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Unterstanding Factors Associated With Anaplastic Lymphoma Kinase Testing Delays in Patients With Non–Small Cell Lung Cancer in a Large Real-World Oncology Database

Eric H. Bernicker, MD; Yan Xiao, MD, PhD; Denise A. Croix, PhD; Baiyu Yang, PhD; Anup Abraham, MPH; Stella Redpath, PhD; Julia Engstrom-Melnyk, PhD; Roma Shah, MPH; Timothy Craig Allen, MD, JD

Context.—With multiple therapeutic options available for patients with advanced non–small cell lung cancer, the timely ordering and return of results to determine therapy are of critical importance.

Objective.—To assess factors impacting anaplastic lymphoma kinase (ALK) test ordering and time to result delivery.

Design.—A retrospective study using a de-identified electronic health record database was performed. Post-diagnosis ALK tests (n = 14,657) were analyzed from 14,197 patients with advanced non–small cell lung cancer diagnosed between January 2015 and May 2019. Time from non–small cell lung cancer diagnosis to ALK sample receipt in the laboratory was a surrogate for test ordering time. Time ordering was considered delayed if order time was more than 20 days. Turnaround time from sample received to test result was calculated and considered delayed if more than 10 days. Multivariable logistic regression was used to assess factors associated with order time and turnaround time delays.

Results.—Median ALK test order time was 15 days, and 36.4% (5,342) of all 14,657 orders were delayed. Factors associated with delays were non–fluorescent in situ hybridization testing, send-out laboratories, testing prior to 2018, nonadenocarcinoma histology, and smoking history. Median turnaround time was 9 days, and 40.3% (5,906) of all 14,657 test results were delayed. Non–fluorescent in situ hybridization testing, tissue sample, and orders combining ALK with other biomarkers were associated with delayed ALK result reporting.

Conclusions.—This study provides a snapshot of real-world ALK test ordering and reporting time in US community practices. Multiple factors impacted both test ordering time and return of results, revealing opportunities for improvement. It is imperative that patients eligible for targeted therapy be identified in a timely fashion.

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The identification of driver alterations that can be targeted with oral tyrosine kinase inhibitors has transformed the care of patients with advanced lung cancer. However, treating patients appropriately is contingent on the timely and accurate identification of the tumor’s mutation profile. Often, patients with lung cancer have very small biopsies or significant comorbid conditions that complicate full genomic profiling. Because targeted therapies have superior response rates over chemotherapy in patients with driver alterations and because immunotherapies often have lower response rates in this population as well, it is essential that actionable mutations (such as epidermal growth factor receptor [EGFR] or gene translocations/fusions (such as ALK or c-ros oncogene 1 [ROS-1]) be identified up front upon diagnosis if patients are to receive the highest quality care.\(^1,2\)

ALK gene translocations/fusions are highly actionable targets that are exquisitely sensitive to treatment with specific ALK inhibitors. They often—but not always—are in patients with light or no smoking history with an adenocarcinoma histology.\(^3\) Along with EGFR-mutated adenocarcinoma, ALK translocation–positive lung cancer...
became a paradigmatic example of rapid and rational drug development for patients with advanced disease, as well as highlighting the need for repeat biopsy upon development of acquired resistance.4

This study was designed to examine test ordering and turnaround time (TAT) for ALK gene translocation/rearrangement/fusion testing. A large cohort of patients with known ALK testing was studied to determine length of time for ALK testing to be ordered, the TAT of the testing, and the factors affecting these times. The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines in place during the majority of this study period suggested a TAT of 10 working days from sample receipt to test reporting (for stage IV patients) as reasonable for allowing the oncologist and patient adequate time to acquire the necessary results to make an informed treatment decision.5

METHODS

Study Design and Data Source

This retrospective observational study used Flatiron Health’s nationwide longitudinal, de-identified database derived from electronic health record (EHR) data from approximately 280 US cancer clinics (approximately 800 sites of care). The Flatiron Health database is composed of de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction6,7 and the majority of patients in the database originate from community oncology settings; relative community to academic proportions may vary depending on study cohort. Institutional review board approval of the study protocol was obtained prior to study conduct, and included a waiver of informed consent.

