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Association of Broad-Based Genomic Sequencing With Survival Among Patients With Advanced Non–Small Cell Lung Cancer in the Community Oncology Setting

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IMPORTANCE Broad-based genomic sequencing is being used more frequently for patients with advanced non–small cell lung cancer (NSCLC). However, little is known about the association between broad-based genomic sequencing and treatment selection or survival among patients with advanced NSCLC in a community oncology setting.

OBJECTIVE To compare clinical outcomes between patients with advanced NSCLC who received broad-based genomic sequencing vs a control group of patients who received routine testing for *EGFR* mutations and/or *ALK* rearrangements alone.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of patients with chart-confirmed advanced NSCLC between January 1, 2011, and July 31, 2016, and who received care at 1 of 191 oncology practices across the United States using the Flatiron Health Database. Patients were diagnosed with stage IIIB/IV or unresectable nonsquamous NSCLC who received at least 1 line of antineoplastic treatment.

EXPOSURES Receipt of either broad-based genomic sequencing or routine testing (*EGFR* and/or *ALK* only). Broad-based genomic sequencing included any multigene panel sequencing assay examining more than 30 genes prior to third-line treatment.

MAIN OUTCOMES AND MEASURES Primary outcomes were 12-month mortality and overall survival from the start of first-line treatment. Secondary outcomes included frequency of genetic alterations and treatments received.

RESULTS Among 5688 individuals with advanced NSCLC (median age, 67 years [interquartile range, 41-85], 63.6% white, 80% with a history of smoking); 875 (15.4%) received broad-based genomic sequencing and 4813 (84.6%) received routine testing. Among patients who received broad-based genomic sequencing, 4.5% received targeted treatment based on testing results, 9.8% received routine *EGFR*/*ALK* targeted treatment, and 85.1% received no targeted treatment. Unadjusted mortality rates at 12 months were 49.2% for patients undergoing broad-based genomic sequencing and 35.9% for patients undergoing routine testing. Using an instrumental variable analysis, there was no significant association between broad-based genomic sequencing and 12-month mortality (predicted probability of death at 12 months, 41.1% for broad-based genomic sequencing vs 44.4% for routine testing; difference −3.6% [95% CI, −18.4% to 11.1%]; $P = .63$). The results were consistent in the propensity score–matched survival analysis (42.0% vs 45.1%; hazard ratio, 0.92 [95% CI, 0.73 to 1.11]; $P = .40$) vs unmatched cohort (hazard ratio, 0.69 [95% CI, 0.62 to 0.77]; log-rank $P < .001$).

CONCLUSIONS AND RELEVANCE Among patients with advanced non–small cell lung cancer receiving care in the community oncology setting, broad-based genomic sequencing directly informed treatment in a minority of patients and was not independently associated with better survival.

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Supplemental content

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Targeted treatments for epidermal growth factor receptor (*EGFR*; 131550 OMIM) mutations and anaplastic lymphoma kinase (*ALK*; 105590 OMIM) rearrangements among patients with advanced non–small cell lung cancer (NSCLC) improve survival compared with chemotherapy.[1,2] Hence, routine testing for *EGFR* and *ALK* alterations should be the standard of care for patients with advanced NSCLC. Broad-based genomic sequencing is distinct from *EGFR/ALK* testing in that it evaluates multigene panels of 30 to hundreds of genes using next-generation sequencing techniques.[3] The National Comprehensive Cancer Network (NCCN) recommends testing using broad-based genomic sequencing to identify rare driver mutations and to assess clinical trial eligibility for other targeted treatments.[4] However, broad-based genomic sequencing has been criticized due to the scarcity of clinically actionable mutations, the unknown effect on patient outcomes,[5] and health care expenditures.[6-10]

There is no evidence that routine use of broad-based genomic sequencing improves survival in large populations of patients with advanced NSCLC treated in the community.[11] The only randomized clinical trial of broad-based genomic sequencing using investigational agents (the SHIVA trial[12]) did not find any improvement in progression-free survival. Similarly, a study conducted by the Lung Cancer Mutational Consortium prospectively used multiplex genotyping to detect 10 oncogenic drivers at 14 academic institutions.[13] This study did not find a significant difference in median survival among 49 patients who received targeted treatment for oncogenic driver mutations other than *EGFR* and/or *ALK* but were only focused on 10 specific mutations. Another retrospective study suggested that broad-based genomic sequencing does improve survival for patients who receive targeted treatment for actionable mutations compared with patients without actionable mutations, but *EGFR/ALK* alterations were included in the broad-based genomic sequencing group.[14]

A better understanding of the incremental benefit of broad-based genomic sequencing compared with routine *EGFR*/*ALK* testing is needed. Thus, testing with broad-based genomic sequencing and its association with improved survival compared with routine *EGFR*/*ALK* alteration testing was studied in a cohort of patients with advanced NSCLC treated in community oncology clinics.

