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Original Article

A rising tide lifts all boats in the personalized cancer care continuum for mNSCLC: bridging inequities in NGS fosters equity in targeted treatment

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Abstract

Background: Next-generation sequencing (NGS) testing in patients with metastatic non-small cell lung cancer (mNSCLC) identifies actionable driver oncogenes (ADO) and targeted treatment (TT). Potential inequities were evaluated in NGS testing and TT in patients with mNSCLC.

Patients and methods: This retrospective study used a nationwide electronic health record–derived deidentified database for patients ≥18 years diagnosed with mNSCLC between 4/2018 and 4/2024, ≥2 recorded visits, and follow-up ≥90 days post diagnosis. For TT, patients must have received NGS testing before first-line (1L) treatment and harbored ≥1 1L ADO.

Results: A total of 15 392 patients with mNSCLC were included: 66% with commercial insurance, 16% with Medicare, 12% with other, 4% with Medicaid, and 3% with other government insurance. Patients with commercial insurance had significantly higher odds of receiving NGS testing vs Medicare, Medicaid, or other insurance. While patient characteristics varied across insurances, the effect of insurance type on NGS testing did not differ by race/ethnicity, age, or socioeconomic status (SES). Site of care was a significant effect modifier, with increased odds of NGS testing for community vs academic settings for commercial, Medicare, and other insurance and decreased odds for Medicaid. When all patients received NGS testing, significantly lower odds of receiving TT occurred for patients with SES 2 vs SES 1 (lowest); higher odds occurred for Asian vs white patients.

Conclusion: Insurance is a key contributor to inequity in NGS testing. When all patients received NGS testing, equity was achieved in patients receiving TT, except those with lower SES, who potentially did not qualify for Medicaid.

Key words: next-generation sequencing; health equity; insurance.

Implications for practice

Insurance is a key contributor to inequity in next-generation sequencing (NGS) testing in patients with metastatic non-small cell lung cancer (mNSCLC) receiving care in community settings; those enrolled in Medicaid were less likely to receive NGS testing vs commercially insured patients. When all patients with mNSCLC had equitable access to NGS testing, we observed a positive downstream effect of more equitable access to targeted therapy, with the exception of patients with lower socioeconomic status not qualified for Medicaid. Insurance is therefore a key consideration to ensure equity from NGS testing to treatment stages in the mNSCLC personalized cancer care journey.

Introduction

Lung cancer is one of the most common cancers, representing 11.7% of all new cancer cases in the United States.[1] Non-small cell lung cancer (NSCLC) is the most common (85%) type of lung cancer, and approximately 30%-40% of patients present with metastatic NSCLC (mNSCLC) at the time of diagnosis.[2] Comprehensive genomic profiling through next-generation sequencing (NGS) is the standard of care for patients with mNSCLC in order to identify actionable driver oncogenes (ADO) and determine if and which optimal targeted treatment (TT) may be needed.[3,4] Over 60% of all patients with NSCLC have oncogenic driver mutations; of those, approximately 75% have an ADO.[5-7] The treatment

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landscape in mNSCLC has rapidly evolved, with various biomarkers recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the detection of ADO (eg, inhibitors of EGFR, ALK, ROS1, BRAF V600E, NTRK1/23/3, RET, MET, HER2, and KRAS G12C).[3]

Despite improved survival outcomes associated with TT for ADO identified via NGS testing,[8,9] inequity in NGS testing remains, especially for Black patients with lung cancer.[10] A systematic review found racial and ethnic disparities in most studies that used genomic testing in patients with NSCLC, with a lower testing rate observed for Black patients.[11] A recent study found that differences within community practices, across community practices, and within community primary providers were also main contributors to racial inequity in NGS testing for Black and Latinx patients.[12]

In addition to race and ethnicity inequities, insurance has been observed as a contributor to inequity in NGS testing. Compared with public insurance plans, biomarker testing was significantly more frequently conducted in patients with private insurance plans and self-pay patients.[13] While the Centers for Medicare & Medicaid Services (CMS) national coverage decision (NCD) should ensure equitable access to NGS testing, the policy did not narrow racial inequity in NGS testing among the Medicare-insured population, especially for Black and Latinx populations.[14] There is a paucity of data on potential inequity in receiving NGS testing by different insurance programs and the potential effect modification by race, socioeconomic status (SES), and practice type. In addition, questions remain if there is any inequity in patients with mNSCLC receiving TT after being identified with ADO through NGS testing.

This study evaluated the following in the mNSCLC personalized care continuum: (1) the potential NGS testing inequity by insurance plans and interactions by site of care, race/ethnicity, and SES and (2) the potential inequity in receiving TT after an ADO was identified through NGS testing in patients with *de novo* mNSCLC.

Patients and methods

A retrospective cohort study was performed using the Flatiron Health electronic health record–derived, US nationwide, deidentified longitudinal database comprising patient-level data originating from ≈280 US cancer clinics (≈800 sites of care) and curated via technology-enabled abstraction.[15,16] The data were deidentified and subject to obligations to prevent reidentification and protect patient confidentiality. This study was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices and applicable regulatory requirements. Review and approval by ethics committees or informed consent from patients included in this study analysis were not required, as the dataset adheres to the Safe Harbor Health Insurance Portability and Accountability Act deidentification rules for the United States and participants confirmed for inclusion were deidentified.