Study Population

Patients with advanced non–small cell lung cancer (NSCLC) (stage IIIB, IIIC, or IV by American Joint Committee on Cancer 7th edition guidelines9) diagnosed from January 2015 to May 31, 2019 (based on the latest data available at the time of this analysis) and receiving an ALK test following NSCLC diagnosis (including up to 14 days before) were included for this analysis. Patients were excluded for the following reasons: missing sample type or smoking status, the first postdiagnosis ALK specimen was received more than 90 days after the date of NSCLC diagnosis, or the ALK test result was received more than 45 days after the sample was received. A patient may have had multiple first postdiagnosis ALK tests performed if specimens were submitted for testing concurrently on different platforms (eg, fluorescent in situ hybridization [FISH] and next-generation sequencing [NGS] ALK tests).

Definitions

In order to understand factors that might impact testing timeliness, we divided testing into 2 distinct periods: the time to test order and time to reporting of results. The following definitions were used in our study. The NSCLC diagnosis date was the date of the first pathology/cytology procedure that confirmed the diagnosis of invasive carcinoma in a lung specimen. The ALK test sample receipt date served as a surrogate for test order date in this analysis. For the purposes of this analysis, we defined a delayed ALK test order as receipt of the ALK test specimen greater than 20 days after NSCLC diagnosis, and a delayed ALK TAT as an ALK test result reported greater than 10 days after sample receipt.

Test methods for ALK were captured in the EHR as FISH, immunohistochemistry (IHC), NGS, or others. The category of others included polymerase chain reaction, sequencing other than NGS, or unknown testing method. We also assessed the type of specimen used for testing (blood versus tissue).

Combination orders indicated that specimens were received for other biomarker testing on the same date of the first ALK test order.

RESULTS

Patient Characteristics

A total of 14 657 postdiagnosis ALK tests from 14 197 NSCLC patients diagnosed from January 2015 to May 31, 2019, were included in the analysis (Table 1). The median age of patients was 69 years (interquartile range, 15 years). Men comprised 50.1% of the patients (7116 of 14 197), and 68.5% of patients (9720 of 14 197) were Caucasian. Patients in this cohort were primarily from community medical centers (93.9%, 13 331 of 14 197).

Delayed ALK Test Ordering

More than one-third of tests (36.4%; 5342 of 14 657) in this cohort had a testing order delay (time to test order was >20 days). Median time from NSCLC diagnosis to ALK test order was 15 days (interquartile range, 19 days) (Figure 1; Table 2). Median ALK test order time was shorter in subgroups with younger age, patients from academic medical centers, FISH test methodology, and in–house pathology laboratories (12, 13, 12, and 11 days, respectively) (Table 2). Median ALK test order time was longer in patients with NSCLC histology not otherwise specified or squamous histology, as well as tests performed using NGS or IHC platform (19, 18, 21, and 18 days, respectively).

As shown in Figure 2, A, when we compared a more recent testing period of 2018–2019 with the 2016–2017 timespan, the percentage of delayed test orders in both FISH and NGS test types decreased (FISH, from 31.4% [1319 of 4201] to 27.5% [707 of 2571]; NGS, from 54.9% [849 of 1546] to 46.5% [906 of 1949]), and the median order time also shortened (FISH, from 12 to 11 days; NGS, from 22 to 19 days). As illustrated in Figure 2, B, the increased number of NGS tests, which had a greater percentage of delayed tests, and the decreased number of FISH tests, which had a smaller percentage of delayed tests, offset each other, resulting in a similar delayed test ordering rate between the 2 time periods.

The proportion of delayed tests was higher in subgroups with older age (≥65 years), known pacer information, non–South regions, community centers, diagnosis year after 2016, smoking history, NSCLC histology not otherwise specified, squamous histology, non-FISH test type, blood sample, non–in–house laboratories, and combination test ordering (Table 2). Upon adjustment of covariates using multivariable logistic regression, the factors that remained associated with a higher risk of delayed test ordering were non–FISH test type, Black (African American) race, smokers, smokers, and clinical characteristics. Continuous variables were summarized with median and interquartile range. Frequency counts and the percentage of patients within each category were reported for categorical variables. Bivariate logistic regression analysis was used to determine the association of patients’ demographic and clinical characteristics with delayed ALK testing. Mixed-effects multivariable logistic regression analysis (with hospital as a random effect) was used to generate adjusted odds ratios and 95% CIs for the factors. For all analyses, significance levels were 2-tailed, and adjusted odds ratios reported with 95% CIs that did not include 1 was considered statistically significant. Statistical analysis was performed using R statistical package version 3.5.3 (R Foundation, Vienna, Austria) and SAS Studio Enterprise version 3.7 (SAS Institute, Cary, North Carolina). All analyses were completed by April 2020.
Table 1. Demographic and Clinical Characteristics of Advanced Non–Small Cell Lung Cancer (aNSCLC) Patients Diagnosed From 2015 Through 2019

