Real-world ALK Testing Trends in Patients With Advanced Non–Small-Cell Lung Cancer in the United States

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Abstract

Real-world data from the United States were used to assess ALK biomarker testing in patients with non–small-cell lung cancer. Between 2011 and 2019, tumors from 61.1% of patients were tested, and 2.8% were ALK-positive (ALK+). Treatment decisions may have been made without guideline-recommended biomarker data as ALK status was not available for nearly 25% of ALK+ patients at treatment initiation.

Introduction: Patients with non–small-cell lung cancer (NSCLC) whose tumors harbor anaplastic lymphoma kinase (*ALK*) rearrangements can be treated with ALK tyrosine kinase inhibitors. We assessed real-world *ALK* biomarker testing and treatment patterns of patients with NSCLC in the United States. **Patients and Methods:** Data were extracted from the Flatiron Health electronic health record-derived deidentified database for patients aged ≥18 years with stage IIIB or IV NSCLC and ≥2 clinic visits between January 2011 and December 2019. **Results:** Among 60,025 eligible patients, tumors from 36,691 (61.1%) patients were tested for *ALK* rearrangements, and 1042 (2.8%) tested positive (*ALK*+). From 2011 to 2019, *ALK* testing rates increased from 33.1% to 73.0%; testing via fluorescence in situ hybridization declined from 68.3% to 32.1% while next-generation sequencing increased from <1% to 52.2%. Although tissue samples were more commonly used than blood (85.1% vs. 13.5% of tests), blood sample testing increased from 0.1% in 2011 to 28.2% in 2019. Median (interquartile range) time from diagnosis of advanced NSCLC to first *ALK*+ test result was 23 (13-43) days, including laboratory processing time of 9 (6-14) days. For the 24.7% of patients with an *ALK*+ test result who began treatment before receiving the positive result, chemotherapy was initiated most often overall until 2018 when immuno-oncology agents became most common. **Conclusion:** Although *ALK* testing in NSCLC increased over time, testing rates among eligible patients did not reach 100% during the study period. Treatment decisions for some patients with NSCLC may have been made without important, guideline-recommended biomarker data.

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Keywords: Biomarker testing, Fluorescence in situ hybridization, Next-generation sequencing, Targeted therapies, Treatment patterns

Introduction

Anaplastic lymphoma kinase gene (*ALK*) rearrangements are found in approximately 3% to 8% of patients with non–small-cell lung cancer (NSCLC).[1-3] Patients with squamous histology type have a lower rate of *ALK* rearrangement (0.92%) than patients with nonsquamous (6.94%) histology types.[2] Results from recent clinical studies suggest that patients whose lung cancers harbor *ALK* rearrangements can achieve significant clinical benefit from treatment with ALK-targeted tyrosine kinase inhibitors (TKIs).[4-9] Based on the demonstrated benefits of these therapies in patients with *ALK*-positive *(ALK*+) NSCLC, guidelines published by the National Comprehensive Cancer Network (NCCN) and others recommend tumor molecular testing for *ALK* rearrangements at time of initial diagnosis and prior to initiation of therapy.[10,11]

Abbreviations: ALK, anaplastic lymphoma kinase; ALK, anaplastic lymphoma kinase gene; Chemo, chemotherapy; EGFR, epidermal growth factor receptor; EHR, electronic health record; FDA, Food and Drug Administration; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IO, immuno-oncology; IQR, interquartile range; NCCN, National Comprehensive Cancer Network (NCCN); NGS, next-generation sequencing; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PCR, polymerase chain reaction; Pd-1, programmed cell death-1; Pd-L1, programmed death-ligand 1; RNA, ribonucleic acid; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; UNK, unknown; US, United States.

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ALK rearrangements can be detected using multiple types of molecular assays, including fluorescence in-situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (PCR), and next-generation sequencing (NGS).[11] FISH was the first widely deployed methodology to determine the presence of *ALK* gene rearrangement. The FDA-approved, ALK [D5F3] CDx IHC assay can also be used as diagnostic assay and does not require confirmation by FISH.[11] NGS allows for the simultaneous detection of multiple alterations in relevant cancer genes in a single test, and in some instances can be used to guide diagnosis and use of targeted treatments.[12]

While targeted therapies have led to significant improvement in the management and prognosis of *ALK*+ NSCLC, acquired resistance to *ALK* TKIs is nearly inevitable. Between 2015 and 2016, immuno-oncology (IO) agents targeting programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) gained regulatory approval in the United States (US) for patients with advanced NSCLC whose tumors express PD-L1 and who have disease progression despite platinum-based chemotherapy or after progression on targeted therapy.[13-15] Subsequent studies showing poor response rates and toxicities associated with PD-1/PD-L1 inhibitor monotherapy and use in combination with *ALK* TKIs in patients with *ALK*+ NSCLC resulted in modifications of treatment guidelines and a requirement for negative *ALK* test results before first-line administration of IO agents.[10,11,16-19]

With the ongoing development of effective therapies targeting specific biomarkers and advancements in biomarker detection technology, vigilance is required to monitor patterns in biomarker testing practices to reveal unmet needs and optimize treatment decisions. In the current study, we assessed real-world patterns of *ALK* testing in community practices in the US in patients with advanced NSCLC.

Patients and Methods

Data Source

This was a retrospective observational study that utilized Flatiron Health's nationwide longitudinal, demographically and geographically diverse, de-identified database comprising electronic health record (EHR) data from over 280 cancer clinics (approximately 800 sites of care).[20,21] The de-identified patient-level data in the EHRs include structured data (eg, laboratory values and prescribed drugs) and unstructured data collected via technology-enabled chart abstraction from physicians' notes and other unstructured documents (eg, biomarker reports). Data provided to third parties are de-identified, and provisions are in place to prevent re-identification and protect patient confidentiality. This study included data from January 1, 2011 through December 31, 2019.