Key Points

Question Is there an association between broad-based genomic sequencing and better survival compared with routine genomic testing (*EGFR*/*ALK* alterations only) among patients with advanced non–small cell lung cancer treated in the community oncology setting?

Findings In this retrospective cohort study that included 191 community oncology practices and 5688 patients, there was no significant association between broad-based genomic sequencing and routine genomic testing on 12-month mortality using instrumental variable analysis (difference, −3.6%) or overall survival using a propensity score–matched analysis (hazard ratio, 0.92).

Meaning Use of broad-based genomic sequencing in the community setting for advanced non–small cell lung cancer may not currently offer a survival advantage.

Methods

Study Design

This retrospective cohort study used the Flatiron Health Database to identify patients diagnosed with stage IIIB/IV or recurrent nonsquamous advanced NSCLC who received first-line antineoplastic treatment and either broad-based genomic sequencing or routine testing (*EGFR* and/or *ALK* only). Broad-based genomic sequencing included any multigene panel testing more than 30 genes. An instrumental variable approach was used as the primary analysis to evaluate differences in 12-month mortality between the broad-based genomic sequencing and routine-tested groups. A propensity score–matched survival analysis was used as a secondary analysis to evaluate differences in overall survival between the groups.

Data Source

The Flatiron Health Database includes deidentified patient-level data obtained under an institutional review board–approved protocol with waiver of informed consent. The Yale Human Investigations Committee determined that this study did not constitute human subjects research. The deidentified data set was generated using both structured and unstructured data. The Flatiron Health Database represents a geographically and demographically diverse population of patients with cancer, their clinicians, and health care institutions. At the time of this analysis, the Flatiron network represented more than 250 cancer clinics with 1.5 million active patients, integrated into a single data warehouse via a cloud-based electronic health record (EHR) platform.[15] All data sets included demographic data, such as age, along with clinical data, such as mutation status and treatment type. This cohort was similar in age, sex, and race to the US population of patients with advanced NSCLC based on 2014 SEER data (eTable 1 in the Supplement). Race was included this study because it is a patient characteristic that has been found to affect survival among patients with lung cancer.[16] Self-identification was the most common source for this information based on fixed categories. Tumor genomic testing results were abstracted from multigene panel sequencing reports in patients' charts.

Study Sample

The study sample included patients who were diagnosed with advanced NSCLC between January 1, 2011, and July 31, 2016, or were diagnosed with early-stage NSCLC and subsequently developed recurrent or progressive disease between those same dates. Each patient had an *ICD-9* or *ICD-10* diagnosis of lung cancer (162.x or C34.x), at least 2 documented clinical visits on or after January 1, 2011, pathology consistent with nonsquamous NSCLC, and confirmation of advanced NSCLC on or after January 1, 2011. All patients received at least 1 line of systemic antineoplastic treatment for advanced NSCLC. Patients with evidence of other concurrent active cancers within 6 months prior to diagnosis of advanced NSCLC, other than nonmelanoma skin cancer, were excluded. A patient must have had documentation in the chart of either broad-based genomic sequencing testing or dedicated *EGFR* testing. If *EGFR*

mutation testing was negative, *ALK* rearrangement testing was required to be included in the routine-tested group. Patients were divided into 2 groups: broad-based genomic sequencing and routine tested (*EFGR* and/or *ALK* testing, but no broad-based genomic sequencing). Routine testing for *EGFR*/*ALK* was considered standard-of-care at the time of this study.