Patients

For the first study objective, impact of insurance on potential inequity in NGS testing, patients were included if they were aged ≥18 years; were diagnosed with mNSCLC (stage IVA or IVB) between April 1, 2018 (post–CMS March 2018 NCD11), and March 30, 2024; had ≥2 recorded visits; and had a follow-up of ≥90 days after metastatic diagnosis. Patients who received care in both community and academic settings and those with unknown insurance type were excluded.

For the second study objective, evaluation of any potential inequity for patients to receive TT after NGS testing, patients were included if they were aged ≥18 years; were diagnosed with mNSCLC (stage IVA or IVB) between April 1, 2018 (post-CMS March 2018 NCD11), and March 30, 2024; had ≥2 recorded visits; had a follow-up of ≥90 days after metastatic diagnosis; had received NGS testing before first-line (1L) treatment initiation; and were identified to harbor an ADO in the 1L setting (ie, ALK, BRAF, EGFR, MET, NTRK, RET, and/or ROS-1) per guideline recommendation at the time this study analysis was conducted in the fourth quarter of 2023.[17] Patients who received care in both community and academic settings, died ≤3 months from metastatic diagnosis, or were enrolled in clinical trials were excluded. To account for different US Food and Drug Administration (FDA) approval timelines of TT, a subanalysis was conducted on the second study objective focusing on patients with mNSCLC harboring an established ADO (eg, EGFR [FDA approved in 2004],[18] ALK [FDA approved in 2011],[19] or ROS-1 [FDA approved in 2016][20]).

Measures

NGS testing information and results were abstracted from electronic health record documentation and reported by testing technology platforms (eg, Illumina HiSeq), specific FDA-approved tests (eg, FoundationOne® CDx), and testing providers (eg, Caris Life Sciences).

Area-level SES was measured on the basis of the census block group data from the American Community Survey (2015-2019) with respect to the Yost Index (incorporating median household income, median home value, median gross rent, percentage of individuals living below 150% poverty line, percentage of individuals considered working class, percentage of unemployed individuals, and education index) and summarized in US population–weighted quintiles, with 1 representing the lowest SES (ie, 20th centile or less) to 5 representing the highest SES (ie, 80th centile or higher).[21,22]

Race/ethnicity was self-reported by patients and categorized as follows: non-Latinx white (white), non-Latinx Black, Latinx, non-Latinx Asian, and Other (Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial).

Insurance type was also self-reported (not sourced from billing transactions) and was categorized in hierarchical order as follows: commercial, including top health insurance companies as listed by the National Association of Insurance Commissioners report as well as any recorded health maintenance organization and preferred provider organizations; Medicare, which captures original Medicare fee-for-service; Medicaid, which includes aliases for state-specific Medicaid programs (eg, Medi-Cal); other government insurance, which includes Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage; and others, which includes patient assistant programs (defined by the Association of Community Cancer Centers; includes both foundation- and pharmaceutical/biotech-supported programs), self-pay, workers' compensation, or unknown payer types.

TTs in this study were specific to ADO in the 1L treatment setting per NCCN Guidelines® recommendation at the time of this study analysis, including ALK, BRAF, EGFR, MET, NTRK, RET, and/or ROS-1.[17]

Statistical analyses

Patient characteristics and demographics were descriptively summarized. Study cohorts by insurance and by race/ethnicity were compared using the Kruskal-Wallis rank sum test for continuous variables and Pearson χ^2 test for categorical variables.

For the first objective on the odds to receive NGS testing considering the CMS Laboratory Date of Service Policy of "14-day rule," for which reimbursement is confined to diagnostic tests ordered within 14 days of inpatient/outpatient discharge,[23] and factoring in the lack of testing order date (but including the sample collection date) available in the database, the odds of receiving an NGS test result during the period up to 90 days after metastatic diagnosis was evaluated. Multivariate regression analysis estimated the odds ratios of NGS testing, with adjustments for age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, SES, histology, smoking status, geographic region, practice type, race/ethnicity, practice volume, and year of advanced diagnosis. To identify potential effect modification, two-way interaction terms between insurance group and race/ethnicity, insurance and SES, and insurance and practice type were included in the multivariate regression analysis to assess the effects of insurance by race/ethnicity, SES, and practice type. Multiple imputation was performed to impute missing values for sex, SES, and smoking status. All other covariates with missing values were included in the model, with missing/unknown as a separate category.

For the second objective, the odds of receiving TT after patients were identified as harboring ADO based on their NGS testing results, to estimate the odds ratios for receiving TT, multivariate additive models were applied, with adjustment for race/ethnicity, SES, insurance group, practice type, practice volume, geographic region, age, sex, histology, smoking status, and ECOG performance status.

All analyses were conducted using R version 4.2.2.

Results

NGS testing inequity by insurance

A total of 15 392 patients with *de novo* mNSCLC met the study criteria (**Figure 1**). The majority of patients had commercial insurance (66%), followed by 16% with Medicare, 12% with other insurance (including unknown, patient assistance program, self-pay, and workers' compensation), 4% with Medicaid, and 3% with other government insurance. Across the different insurance plans, statistically significant differences were observed in age, sex, SES, race/ethnicity, practice type, histology, smoking status, ECOG performance status, and year of advanced diagnosis (**Table 1**). There was a higher proportion of non-Latinx Black patients who had Medicaid (19%) vs commercial (9.7%), Medicare (11%), other insurance (12%), and other government insurance (11%). Similar results were observed for Latinx patients (Medicaid 9.2% vs 1.7%-6.7% for all other insurance types). There was also a higher proportion of patients with a history of smoking in the Medicaid cohort and other government insurance cohorts (88% for each vs 80%-83% in all other insurance types).