Patient Population

Patients were included in the analysis if they met the following criteria: (1) age ≥18 years, (2) confirmed diagnosis of advanced NSCLC, defined as clinical stage IIIB or IV, and (3) ≥ 2 clinic visits within the Flatiron Network between January 1, 2011 and December 31, 2019. The majority of clinic visits were from the community setting.

Outcomes

Baseline Demographic and Clinical Characteristics. Patient demographic and clinical characteristics were summarized based on *ALK* testing status (performed or not performed) and *ALK* test result received (positive or negative).

ALK Testing Patterns. Assessments of *ALK* testing patterns included proportions of patients tested for *ALK* rearrangements, *ALK* testing methodologies, sample types used for *ALK* testing, and timing of *ALK* test, including the time from diagnosis of advanced NSCLC to obtaining the *ALK* test result, and laboratory processing time, defined as the period between the testing laboratory obtaining the test sample and providing a positive or negative *ALK* test result. A sensitivity analysis for the years 2016-2019 was conducted to account for changes in technology and testing practices over the study period (2011-2019).

Treatment Patterns Before and After ALK Test Results. Systemic treatments for patients who underwent *ALK* testing were evaluated to determine the proportion of patients who initiated treatment before an *ALK*+ test result was received, the treatment class(es) used during that period, line of treatment when the *ALK*+ test result was received, and treatment administered after the *ALK*+ test result was received. Assessment of PD-L1 testing patterns and timing of PD-L1 testing was also performed.

Statistical Analysis

Patient demographics and clinical characteristics, treatment patterns, and clinical outcomes were analyzed descriptively. *ALK* testing patterns were summarized by year and for the overall analysis period.

Results

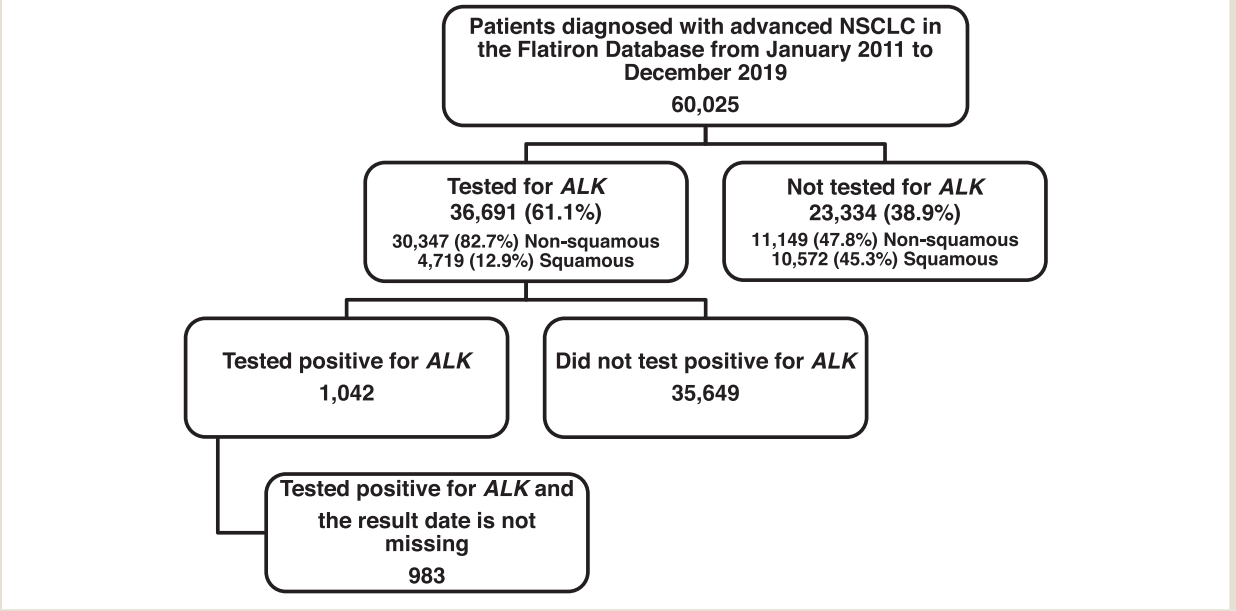
Patients

A total of 60,025 adult patients with stage IIIB or IV NSCLC were eligible for this study. Of these, the majority (69.1%) had tumors with nonsquamous cell histology, 86.6% had a history of smoking, and most had stage IV disease at initial diagnosis (61.8% vs. 20.5% at stage III, 5.2% at stage II, and 9.0% at stage I).

Tumors from 36,691 (61.1%) patients were tested at least once for *ALK* alterations during the analysis period, and tumors from 23,334 (38.9%) patients were not tested (Figure 1). About 30.9% (n = 4719) of patients with squamous histology and 73.1% (n = 30,347) of patients with nonsquamous histology were tested for *ALK* alterations (Table S1). Testing rates were similar regardless of smoking status.

Among patients who underwent *ALK* testing, the median age was 69.0 (interquartile range [IQR]: 61-76) years, 45.1% were female, 62.1% were White, 66.6% had stage IV disease, 84.2% had a history of smoking, 82.7% had nonsquamous histology, 12.9% had squamous histology, and histology was not specified in 4.4% of patients. Patients who were not tested for *ALK* had a median age of 70.0 (IQR: 63-77) years, 39.7% were female, 63.5% were White, 54.4% had stage IV disease, 90.4% had a history of smoking, 47.8% had nonsquamous histology, 45.3% had squamous histology, and histology was not specified in 6.9% of patients (Table 1).

Figure 1 Patient sample selection. Abbreviations: *ALK* = anaplastic lymphoma kinase gene; NSCLC = non–small-cell lung cancer.