Construction of Variables

Cohort characteristics included age at advanced diagnosis, year of diagnosis, sex, race, smoking status, insurance source, median household income at the zip code level, stage at diagnosis, and *EGFR*/*ALK* alteration status. Comorbidities were assessed using *ICD-9* and *ICD-10* diagnosis codes using the categories outlined by Elixhauser et al.[17] The number of comorbidities was summed to create a comorbidity score (0, 1-2, ≥3 comorbidities). Treatment informed by broad-based genomic sequencing was defined as the receipt of targeted treatment for a specific mutation other than *EGFR*/*ALK* identified with broad-based genomic sequencing. The mortality variable was generated as previously described[18] with a sensitivity of 82.5% and specificity of 96.4%, benchmarked against the National Death Index. For other variables, characterization of data quality was performed at the individual item level including completeness and, when appropriate, accuracy based on double-data abstraction. Data quality of each variable was considered before incorporation into the analysis.

Outcomes

The primary outcome was 12-month mortality from the start of first-line treatment for the instrumental variable analysis. For the propensity score–matched survival analysis, the outcome was overall survival, defined as the time from the start of first-line treatment to the date of death, last follow-up, or data cut-off date of July 31, 2016. Secondary outcomes included the frequency of specific genetic alteration as well as treatments received. Among patients undergoing broad-based genomic sequencing, receipt of targeted treatments that were associated with specific mutations other than *EGFR or ALK* alterations defined "BGS-informed treatment."

Statistical Analysis

The distribution of cohort characteristics and treatment types received between the broad-based genomic sequencing and routine-tested groups was compared using χ^2 tests. For the survival analysis, patients undergoing broad-based genomic sequencing must have received testing prior to either first-, second-, or third-line treatment to avoid survivor bias of patients who received testing prior to their fourth or fifth line of treatment. All patients must have had 12 months of follow-up from the start date of their first line of systemic treatment (ie, started first-line treatment before July 31, 2015). An instrumental variable analysis was used to compare 12-month mortality between patients who received broad-based genomic sequencing vs routine testing. An instrumental variable analysis is used to account for unmeasured confounders in health services research.[19] The instrument is a known factor that is associated with the primary independent variable (broad-based genomic sequencing) but is only associated with the outcome (12-month mortality) through its effect on the independent variable.[20] The instrument used was the rate of broad-based genomic sequencing (number of patients who received broad-based genomic sequencing/total patients per practice) at the practice where the patient received care.[21,22] The association between rate of broad-based genomic sequencing (categorized into quartiles) and receipt of broad-based genomic sequencing testing was determined using a linear probability model. The association between practice rate of broad-based genomic sequencing and overall survival was determined using a Cox proportional hazards model. For an instrument to be valid, the association between broad-based genomic sequencing rate and the receipt of broad-based genomic sequencing testing should be strong, and the association between broad-based genomic sequencing testing practice rate and overall survival should be weak. A bivariate probit regression with broad-based genomic sequencing testing practice rate as the instrument and 12-month mortality as the dichotomous dependent variable was used to estimate the marginal effects of broad-based genomic sequencing on 12-month mortality. The difference in predicted probability of 12-month mortality between groups was reported.[23]

As a sensitivity analysis, propensity score matching was used to address potential confounding due to the significantly different cohort characteristics. Similar to the instrumental variable analysis, the propensity score sample was restricted to patients who received broad-based genomic sequencing prior to their third line of treatment. In addition, medical practices where none of the patients received broad-based genomic sequencing were excluded. A multivariable logistic regression analysis was used to estimate the probability of receiving broad-based genomic sequencing (from 0 to 1), the propensity score, based on age, race, sex, smoking status, income quartile, stage, year of diagnosis, *EGFR* or *ALK* mutation, broad-based genomic sequencing practice rate, number of comorbidities, receipt of only 1 line of treatment, and receipt of immunotherapy in line 1 or 2 vs line 3 or 4 of treatment. Due to significant survival bias conferred by certain patient characteristics, 4 covariates were set as exact covariate matches: *EGFR* or *ALK* mutation, receipt of only 1 line of treatment, year of diagnosis, and receipt of immunotherapy. For the variables with missing data (race, smoking status, income quintile, and stage), a missing indicator method was used because the missing variables were not missing at random.[24-26] One-to-one matching was performed using a nearest neighbor algorithm with a caliper of 0.1 standard deviations. Survival outcomes were estimated by the Kaplan-Meier method for each group (time 0 = start of first line) and were compared using the log-rank test. The association of broad-based genomic sequencing with survival was tested with a mixed-effects Cox proportional hazards model with practice site as a random effect. The proportional hazards assumption was tested graphically and statistically and was satisfied using both log (-log [survival]) curves and Schoenfeld residuals. Marginal adjusted hazard ratio and adjusted 95% CI were reported using a robust variance estimator to account for the matched nature of the data. All statistical tests were 2-sided, with a P value <.05 considered statistically significant. SAS 9.4,

