Published in final edited form as:

J Clin Pathw. 2018 ; 4(1): 49–54. doi:10.25270/jcp.2018.02.00001.

Patterns of Biomarker Testing Rates and Appropriate Use of Targeted Therapy in the First-Line, Metastatic Non-Small Cell Lung Cancer Treatment Setting

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Abstract

Despite clear clinical benefit and guideline recommendations for predictive biomarker testing and subsequent first-line targeted therapy treatment in patients with non-small cell lung cancer (NSCLC), there is evidence that testing has not been widely embraced in the clinical setting.

This study uses clinical pathways to understand biomarker testing patterns and ensuing first-line treatment decisions. Data of patients with metastatic NSCLC were analyzed for testing rates and treatment selection at 7 cancer programs using data input by providers into the pathways software. Findings were analyzed by type of provider (community or academic). Among providers using clinical pathways, biomarker testing rates were high and appropriate selection of targeted therapy was observed. Clinical pathways can act as a tool to assist oncology practices to promote testing of key biomarkers and subsequent selection of appropriate therapy.

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Disclosures:

Research support provided by Via Oncology, LLC. The opinions expressed by the authors contributing to this article submission do not necessarily reflect the opinions of the institutions with which the authors are affiliated. This work was previously presented at the 2017 American Society of Clinical Oncology Annual Meeting.

Keywords

biomarker testing; non-small cell lung cancer; clinical pathways; targeted therapy

In 2017, lung and bronchus cancer was the second-most common cancer type in the United States, representing 13% of all new cancer cases.¹ Of the estimated 222,550 lung and bronchus cancer cases diagnosed in 2017, approximately 80% to 85% were non-small cell lung cancer (NSCLC).^{1,2} The vast majority of patients with NSCLC are diagnosed in the metastatic stage.¹

While advancements in chemotherapy regimens have improved the overall survival rate in the past 3 decades, the 5-year, overall survival rate remains low (~17%).^{1,3} Advancements in diagnosis and treatment of NSCLC are critical to improving survival. The recent identification of some of the driver mutations for NSCLC has allowed for more individualized targeted treatment options as compared with traditional cytotoxic chemotherapies. As a result, it is now a standard recommendation that patients with advanced NSCLC undergo routine molecular testing for identification of certain known genomic abnormalities, most notably, rearrangements of *anaplastic lymphoma kinase (ALK)* and mutations of *epidermal growth factor receptor (EGFR)*.^{4,5} Tyrosine kinase inhibitors (TKIs) that target these abnormalities have provided greater clinical benefit with improved survival compared with cytotoxic treatments in patients with NSCLC. For instance, patients with NSCLC with somatic mutations in *EGFR* are demonstrated to have improved progression-free survival when treated with EGFR-targeted therapies compared with platinum-based chemotherapy.⁶⁻⁹ Similar results have been noted with treatments that target ALK and/or c-ros oncogene 1 (ROS1) rearrangements in patients with NSCLC bearing these molecular abnormalities.^{8,10-12} More recently, patients with NSCLC and bearing the *BRAF* V600 mutation have demonstrated clinical response to BRAF/MEK inhibitor therapy.¹³

In patients lacking these specific genomic abnormalities or in those who have progression after treatment with targeted therapy, expression of programmed death ligand 1 (PD-L1) may provide guidance regarding the use of immune checkpoint inhibitors that have provided major treatment responses across numerous cancer types, including NSCLC.¹⁴⁻¹⁶ PD-L1 expression does not have a universal standard, making it a less-than-ideal biomarker, but it is currently the best available method with which to assess a patient with NSCLC's candidacy for treatment with pembrolizumab. Use of single-agent pembrolizumab in the first-line, NSCLC metastatic setting requires PD-L1 expression levels of 50% or more.¹⁴

The availability of treatments that specifically target genetic alterations leading to superior outcomes has led to the issuance of guidelines by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommending testing for *EGFR* and *ALK* mutations and/or translocations at diagnosis of advanced stage NSCLC. Furthermore, the guidelines state that testing for alterations in *EGFR* and *ALK* should be prioritized over other molecular predictive tests.⁴ Additionally, the National Comprehensive Cancer Network® (NCCN) strongly recommends that patients with metastatic NSCLC undergo molecular testing for *EGFR* or *ALK* alterations and, if positive, receive targeted therapy in the first-line setting. The NCCN also

recommends testing for *ROS1* and *BRAF* as part of broad molecular profiling, in addition to PD-L1 expression levels, to guide first-line treatment decisions.