An increasing trend in NGS testing rates was observed over time across all insurance types between 2018 and 2024 (**Figure 2A**). For all insurance types, NGS testing rates were between 73% and 100% in the first half of 2024 that was

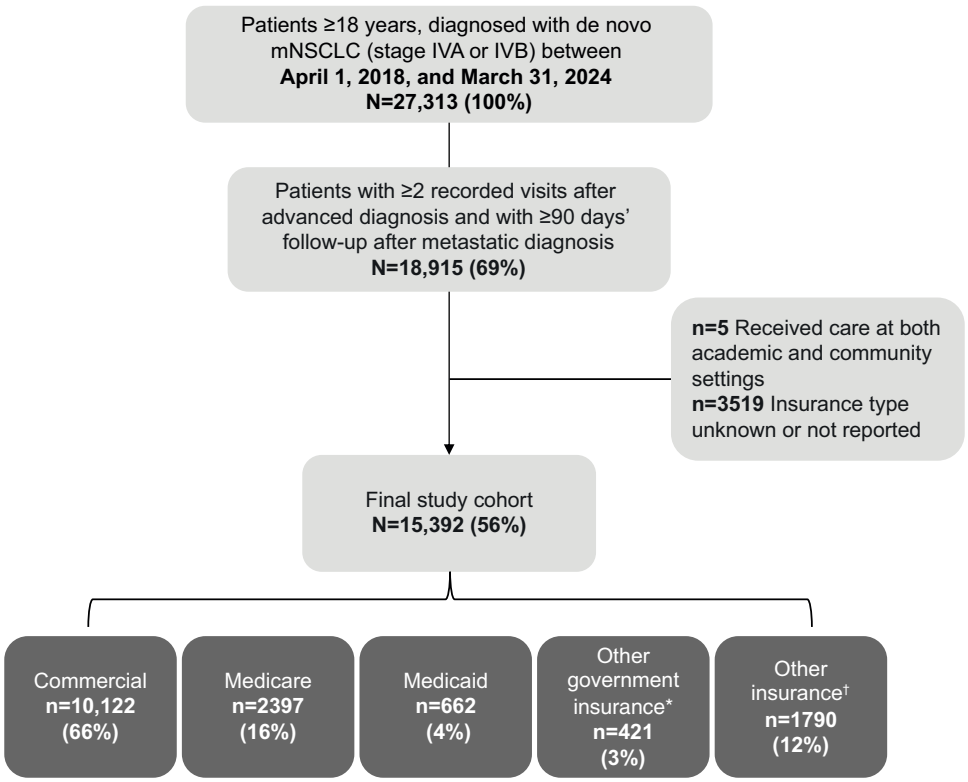

Figure 1. Patient attrition. mNSCLC, metastatic non-small cell lung cancer. * Other government insurance included Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage. † Other insurance programs included other payer type unknown, patient assistance program, self-pay, and workers' compensation.

Table 1. Characteristics among patients with mNSCLC by insurance type.