| Characteristic                  | No. (%) of Patients | No. (%) of ALK Tests |
|--------------------------------|---------------------|----------------------|
| Age, y                         |                     |                      |
| 18–49                          | 512 (3.6)           | 535 (3.7)            |
| 50–64                          | 4235 (29.8)         | 4376 (29.9)          |
| 65+                            | 9450 (66.6)         | 9746 (66.5)          |
| Sex                            |                     |                      |
| Female                         | 7081 (49.9)         | 7327 (50.0)          |
| Male                           | 7116 (50.1)         | 7330 (50.0)          |
| Race                           |                     |                      |
| White                          | 9720 (68.5)         | 10 039 (68.5)        |
| Black or African American      | 1150 (8.1)          | 1179 (8.0)           |
| Other race                     | 1784 (12.6)         | 1831 (12.5)          |
| Unknown                        | 1543 (10.9)         | 1608 (11.0)          |
| Region                         |                     |                      |
| South                          | 5881 (41.4)         | 6044 (41.2)          |
| Northeast                      | 2803 (19.7)         | 2897 (19.8)          |
| West                           | 2253 (15.9)         | 2350 (16.0)          |
| Midwest                        | 2153 (15.2)         | 2233 (15.2)          |
| Unknown                        | 1107 (7.8)          | 1133 (7.7)           |
| Practice type                  |                     |                      |
| Community                      | 13 331 (93.9)       | 13 776 (94.0)        |
| Academic                       | 866 (6.1)           | 881 (6.0)            |
| Year of aNSCLC diagnosis       |                     |                      |
| 2015                           | 2704 (19.0)         | 2776 (18.9)          |
| 2016–2017                      | 6444 (45.4)         | 6637 (45.3)          |
| 2018–2019                      | 5049 (35.6)         | 5244 (35.8)          |
| Smoking status                 |                     |                      |
| History of smoking             | 12 044 (84.8)       | 12 424 (84.8)        |
| No history of smoking          | 2153 (15.2)         | 2233 (15.2)          |
| Histology type                 |                     |                      |
| Nonsquamous                    | 11 626 (81.9)       | 11 975 (81.7)        |
| NSCLC NOS                      | 664 (4.7)           | 697 (4.8)            |
| Squamous                       | 1907 (13.4)         | 1985 (13.5)          |
| aNSCLC type                    |                     |                      |
| De novo                        | 11 979 (84.4)       | 12 351 (84.3)        |
| Recurrent                      | 2027 (14.3)         | 2111 (14.4)          |
| Unknown                        | 191 (1.3)           | 195 (1.3)            |
| Total                          | 14 197 (100.0)      | 14 657 (100.0)       |

Abbreviation: NSCLC NOS, non–small cell lung cancer not otherwise specified.

and nonsmokers with NSCLC histology not otherwise specified; tests performed in-house and patients diagnosed in recent years (2018–2019) were less likely to have delayed test ordering (Figure 3).

Delayed ALK Testing TAT

For analysis purposes in this study, we defined ALK delayed TAT as the receipt of test results greater than 10 days after sample receipt. Within this cohort, 40.3% (5906) of all 14 657 ALK tests had delayed TAT (Figure 4; Table 3). Median ALK testing TAT was 9 days (interquartile range, 7 days) (Table 3). Next-generation sequencing and IHC test types had the highest rate of delayed TAT (66.8% [2641 of 3952] and 48.3% [246 of 509], respectively), and longer median TAT (12 and 10 days, respectively). A subgroup analysis of NGS test type showed that the rate of delayed TAT (73% [2143 of 2917] versus 48% [498 of 1035]) and median TAT (13 versus 10 days) were poorer in NGS tests with tissue samples than with blood samples (Figure 5).

In bivariate logistic analysis, delayed ALK test TAT was associated with test-related factors (type of test, sample, laboratory, and order), and other factors including region, practice type, diagnosis year, and histology type (Table 3). In multivariable logistic regression analysis, only test-related factors were independently associated with delayed ALK test TAT (Figure 6). Compared with FISH testing, TAT of NGS testing was 6.8 times more likely to be delayed, and IHC testing TAT was 2.5 times more likely to be delayed. When comparing specimens used for ALK testing, tissue specimens were 3.7 times more likely to have delayed TAT than TAT from blood specimens.