A recent international survey of oncologists assessed the degree to which a patient with NSCLC's genetic makeup impacted first-line treatment decisions by providers. The majority (60%) of oncologists in North America did not base their treatment decision on a patient's genetic mutation subtype. Despite ordering mutation tests, 21% of North American-based oncologists determined the treatment regimen for their patients before the mutation test results were available. Overall, 23% of respondents did not consider *EGFR* mutation subtypes in making treatment decisions.¹⁸ An analysis of real-world patterns of *EGFR* testing and treatment based on a random sample of patients with NSCLC in the Surveillance Epidemiology and End Results (SEER) data base found that less than a quarter of the stage IV, adenocarcinoma patients received *EGFR* testing, and less than half with stage IV, *EGFR*-positive disease received targeted therapy.¹⁹ A separate study examining PD-L1 testing patterns and nivolumab and pembrolizumab use for all lines of metastatic NSCLC treatment found that, prior to receiving either nivolumab or pembrolizumab, 11.3% of patients were tested for PD-L1 expression.²⁰

Despite clear evidence of the clinical benefits associated with molecular testing and the universal recommendations calling for molecular testing to guide treatment decisions, it is apparent that resources and processes are urgently needed to ensure appropriate implementation of molecular testing in the NSCLC-treatment setting.

One strategy to promote testing of actionable biomarkers and appropriate use of targeted agents is through the use of clinical pathways. Clinical pathways have been adopted in various fields of medicine, including congestive heart failure, pneumonia, chronic obstructive pulmonary disease, stroke, asthma, and deep vein thrombosis.^{21–26} A recent study in breast cancer demonstrated that clinical pathways have the ability to standardize clinical practice patterns and rapidly promote change consistent with current evidence-based guidelines.²⁷ Another breast cancer study demonstrated that clinical pathways can be used to measure adoption of diagnostic testing and the use of appropriate therapy based on the results of diagnostic testing.²⁸

In order to explore the ability of clinical pathways to promote testing of key biomarkers and subsequent appropriate use of targeted agents as treatment in patients with metastatic NSCLC, authors performed a retrospective data analysis to compare biomarker testing rates with treatment decisions at academic and community cancer programs utilizing the Via Oncology clinical pathways software program, the Via Portal.

Methods

Protected health information was not reviewed or exchanged as part of this analysis. Institutional Review Board approval was not required. The study took place from January 1, 2017 through March 31, 2017, at the following 7 cancer programs: Aurora Health Care, The Center for Cancer and Blood Disorders, City of Hope, Tennessee Oncology, Oregon Health & Science University, The University of Chicago Medicine, and UPMC Hillman Cancer

Center. Three of these cancer programs, Aurora Health Care, The Center for Cancer and Blood Disorders, and Tennessee Oncology, identify themselves as community centers whereas the others include both community and academic practitioners. Designation of a provider as an academic or community practitioner was provided by the individual cancer centers.

These cancer programs utilized the Via Portal, a patient specific, point-of-care decision support software through which providers access evidence-based clinical pathways known as Via Pathways. Providers navigate the disease-specific decision support in their daily practice through the web-based pathway platform. Providers are prompted to input data on biomarker mutation, rearrangement, and translocation expression.