Characteristic*	Overall *N*=15 392	Commercial *n*=10 122	Medicare *n*=2397	Medicaid *n*=662	Other government insurance† *n*=421	Other‡ *n*=1790	*P* value§
Age, median (IQR), years	69 (55-83)	69 (55-83)	73 (62-84)	63 (50-76)	72 (56-88)	64 (50-78)	<.001
Sex							<.001
Female	7783 (51%)	5227 (52%)	1217 (51%)	342 (52%)	159 (38%)	838 (47%)	
Male	7607 (49%)	4894 (48%)	1179 (49%)	320 (48%)	262 (62%)	952 (53%)	
Missing	≤5 (< 1%)	≤5 (< 1%)	≤5 (< 1%)	0	0	0	
Histology							<.001
Non-squamous cell carcinoma	11,889 (77%)	7857 (78%)	1823 (76%)	485 (73%)	303 (72%)	1421 (79%)	
Squamous cell carcinoma	2866 (19%)	1829 (18%)	485 (20%)	142 (21%)	102 (24%)	308 (17%)	
NSCLC histology NOS	637 (4.1%)	436 (4.3%)	89 (3.7%)	35 (5.3%)	16 (3.8%)	61 (3.4%)	
Smoking status							<.001
History of smoking	12,633 (82%)	8261 (82%)	1992 (83%)	582 (88%)	372 (88%)	1426 (80%)	
No history of smoking	2747 (18%)	1852 (18%)	403 (17%)	80 (12%)	49 (12%)	363 (20%)	
Missing	12 (< 1%)	9 (1%)	≤5 (< 1%)	0	0	≤5 (< 1%)	
ECOG performance status							<.001
0	4484 (29%)	3069 (30%)	610 (25%)	146 (22%)	116 (28%)	543 (30%)	
1	5853 (38%)	3890 (38%)	901 (38%)	248 (37%)	169 (40%)	645 (36%)	
2	2074 (13%)	1300 (13%)	392 (16%)	111 (17%)	52 (12%)	219 (12%)	
3 or 4	666 (4.3%)	413 (4.1%)	123 (5.1%)	49 (7.4%)	15 (3.6%)	66 (3.7%)	
Unknown	2315 (15%)	1450 (14%)	371 (15%)	108 (16%)	69 (16%)	317 (18%)	
Year of advanced diagnosis							<.001
2018	2145 (14%)	1333 (13%)	424 (18%)	88 (13%)	46 (11%)	254 (14%)	
2019	2698 (18%)	1688 (17%)	518 (22%)	116 (18%)	67 (16%)	309 (17%)	
2020	2459 (16%)	1624 (16%)	400 (17%)	97 (15%)	87 (21%)	251 (14%)	
2021	2568 (17%)	1722 (17%)	398 (17%)	92 (14%)	65 (15%)	291 (16%)	
2022	2511 (16%)	1691 (17%)	325 (14%)	132 (20%)	73 (17%)	290 (16%)	
2023	2419 (16%)	1642 (16%)	261 (11%)	115 (17%)	71 (17%)	330 (18%)	
2024	592 (3.8%)	422 (4.2%)	71 (3.0%)	22 (3.3%)	12 (2.9%)	65 (3.6%)	
Area-level SES index¶							<.001
1 Lowest SES	2569 (18%)	1603 (17%)	360 (16%)	200 (33%)	78 (20%)	328 (20%)	
2	2758 (19%)	1806 (19%)	374 (17%)	148 (24%)	87 (22%)	343 (21%)	
3	3056 (21%)	2012 (21%)	476 (21%)	106 (17%)	85 (22%)	377 (23%)	
4	3148 (22%)	2119 (22%)	484 (22%)	103 (17%)	84 (22%)	358 (21%)	
5 Highest SES	2795 (20%)	1890 (20%)	534 (24%)	53 (8.7%)	54 (14%)	264 (16%)	
Missing	1066	692	169	52	33	120	
Race/ethnicity							<.001
Non-Latinx white	9648 (63%)	6409 (63%)	1625 (68%)	333 (50%)	276 (66%)	1005 (56%)	
Non-Latinx Black	1622 (11%)	977 (9.7%)	255 (11%)	125 (19%)	46 (11%)	219 (12%)	
Latinx	588 (3.8%)	343 (3.4%)	57 (2.4%)	61 (9.2%)	7 (1.7%)	120 (6.7%)	
Non-Latinx Asian	558 (3.6%)	358 (3.5%)	82 (3.4%)	35 (5.3%)	10 (2.4%)	73 (4.1%)	
Non-Latinx other	800 (5.2%)	532 (5.3%)	93 (3.9%)	41 (6.2%)	21 (5.0%)	113 (6.3%)	
Missing	2176 (14%)	1503 (15%)	285 (12%)	67 (10%)	61 (14%)	260 (15%)	
Practice type#							<.001
Academic	2896 (19%)	1769 (17%)	655 (27%)	125 (19%)	39 (9.3%)	308 (17%)	
Community	12,496 (81%)	8353 (83%)	1742 (73%)	537 (81%)	382 (91%)	1482 (83%)	
Geographic region							<.001
South	6159 (40%)	3964 (39%)	910 (38%)	298 (45%)	248 (59%)	739 (41%)	
Northeast	2093 (14%)	1392 (14%)	346 (14%)	98 (15%)	25 (5.9%)	232 (13%)	
Midwest	1619 (11%)	1164 (11%)	194 (8.1%)	49 (7.4%)	35 (8.3%)	177 (9.9%)	
West	2162 (14%)	1514 (15%)	240 (10%)	72 (11%)	67 (16%)	269 (15%)	
Missing	3359 (22%)	2088 (21%)	707 (29%)	145 (22%)	46 (11%)	373 (21%)	

Table 1. Continued

Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including ≤5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification. If it was possible to calculate ≤5 cell value using column total, the next higher number was used for both rows.
* All values are *n* (%) unless otherwise indicated.
†Other government insurance included Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage.
‡ Other insurance programs included other payer type unknown, patient assistance program, self-pay, and workers' compensation.
§ Kruskal-Wallis rank sum test; Pearson X^2 test.
¶ SES index is based on where patients reside.
# Practice type is categorized based on visits closest to advanced diagnosis date.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mNSCLC, metastatic non-small cell lung cancer; NOS, not otherwise specified; SES, socioeconomic status.

evaluated. Patients with commercial insurance were more likely to receive NGS testing vs all other insurance types; these results were all statistically significant except for commercial vs other government insurance (**Figure 2B**).

Within each people of color race/ethnicity, we observed a higher proportion of patients enrolled in Medicaid (Supplementary Table S1). Within the lower SES levels, we observed a higher proportion of patients enrolled in Medicaid (Supplementary Table S2). When two-way interactions were modeled between insurance type and each of race/ethnicity, SES, and site of care, patients with commercial insurance were less likely to receive NGS testing if they were non-Latinx Black, non-Latinx Asian, or non-Latinx Other (vs non-Latinx white); for Medicare and Medicaid, similar results were observed for non-Latinx Black patients (**Supplementary Table S3**). For commercial, Medicare, and other insurance, patients were less likely to receive NGS testing in a community practice vs an academic setting; for Medicaid, the opposite was observed, with patients more likely to receive NGS testing in a community practice. A significant interaction effect was only observed for insurance type by site of care, where the odds ratio of NGS testing in community vs academic setting was significantly lower for patients with Medicaid compared with commercial insurance (odds ratio: 0.18; 95% CI: 0.11, 0.31; **Supplementary Table S4**). Race/ethnicity, age, and SES had no interaction effects on the relationship between insurance plan and odds of receiving NGS testing.

