epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, c-ros oncogene 1 (ROS1) rearrangements, B-Raf proto-oncogene (BRAF) mutations, programmed death-ligand 1 (PD-L1) expression, and *neurotrophic tyrosine kinase* (*NTRK*) gene fusions [3] [4]. The use of targeted therapy is associated with improved outcomes in patients with advanced disease with identified gene alterations, and national guidelines recommend routine biomarker testing in patients with NSCLC so that those with gene alterations can receive treatment with effective targeted therapies [3] [4].

EGFR mutations are observed in approximately 40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively [5]. Mutations in exons 18 - 21 confer sensitivity to EGFR-tyrosine kinase inhibitors (TKIs) such as afatinib, erlotinib, and gefitinib. In patients with known EGFR mutations, frontline treatment with EGFR-TKIs is recommended. However, in approximately 50% of patients with EGFR mutation-positive NSCLC, a secondary mutation, EGFR T790M, develops, conferring resistance to first- and second-generation EGFR-TKI treatments [6]-[11]. Osimertinib, a third-generation, irreversible, oral EGFR-TKI, potently and selectively inhibits both EGFR sensitizing mutations and EGFR T790M, and has demonstrated efficacy in NSCLC central nervous system metastases [12]-[17]. Thus, continued biomarker testing in EGFR mutation-positive patients after progression on an EGFR-TKI may help identify patients who can continue to benefit from additional targeted therapies.

The primary objective of this study was to examine the rate of documented biomarker testing, including EGFR, EGFR T790M, ALK, ROS1, PD-L1, and BRAF, for patients with advanced NSCLC being treated in a US community oncology setting during the study. The secondary objective was to examine patient, disease, and provider factors associated with documented biomarker testing in patients with NSCLC in a real-world setting.

2. Materials and Methods

2.1. Study Design and Data Sources

This was a retrospective observational study among patients who received care within a US Oncology Network clinic between January 1, 2012 and May 31, 2017. The US Oncology Network is affiliated with approximately 1400 physicians in more than 60 community oncology practices in over 450 sites of care across 25 states in the US. Patients were identified from practices using the iKnowMed (iKM) electronic health record (EHR) system. iKM is an oncology-specific EHR system that captures outpatient practice encounter history. Within the EHR, many data elements, including specific tumor biomarkers (EGFR, ALK, ROS1, PD-L1, and BRAF), are documented within structured data fields. Demographic and disease characteristic data including age, sex, race, smoking history, Eastern Cooperative Oncology Group performance status, histology, tumor biomarker status, and year of diagnosis were collected via programmatic queries of the iKM database. Eligible patients were at least 18 years of age at diagnosis of NSCLC, with Stage IV disease, and with at least two visits during the study period (January 2012 to May 2017). Patients enrolled in clinical trials at any time during the study period, and patients with other documented primary cancer diagnoses during the study period were excluded. The index date was defined as the date of Stage IV NSCLC diagnosis. The US Oncology Institutional Review Board approval was obtained for the study.

2.2. Statistical Analysis

Standard descriptive statistics were used for continuous and categorical study variables. Characteristics were calculated and compared using standard significance testing, such as chi-squared/Fisher's exact test (for categorical variables), and t-test/Mann-Whitney U test/ANOVA/Kruskal-Wallis test (for the continuous variables). Patients were examined overall and by histology. Rates of documented biomarker testing were calculated, overall and by year. All patients who met the eligibility criteria and had results from documented biomarker testing were included. The actual testing date for each patient was also collected. Multivariable stepwise logistic regression analysis was conducted to identify characteristics associated with documented biomarker testing. The stepwise model building process used a type 3 p-value for entry of 0.20 and type 3 p-value for retention of 0.10. Odds ratios and 95% confidence intervals (CIs) were reported. For any significance testing, an alpha of 0.05 was used unless otherwise stated or requested. The analyses were conducted using SAS® (SAS Institute Inc., Version 9.4, Cary, NC, US).

3. Results

3.1. Patient Characteristics

There were 14,461 patients with advanced NSCLC meeting eligibility during the 5-year study period. Table 1 describes the demographic and clinical characteristics

Table 1. Demographic and clinical characteristics among patients with NSCLC, overall and by histologic type.