Clinicians provided the status of *EGFR*, *ALK*, and *ROS1* expression for patients presenting with nonsquamous NSCLC during the entire analysis period from January 1, 2017 through March 31, 2017. *BRAF* mutation status was not collected because at the time of the analysis there were no targeted therapies approved for patients with this mutation. Clinicians provided the status of PD-L1 expression for both nonsquamous and squamous presentations during a portion of the analysis period from January 13, 2017 through March 31, 2017. PD-L1 status was collected for a shorter period of time because PD-L1 inhibitors had only recently been approved for first-line use (October 2016) and added to the pathway in January 2017.

Data were extracted from the pathway platform. A retrospective review of de-identified data for patients with metastatic NSCLC preparing to receive first-line treatment from January 2017 through March 2017 was performed.

Recorded responses were used to compare biomarker testing rates. Results were analyzed in total and subsequently by type of provider (ie, community providers vs academic providers who specialize in lung cancer) to determine if the testing rates remained consistent across providers in different settings who use the clinical pathways program. A 2-sided Fisher's exact test was used to test for statistical significance. A *P*-value of .05 was considered statistically significant.

Results

Provider decisions were made for 379 unique patients. Within this population, 304 decisions were made for patients with nonsquamous disease (253 decisions by community providers and 51 decisions by academic providers) while the remaining decisions were for patients with squamous disease (85 decisions by community providers and 7 decisions by academic providers).

A provider may make multiple decisions for a patient within the pathways program for the same line of therapy if a patient is unable to start a treatment due to insurance issues, needs to change treatment based on the results of a biomarker test, is unable ultimately to accrue to a clinical trial that was selected, is unable to travel to the clinic on the required schedule, and so on. A total of 396 first-line treatment decisions for patients with metastatic NSCLC were included in the final analysis, 338 from community providers and 58 from academic

providers. Throughout this article, all n values refer to the number of treatment decisions unless otherwise noted.

Fifty-eight decisions were made at Aurora Health Care, 36 at City of Hope, 26 at Oregon Health & Science University, 61 at Tennessee Oncology, 41 at The Center for Cancer and Blood Disorders, 21 at The University of Chicago Medicine, and 153 at UPMC Hillman Cancer Center.

The rates of biomarker testing are depicted in Table 1. Testing rates for *ALK*, *EGFR*, and *ROS1* were 94% (n = 285), 95% (n = 288), and 88% (n = 267), respectively, in the overall nonsquamous NSCLC population (N = 304) and ranged from 85% to 100% within the academic and community settings.

Testing data for PD-L1 was available for 327 decisions for patients with nonsquamous and squamous NSCLC. Data was unavailable for 69 decisions: 13 decisions in the academic setting, 56 decisions in the community setting. The PD-L1 testing rates were lower than that observed for the other biomarkers, with an overall testing rate of 57% (n = 187) (62% (n = 28) vs 56% (n = 159) in the academic and community settings, respectively. A statistically significant difference was observed between the *ROS1* testing rates of academic and community providers ($P = .0015$). No significant differences in testing rates for *ALK*, *EGFR*, and PD-L1 were found between academic and community providers.

The 396 first-line treatment decisions for patients presenting with and without actionable biomarkers were analyzed (Table 2). Of the patients presenting with an actionable *ALK*, *EGFR*, or *ROS1* mutation, 96.8% (n = 61) were prescribed an appropriate targeted therapy, and the remaining 3.2% (n = 2) were referred to a clinical trial. For some patient decisions, providers indicated patients had positive results for multiple tests. There were 7 decisions for patients with a PD-L1 expression of 1%–49% who were also *EGFR* sensitizing and 1 decision for a patient with a PD-L1 expression of 1%–49% TPS who was also *ALK* positive. There were 3 decisions for patients with a PD-L1 expression of 50% TPS who were also *EGFR* sensitizing and 1 decision for a patient with a PD-L1 expression of 50% TPS who was also *ALK* positive. For these decisions, providers documented that the patients were to receive TKIs.