Of patients who were tested, 1042 (2.8%) were positive and 35,649 (97.2%) were negative for *ALK* rearrangements. Among patients with an *ALK*+ test result, the median age was 63.0 (IQR: 54-72) years, 50.2% were female, 60.4% were White, 71.8% had stage IV disease, 46.7% had a history of smoking. 92.5% had nonsquamous histology, 3.6% had squamous histology, and histology was not specified in 3.8% of patients. Among patients with a negative *ALK* test result, the median age was 69.0 (IQR: 61-76) years, 45.0% were female, 62.2% were White, 66.4% had stage IV disease, 85.3% had a history of smoking, 82.4% had nonsquamous histology, 13.1% had squamous histology, and histology was not specified in 4.4% of patients (Table 1).

ALK Testing Patterns

The median time from diagnosis of advanced NSCLC to the date of the first *ALK*+ test result was 23 (IQR: 13-43) days (Table 2). The latency between diagnosis and the first *ALK*+ test result was similar between 2016 and 2019 (median: 25 days; IQR: 14-45) and for the entire study period (Table S2).

Over the duration of the analysis period, the rate of *ALK* testing increased from 33.1% in 2011 to 73.0% in 2019. Testing was lower for patients with squamous compared to nonsquamous histology. *ALK* testing rates increased over time for patients with nonsquamous (41.6%-81.6%) and squamous histology (13.6%-50.4%). Testing rates increased more rapidly among patients with squamous histology, with the largest increase occurring from 2016 to 2018 (31.2%-50.8%) (Figure 2).

The proportion of tests performed using FISH declined from 83.8% in 2012 to 32.1% in 2019. Conversely, the proportion of tests performed using NGS increased from 0.2% in 2011 to 52.2% in 2019 (Figure 3A). These patterns of *ALK* sequencing technology usage were reflected among patients with an *ALK*+ test result (Figure 3B). The proportion of tests that were positive for *ALK* alterations differed by sequencing technology, with 0.9% of PCR, 2.1% of NGS, and 3.0% of FISH tests reporting *ALK*+ results (Table S3).

ALK Testing by Sample Type

Over the duration of the analysis period, sample types used for *ALK* testing were distributed as 85.1% solid tissue (biopsy) samples and 13.5% blood (liquid biopsy) (Table S4). The proportion of *ALK* tests performed using blood samples increased from 0.1% in 2011 to 28.2% in 2019, with the largest increase occurring from 2015 to 2019 (5.2%-28.2%). An opposing trend was observed with the use of tissue samples, which decreased from 98.0% in 2011 to 71.2% in 2019 (Figure 4). Patients may have had more than one test and the frequency of blood sample testing increased with repeat *ALK* testing, as only 9.1% of tests used to obtain a first *ALK* test result were performed on blood samples, compared to 28.4 and 38.6% of tests used to obtain second and third *ALK* test results, respectively (Table S4).

The latency between the diagnosis of advanced NSCLC and the first *ALK*+ test result differed by sample type. Specifically, the first *ALK*+ test result was obtained at a median 22 (IQR: 13-40.5) days after diagnosis when tissue samples were used, compared to 30.5 (IQR: 17-69) days when blood samples were used. Although laboratory processing time was similar for both sample types, time from diagnosis to blood test date, and consequently test result, was longer (Table 2).

As shown in Figure 5, over the duration of the analysis period, relative frequencies of testing methods were unique to the sample

Table 1 Baseline Demographics and Clinical Characteristics by *ALK* Status ($N = 60,025$)

	Tested for *ALK*		*ALK*+ Test Result	
	Yes[a] ($n = 36,691$)	No ($n = 23,334$)	Yes ($n = 1042$)	No ($n = 35,649$)
Age at advanced diagnosis, median (IQR)	69.0 (61-76)	70.0 (63-77)	63.0 (54-72)	69.0 (61-76)
Practice type, *n* (%)				
Academic	2747 (7.5)	2062 (8.8)	141 (13.5)	2606 (7.3)
Community	30,135 (82.1)	19,492 (83.5)	826 (79.3)	29,309 (82.2)
Missing	3809 (10.4)	1780 (7.6)	75 (7.2)	3734 (10.5)
Sex, *n* (%)				
Female	16,552 (45.1)	9256 (39.7)	523 (50.2)	16,029 (45.0)
Male	16,329 (44.5)	12,294 (52.7)	444 (42.6)	15,885 (44.6)
Missing	3810 (10.4)	1784 (7.6)	75 (7.2)	3735 (10.5)
Race, *n* (%)				
White	22,797 (62.1)	14,809 (63.5)	629 (60.4)	22,168 (62.2)
Black or African American	2721 (7.4)	1835 (7.9)	66 (6.3)	2655 (7.4)
Asian	986 (2.7)	400 (1.7)	61 (5.9)	925 (2.6)
Other/missing[b]	10,187 (27.7)	6290 (26.9)	286 (27.5)	9901 (27.7)
Disease stage at diagnosis, *n* (%)				
I	3051 (8.3)	2328 (10.0)	66 (6.3)	2985 (8.4)
II	1837 (5.0)	1311 (5.6)	54 (5.2)	1783 (5.0)
III	6374 (17.4)	5934 (25.4)	161 (15.5)	6213 (17.4)
IV	24,423 (66.6)	12,700 (54.4)	748 (71.8)	23,675 (66.4)
Not reported/other	1006 (2.7)	1061 (4.5)	13 (1.2)	993 (2.8)
Ever smoker, *n* (%)				
Yes	30,886 (84.2)	21,096 (90.4)	487 (46.7)	30,399 (85.3)
No/missing[c]	5805 (15.8)	2238 (9.6)	555 (53.3)	5250 (14.7)
Histology, *n* (%)				
Nonsquamous cell carcinoma	30,347 (82.7)	11,149 (47.8)	964 (92.5)	29,383 (82.4)
Squamous cell carcinoma	4719 (12.9)	10,572 (45.3)	38 (3.6)	4681 (13.1)
Not specified	1625 (4.4)	1613 (6.9)	40 (3.8)	1585 (4.4)

Abbreviations: *ALK* = anaplastic lymphoma kinase gene; IQR = interquartile range.
[a] Sequential testing is not routine; therefore 20% of patients received >1 test. 80% tested once, 16% twice, 3.1% 3 times, and 0.8% >3 times.
[b] <5 of *ALK*+ patients identified as Hispanic or Latino, which could not be reported separately.
[c] <5 *ALK*+ patients had missing smoking history, which could not be reported separately.