	Overall (N = 14,461)	Non-Squamous (N = 9,359)	Squamous (N = 2,527)	Unspecified Non-Small Cell Cancer (N = 471)	Not Documented (N = 2,104)
Age, years					
Median (Min, Max)	69.3 (21.5, 90+)	68.9 (21.5, 90+)	71.0 (28.4, 90+)	68.6 (34.9, 90+)	69.5 (30.3, 90+)
Sex, n (%)					
Female	6901 (47.7)	4694 (50.2)	967 (38.3)	215 (45.6)	1025 (48.7)
Male	7560 (52.3)	4665 (49.8)	1560 (61.7)	256 (54.4)	1079 (51.3)
Race, N (%)					
White	10,949 (75.7)	7052 (75.4)	2006 (79.4)	367 (77.9)	1524 (72.4)
Black	1271 (8.8)	804 (8.6)	213 (8.4)	48 (10.2)	206 (9.8)
Asian	372 (2.6)	284 (3.0)	31 (1.2)	6 (1.3)	51 (2.4)
Other	159 (1.1)	103 (1.1)	28 (1.1)	7 (1.5)	21 (1.0)
Not documented	1710 (11.8)	1116 (11.9)	249 (9.9)	43 (9.1)	302 (14.4)
Smoking History, N (%)					
Former	8652 (59.8)	5541 (59.2)	1648 (65.2)	298 (63.3)	1165 (55.4)
Current	2619 (18.1)	1559 (16.7)	553 (21.9)	95 (20.2)	412 (19.6)
Never	2115 (14.6)	1637 (17.5)	156 (6.2)	45 (9.6)	277 (13.2)
Not documented	1075 (7.4)	622 (6.6)	170 (6.7)	33 (7.0)	250 (11.9)
ECOG Performance Status at Index, N (%)					
0	477 (3.3)	356 (3.8)	61 (2.4)	10 (2.1)	50 (2.4)
1	6277 (43.4)	4254 (45.5)	1083 (42.9)	197 (41.8)	743 (35.3)
2	4009 (27.7)	2598 (27.8)	772 (30.6)	146 (31.0)	493 (23.4)
3+	1236 (8.5)	802 (8.6)	218 (8.6)	49 (10.4)	167 (7.9)
Not documented	2462 (17.0)	1349 (14.4)	393 (15.6)	69 (14.7)	651 (30.9)
Practice Patient Volume (NSCLC Patients Treated/Year), N (%)					
<50	4519 (31.3)	2957 (31.6)	804 (31.8)	144 (30.6)	614 (29.2)
50 - 99	5518 (38.2)	3638 (38.9)	1002 (39.7)	162 (34.4)	716 (34.0)
100 - 149	1135 (7.8)	742 (7.9)	196 (7.8)	42 (8.9)	155 (7.4)
150+	903 (6.2)	622 (6.6)	122 (4.8)	30 (6.4)	129 (6.1)
Not documented	2386 (16.5)	1400 (15.0)	403 (15.9)	93 (19.7)	490 (23.3)
Practice Physician Size, N (%)					
Small (0 - 5 physicians)	3124 (21.6)	1983 (21.2)	617 (24.4)	113 (24.0)	411 (19.5)
Medium (6 - 10 physicians)	6360 (44.0)	4222 (45.1)	1092 (43.2)	185 (39.3)	861 (40.9)
Large (>10 physicians)	2296 (15.9)	1590 (17.0)	346 (13.7)	70 (14.9)	290 (13.8)
Not documented	2681 (18.5)	1564 (16.7)	472 (18.7)	103 (21.9)	542 (25.8)
Practice Region, N (%)					
South	8852 (61.2)	5589 (59.7)	1654 (65.5)	275 (58.4)	1334 (63.4)
West	3088 (21.4)	2033 (21.7)	499 (19.7)	105 (22.3)	451 (21.4)
Midwest	1513 (10.5)	1043 (11.1)	219 (8.7)	48 (10.2)	203 (9.6)
Northeast	1008 (7.0)	694 (7.4)	155 (6.1)	43 (9.1)	116 (5.5)

ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; NSCLC, non-small cell lung cancer.

of the patients overall, and by histologic subtype. Most patients (64.7%) had non-squamous histology, consisting of 59.8% of patients (n = 8644) with adenocarcinoma. The median age at diagnosis was 69.3 years. Most patients were treated at medium-sized practices with six to ten physicians.