Inequity in TT

A total of 1811 patients with mNSCLC who received NGS testing prior to 1L TT initiation and harbored ≥1 ADO (ALK, BRAF, EGFR, MET, NTRK, RET, and/or ROS1) met the study criteria (**Figure 3**, **Table 2**). Of these patients, 54% self-reported as non-Latinx white, 15% had race/ethnicity missing, 12% were Asian, 8% were non-Latinx Black, 6% were Latinx, and 5% reported as "other" race/ethnicity (**Table 3**). Overall, 95% had non-squamous NSCLC, 2% had squamous NSCLC, and 2% had histology not otherwise specified. There were significant differences by race/ethnicity in age at diagnosis, SES, insurance type, practice type, and smoking status. A higher proportion of non-Latinx Black (33%) and Latinx patients (30%) were in the lowest SES 1 compared with other race/ethnicities (range, 7.3%-14%). For insurance types, a higher proportion of non-Latinx Black (4.2%), Latinx (5.2%), and non-Latinx Asian (7.0%) patients had Medicaid compared with patients of other race/ethnicities (range, 1.1%-3.0%). Other insurance and other government insurance categories were combined to preserve sample size. EGFR (63%) was the most common 1L ADO, with the highest proportion observed in non-Latinx Asian patients (86%), followed by Latinx (70%) and missing race/ethnicity (67%; **Table 2**). Across race/ethnicity, the mean time from advanced diagnosis to NGS testing result date was 22 days (range: 20-26 days), and mean time from advanced diagnosis to 1L TT initiation: 39 days (range: 35-47 days).

Of patients with mNSCLC harboring ≥1 1L ADO, Asian vs white, Medicare vs commercial, and no smoking history vs smoking history were more likely to receive 1L TT; those patients in SES 2 (ie, 21st-40th centile) vs lowest SES 1 (ie, ≤20th centile/lowest), community vs academic, and squamous vs non-squamous were less likely to receive 1L TT (**Figure 4A**). A total of 1347 patients with mNSCLC harbored an established ADO (EGFR, ALK, or ROS-1). Of these patients, Asian vs white patients were more likely to receive 1L TT, while SES 2 (ie, 21st-40th centile) vs SES 1 (ie, ≤20th centile/lowest) and squamous vs non-squamous were less likely to receive 1L TT (**Figure 4B**).

Discussion

In this study, we evaluated inequities in the personalized cancer care continuum for patients with mNSCLC, from NGS testing to treatment in routine US clinical care settings.

At the NGS testing stage, while all insurance plans have increased adoption of NGS testing over time for patients with mNSCLC, we observed that patients with commercial insurance had significantly higher odds of receiving NGS testing compared with patients with Medicare, Medicaid, and other insurance types. These findings were consistent with a study that also showed that biomarker testing rates were higher for commercially insured patients vs the Medicare Advantage population (49% vs 44%; $P < .01$)[24] as well as another study that observed that Medicaid patients were less likely to receive biomarker testing compared with patients who had commercial insurance.[25,26]

Even though significant differences were observed across insurance plans by patient characteristics evaluated, our findings suggest that race/ethnicity, age, and SES have no effect modification on the association between insurance plan and odds of receiving NGS testing. However, site of care was a significant effect modifier where Medicaid patients were significantly less likely to receive NGS testing vs commercially insured patients in community vs academic settings. This was consistent with the literature showing that community vs academic centers have lower biomarker testing rates.[27] Opportunities remain to reduce the complexity of ordering and interpreting biomarker tests in all centers where NGS testing occurs, overcome insufficient tissue availability for biomarker testing, and address operational challenges on the multidisciplinary cancer care team to provide all patients with equitable care.[27]

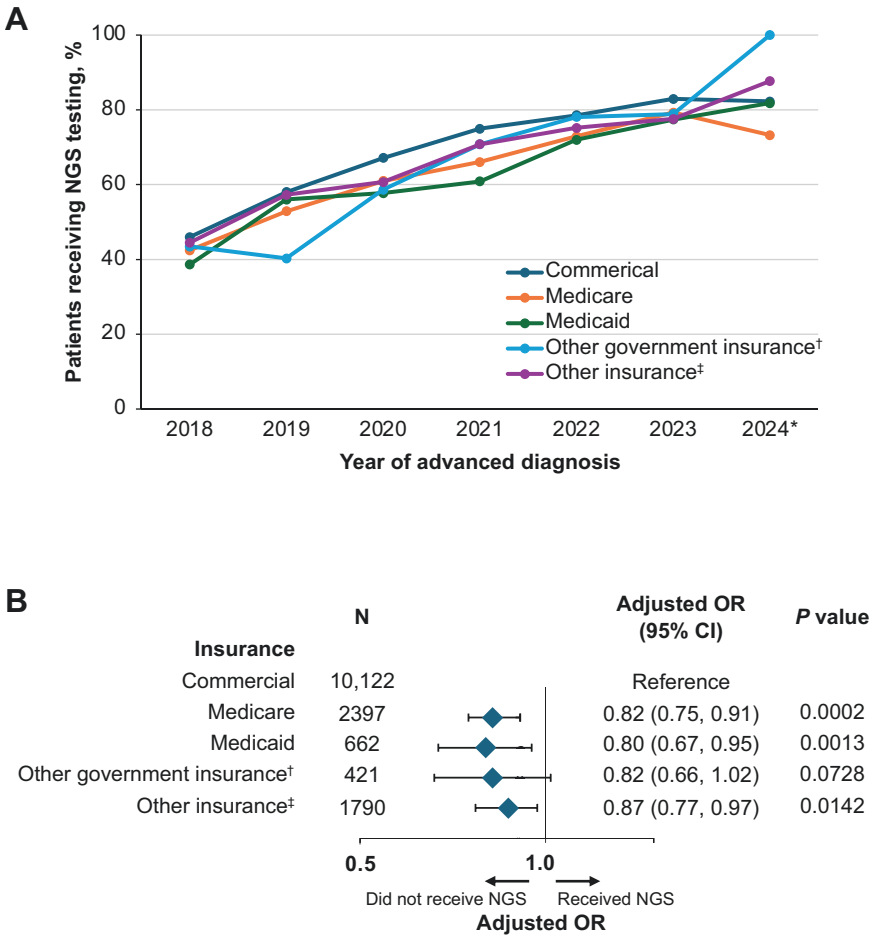

Figure 2. (A) NGS testing over time and **(B)** odds of patients with mNSCLC receiving NGS testing by insurance type. mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; OR, odds ratio. * 2024 included only the period from January 2024 to the end of June 2024. † Other government insurance included Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage. ‡ Other insurance programs included other payer type unknown, patient assistance program, self-pay, and workers' compensation.