Table 1. Characteristics of the Full Sample of Patients With Advanced Non–Small Cell Lung Cancer (N = 5688)

	No. (%)		
Total	Broad-Based Genomic Sequencing (n=875)	Routine Testing (n=4813)	*P* Value[a]
Age at diagnosis, y			
≤45	41 (4.7)	89 (1.9)	<.001
46-55	106 (12.1)	588 (12.2)	
56-65	277 (31.7)	1367 (28.4)	
66-75	307 (35.1)	1642 (34.1)	
76-85	144 (16.5)	1127 (23.4)	
Sex			
Male	407 (46.5)	2247 (46.7)	.93
Female	468 (53.5)	2566 (53.3)	
Race/ethnicity			
Non-Hispanic white	594 (67.9)	3023 (62.8)	<.001
Non-Hispanic black	49 (5.6)	380 (7.9)	
Hispanic or Latino	28 (3.2)	166 (3.5)	
Asian	39 (4.5)	172 (3.6)	
Other	98 (11.2)	377 (7.8)	
Unknown	67 (7.7)	695 (14.4)	
Comorbidity count[b]			
0	540 (61.7)	3092 (64.2)	.27
1-2	279 (31.9)	1404 (29.2)	
≥3	56 (6.4)	317 (6.6)	
Smoking status[c]			
No history of smoking	>218 (>24.9)	826 (17.2)	<.001
History of smoking	652 (74.5)	3891 (80.8)	
Unknown	<5 (<0.6)	96 (2.0)	
Insurance			
Commercial	364 (41.6)	1778 (36.9)	.10
Medicare	146 (16.7)	912 (19.0)	
Medicaid	7 (0.8)	53 (1.1)	
Other payer	116 (13.3)	646 (13.4)	
Unknown	242 (27.7)	1424 (29.6)	
Income, by quintile			
1 (lowest)	71 (8.1)	484 (10.1)	<.001
2	95 (10.9)	637 (13.2)	
3	163 (18.6)	927 (19.3)	
4	177 (20.2)	1037 (21.6)	
5 (highest)	357 (40.8)	1612 (33.5)	
Unknown	12 (1.4)	116 (2.4)	
Stage at diagnosis			
I	53 (6.1)	291 (6.1)	.61
II	33 (3.8)	179 (3.7)	
III	140 (16.0)	698 (14.5)	
IV	630 (72.0)	3504 (72.8)	
Unknown	19 (2.2)	141 (2.9)	
Year of diagnosis			
2011	33 (3.8)	418 (8.7)	<.001
2012	39 (4.5)	823 (17.1)	
2013	123 (14.1)	988 (20.5)	
2014	194 (22.2)	1139 (23.7)	
2015	317 (36.2)	1054 (21.9)	
2016	169 (19.3)	391 (8.1)	

(continued)

Table 1. Characteristics of the Full Sample of Patients With Advanced Non–Small Cell Lung Cancer (N = 5688) (continued)

Total	No. (%)		P Value[a]
	Broad-Based Genomic Sequencing (n=875)	Routine Testing (n=4813)	
EGFR status[d]			
Total tested	875 (100)	4813 (100)	
Positive	>175 (>20.0)	852 (17.7)	<.001
Negative	695 (79.4)	3830 (79.6)	
Unknown	<5 (<0.6)	131 (2.7)	
ALK status			
Total tested	863 (98.6)	5412 (94.5)	
Positive	35 (4.0)	176 (3.7)	<.001
Negative	817 (93.4)	4091 (85.0)	
Unknown	23 (2.6)	546 (11.3)	
Timing of broad-based genomic sequencing			
Before first-line treatment	310 (35.8)		
Before second-line treatment	366 (42.3)		
Before third-line treatment	116 (13.4)		
Before fourth-line treatment	46 (5.3)		
Before fifth-line treatment	28 (3.2)		

[a] χ^2 Test for the distribution of cohort characteristics between broad-based genomic sequencing and routine-tested groups.

[b] Comorbidities were assessed using *ICD-9* and *ICD-10* diagnosis codes using the comorbidity categories outlined by Elixhauser et al.[18] The number of conditions a patient had was summed to create a comorbidity score: 0, 1-2, or ≥3 comorbidities.