3.2. Testing Patterns

Less than half of patients overall and in all histology groups had documentation of EGFR testing (Table 2). The lowest proportion of patients tested for a EGFR

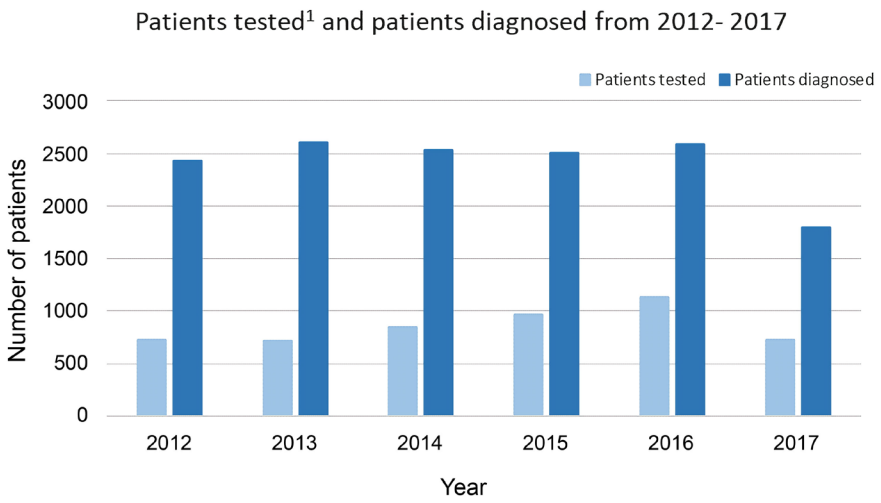
Table 2. Documented mutation testing and test results among patients with NSCLC for full study period, overall and by histologic type.

	Overall (N = 14,461)	Non-Squamous (N = 9,359)	Squamous (N = 2,527)	Unspecified Non-Small Cell Cancer (N = 471)	Not Documented (N = 2,104)
EGFR Status, N (%)					
Patients tested	5132 (35.5)	4456 (47.6)	358 (14.2)	120 (25.5)	198 (9.4)
Negative	4098 (79.9)	3500 (78.5)	330 (92.2)	111 (92.5)	157 (79.3)
Positive[1]	1016 (19.8)	938 (21.1)	28 (7.8)	9 (7.5)	41 (20.7)
Tested, but result unknown	18 (0.4)	18 (0.4)	0	0	0
No documented testing	9329 (64.5)	4903 (52.4)	2169 (85.8)	351 (74.5)	1906 (90.6)
ALK Status, N (%)					
Patients tested	4752 (32.9)	4121 (44.0)	337 (13.3)	119 (25.3)	175 (8.3)
Negative	4448 (93.6)	3849 (93.4)	322 (95.5)	111 (93.3)	166 (94.9)
Positive	204 (4.3)	189 (4.6)	8 (2.4)	1 (0.8)	6 (3.4)
Tested, but result unknown	100 (2.1)	83 (2.0)	7 (2.1)	7 (5.9)	3 (1.7)
No documented testing	9709 (67.1)	5238 (56.0)	2190 (86.7)	352 (74.7)	1929 (91.7)
ROS1 Status, N (%)					
Patients tested	820 (5.7)	712 (7.6)	91 (3.6)	15 (3.2)	2 (0.1)
Negative	797 (97.2)	690 (96.9)	91 (100.0)	14 (93.3)	2 (100.0)
Positive	23 (2.8)	22 (3.1)	0	1 (6.7)	0
No documented testing	13,641 (94.3)	8647 (92.4)	2436 (96.4)	456 (96.8)	2102 (99.9)
PD-L1 Status, N (%)					
Patients tested	831 (5.7)	673 (7.2)	135 (5.3)	19 (4.0)	4 (0.2)
Negative	487 (58.6)	402 (59.7)	78 (57.8)	7 (36.8)	0
Positive	344 (41.4)	271 (40.3)	57 (42.2)	12 (63.2)	4 (100.0)
No documented testing	13,630 (94.3)	8686 (92.8)	2392 (94.7)	452 (96.0)	2100 (99.8)
BRAF Status, N (%)					
Patients tested	16 (0.1)	15 (0.2)	0	1 (0.2)	0
Negative	13 (81.3)	13 (86.7)	0	0	0
Positive	3 (18.8)	2 (13.3)	0	1 (100.0)	0
No documented testing	14,445 (99.9)	9344 (99.8)	2527 (100.0)	470 (99.8)	2104 (100.0)