Table 2 Time From Advanced Diagnosis Date to First *ALK* Test Date and Laboratory Processing Time

Test	Advanced Diagnosis to First *ALK*+ Test			Laboratory Receipt to First *ALK*+ Test Result			Total Advanced Diagnosis to First *ALK*+ Result		
	All ($n = 957$)	Tissue ($n = 903$)	Blood ($n = 48$)	All ($n = 957$)	Tissue ($n = 903$)	Blood ($n = 48$)	All ($n = 983$)	Tissue ($n = 912$)	Blood ($n = 48$)
Median (IQR) time (days)	9 (0-27)	9 (0-25)	23.5 (7-60)	9 (6-14)	9 (6-14)	9.5 (7-12.5)	23 (13-43)	22 (13-40.5)	30.5 (17-69)

Abbreviations: *ALK* = anaplastic lymphoma kinase gene; IQR = interquartile range.

type used, whereby most testing on tissue samples was performed using FISH (71.1%) followed by NGS (20.9%). When blood samples were tested, the most common testing methods were NGS (69.3%) followed by PCR (23.7%).

Treatment Patterns Before and After ALK Test Results

Among patients with at least one *ALK*+ test result ($n = 983$), 243 (24.7%) had initiated therapy prior to receiving their first *ALK*+ test result (Table 3). Most of these patients received their *ALK*+ test result prior to first-line therapy (Figure 6A). From 2011 to 2016, chemotherapy was the most common treatment for patients with *ALK*+ NSCLC who had not yet received their *ALK*+ test result, and in 2017 chemotherapy and IO agents were used at the same frequency in this patient population. From 2018 to 2019, IO agents were the most commonly initiated treatment for patients with *ALK*+ NSCLC who had not yet received the *ALK* test result (Figure 6B). Of the 983 patients with an *ALK*+ test result, 742 (75.5%) received an ALK TKI after their *ALK*+ test result. Among the 243 patients who initiated treatment prior to their *ALK*+ test result, 194 (79.8%) received an ALK TKI, including

Figure 2 *ALK* testing rates and ALK TKI FDA approvals, by year of advanced diagnosis. Abbreviations: 1L = first-line; ALK = anaplastic lymphoma kinase; *ALK* = anaplastic lymphoma kinase gene; FDA = Food and Drug Administration; TKI = tyrosine kinase inhibitor.

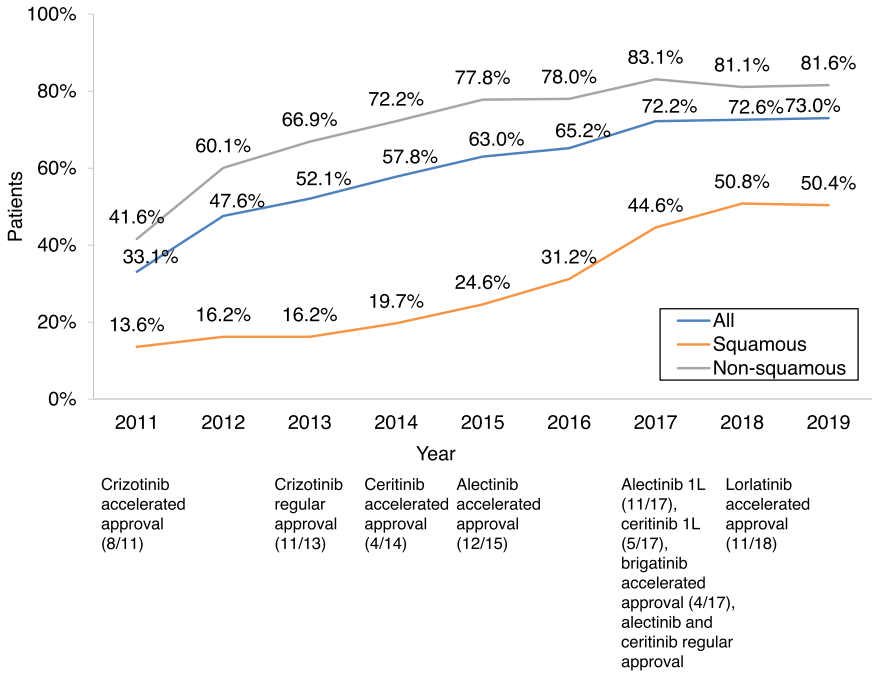


Table 3 Treatment Patterns After *ALK* Test Result

	N	ALK TKI Received After *ALK*+ Test Result *n* (%)	Treatment Latency[a] (Median [IQR] Days)
Patients with *ALK*+ test result	983	742 (75.5)	22 (10-55)
Patients who initiated treatment prior to *ALK* test result	243	194 (79.8)	32.5 (15-93)
Treatment received prior to test result			
ALK TKI	28[b]	25 (89.3)	
IO included[c]	57	36 (63.2)	
EGFR TKI	6	5 (83.3)	
Chemotherapy	144	123 (85.4)	
Other	8	5 (62.5)	