DISCUSSION

Molecular biomarker testing has existed in some form for almost a decade and a half, and for at least the last 5 years molecular biomarker testing has been standard of care in rendering a complete diagnosis in patients with NSCLC, even as the breadth of that testing has grown with time to include new actionable biomarkers that signal tyrosine kinase inhibitor therapies beyond EGFR mutations or ALK gene translocation/fusion, such as ROS-1 gene translocation/fusion. Even so, in many cases molecular testing has not been performed, or has been performed incompletely and/or untimely. Non–small cell lung cancer patients are typically very ill; even relatively short delays in biomarker testing can trigger anxious physicians to institute, and anxious patients to accept, non–molecular-targeted therapy, primarily chemotherapy, as initial treatment. With the growth of immunotherapy in frontline settings and the recognition that tyrosine kinase inhibitors following immunotherapy could increase patient risk for significant immune toxicities such as pneumonitis, the potential harm of starting therapy prior to genomic result reporting has become an increasingly urgent problem. It has taken a significant amount of time to increase the testing rates already, and will take even longer to increase rates to those that most patients and advocates would consider as acceptable. The very small size of tumor biopsies has been an issue for many years; however, the availability of NGS panels and cell-free DNA assays has provided opportunities to better test patients upon NSCLC diagnosis and provide timely therapy. Yet the slow adoption of broad testing for advanced lung cancer remains frustrating. A number of meaningful therapies have rapidly become available for a wide number of driver mutations. However, the triggering of such therapy is contingent upon molecular identification, beyond histologic classification, requiring multidisciplinary optimization of workflow for timely, accurate molecular testing and consequent timely, accurate therapy.

Timely delivery of test results is recognized as a barrier to optimal therapy. In a recent global survey, 22% of treating physicians reported delays of greater than 10 days in receiving testing results. This is a global concern, as the median length of time from diagnosis to treatment initiation ranges from 23 to 41 days depending on locality. In a retrospective study at one Canadian institution, a wide range of biomarker test TAT was observed (from availability
25 days prior to initial oncology assessment to 21 days after initial oncologist meeting). Only a handful of studies have reported that TAT in NSCLC testing meets guideline recommendations. One difficulty in comparing studies assessing testing and treatment delays is the lack of standardized definitions for diagnosis/treatment intervals.24,28

In our study, we wanted to take a closer look at the diagnostic steps within a US cohort to determine current time to testing results as well as factors that might impact testing orders and TAT. Better understanding of delays and associated factors will allow institutions to assess their workflow and implement measures to decrease delays to meet guidelines for molecular testing in NSCLC if they are not currently meeting guidelines.

Guidelines suggest that patients with advanced NSCLC be tested for actionable driver alterations within 14 calendar days or 10 working days of specimen receipt in the testing laboratory. To assess if these guidelines are being met for ALK, we looked at 2 distinct time points to understand testing and associated factors. We looked first at the time interval for ALK tests to be ordered. In our study, the median time from NSCLC diagnosis to ALK test ordering (as captured by specimen receipt) was 15 days. Some of this delay may be attributable to billing issues; however, more than one-third of ALK tests were delayed (eg, order time >20 days) and this was essentially equivalent regardless of insurance type (see Table 2 for reference). Such a large number of test order delays in this cohort was unexpected. Delays may be partially due to sending to outside laboratories. It is possible that the delays may be attributable to the date of service rule for inpatient services. The date of service regulation, 42 CFR §414.510, also called the 14-day rule, is a Centers for Medicare & Medicaid Services regulation that requires laboratories to bill a hospital or hospital-owned facility for certain clinical laboratory services.
Table 2. Percentage of Delayed ALK Test Orders and Median ALK Test Order Time by Advanced Non–Small Cell Lung Cancer (aNSCLC) Patients’ Demographic and Clinical Characteristics