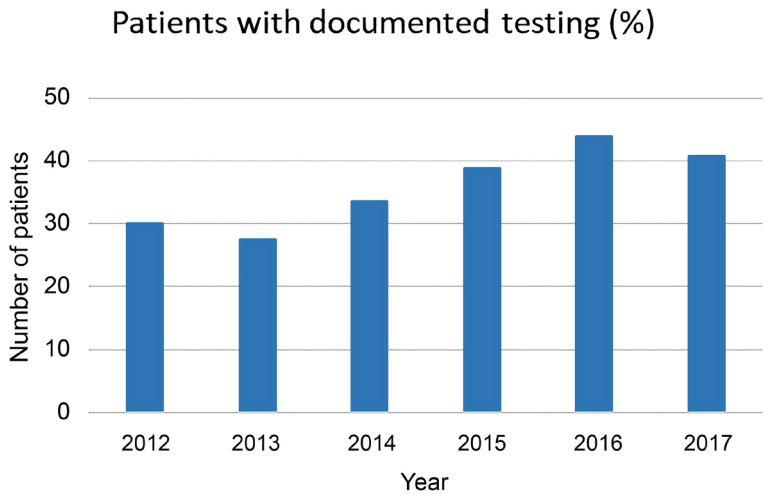
The denominator for the proportion of patients with negative/positive/result unknown mutation test results is the number of patients tested. Percentages may not add up to 100 due to rounding. [1]Information on whether mutation was sensitizing was provided if available in iKM. Positive results include EGFR-TKI sensitizing mutation (+) n = 511; EGFR-TKI non-sensitizing mutation (+) n = 67; T790M n = 39. ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; ROS1, c-ros oncogene 1.

mutation were those with squamous cell carcinoma (14.2%) or no documented histology (9.4%). Of those with documentation of EGFR mutation testing, 19.8% were positive, and those with non-squamous histology had the highest proportions of EGFR mutation positive patients (21.1%). Of those with and without documented EGFR mutation testing, 7.0% in the overall group were positive.

EGFR testing rates from diagnosis to the end of the study period were 35.5% overall, with an increase in rates observed over time: 30.0% in 2012 to 44.0% in 2016 ($p < 0.001$) (Figure 1(a), Figure 1(b)). Data for 2017 was only available for the partial year. During the 5-year study period, the proportion of patients tested for EGFR mutations was at its highest point in 2016. Among these patients tested in 2016, 19.4% tested positive (data not shown). Data on testing for



(a)



(b)

Figure 1. (a) Patients diagnosed and patients tested for EGFR mutations by year*. *Data for 2017 was a partial year; (b) proportion of patients with documented EGFR mutation testing by year*. Data are as documented in the EHR. Lack of documentation does not necessarily confirm that the patient was not tested. *Data for 2017 was a partial year. EGFR, epidermal growth factor receptor; EHR, electronic health record.

the EGFR T790M mutation specifically in the EHR were available for 2016 and 2017 only (data not shown). Of the known EGFR mutation-positive patients, 9.5% and 10.8% were tested for EGFR T790M in 2016 and 2017 respectively.

Similarly, 32.9% of patients overall had documentation of ALK status testing. Of those with documented mutation testing, few had an ALK-positive status (4.3% overall).

ROS1 or PD-L1 status testing was documented during the study period in 5.7% of patients. Among those who did, most were negative for a ROS1 mutation (97.2%) and PD-L1 expression (58.6%). BRAF testing was conducted in 0.1% of patients. Testing would not have been performed for these biomarkers during the earlier years of this study when these tests were not yet available or actionable.