Our findings underscore the variability of insurance coverage for NGS testing, which contributes to inequities in patient care. Commercial insurances provide variable coverage based on factors such as FDA labeling, clinical efficacy of tests, NCCN Guidelines, and peer-reviewed published data and may require prior authorization.[25,28,29] In contrast, Medicare covers all FDA-approved oncology NGS tests; however, some medical administrative contractors have had issues with limits on the timing and frequency of testing.[30,31] For Medicaid, each state has a different coverage policy, and many state Medicaid plans lack explicit coverage policies regarding biomarker testing.[25,32,33] For other government insurance plans, NGS testing is covered by an agreement with a national laboratory and Foundation Medicine; the coverage varies by plan, patient diagnosis, and other factors.[34,35]

Since 2021, several states in the United States have passed legislation to mandate coverage for biomarker testing. As of July 2024, 20 states (Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maryland, Minnesota, New Mexico, New York, Oklahoma, Pennsylvania, Rhode Island, and Texas) have instituted legislation for insurance to cover comprehensive biomarker testing, such as NGS testing.[36] However, this legislation varies by state: some are Medicaid oriented only, some are Medicaid and commercial payers, and some are commercial payer only[37]; the legislation does not consider patient affordability but defers to insurers' discretion over cost sharing.[38,39] As highlighted by a large cohort of oncologists in the United States, a patient's insurance coverage and out-of-pocket costs were key factors in the oncologists' treatment decisions for the patient.[40] Although a recent study observed that the out-of-pocket costs for patients with cancer represented about 3% of the overall total cost of care, patient cost-sharing can vary by insurance plan, and data remain limited on patient affordability of NGS testing.[41] Opportunities remain to refine state Medicaid coverage policy and patient out-of-pocket cost-sharing design across all insurance types.[32]

At the treatment stage, when all patients with mNSCLC received NGS testing to identify their ADO before 1L treatment initiation, the inequity by race and inequity by insurance observed at the NGS testing stage no longer applied. This reinforces the importance of receiving timely NGS testing results to inform the appropriate TT for patients with mNSCLC, which was previously demonstrated to be a common barrier for precision oncology.[42] Significantly lower odds of receiving TT were observed for patients with SES 2 (ie, 21st-40th centile) vs SES 1 (ie, ≤20th centile/lowest; adjusted HR: 0.53, $P = .0418$ for mNSCLC with any ≥1 ADO and 0.37, $P = .0363$ for mNSCLC with historical ADO [EGFR, ALK, or ROS-1]) and those receiving care in community vs

academic centers. These results may reflect financial challenges in patient populations that are most likely to encounter the Medicaid coverage gap, which include patients with lower SES who are not eligible for Medicaid and cannot afford private insurance.[43] For patients receiving care in community centers, the lack of receiving TT may reflect referral bias or underuse of TT due to operational and/or financial challenges.[44] The significantly higher odds of receiving TT by race (Asian vs white), histology (non-squamous vs squamous), and smoking history (non-smoker vs smoker) reflects the known characteristics of patients with mNSCLC who are most likely to have an ADO and may signify that providers are more cognizant of the need for NGS testing when these factors are present. Similar findings for lower odds of TT in SES 2 vs SES 1 and higher odds of TT in Asian vs white patients in the subcohort with historical ADO underscore that better insurance coverage and design is an area of opportunity to ensure equitable access to TT in mNSCLC.

Our findings were limited by the data available. Reasons for not getting NGS tested and/or receiving TT were not available, and NGS may not have been conducted due to insufficient tissue, lack of reflex testing, insurance denial, lack of affordability, patient refusal or contraindication, and other reasons. While area-level SES, insurance, and race/ethnicity data were included in this study, additional information on social determinants of health, such as cultural barriers, language proficiency, health literacy, proximity to healthcare providers, support systems, and economic stability, was not available. In addition, data on patient race/ethnicity and insurance were self-reported and subjective to misclassification, and approximately 15% of race/ethnicity data were missing. We also did not have details on the list of payers included in the commercially insured cohort to further discern if certain aspects of coverage policies hindered patient access to NGS testing. For example, a recent study found that many commercial insurance policies were more restrictive on the number of genes that could be tested vs what is recommended in the NCCN Guidelines, especially for certain cancer types, including NSCLC.[45] Future studies are warranted to further understand variability and inequity in coverage and patient affordability for NGS testing. Finally, findings observed in this study are reflective of the predominantly community setting from the Flatiron Health Network and may not be generalizable to broader cancer care practices in the US or outside of the US.