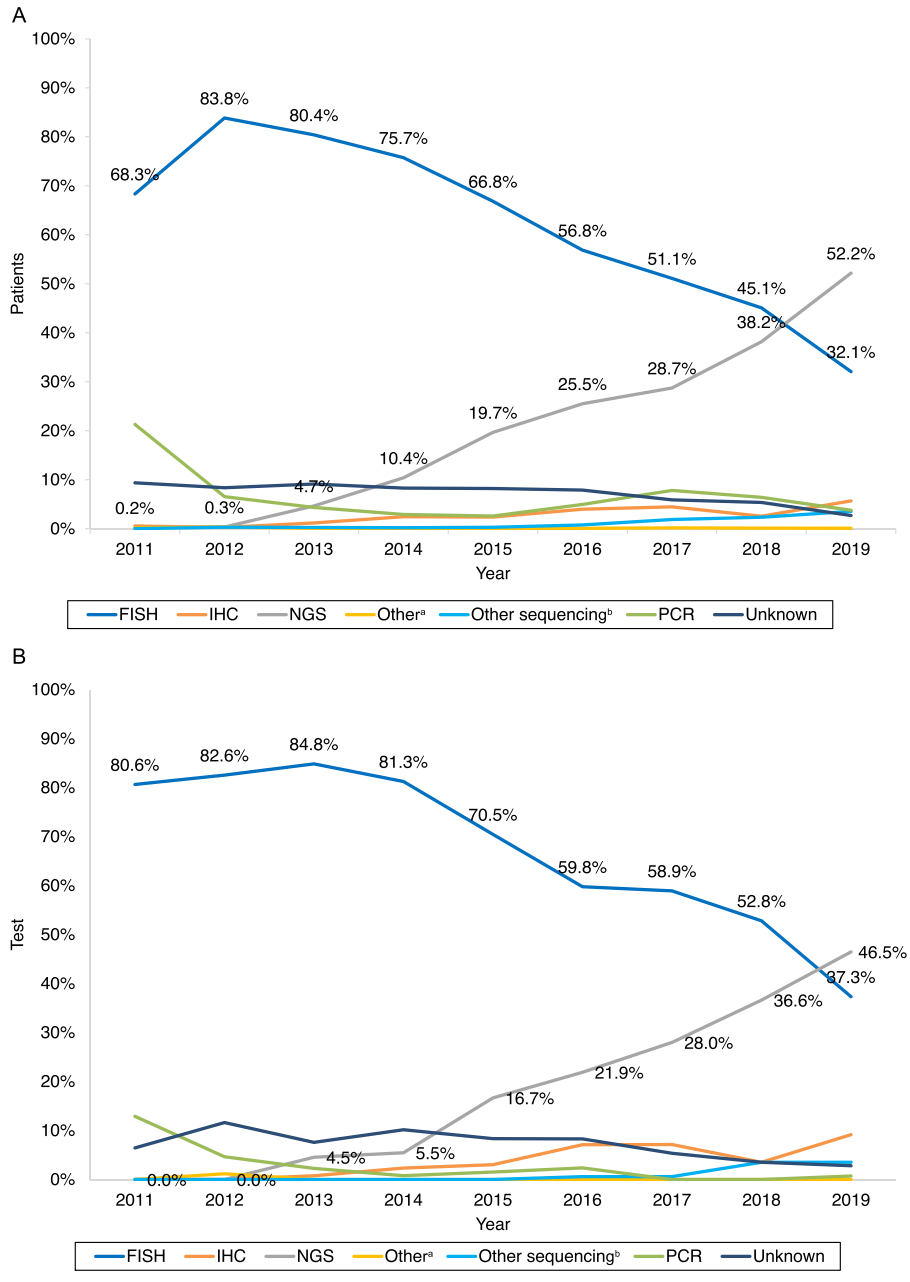
Abbreviations: ALK = anaplastic lymphoma kinase; *ALK* = anaplastic lymphoma kinase gene; EGFR = epidermal growth factor receptor; IO = immuno-oncology; IQR = interquartile range; TKI = tyrosine kinase inhibitor.
[a] Defined as the date of first use of ALK TKI minus the date of *ALK*+ test result among patients who initiated ALK TKI treatment after *ALK* test result.
[b] Five additional patients used both ALK and IO, total is 33.
[c] Note: the majority of these patients (46 out of 57) received an IO/chemotherapy combination.

123/144 (85.4%) patients who had originally initiated chemotherapy. Among patients who received an ALK TKI, treatment latency (median number of days from *ALK*+ test result to initiation of ALK TKI) was 22 days (IQR: 10-55). Among patients who initiated treatment prior to *ALK* test result, treatment latency was 32.5 days (IQR: 15-93) (Table 3). Details of the line of therapy when first ALK TKI was received are presented in Tables S5 and S6.

PD-L1 Testing

An analysis of PD-L1 testing patterns in patients with advanced NSCLC revealed that between 75.4% and 77% of these patients had been tested for PD-L1 expression each year since 2017 (**Figure S1**). Median time from advanced diagnosis date to first PD-L1 test was 12 (IQR: 3-38.5) days, and time to first positive PD-L1 test was 20.5 (IQR: 10-36.5) days (Table S7). Among patients with a first *ALK*+ test result (n = 983), 158 (16.1%) received their first positive PD-L1 test result (defined as "PD-L1 positive" in patient chart review or PD-L1 tumor proportion score [TPS] > 1%) before their *ALK*+ test result. Of the 243 patients who initiated any treatment before receiving their first *ALK*+ test result, 41 (16.9%) had tested positive for PD-L1 prior to receiving the *ALK*+ test result. Of the 57 patients who initiated IO therapy

Figure 3 *ALK* sequencing technology usage, by year of test result for (A) all patients, and (B) all patients with an *ALK*+ test result [a]"Other" included testing types that represented a small proportion of tests, including proteomics, mass spectrometry, and FISH. [b]"Other sequencing" defined as sequencing methods other than NGS, including RNA sequencing, whole transcriptome shotgun sequencing, Sanger sequencing, direct sequencing, or if a sequencing test was performed just to test one gene, as opposed to a large panel of genes. Abbreviations: *ALK* = anaplastic lymphoma kinase gene; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NGS = next-generation sequencing; PCR = polymerase chain reaction; RNA = ribonucleic acid.



prior to receiving their first *ALK*+ test result, 42 (73.7%) had received their first PD-L1 result, of whom 27 (47.4%) had received a positive PD-L1 test prior to obtaining their *ALK*+ test result (Table S8).