3.3. Predictors of Testing

In a multivariate logistic regression analysis, several parameters were strongly associated with higher documented EGFR mutation testing rates (Table 3). Patients with a non-squamous histology (including adenocarcinoma and bronchioalveolar) were more likely to have been tested for EGFR compared with patients with a squamous histology ($p < 0.0001$). The likelihood of being tested increased with more recent diagnoses, increasing by 2.8-fold from 2013 to 2017 ($p < 0.0001$). A larger practice size ($p = 0.0097$) and volume (<50 patients versus ≥ 50 patients; $p < 0.0001$) were also associated with higher documented testing rates, as were nonsmoking status (former or never) compared with current smokers ($p < 0.0001$), being female ($p = 0.005$), and practice region ($p = 0.013$). Race had no effect on documented EGFR testing rates.

A similar analysis was performed for documented ALK mutation testing rates with comparable results observed (Table 4). Factors associated with having documented ALK testing included adenocarcinoma and bronchioalveolar histologies

Table 3. Multivariable model examining associations between patient and practice level characteristics and documented EGFR mutation testing.

	Characteristic	Total	Odds Ratio (95% CI)	p-Value
Age	Per year increase	8423	0.99 (0.99 - 0.99)	**<0.0001**
Histology	Squamous (reference)	1721	.	**<0.0001**
	Adenocarcinoma	5930	5.05 (4.38 - 5.82)	
	Other	523	1.52 (1.19 - 1.94)	
	Adenosquamous	178	3.55 (2.53 - 4.99)	
	Bronchioloalveolar carcinoma	71	5.56 (3.36 - 9.22)	
Practice Region	South (reference)	5288	.	**0.0013**
	West	1767	0.95 (0.84 - 1.07)	
	Midwest	880	1.33 (1.13 - 1.57)	
	Northeast	488	0.93 (0.75 - 1.15)	

Continued

Practice size	Small (reference)	2327	.	**0.0097**
	Medium	4465	1.135 (1.00 - 1.29)	
	Large	1631	1.33 (1.11 - 1.60)	
Practice Volume	<50 (reference)	2994	.	**<0.0001**
	50 - 99	4007	0.80 (0.71 - 0.91)	
	100 - 149	824	0.94 (0.77 - 1.15)	
	150+	598	0.60 (0.41 - 0.75)	
Smoking Status	Current (reference)	1631	.	**<0.0001**
	Former	5439	1.35 (1.19 - 1.53)	
	Never	1353	2.00 (1.70 - 2.36)	
Sex	Male (reference)	4402	.	**0.0005**
	Female	4021	1.19 (1.08 - 1.30)	
Race	White (reference)	7345	.	0.0769
	Black	700	0.97 (0.82 - 1.16)	
	Asian	266	1.30 (0.99 - 1.72)	
	Other	112	1.47 (0.97 - 2.22)	
Year of Diagnosis	2012 (reference)	952	.	**<0.0001**
	2013	1403	1.34 (1.11 - 1.63)	
	2014	1479	1.86 (1.54 - 2.24)	
	2015	1579	2.56 (2.13 - 3.08)	
	2016	1663	3.10 (2.57 - 3.72)	
	2017	1347	3.77 (3.11 - 4.56)	

Table 4. Multivariable model examining associations between patient and practice level characteristics and documented ALK mutation testing.

	Characteristic	Total	Odds Ratio (95% CI)	p-Value
Age	Per year increase	8423	0.99 (0.98 - 0.99)	**<0.0001**
Histology	Squamous (reference)	1721	.	**<0.0001**
	Adenocarcinoma	5930	4.78 (4.13 - 5.52)	
	Other	523	1.58 (1.23 - 2.02)	
	Adenosquamous	178	3.84 (2.73 - 5.41)	
	Bronchioloalveolar carcinoma	71	4.53 (2.73 - 7.50)	
Practice Region	South (reference)	5288	.	**0.0009**
	West	1767	0.98 (0.87 - 1.11)	
	Midwest	880	1.36 (1.16 - 1.60)	
	Northeast	488	0.92 (0.74 - 1.14)	
Practice Size	Small (reference)	2327	.	**0.035**
	Medium	4465	1.11 (0.98 - 1.25)	
	Large	1631	1.28 (1.06 - 1.54)	