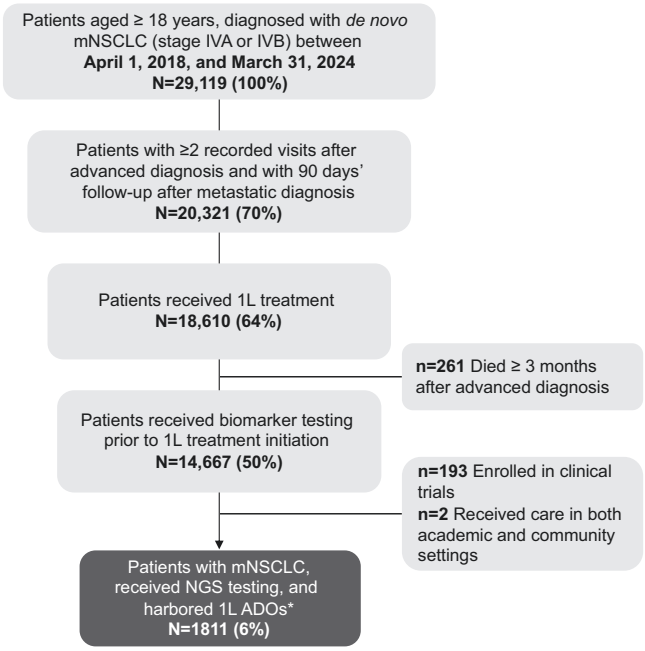

Figure 3. Patient attrition. 1L, first line; ADO, actionable driver oncogene; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing. * ADO included EGFR, ALK, ROS-1, BRAF, MET, NTRK, and RET.

Conclusions

Findings from our study provided important insights to strive for health equity in personalized care in mNSCLC. We uncovered insurance as a key contributor to inequity in NGS

Table 2. Actionable driver oncogene mutation distribution among patients with mNSCLC who received NGS testing before 1L treatment initiation.

1L ADO, *n* (%)	Overall *N*=1811	Non-Latinx white *n*=970	Non-Latinx Black *n*=145	Latinx *n*=116	Non-Latinx Asian *n*=214	Non-Latinx other *n*=95	Missing race/ethnicity *n*=271
ALK	158 (8.7%)	90 (9.3%)	16 (11%)	10 (8.6%)	11 (5.1%)	≤5 (< 5%)	27 (10.0%)
BRAF	137 (7.6%)	93 (9.6%)	14 (9.7%)	≤5 (< 4%)	≤5 (< 3%)	8 (8.4%)	14 (5.2%)
MET	149 (8.2%)	96 (9.9%)	14 (9.7%)	8 (6.9%)	≤5 (< 3%)	9 (9.5%)	17 (6.3%)
EGFR	1149 (63%)	552 (57%)	90 (62%)	81 (70%)	183 (86%)	61 (64%)	182 (67%)
NTRK1	≤5 (< 1%)	≤5 (< 1%)	≤5 (< 4%)	≤5 (< 4%)	≤5 (< 3%)	≤5 (< 5%)	≤5 (< 2%)
NTRK2	≤5 (< 1%)	≤5 (< 1%)	≤5 (< 4%)	≤5 (< 4%)	≤5 (< 3%)	≤5 (< 5%)	≤5 (< 2%)
NTRK3	≤5 (< 1%)	≤5 (< 1%)	≤5 (< 4%)	≤5 (< 4%)	≤5 (< 3%)	≤5 (< 5%)	≤5 (< 2%)
RET	40 (2.2%)	31 (3.2%)	≤5 (< 4%)	≤5 (< 4%)	≤5 (< 3%)	≤5 (< 5%)	≤5 (< 2%)
ROS1	40 (2.2%)	25 (2.6%)	≤5 (< 4%)	≤5 (< 4%)	≤5 (< 3%)	≤5 (< 5%)	≤5 (< 2%)
≥1 aforementioned ADO	134 (7.4%)	81 (8.4%)	6 (4.1%)	9 (7.8%)	7 (3.3%)	10 (11%)	21 (7.7%)

Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including ≤5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification. If it was possible to calculate ≤5 cell value using column total, the next higher number was used for both rows.
1L, first line, ADO, actionable driver oncogene; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing.

Table 3. Characteristics among patients with mNSCLC who received NGS and harbored ADO by race/ethnicity.