[c] Some cell sizes are obscured to protect patient privacy. Flatiron prohibits the display of cells containing fewer than 5 patients, as well as the display of information that could be used to determine a cell size containing <5 patients through subtraction or multiplication.

Table 2. Survival Results for Instrumental Variable and Propensity Score Matched Analyses[a]

	Broad-Based Genomic Sequencing	Routine Testing
Instrumental variable (n = 3587)[b]		
Predicted probability of death at 12 months[c], No. (%)	143 (41.1)	1439 (44.4)
Difference in predicted probability of death at 12 months%, [c]	−3.64 (−18.40 to 11.12)	
P value	.63	
Propensity score matched sample, Cox model (n = 1038)[d]		
Overall deaths, No. (%)	218 (42.0)	234 (45.1)
Hazard ratio (95% CI)	0.92 (0.73 to 1.11)	
P value	.40	

[a] Broad-based genomic sequencing performed before third-line treatment and had 12 months of follow-up from the start of first-line treatment. Routine testing performed at any time.

[b] Adjusted for all variables in Table 1.

[c] Time zero = from start of first-line treatment

[d] Mixed-effect Cox model with practice site as a random effect.

Stata version 14 (StataCorp LP), and R version 3.3.1 (R-project, Institute for Statistics and Mathematics: packages *lubridate V1.6.0*, *MatchIt V2.4-21*, *Survival version 2.3, coxphw V4.0.0, coxme V2.2-7*) were used to conduct all analyses.

Results

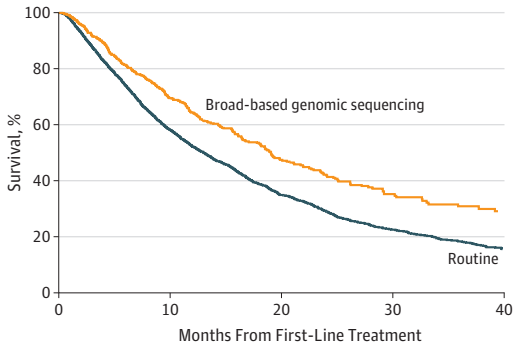
Baseline Characteristics

In the study sample, 5688 individuals with advanced NSCLC received broad-based genomic sequencing or routine testing; 875 (15.4%) received broad-based genomic sequencing (**Table 1**). The median age was 67 years (interquartile range, 41-85), the majority was white (63.6% vs 7.5% black vs 13.4% unknown race) and had a history of smoking (79.9%). Due to predetermined inclusion criteria, the entire sample received *EGFR* testing, while 95% received *ALK* testing. The majority of *ROS-1* (165020 OMIM), *KRAS* (190070 OMIM), and *PDL-1* (605402 OMIM) testing was performed among patients within the broad-based genomic sequencing group. There was a significant association between the receipt of immunotherapy and the receipt of broad-based genomic sequencing (adjusted odds ratio for receipt of immunotherapy among broad-based genomic sequencing vs routine-tested patients adjusted for age, sex, race, cancer stage, smoking status, income, comorbidities, and *EGFR/ALK* alteration status: 2.48 [95% CI, 2.0-3.0], *P* < .001). Receipt of immunotherapy within the first 4 lines of treatment was significantly associated with improved survival (adjusted hazard ratio, 0.41 [95% CI, 0.36-0.47], *P* < .001).

Survival

For the instrumental variable analysis, 49.2% of routine-tested patients died at 12 months vs 30.5% of patients receiving broad-based genomic sequencing (*P* < .001). The association between practice rates of broad-based genomic sequencing and receipt of testing was highly correlated (*P* < .001; F statistic = 495.6). Although there was significant variation in the use of broad-based genomic sequencing—0% to 100% of patients treated across practice sites—there was no significant difference in broad-based genomic sequencing practice quartiles and overall survival (hazard ratios ranged from 0.95 to 1.02, *P* = .43) or 12-month mortality (odds ratios, 0.82-1.13, *P* = .68), indicat-

Figure 1. Kaplan-Meier Estimates of Patients With Broad-Based Genomic Sequencing vs Routine Testing (N = 5688)