Discussion

This study assessed real-world *ALK* testing patterns and treatment in 60,025 patients with advanced NSCLC, a similar number of patients compared with other reports of advanced NSCLC in

Figure 4 Sample types used for *ALK* testing, by year of test result. Abbreviation: *ALK* = anaplastic lymphoma kinase gene.

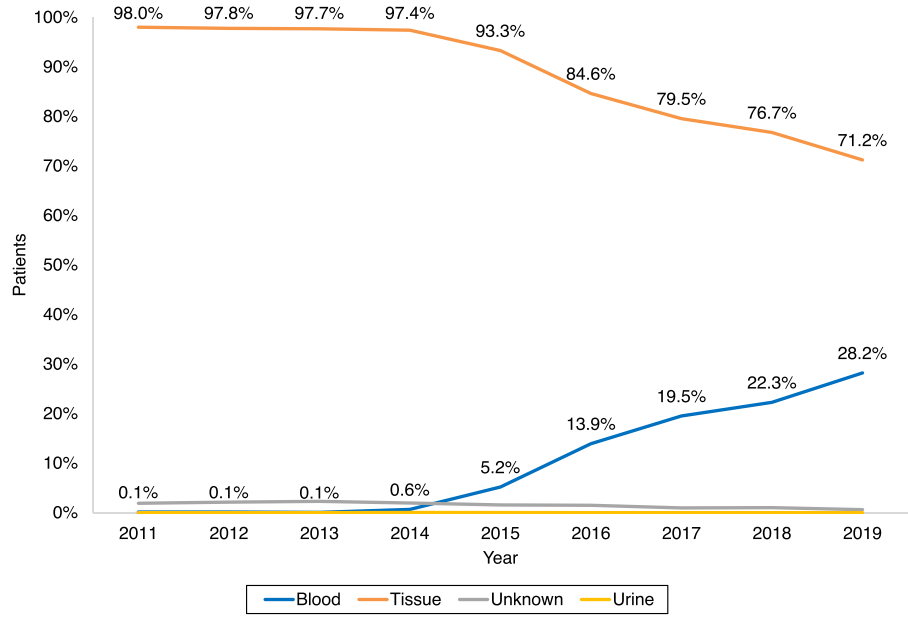


Figure 5 Frequency of *ALK* testing by sequencing technology, by sample type during the analysis period. Abbreviations: *ALK* = anaplastic lymphoma kinase gene; FISH = fluorescence in situ hybridization; NGS = next-generation sequencing; PCR = polymerase chain reaction.

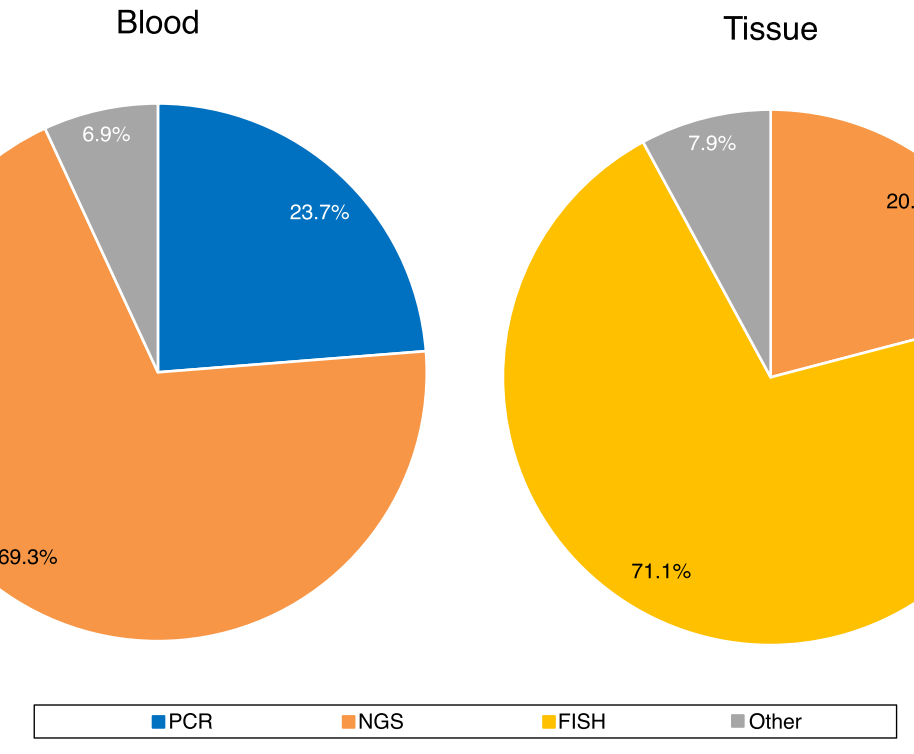
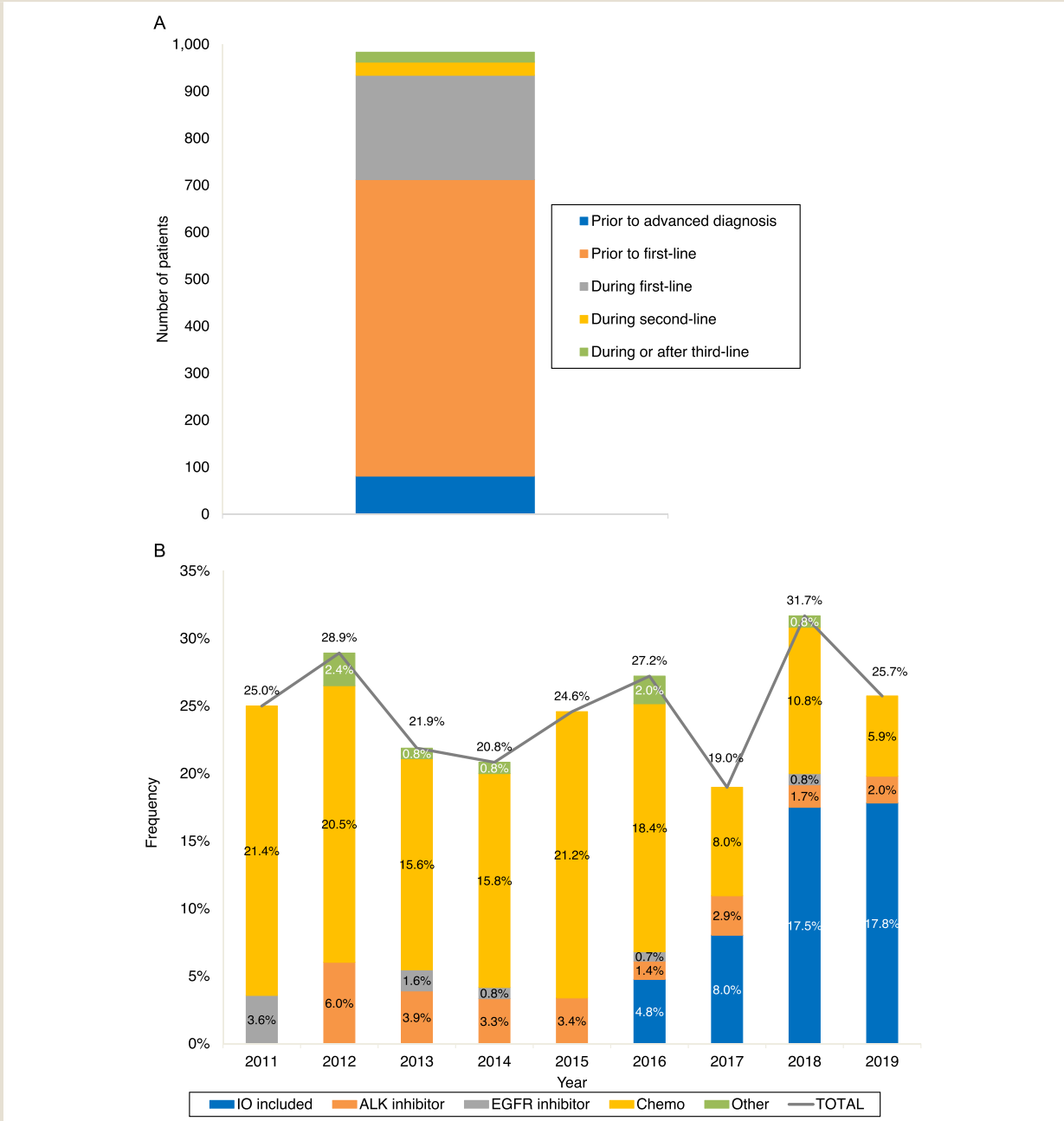