Continued

Practice Volume	<50 (reference)	2994	.	**<0.0001**
	50 - 99	4007	0.87 (0.77 - 0.99)	
	100 - 149	824	1.09 (0.89 - 1.33)	
	150+	598	0.50 (0.39 - 0.63)	
Smoking Status	Current (reference)	1631	.	**<0.0001**
	Former	5439	1.29 (1.13 - 1.46)	
	Never	1353	1.63 (1.38 - 1.91)	
Gender	Male (reference)	4402	.	0.0522
	Female	4021	1.10 (0.99 - 1.21)	
Year of Diagnosis	2012 (reference)	952	.	**<0.0001**
	2013	1403	1.26 (1.03 - 1.53)	
	2014	1479	1.80 (1.48 - 2.18)	
	2015	1579	2.50 (2.07 - 3.02)	
	2016	1663	3.27 (2.71 - 3.95)	
	2017	1347	4.22 (3.47 - 5.13)	

($p < 0.0001$), nonsmoking status ($p < 0.0001$), and practice size ($p = 0.035$), volume ($p < 0.0001$), and region ($p = 0.0009$). The likelihood of testing again increased with more recent diagnoses: those diagnosed in 2017 were 3.3 times more likely to have had ALK testing as those diagnosed in 2013 ($p < 0.0001$). Unlike EGFR mutation testing rates, gender had no significant association with documented ALK mutation testing rates.

Testing rates for other biomarkers were low, therefore a predictive modelling was not performed.

4. Discussion

Although clinical practice guidelines recommend biomarker testing in all NSCLC patients, little is known about actual testing rates in the real-world setting, particularly in community settings. In our study, testing rates for EGFR mutations specifically were 35% overall, with an increase observed over time from 30% in 2012 to 41% in 2016. The testing rate for ALK rearrangements was 33% overall.

It was not unreasonable that testing rates for the other actionable biomarkers in our study were low, given the timeframe of this study in relation to the approval of other targeted therapies for ROS1, BRAF, and PD-L1. This study evaluated testing in the years between 2012 and 2017. PD-L1 inhibitors for the treatment of NSCLC became available in 2015, and the recommendations for PD-L1 testing have changed over time. Similarly, targeted therapy for the treatment of ROS1-positive NSCLC and BRAF-positive NSCLC became available in 2016 and 2017, respectively. Also, *NTRK* gene fusion testing was not included in

this study as this test was added to the guidelines after the study was completed. However, biomarker testing remains important in the management of advanced NSCLC to identify patients eligible for targeted therapies which may improve their outcomes.

In one study by McKeage *et al.*, the real-world uptake of EGFR mutation testing was assessed during the implementation of updated testing guidelines in a registry cohort from New Zealand. From 2010 to 2014, 1857 non-squamous NSCLC patients were identified as being eligible for EGFR testing [18]. Testing occurred in 27% of patients. Testing rates increased during the study period from <5% to 67% of patients ($p < 0.0001$). It was demonstrated that testing for EGFR mutations was associated with increased survival (adjusted hazard ratio = 0.76 [95% CI 0.65 - 0.89]; log-rank $p < 0.0001$), which was thought to be driven by longer survival in the EGFR mutation-positive patients receiving targeted therapy. This reinforces the need for testing in the NSCLC population to determine which patients are candidates for targeted therapies.

Reasons for not performing EGFR mutation testing in the McKeage study included a lack of availability of specimens. This may likely have also played a role in the present study. Surgery- or biopsy-obtained tumor tissue may not always be available, and testing may be a challenge if samples are small. Additionally, performing invasive procedures may pose a risk for some patients. It has been reported that 20% - 30% of patients are not able to provide tumor samples at diagnosis [19]. Therefore, other methods such as using circulating free tumor-derived DNA from plasma have been tested. Additionally, the use of large-scale sequencing strategies, such as next-generation sequencing, allows for the detection of multiple molecular targets simultaneously. Targeted educational interventions are needed regarding how and when biomarker testing should be performed to optimize and support personalized treatment for NSCLC. We observed that non-squamous histology, larger practice size, and nonsmoking status were strongly associated with higher documented EGFR mutation testing rates in our study. This mutation is often found in nonsmoking women from East Asian decent with non-squamous histology [2]. Increased knowledge and education regarding patient and clinical characteristics associated with specific gene alterations may also improve testing rates.