| Characteristic                      | No. (%) of ALK Tests | Order Time, Median (IQR), d | Delayed Tests, % |
|-------------------------------------|----------------------|-----------------------------|------------------|
| **Age, y**                          |                      |                             |                  |
| 18–49                               | 535 (3.7)            | 12 (20)                     | 32.3             |
| 50–64                               | 4376 (29.9)          | 14 (19)                     | 35.1             |
| 65+                                 | 9746 (66.5)          | 16 (19)                     | 37.3             |
| **Sex**                             |                      |                             |                  |
| Female                              | 7327 (50.0)          | 15 (19)                     | 35.8             |
| Male                                | 7330 (50.0)          | 15 (20)                     | 37.1             |
| **Race**                            |                      |                             |                  |
| White                               | 10 039 (68.5)        | 15 (19)                     | 36.0             |
| Black                               | 1179 (8.0)           | 15 (20)                     | 36.7             |
| Other                               | 1831 (12.5)          | 15 (20)                     | 37.8             |
| Unknown                             | 1608 (11.0)          | 16 (19)                     | 37.7 b           |
| **Insurance**                      |                      |                             |                  |
| Medicaid and Medicare               | 6826 (46.6)          | 15 (19)                     | 35.9             |
| Commercial health plan              | 5278 (36.0)          | 15 (19)                     | 36.8             |
| Other payers                        | 2032 (13.9)          | 15 (22)                     | 39.6             |
| Unknown                             | 521 (3.6)            | 14 (16)                     | 28.2 b           |
| **Region**                          |                      |                             |                  |
| South                               | 6044 (41.2)          | 14 (19)                     | 33.5             |
| Northeast                           | 2897 (19.8)          | 16 (19)                     | 37.7 b           |
| West                                | 2350 (16.0)          | 17 (20)                     | 41.8 b           |
| Midwest                             | 2233 (15.2)          | 16 (19)                     | 39.1 b           |
| Unknown                             | 1133 (7.7)           | 13 (16)                     | 32.9             |
| **Practice type**                   |                      |                             |                  |
| Community                           | 13 776 (94.0)        | 15 (19)                     | 36.7             |
| Academic                            | 881 (6.0)            | 15 (16)                     | 31.9             |
| **Year of aNSCLC diagnosis**        |                      |                             |                  |
| 2015                                | 2776 (18.9)          | 14 (19)                     | 33.8             |
| 2016–2017                           | 6637 (45.3)          | 15 (20)                     | 37.7 b           |
| 2018–2019                           | 5244 (35.8)          | 15 (18)                     | 36.2             |
| **Smoking status**                  |                      |                             |                  |
| No history of smoking               | 2233 (15.2)          | 14 (17)                     | 33.8             |
| History of smoking                  | 12 424 (84.8)        | 15 (20)                     | 36.9             |
| **Histology type**                  |                      |                             |                  |
| Nonsquamous                         | 11 975 (81.7)        | 14 (18)                     | 34.7             |
| NSCLC NOS                            | 697 (4.8)            | 19 (20)                     | 44.8 b           |
| Squamous                            | 1985 (13.5)          | 18 (21)                     | 43.9 b           |
| **aNSCLC type**                     |                      |                             |                  |
| Recurrent                           | 2111 (14.4)          | 16 (21)                     | 39.7             |
| De novo                             | 12 351 (84.3)        | 15 (19)                     | 35.9 b           |
| Unknown                             | 195 (1.3)            | 17 (25)                     | 37.9             |
| **Test type**                       |                      |                             |                  |
| FISH                                | 8886 (60.6)          | 12 (18)                     | 29.9             |
| NGS                                 | 3952 (27.0)          | 21 (20)                     | 50.4 b           |
| IHC                                 | 509 (3.5)            | 18 (19)                     | 42.2 b           |
| Others                              | 963 (6.6)            | 16 (19)                     | 40.4 b           |
| Unknown                             | 347 (2.4)            | 9 (21)                      | 26.5             |
| **Sample type**                     |                      |                             |                  |
| Tissue                              | 12 888 (87.9)        | 15 (18)                     | 35.4             |
| Blood                               | 1769 (12.1)          | 17 (21)                     | 43.9 b           |

Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; IQR, interquartile range; NGS, next-generation sequencing; NSCLC NOS, non–small cell lung cancer not otherwise specified.

a The first subgroup under each characteristic is the reference group for the comparison of the rate of delayed test order.
b Bivariate analysis with delayed ALK test order as outcome: P < .001.
c Combination test was defined as the sample of at least one of the other biomarkers (including epidermal growth factor receptor [EGFR], c-ros oncogene 1 [ROS1], KRAF, BRAF, and programmed death ligand-1 [PD-L1]) being received the same day as the ALK test.

and the technical component of pathology services provided to Medicare patients when those services are ordered less than 14 days after a patient’s hospital discharge.²⁰ Our study period straddled the time when the 14-day rule was changed, so it is possible that this rule delayed test orders. However, the median order time for patients with Medicaid and Medicare (the bulk of the patient population; Table 2) was the same as for commercial health payers. A recent cohort study in Germany reflected that reimbursement concerns were not an issue in a study in which TATs were achieved.²⁷ Sequential order of testing and waiting for the results of one test before ordering the next is not likely to blame for order delays in this cohort, as the majority of orders for ALK testing in this group were combination orders (13 895 of 14 657; 94.8%).