Figure 6 Treatment characteristics of patients with *ALK*+ test result. (A) Line of therapy patients were receiving when the *ALK*+ test result was obtained, and (B) frequencies, by year of test result, of treatment types initiated by patients who were *ALK*+ but had yet to receive the *ALK* test result *28 patients who received *ALK*+ test result and initiated first-line treatment on the same day were considered "During first-line." Abbreviations: ALK = anaplastic lymphoma kinase; *ALK* = anaplastic lymphoma kinase gene; chemo = chemotherapy; EGFR = epidermal growth factor receptor; IO = immuno-oncology; TKI = tyrosine kinase inhibitor.



the Flatiron database.[22] Findings showed that *ALK* testing rates in patients with advanced NSCLC steadily increased over time from 33% in 2011 to 73% in 2019, but universal testing was not reached. Considering histological subtype by year of diagnosis, *ALK* testing rates in patients with squamous histology increased from 13.6% in 2011 to 50.4% in 2019. *ALK* testing rates in patients with nonsquamous histology increased from 41.6% in 2011 to 81.6% in 2019. As the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) only recommend biomarker testing in select patients with nonsquamous histology,[11]

the value of *ALK* testing rates in patients with squamous histology is unclear.

In line with the current study, increases in *ALK* testing rates over time have been reported previously.[23-28] These increases in *ALK* testing rates were likely influenced by several factors, including advances in testing methodologies that allow for more accurate detection of *ALK* rearrangements, recent development and approval of effective treatments targeting *ALK* rearrangements, and the addition of and/or updates to clinical treatment guidelines that have included biomarker testing recommendations since 2012.[10,11] Although early guidelines primarily recommended testing in adenocarcinomas,[10] current guidelines recommend biomarker testing at initial diagnosis in all metastatic nonsquamous cell disease, including NSCLC not otherwise specified (NOS).[11] Factors reported in the literature that are associated with a lower likelihood of *ALK* testing have been identified as histology (squamous or NSCLC diagnosed as NOS due to uncertain histological subtype compared to nonsquamous histology), a history of smoking (for nonsquamous histology), decreased Eastern Cooperative Oncology Group performance status at diagnosis, earlier stage disease at initial NSCLC diagnosis, advanced diagnosis prior to 2016, older age (≥50 years), male sex, noncommercial insurance, smaller practice size and volume, and non-Western US regions.[24,25,29]

Similar to other studies,[23,26,28] the present analysis showed that NGS became the predominant *ALK* testing method in 2018, replacing FISH. This trend is likely to continue as numerous NGS methodologies allow detection of a significant number of actionable gene alterations; and current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC recommend broad molecular profiling.[11] IHC and FISH have some disadvantages compared to NGS. Background staining of other cells by IHC may result in false positive interpretation;[30] while FISH is limited by technical challenges such as signal instability and challenges with scoring.[31] However, IHC and FISH may detect some *ALK* rearrangements not identified by NGS, with discrepancies commonly related to the highly complex genomic rearrangements found in the clinical specimens.[32]