One study reported an increase in EGFR testing after implementation of reflex testing, defined as a request for EGFR testing by the pathologist at the time of non-squamous NSCLC diagnosis [20]. From 2010 to 2014, of 2214 patients from seven centers in Canada that had EGFR testing, 1330 patients were tested before implementation of reflex testing and 884 patients were tested after. During this time, the proportion of pathologists requesting mutation testing increased from 4% to 53%, whereas the proportion of mutation testing requested by medical oncologists decreased from 95% to 46% ($p < 0.001$). There was a significant increase in the number of patients tested per center per month ($p < 0.001$). Thus, it was observed that reflex testing could help increase awareness and reduce bar-

riers to testing.

Testing data for EGFR T790M in this study was only available for 2016 and 2017, reflecting the approval timing for the EGFR T790M mutation test. The testing rate overall was low, with less than 10% of known EGFR mutation-positive patients receiving testing for EGFR T790M during the study period. With the recent availability of additional targeted therapy options, including third-generation EGFR-TKIs such as osimertinib, in patients who develop resistance following first- and second-generation EGFR-TKIs, increased awareness of new treatment options will help support ongoing personalized therapy in advanced NSCLC.

In our study, 33% of patients received ALK status testing. Lower testing rates have been reported in other studies with newly diagnosed advanced NSCLC; ALK status was tested in 18% of patients in the international PIvOTAL observational study (n = 1440) [21] and in 17% of patients in a retrospective Japanese study (n = 175) [22]. The other biomarkers tested in this study have more recently been added to the advanced NSCLC guidelines so there are few studies analyzing testing rates to compare with our data. The recommended timing for when to conduct biomarker testing in NSCLC has also evolved over the years. At the time that this study was performed, biomarker testing was recommended for all patients with Stage IV NSCLC. Improved understanding and better dissemination of updates to guideline recommendations for testing timing and methods may also improve testing rates overall.

Limitations of this study include the retrospective observational nature of the study with data extracted from a database, and the potential for under-reported testing. Availability of biomarker testing required that results were directly entered into the specific structured EHR fields. Results available through scanned documents or progress notes may not have been entered into the specific fields in the EHR, and therefore reasons for not testing could not be investigated. The low rate of EGFR mutation testing (35%) was likely a consequence of this structured data extraction methodology, as well as a general lack of documentation. Also, biomarker testing rates were captured when some therapies were not approved, thereby impacting what biomarkers were actionable for documentation as structured data in the EHR. Furthermore, at the time of the study, osimertinib was not approved as first-line treatment for EGFR mutated NSCLC patients which may have an impact on translating these data to current practice. Strengths of this study include the large sample size of over 14,000 advanced NSCLC patients evaluated in community oncology practices across the US, reflecting real-world community practice and testing patterns.

5. Conclusion

Between 2012 and 2016, EGFR mutation testing rates steadily increased over time in patients with Stage IV NSCLC but remained less than 50%. Testing rates for ALK, ROS1, PD-L1, and BRAF were lower, ranging from <1% to 33%. Our data, therefore, suggest that opportunities exist to improve biomarker testing

uptake and education in advanced NSCLC in the real world. The reasons for not testing should be identified to understand actions needed to improve biomarker testing rates.

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Conflicts of Interest

Eric Nadler reports a consulting or advisory role for Merck, and participation in speakers' bureau for Merck, Genentech, and AstraZeneca. Janet Espirito and Jamyia Clark are McKesson employees and shareholders. Melissa Pavilack is an AstraZeneca employee. Ancilla Fernandes is an AstraZeneca employee and shareholder. All authors critically reviewed the manuscript and approved the final version for submission.

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