Among decisions where providers documented that the patient had a PD-L1 expression of 1%–49% TPS (52 total), chemotherapy was selected in 65.4% (n = 34) of decisions and immunotherapy was selected in 9.6% (n = 5) of decisions. Among decisions where providers documented that the patient had a PD-L1 expression of 50% TPS (62 total), immunotherapy was selected in 87.1% (n = 54) of decisions. The overall treatment trends remained consistent when analyzed by academic vs community settings (data not shown).

Discussion

This retrospective analysis of data from academic and community cancer centers employing clinical pathways demonstrates high rates of molecular testing and appropriate first-line treatment decisions based on biomarker expression. Identification of these known actionable mutations upon diagnosis of metastatic NSCLC drove appropriate selection of optimal first-

line therapy. The results from this analysis support the use of clinical pathways to address some of these challenges.

In our current study, overall testing rates for patients in both settings for *ALK*, *EGFR*, and *ROS1* were 94% (n = 285), 95% (n = 288), and 88% (n = 267), respectively, for treatment decisions (N = 304) in the nonsquamous NSCLC population. Rates ranged from 85% to 100% within the academic and community settings. The overall testing rate for PD-L1 when the data was available (n = 327) was 57% in the first-line setting regardless of histology. While a statistically significant difference was observed between the *ROS1* testing rates of academic and community providers ($P = .0015$), no significant differences ($P > .05$) in testing rates for *ALK*, *EGFR*, and PD-L1 were found between academic and community providers. These findings largely aligned with the authors' hypothesis that similar practice patterns would be observed across academic and community providers utilizing a clinical pathways decision support software program.

It should be noted that routine testing for biomarker expression was not mandatory within the clinical pathway used in this study, and clinicians could also have chosen to use a therapy not recommended by the pathway. However, the compliance rates reported demonstrate that using clinical pathways to prompt clinicians for biomarker testing results and providing them with literature-supported treatment options may be an effective mechanism for increasing adherence to appropriate treatment and diagnostic guidelines. In this study, clinical pathways provided consistent rates of biomarker testing and appropriate first-line therapy regardless of the treatment setting, with consistently high rates of best practices being followed in both academic and community treatment centers.

This study also demonstrates that providers selected the appropriate targeted therapies for patients based on their test results. Providers were more likely to select an immunotherapy if the patient had a PD-L1 expression of 50% and more frequently selected chemotherapy for patients with lower levels of expression, indicating that the level of expression may have factored into their decision-making process as well. However, it should be noted that this study relied on data reported by providers into the Via Portal and did not compare these data with actual medical record data to confirm accuracy.

A limitation of this study is the lack of baseline data of testing rates and appropriate treatment selection based on biomarker results prior to implementation of the clinical pathways at the sites evaluated. However, these rates can be compared to the average testing rates of various other sites. A review of 15 community oncology cancer centers showed biomarker testing of *ALK*, *EGFR*, and *ROS1* at 69%, 65%, and 25%, respectively, over a two-year period ending in 2015.²⁹ A separate analysis from the Montefiore Medical Center showed testing rates of *ALK* and *EGFR* at 62% and 23%, respectively, from 2009 to 2013.³⁰ A 5-year analysis demonstrated very low (~11%) testing rates for PD-L1 in 2016, but authors noted that rates of testing markedly increased following US Food and Drug Administration-approval of nivolumab and pembrolizumab.²⁰ Similar results have been noted in academic centers. In a 3-year retrospective review of patients with advanced NSCLC seen at Princess Margaret Cancer Centre in 2013, 72% were tested for expression of molecular alterations, but only 21% of patients had biomarker results available at their initial

oncology consultation. This delay in biomarker testing led to inappropriate treatment decisions, with 19% of patients with activating *EGFR* or *ALK* mutations initiating chemotherapy prior to their biomarker results availability.³¹ The authors recognize that none of these studies are contemporaneous with our data, limiting comparisons.

Another limitation of this study is the number of academic provider decisions that were included in the analysis. There were many more decisions in the community provider group which may limit the generalizability of the results. A larger sample size of academic providers may make these results more generalizable.