Using in-house pathology laboratories was associated with lower risk of delay in test ordering. Although in-house pathology laboratory testing is usually faster, many centers do not have the capacity to build and validate these tests, and using send-out commercial laboratories continues to be these centers’ only practical option to be a part of the testing landscape. ALK testing sent to outside laboratories necessitates attention to logistical concerns, payment questions, efficient communication, and shipping time, which can subsequently impact TAT. Another factor associated with lower risk of delayed test ordering was testing in recent years (2018–2019), suggesting that over the years, providers are being increasingly aware that tests should be ordered in a timely fashion.

Delays in test ordering led to speculation that there is little reflex testing in place; unfortunately, we were unable to distinguish between reflex orders and request orders in the EHR information, so we cannot definitely determine this. The fact that smokers and nonsmokers with not otherwise specified histology were more likely to have delays is concerning, as it has been recognized since the first College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines in 2013 that tobacco use should not serve as a
discriminative function in determining testing\textsuperscript{5} and that likewise nonsmokers with squamous cancers should be considered for biomarker testing. The delay in test ordering for Black patients needs to be studied further to gauge if some of the issue is insurance related or related to the severity of comorbid medical illnesses.

This delay in test ordering has profound implications for patient therapy options. Some delays are inevitable and are related to workflow; however, this data set suggests that frequently orders for testing for ALK and other alterations did not originate until the patient actually was seen by an oncologist, in many cases 2 to 3 weeks after NSCLC

| Characteristics                          | OR  | 95% CI |
|-----------------------------------------|-----|--------|
| NGS vs. FISH                            | 2.4 | 2.2 2.6 |
| IHC vs. FISH                            | 1.7 | 1.4 2.1 |
| Other test types vs. FISH               | 1.5 | 1.3 1.8 |
| Other labs vs. In-house pathology lab   | 1.3 | 1.1 1.5 |
| 2016-2017 vs. 2015                      | 1.1 | 0.9 1.2 |
| 2018-2019 vs. 2015                      | 0.9 | 0.8 1.0 |
| Smoker/NSCLC NOS vs. Nonsmoker/Non-squamous | 1.6 | 1.3 2.0 |
| Smoker/Squamous vs. Nonsmoker/Non-squamous | 1.6 | 1.3 1.8 |
| Smoker/Non-squamous vs. Nonsmoker/Non-squamous | 1.2 | 1.0 1.3 |
| Nonsmoker/NSCLC NOS vs. Nonsmoker/Non-squamous | 1.8 | 1.1 2.9 |
| Nonsmoker/Squamous vs. Nonsmoker/Non-squamous | 1.2 | 0.8 1.9 |
| Black or African American vs. White     | 1.2 | 1.1 1.4 |
| Other races vs. White                   | 1.1 | 0.9 1.2 |

Figure 3. Factors associated with delayed ALK test order in advanced non–small cell lung cancer patients diagnosed from 2015 through 2019. Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC NOS, non–small cell lung cancer not otherwise specified; OR, odds ratio.

Figure 4. Time from ALK test order to result (turnaround time [TAT]). The histogram illustrates the frequency distribution of ALK test TAT. Delayed ALK TAT was defined as an ALK test result reported more than 10 days after sample receipt.
diagnosis. Others have also documented that patients are being seen by oncologists prior to having molecular test results available.\textsuperscript{14,15,22,32}

After assessment of time to order, we evaluated the length of time to return test results. In our cohort, after ordering, 40% of ALK tests had a TAT of greater than 10 days. This further delay increases the probability that a patient with NSCLC will begin cytotoxic therapy rather than ALK tyrosine kinase inhibitors. Factors associated with delayed TAT in receiving testing results were an NGS panel or IHC (compared with FISH), tissue sample type, and combination test.