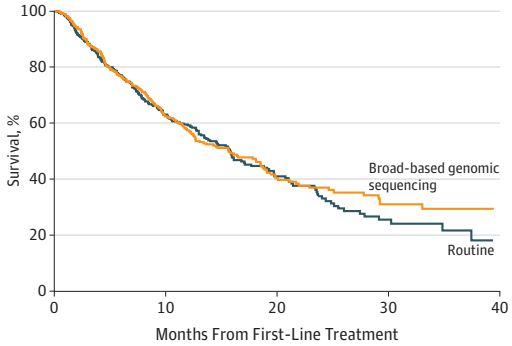


No. at risk

Testing method					
Broad-based genomic sequencing	875	363	146	63	31
Routine	4813	2018	831	350	132

Log-rank $P < .001$. Broad-based genomic sequencing indicated by >30 genes on testing platform. Routine testing included *EGFR* mutations and/or *ALK* rearrangements. Median length of follow-up for broad-based genomic sequencing group = 8.32 months (IQR, 3.68-16.12); for routine-tested group = 8.13 months (IQR, 3.62-15.92).

Figure 2. Kaplan-Meier Estimates of Patients With Broad-Based Genomic Sequencing vs Routine Testing Propensity Score–Matched Sample (n = 1038)



No. at risk

Testing method					
Broad-based genomic sequencing	515	195	64	23	8
Routine	513	192	66	18	<5

Log-rank $P = .50$. Broad-based genomic sequencing indicated by >30 genes on testing platform. Routine testing included *EGFR* mutations and/or *ALK* rearrangements. Median length of follow-up for broad-based genomic sequencing group = 7.63 months (IQR, 3.23-13.55); for routine-tested group = 6.97 months (IQR, 3.0-13.85).

ing a valid instrumental variable. The instrumental variable analysis had 83.7% power to detect an absolute difference of 12.4% in 12-month mortality between the groups. Using the instrumental variable analysis, there was no significant association between broad-based genomic sequencing and 12-month mortality (difference in the predicted probability of death at 12 months between the groups: −3.6% [95% CI, −18.4% to 11.1%]; $P = .63$; **Table 2**). The predicted probability of 12-month mortality for routine-tested patients was 44.4% (95% CI, 42.9%-45.9%) compared with 41.1% (95% CI, 27.7%-54.5%) for patients receiving broad-based genomic sequencing.

Using Kaplan-Meier survival analyses among the full sample, there was a significant difference between the 2 cohorts in the unadjusted survival curves (hazard ratio, 0.69 [95% CI, 0.62-0.77]; log-rank $P < .001$; **Figure 1**). The propensity score analysis had 80% power to detect a hazard ratio of 0.86 between the groups. Propensity-based matching produced 519 matched pairs with well-matched characteristics and balance, with standardized differences in patient characteristics of ≤0.10 (eTable 2 in the Supplement). The majority of the sample (81.2%) had complete data. Rates of immunotherapy use were 21.2% in both groups. Among the propensity score–matched sample, overall survival of the broad-based genomic sequencing cohort compared with the routine-tested cohort was not significantly different, as assessed using both a log-rank test ($P = .50$; **Figure 2**) and Cox proportional hazards model (hazard ratio, 0.92 [95% CI, 0.73-1.11]; $P = .40$; Table 2).

Genetic Mutations Detected

Among 875 patients in the broad-based genomic sequencing group, the majority had testing completed prior to either their first (35.8%) or second (42.3%) line of treatment. Among 875 broad-based genomic sequencing tested patients, 778 patients had a genetic mutation identified (88.9%). Among 247 unique genetic mutations identified, *TP53* was the most common (55.1% of mutations detected), followed by *KRAS* (34.2%), *EGFR* (21.9%), *CDKN2A* (15.7%), and *STK11* (12.2%) (eTable 3 in the Supplement). The most common actionable alterations other than *EGFR* and *ALK* found on broad-based genomic sequencing for which patients received targeted treatment were *BRAFV600E*, *MET*, and *ERBB2* (eTables 4, 5 and 6 in the Supplement). The majority of broad-based genomic sequencing tests reported on 315 genetic mutations (59.5%, eTable 7 in the Supplement). Overall, there was high concordance (98%-99.1%) between 399 *EGFR* and 330 *ALK* tests performed in patients who received both broad-based genomic sequencing testing in addition to routine testing.