Conclusion

The rapidly changing recommendations and increasing knowledge of various actionable biomarkers in cancer care are significant challenges for providers. This study demonstrates high adherence to recommended biomarker testing in the metastatic NSCLC setting and appropriate selection of targeted agents. Clinical pathways can act as a tool to assist oncology practices to promote testing of key biomarkers and subsequent selection of appropriate therapy, lending to standardization of care, quality assurance measurements, and optimal management of patients with NSCLC.

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Table 1.

Rates of Biomarker Testing Prior to Therapy in Patients with Metastatic NSCLC by Treatment Setting

Nonsquamous NSCLC	Decisions in Academic Setting (n = 51)	Decisions in Community Setting (n = 253)	Total # of Decisions (N = 304)
ALK Test Status			
Awaiting test results	6	74	80
Did not order test	0	19	19
Negative	42	157	199
Positive	3	3	6
ALK testing rate, n (%)	51 (100)	234 (92)	285 (94)
EGFR Test Status			
Awaiting test results	6	76	82
Did not order test	0	16	16
Negative/wild type	19	100	119
Non-sensitizing	7	27	34
Sensitizing	19	34	53
EGFR testing rate, n (%)	51 (100)	237 (94)	288 (95)
ROS1 Test Status			
Awaiting test results	6	72	78
Did not order test	0	37	37
Negative	43	142	185
Positive	2	2	4
ROS1 testing rate, n (%)	51 (100) ^a	216 (85) ^a	267 (88)
Nonsquamous and Squamous NSCLC	Decisions in Academic Setting (n = 45)	Decisions in Community Setting (n = 282)	Total # of Decisions (N = 327)^b
PD-L1 Test Status			
Negative	15	57	72
Positive (≥ 50% TPS)	8	55	63
Positive (1%–49% TPS)	5	47	52
Did not order test	17	123	140
PD-L1 testing rate, n (%)	28 (62)	159 (56)	187 (57)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

^a*P* = .0015 for academic vs community settings.

^b Testing data for PD-L1 was not gathered in the first-line setting for part of the analysis period. Data for 69 decisions total (13 in the academic setting, 56 in the community setting) were excluded from the testing rate analysis.

Table 2.

First-Line Treatment Decisions (N = 396) by Patient Presentation for Patients With Metastatic NSCLC

Patient Presentation	# of Chemotherapy Decisions	# of Clinical Trial Decisions	# of TKI Decisions	# of Immunotherapy +/- Chemotherapy ^a Decisions
<i>ALK</i> positive ^b	0 (0)	0 (0)	6 (100%)	0 (0)
<i>EGFR</i> sensitizing ^b	0 (0)	2 (3.8)	51 (96.2%)	0 (0)
<i>ROS1</i> positive	0 (0)	0 (0)	4 (100%)	0 (0)
PD-L1 1–49% TPS ^b	34 (65.4%)	4 (7.7%)	9 (17.3%)	5 (9.6)
PD-L1 ≥50% TPS ^b	3 (4.8%)	1 (1.6%)	4 (6.5%)	54 (87.1)
No actionable biomarker	198 (85.7%)	15 (6.5%)	1 (0.4%)	17 (7.4)
Total	235 (57.6%)	22 (5.4%)	75 (18.4%)	76 (18.6%)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TPS, tumor proportion score; TKI, tyrosine kinase inhibitor.

^aOne decision was for combination immunotherapy plus chemotherapy (ie, pembrolizumab, pemetrexed, and carboplatin); all others were for single-agent immunotherapy regimens.

^bSome patients are counted in under multiple patient presentations. Of those with a PD-L1 expression of 1%–49% TPS, 7 were also *EGFR* sensitizing and 1 was *ALK* positive. Of those with a PD-L1 expression of ≥50% TPS, 3 were also *EGFR* sensitizing and one was *ALK* positive. For these patients, providers documented that the patient was to receive a TKI.