Interestingly, TAT for IHC was essentially equivalent to NGS. Rapidity of test TAT has been considered a significant advantage of IHC testing. It is unclear from the data whether small tissue sample size requiring rebiopsy or reagent issues were causative factors in the IHC TAT. An IHC TAT delay may also be attributable to the pathologist waiting for results from molecular testing prior to case sign-out or for confirmatory testing of IHC results. As the standard of care is to sign out the case and add molecular results as addendums, one would hope that a positive ALK result would not be delayed so that the treating physician would be able to start the insurance approval process. There were a small number of patients who had their first postdiagnosis ALK tests performed on multiple platforms on the same date (14 657 tests for 14 197 patients, or 460 additional tests). We do not know if the ALK testing by IHC was then confirmed by FISH, which could potentially account for delay of IHC reporting. Because of the data structure, we are unable to determine if these duplicate tests (460 of 14 657; 3.14% of total tests) delayed reporting of any of the tests. Given the increasing use of NGS, this delay in ALK IHC TAT is less of an issue in the current environment. Although NGS ALK TAT was much greater than ALK TAT for FISH and IHC specimens in our cohort, we anticipate that as NGS becomes more mainstream one should expect this difference to decrease, and even potentially switch.

Although only a small percentage of testing was reported at academic centers, the TAT delays between academic and community practices were relatively modest, showing less than a 5% difference. This reinforces that academic practices have challenges themselves in providing nondelayed ALK TAT for their patients, and that community practices have in fact have provided ALK TAT almost on par with academic practices. When comparing testing sites, TAT delays for send-out laboratories were only about 3% greater than ALK TAT at academic centers, the TAT delays between academic and community practices were relatively modest, showing less than a 5% difference. This reinforces that academic practices have challenges themselves in providing nondelayed ALK TAT for their patients, and that community practices have in fact have provided ALK TAT almost on par with academic practices. When comparing testing sites, TAT delays for send-out laboratories were only about 3% greater than ALK TAT for in-house pathology laboratories. This suggest that issues involved in delayed TAT must go beyond delays due to shipping, and likely are shared issues such as efficient communication and payment.

The vast majority of the testing in this cohort was performed on tissue specimens (12 888 of 14 657; 87.9%); the remainder of tests were performed on blood samples (1769 of 14 657; 12.1%). Various forms of testing (FISH, NGS, and others such as polymerase chain reaction) were used on blood specimens. Although it is possible to perform FISH on circulating tumor cells,\textsuperscript{33,34} because the majority of testing was performed in the community setting, we do not anticipate that this was being routinely performed. It is also not possible to determine if these tests were used in situations of limited tissue or to avoid rebiopsy. Slightly fewer blood specimen tests were delayed for reporting (571 of 1769; 32.3%) compared with tissue-based specimens (5335 of 12 888; 41.4%). ALK testing via blood might go directly to an outside laboratory and bypass the institution’s in-house processing, whereas tissue specimens would be submitted and processed at an institution’s in-house pathology laboratory, from which they would likely then be sent to a reference laboratory for ALK testing, thus increasing the issues of communication, payment, and testing logistics that could increase TAT.

### Table 3. Percentage of Delayed ALK Test Results and Median ALK Test Turnaround Time (TAT) by Advanced Non–Small Cell Lung Cancer (aNSCLC) Patients’ Demographic and Clinical Characteristics\textsuperscript{a}