Treatments Received

All patients received first-line treatment, but only 2688 (47.3%) received second-line treatment. The receipt of targeted treatment and chemotherapy in the first-line treatment setting were similar between routine-tested and broad-based genomic sequencing groups. However, patients receiving broad-based genomic sequencing were more likely to receive immunotherapy (4.0%) or clinical trial regimens (0.6%) than routine-tested patients (1.7% and 0.4%, respectively; $P < .001$ for both comparisons) (**Table 3**). Among patients without documented *EGFR* mutations or *ALK* rearrangements, the percentage receiving targeted treatment first-line was higher among the broad-based genomic sequencing group (8.3%) vs routine-tested (4.7%) ($P < .001$) (eTable 8 in the Supplement). Among broad-based genomic sequencing patients, 36 (4.5%) received broad-based genomic sequencing informed targeted treatment, 75 (9.8%) received *EGFR*/*ALK* targeted treatment, and 674 (85.1%) received no targeted treatment (Table 3).

Table 3. Treatments Received by Patients With Advanced Non–Small Cell Lung Cancer

Treatment Type	No. (%) Broad-Based Genomic Sequencing[a] (n = 875)	No. (%) Routine Testing (n = 4813)	*P* Value[b]
First-line treatment			
Total[c]	875 (100.0)	4813 (100.0)	
Targeted treatment	161 (18.4)	879 (18.3)	.94
Chemotherapy ± anti-VEGF	674 (77.0)	3835 (79.7)	.07
Immunotherapy	35 (4.0)	81 (1.7)	<.001
Clinical trial	5 (0.6)	18 (0.4)	.01
Second-line treatment			
Total	481 (55.0)	2207 (45.9)	
Targeted treatment	97 (20.2)	421 (19.1)	.45
Chemotherapy ± anti-VEGF	250 (52.0)	1477 (66.9)	<.001
Immunotherapy	128 (26.6)	289 (13.1)	<.001
Clinical trial	6 (1.3)	20 (0.9)	<.001
Total broad-based genomic sequencing testing before third-line treatment	792		
No broad-based genomic sequencing–informed targeted treatment	674 (85.1)		
Broad-based genomic sequencing–informed treatment	36 (4.5)		
EGFR/ALK targeted treatment	75 (9.5)		
Missing report	7 (0.9)		

Abbreviation: VEGF, vascular endothelial growth factor.

[a] Broad-based genomic sequencing testing performed before first, second, third, fourth, fifth, sixth, or seventh line of treatment.

[b] χ^2 Test for the distribution of treatment types between broad-based genomic sequencing and routine-tested groups.

[c] All patients received first-line treatment.

Discussion

Using 2 different survival analysis techniques, broad-based genomic sequencing was not associated with better survival than routine *EGFR* and/or *ALK* testing among patients with advanced NSCLC receiving treatment in the community oncology setting. Less than 5% of patients received broad-based genomic sequencing –informed treatment for a non-*EGFR* mutation or *ALK* rearrangement. These results stand in contrast to prior studies, which did not account for routine testing for *EGFR* and/or *ALK* as a comparison group, or use robust analytic techniques to account for both measured and unmeasured confounders.[27,28] Although in unadjusted survival estimates broad-based genomic sequencing was associated with better survival, differential receipt of immunotherapy between the 2 groups was an important confounder that, when accounted for, diminished the survival difference between the groups. Immunotherapy is associated with both broad-based genomic sequencing and with survival. However, treatment with immunotherapy is not directly caused by broad-based genomic sequencing, given that there is no single genetic alteration in a broad-based genomic sequencing report that directs a clinician to give immunotherapy. A clinician obtains PDL-1 testing, rather than broad-based genomic sequencing, to guide the use of single-agent immunotherapy (pembrolizumab) in the first-line treatment setting. Because treatment with immunotherapy is not directly caused by broad-based genomic sequencing, but is associated with both broad-based genomic sequencing and with survival, it was an important confounder requiring adjustment in the analyses. Overall, these findings suggest more effective targeted treatments may be needed to demonstrate improved population-level outcomes using broad-based genomic sequencing.

The paucity of clinically actionable mutations/rearrangements in advanced NSCLC other than *EGFR* or *ALK* in this study is consistent with the observed prevalence of "treatable" mutations seen in other cohorts.[29] The NCI-MATCH trial has exceeded enrollment targets, yet only 9% of tested patients had a gene mutation matching 1 of the 10 initially available treatment arms, while only 5% of tested patients actually received treatment assignments.[30] In addition, among 10 000 patients in the MSK-IMPACT trial, only 11% were enrolled in genomically matched clinical trials.[31]

Furthermore, expedited drug development is needed to iteratively target new molecular subgroups in the clinical trial setting. Initial results of Lung-MAP,[32] a large genomically matched national trial using targeted agents, including *FGFR* inhibitor AZD4547,[33] CDK 4/6 inhibitor palbociclib,[34] and PI3K inhibitor taselisib,[35] have been negative. There is limited availability of targeted treatments that are both effective and have minimal toxicity to target an ever-expanding list of tumor mutations.