This study found that the turnaround time between diagnosis of advanced NSCLC and *ALK*+ test result was 3 to 4 weeks, exceeding the 2 weeks (10 working days) recommended by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology.[33] The delay in obtaining biomarker testing results may have been a factor leading to treatment initiation before confirmation of an *ALK* test result in approximately 25% of patients with an *ALK*+ test result in the present study. Evidence to support the need for timely *ALK* status confirmation was revealed in a recent chart review showing that patients who were diagnosed with advanced NSCLC and had biomarker results available at the initial oncology consultation could reach a treatment decision immediately (median of 0 days), compared to a significant delay of 22 days ($P = .0008$) when biomarker results were not yet available, which was in turn was associated with a delay in initiating treatment.[34]

Biomarker testing of lung cancer specimens for gene rearrangement is important for the identification of potential efficacious targeted therapies and avoidance of therapies unlikely to provide clinical benefit or which cause unnecessary toxicity. Data from the present study showed that nearly one quarter of patients whose tumors would eventually be confirmed as *ALK*+ began treatment, most often chemotherapy, before receiving the result. A recent study demonstrated that initiation of chemotherapy before an ALK TKI in patients with *ALK*+ NSCLC was associated with a 30% increased risk of remaining untreated with an ALK TKI by 3 weeks after the *ALK* test result was received, and a 3-week delay in ALK TKI initiation more than doubled the risk of mortality.[35] In another real-world analysis, 94% of patients with *ALK*+ NSCLC who had been tested before initiating first-line therapy received targeted therapy compared to 65% of patients who had been tested after first-line therapy was underway.[36]

In the 243 patients initiating treatment prior to *ALK* test results in the present study, 6 patients received an epidermal growth factor receptor (EGFR) TKI. Of these, all but 1 patient was diagnosed between 2011 and 2014 when *ALK* testing was less well recognized as a target biomarker. Although all 6 patients were tested for *EGFR* status, only 1 tested positive. It is unknown why these patients were initiated on an EGFR TKI despite the negative *EGFR* mutation testing result in 5 of 6 patients.

In the present study, beginning in 2016, the use of IO steadily increased to become the predominant first-line therapy by 2018 among patients who had not yet received their *ALK*+ test result. This likely reflected the prevailing standard of care with the approval of 3 IO agents.[13-15] Although evidence addressing IO therapy in patients in *ALK*+ NSCLC is limited, several analyses have demonstrated the relative lack of efficacy of IO monotherapy in these patients.[16-18] Additionally, IO treatment is associated with unique immune-mediated adverse events that are not seen with traditional chemotherapy.[11] Severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, dermatologic reactions, and nephritis with renal dysfunction have been reported with IO use.[37,38] There is potential for increased adverse events when IO therapy is used sequentially or in combination with ALK TKIs.[19,39-42]

PD-L1 expression in tumors has been used to select patients more likely to respond to PD-1/PD-L1 inhibitor treatment.[43] Among all patients with *ALK*+ NSCLC in the present study, 16.1% of patients received a positive PD-L1 test result before their *ALK*+ test result, whereas 47.4% of patients who initiated IO therapy prior to receiving their first *ALK*+ test result received a positive PD-L1 test result before their *ALK*+ test result. As PD-1/PD-L1 inhibitors are not recommended as first-line therapy in patients with *ALK*+ NSCLC, the finding that a substantial proportion of patients in this study initiated IO therapy prior to receiving *ALK*+ test results highlights the importance of performing biomarker testing immediately on diagnosis of advanced NSCLC, and the need for prioritization of therapies with the greatest potential for effectiveness in patients with *ALK*+ NSCLC.

Limitations

This study was limited by the retrospective design, the nature of observational data, and the retrospective investigation of medical records, for which quality control can vary. In this particular dataset,

certain elements, such as dates of events, were frequently missing, and whether patients received multiple *ALK* tests and/or when such tests were performed were not always conclusive. Data granularity was limited for some variables, including detailed breakdown of PD-L1 levels, and specifics on type of NGS and FISH testing. As *ALK* rearrangements occur in both nonsmokers and smokers, it is essential to perform biomarker testing for all cases of NSCLC to guarantee complete identification of clinically relevant oncogenic drivers.

Conclusion

This real-world analysis revealed that testing for *ALK* rearrangements increased over time but had not reached 100% by the end of the study period (2019), despite treatment guideline recommendations. Further, 24.7% of patients with a first *ALK*+ test result initiated therapy prior to receiving the *ALK*+ test result. There is an unmet need for comprehensive and timely biomarker testing to ensure necessary molecular data is available for therapeutic planning and informed treatment decision making in patients with *ALK*+ NSCLC.

Clinical Practice Points

- Identification of *ALK* rearrangements in patients with advanced NSCLC helps select those patients who will derive benefit from ALK TKI therapy.
- Clinical practice guidelines recommend molecular profiling that includes ALK testing in patients with NSCLC.
- Real-world data from over 60,000 patients in the US showed the rate of ALK testing in advanced NSCLC increased from 33% to 73% between 2011 and 2019, indicating that more than a quarter of patients with NSCLC are not receiving recommended biomarker testing.
- Despite advancements in ALK testing technology, the median time between diagnosis of advanced NSCLC and obtaining an ALK-positive (ALK+) test result was 23 days.
- Due to delays between NSCLC diagnosis and receipt of ALK test results, nearly 25% of patients with ALK+ tumors initiated therapy prior to knowing ALK status.
- Delays in obtaining test results may have affected treatment decisions for some patients with ALK+ NSCLC; until 2018, prior to receiving an ALK+ test result, the most frequently initiated treatment was chemotherapy, followed by immuno-oncology therapy.

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Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.09.010.

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