| Characteristic | No. (%) of ALK Tests | Turnaround Time, Median (IQR), d | Delayed TAT, % |
|---------------|----------------------|----------------------------------|---------------|
| Region        |                      |                                  |               |
| South         | 6044 (41.2)          | 9 (7)                            | 40.5          |
| Northeast     | 2897 (19.8)          | 9 (8)                            | 42.0          |
| West          | 2350 (16.0)          | 9 (7)                            | 42.0          |
| Midwest       | 2233 (15.2)          | 9 (7)                            | 38.1          |
| Unknown       | 1133 (7.7)           | 8 (7)                            | 35.7          |
| Practice type |                      |                                  |               |
| Community     | 13 776 (94.0)        | 9 (7)                            | 40.6          |
| Academic      | 881 (6.0)            | 8 (7)                            | 35.8          |
| Year of aNSCLC diagnosis |                |                                  |               |
| 2015          | 2776 (18.9)          | 8 (6)                            | 35.9          |
| 2016–2017     | 6637 (45.3)          | 9 (7)                            | 39.1          |
| 2018–2019     | 3244 (22.8)          | 10 (7)                           | 44.2\textsuperscript{b} |
| Histology type|                      |                                  |               |
| Nonsquamous   | 11 975 (81.7)        | 9 (7)                            | 39.3          |
| NSCLC NOS     | 697 (4.8)            | 10 (7)                           | 43.6          |
| Squamous      | 1985 (13.5)          | 10 (7)                           | 44.9\textsuperscript{b} |
| Test type     |                      |                                  |               |
| FISH          | 8886 (60.6)          | 8 (5)                            | 29.3          |
| NGS           | 3952 (27.0)          | 12 (5)                           | 66.8\textsuperscript{b} |
| IHC           | 509 (3.5)            | 10 (8)                           | 48.3\textsuperscript{b} |
| Others/unknown| 1310 (8.9)           | 7 (9)                            | 31.5          |
| Sample type   |                      |                                  |               |
| Tissue        | 12 888 (87.9)        | 9 (8)                            | 41.4          |
| Blood         | 1769 (12.1)          | 8 (7)                            | 32.3\textsuperscript{b} |
| Laboratory type|                      |                                  |               |
| Other laboratories/unknown |     | 13 007 (88.7)                  | 9 (7)         | 40.7          |
| In-house pathology laboratory |        | 1650 (11.3)                     | 8 (9)         | 37.3          |
| Order type    |                      |                                  |               |
| Combination\textsuperscript{c} | 13 895 (94.8)  | 9 (7)                            | 41.2          |
| Single        | 762 (5.2)            | 6 (6)                            | 24.5\textsuperscript{b} |
| Total         | 14 657 (100.0)       | 9 (7)                            | 40.3          |

Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; IQR, interquartile range; NGS, next-generation sequencing; NSCLC NOS, non–small cell lung cancer not otherwise specified.

\textsuperscript{a} The first subgroup under each characteristic is the reference group for the comparison of the rate of delayed test order.

\textsuperscript{b} Bivariate analysis with delayed ALK test result as outcome, \( P < .001 \).

\textsuperscript{c} Combination test was defined as the sample of at least one of the other biomarkers (including epidermal growth factor receptor [EGFR], c-ros oncogene 1 [ROS1], KRAS, BRAF, and programmed death ligand-1 [PD-L1]) being received the same day as the ALK test.
The use of NGS testing during the study time period steadily increased to more than one-third (1941 of 5208; 37.3%) of all testing in the latest time period analyzed (Figure 2, B, for reference). This rate suggests that NGS is becoming more widely used in the community setting, as earlier studies showed that a minority (15.4%–21.2%) of testing in community settings was performed with NGS.25,35 Next-generation sequencing panel testing was not a practical option in past years; however, as multiple mutations continue to be discovered and multiple targeted therapies are approved by the US Food and Drug Administration, single-gene testing using kits have become less practical; sequential testing generally takes longer, and is associated with higher levels of tissue exhaustion. And increasingly, NGS has been shown to be more cost-effective than sequential gene testing.36 As this is a retrospective study using an EHR database, we recognize that an inherent limitation is the reliance on information contained herein as documented in the EHR and the inability to determine if reflex testing was being performed, along with other limitations that have already been stated. Nevertheless, the large number of patients in this database and the ability to look at details on test ordering and TAT for 14 657 ALK tests provides significant information across the United States on the real-world testing environment, particularly in the community setting where the majority of care is delivered.31

Our study indicates that ordering and return of test results in patients with NSCLC (as measured for ALK rearrangements/translocations/fusions) is not occurring in a timely fashion for a significant number of patients. It is imperative that patient care teams involved in the treatment of patients with NSCLC develop pathways for handling biopsy samples in order to ensure that all NSCLC patients have the best option for receiving appropriate initial therapy, with the highest chance of clinical response. The status quo approach to incomplete and/or untimely testing should not continue; our patients deserve better.37 A static approach to testing does not support the evolving standard required in caring for these patients, and stakeholders must continue to work as a team to address the roadblocks to complete and timely molecular biomarker testing—financial, tissue sample adequacy, communication, educational, and logistic—so that patient care can continue to improve. Racial and socioeconomic factors, among other factors, must also be taken into account in order to ensure equity in accessing targeted therapies or clinical trial enrollment. Medical oncologists, pathologists, and radiologists need to work together in a multidisciplinary fashion in their institutions to develop efficient pathways for optimal collection and testing of biopsy tissue. Comprehensive testing delivered in a timely fashion will enable maximal patient treatment options.
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