This study focused mainly on community-based practice, rather than large academic centers where broad-based genomic sequencing may be part of research protocols. However, even if broad-based genomic sequencing is performed and there is a potential clinical trial with targeted therapy available, the number of patients treated in the community setting who have access to clinical trials for advanced NSCLC remains low.[36,37] Improved access to research clinical trials in the community setting may improve use of mutational data. Given the paucity of targeted agents, efforts to increase access to broad-based genomic sequencing should be paired with efforts to facilitate clinical trial enrollment.

This study highlights how broad-based genomic sequencing has disseminated beyond traditional research settings ahead of a demonstrated association with better survival. Drug therapy for advanced NSCLC has evolved rapidly and the use of immunotherapy such as pembrolizumab has become more common since

the dates of data collection for this study. However, PDL-1 screening for the potential benefits of pembrolizumab in the first-line treatment setting does not require broad-based genomic sequencing. The growing use of broad-based genomic sequencing in the community setting may be due to several reasons including the ease and cost associated with ordering a single test rather than multiple tests to obtain standard biomarker results, perception of benefit by physicians and patients, attempts to conserve tissue samples, and the hope of prolonged survival if an oral targeted treatment is available. Cost is particularly important because Medicare recently approved coverage of US Food and Drug Administration–approved broad-based genomic sequencing for any solid tumor type.[38]

The lack of an association between broad-based genomic sequencing and survival is likely multifactorial. First, there were few genetic alterations identified with available targeted treatments. Second, even among those patients for whom targeted treatments were available, the treatments may not yield a substantial survival benefit or patients may not have had access to targeted agents due to financial barriers. Decision support for clinicians once they receive broad-based genomic sequencing results may also be needed. Targeted therapies also may be prohibitively expensive for patients treated in the community, resulting in financial burden and limiting drug access, requiring transparency and payment reform in drug pricing.[39]

Limitations

This study has several limitations. First, this study is limited by a relatively small number of patients who received broad-based genomic sequencing, with the majority being of non-Hispanic white race and having relatively few comorbidities (<3) and commercial insurance, highlighting an issue of limited access of technology to minorities and patients with multiple comorbid conditions and/or noncommercial insurance. Second, comorbidities may have been underestimated using *ICD* codes only in oncology-focused EHR data. Third, use of structured EHR data to identify treatment in clinical trials likely underestimates clinical trial enrollment, and receipt of oral targeted treatment may also have been missed because it is difficult to capture oral usage comprehensively through structured EHR data. Since EHR data are captured during routine care, they are less complete and potentially less accurate than clinical trial data regarding factors such as mortality, performance status, and quality of life; missing mortality data may have biased the results. However, there is no reason to believe that the validity of the approach to ascertaining mortality would be systematically biased according to broad-based genomic sequencing status. Because there is no gold standard data against which to compare most EHR data, it is not possible to report sensitivity and specificity for most EHR-based variables. However, the data abstraction process was optimized through the use of an explicit abstraction protocol and trained abstractors.

Fourth, the data cutoff date may underestimate the number of patients who ultimately did receive second-line treatment. Fifth, evaluating whether clinicians had access to the broad-based genomic sequencing data and offered patients informed therapy was not routinely documented, limiting the understanding of clinician decision-making with broad-based genomic sequencing results. Sixth, the assessment of *EGFR* mutations and *ALK* rearrangements may have differed between the routine-tested and broad-based genomic sequencing groups. However, the study found high concordance among patients who received both types of testing and is therefore an unlikely source of any outcome differences. Seventh, other outcomes such as overall response rate, progression-free survival, and patient-reported outcomes were not measured. Eighth, future studies should assess whether there is a small incremental benefit between broad-based genomic sequencing–tested and routine-tested patients that this study was not powered to detect, and whether the effectiveness of broad-based genomic sequencing changes when newer targeted agents become available.

Conclusions

Among patients receiving care for advanced NSCLC in the community oncology setting, broad-based genomic sequencing directly informed treatment in a minority of patients and was not independently associated with better survival.

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