Characteristic*	Overall *n* = 1811	Non-Latinx white *n* = 970	Non-Latinx Black *n* = 145	Latinx *n* = 116	Non-Latinx Asian *n* = 214	Non-Latinx other *n* = 95	Missing race/ethnicity *n* = 271	*P* value†
Age, median (IQR), years	69 (53-85)	69 (54-84)	67 (51-83)	63 (41-85)	69 (53-85)	70 (53-87)	72 (57-87)	<.001
Sex								.4
Female	1173 (65%)	608 (63%)	101 (70%)	76 (66%)	142 (66%)	60 (63%)	186 (69%)	
Male	638 (35%)	362 (37%)	44 (30%)	40 (34%)	72 (34%)	35 (37%)	85 (31%)	
Histology								>.9
Non-squamous cell carcinoma	1722 (95%)	921 (95%)	137 (94%)	110 (95%)	≥201 (> 94%)	94 (99%)	258 (95%)	
Squamous cell carcinoma	45 (2.5%)	25 (2.6%)	≤5 (< 3.4%)	≤5 (< 4.3%)	≤5 (2.3%)	≤5 (< 5.2%)	8 (3.0%)	
NSCLC histology NOS	44 (2.4%)	24 (2.5%)	≤5 (< 3.4%)	≤5 (< 4.3%)	7 (3.3%)	≤5 (< 5.2%)	≤5 (≤ 1.8%)	
Smoking status								<.001
History of smoking	827 (46%)	503 (52%)	60 (41%)	50 (43%)	60 (28%)	46 (48%)	108 (40%)	
No history of smoking	983 (54%)	466 (48%)	85 (59%)	66 (57%)	154 (72%)	49 (52%)	163 (60%)	
Missing	≤5 (< 1%)	≤5 (< 1%)	0	0	0	0	0	
ECOG performance status								.005
0	589 (33%)	314 (32%)	40 (28%)	33 (28%)	80 (37%)	24 (25%)	98 (36%)	
1	648 (36%)	350 (36%)	58 (40%)	39 (34%)	84 (39%)	35 (37%)	82 (30%)	
2	195 (11%)	103 (11%)	24 (17%)	11 (9.5%)	20 (9.3%)	10 (11%)	27 (10.0%)	
3 or 4	54 (3.0%)	21 (2.2%)	≤5 (< 3.4%)	≤5 (< 4.3%)	9 (4.2%)	6 (6.3%)	12 (4.4%)	
Unknown	325 (18%)	182 (19%)	19 (13%)	31 (27%)	21 (9.8%)	20 (21%)	52 (19%)	
Year of advanced diagnosis								<.001
2018	141 (7.8%)	86 (8.9%)	13 (9.0%)	≤5 (< 4.3%)	17 (7.9%)	10 (11%)	11 (4.1%)	
2019	269 (15%)	162 (17%)	18 (12%)	11 (9.5%)	28 (13%)	20 (21%)	30 (11%)	
2020	272 (15%)	123 (13%)	17 (12%)	27 (23%)	39 (18%)	26 (27%)	40 (15%)	
2021	331 (18%)	171 (18%)	24 (17%)	21 (18%)	38 (18%)	21 (22%)	56 (21%)	
2022	359 (20%)	181 (19%)	34 (23%)	27 (23%)	46 (21%)	8 (8.4%)	63 (23%)	
2023	375 (21%)	209 (22%)	32 (22%)	26 (22%)	41 (19%)	9 (9.5%)	58 (21%)	
2024	64 (3.5%)	38 (3.9%)	7 (4.8%)	≤5 (< 4.3%)	≤5 (< 2.3%)	≤5 (< 5.2%)	13 (4.8%)	
Area-level SES index‡								<.001
1 Lowest SES	199 (12%)	66 (7.3%)	44 (33%)	32 (30%)	17 (8.4%)	11 (14%)	29 (12%)	
2	284 (17%)	142 (16%)	25 (19%)	20 (19%)	39 (19%)	14 (18%)	44 (17%)	
3	361 (22%)	189 (21%)	30 (22%)	20 (19%)	41 (20%)	14 (18%)	67 (27%)	
4	414 (25%)	256 (28%)	21 (16%)	20 (19%)	50 (25%)	19 (25%)	48 (19%)	
5 Highest SES	420 (25%)	254 (28%)	15 (11%)	14 (13%)	55 (27%)	18 (24%)	64 (25%)	
Missing	133	63	10	10	12	19	19	
Practice type§								<.001
Academic	444 (25%)	306 (32%)	38 (26%)	39 (34%)	35 (16%)	17 (18%)	9 (3.3%)	
Community	1367 (75%)	664 (68%)	107 (74%)	77 (66%)	179 (84%)	78 (82%)	262 (97%)	
Geographic region								
South	518 (40%)	290 (46%)	73 (71%)	26 (40%)	47 (27%)	25 (33%)	57 (22%)	
Northeast	278 (21%)	137 (22%)	19 (18%)	9 (14%)	62 (36%)	≤5 (< 5.2%)	48 (19%)	
Midwest	204 (16%)	143 (22%)	7 (6.8%)	7 (11%)	20 (11%)	18 (24%)	9 (3.5%)	
West	307 (23%)	66 (10%)	≤5 (< 3.4%)	23 (35%)	45 (26%)	29 (39%)	140 (55%)	
Missing	504	334	42	51	40	20	17	
Insurance type								<.001
Commercial	1045 (58%)	581 (60%)	72 (50%)	52 (45%)	120 (56%)	57 (60%)	163 (60%)	
Medicare	186 (10%)	111 (11%)	13 (9.0%)	7 (6.0%)	23 (11%)	≤10 (< 11%)	25 (9.2%)	
Medicaid	54 (3.0%)	18 (1.9%)	6 (4.1%)	6 (5.2%)	15 (7.0%)	≤5 (< 5.2%)	8 (3.0%)	
Other insurance¶	189 (10%)	89 (9.2%)	28 (19%)	19 (16%)	19 (8.9%)	9 (9.5%)	25 (9.2%)	
Not reported	337 (19%)	171 (18%)	26 (18%)	32 (28%)	37 (17%)	21 (22%)	50 (18%)	

Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including ≤5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification. If it was possible to calculate ≤5 cell value using column total, the next higher number was used for both rows.
* All values are *n* (%) unless otherwise indicated.
† Kruskal-Wallis rank sum test; Pearson X^2 test.
‡ SES index is based on where patients reside.
§ Practice type is categorized based on visits closest to advanced diagnosis date.
¶ Included 164 patients with other insurance and 25 with other government insurance. Other insurance and other government insurance categories were combined to preserve sample size. Other insurance programs included other payer type unknown, patient assistance program, self-pay, and workers' compensation. Other government insurance included Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage.
Abbreviations: ADO, actionable driver oncogene; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; NOS, not otherwise specified; SES, socioeconomic status.

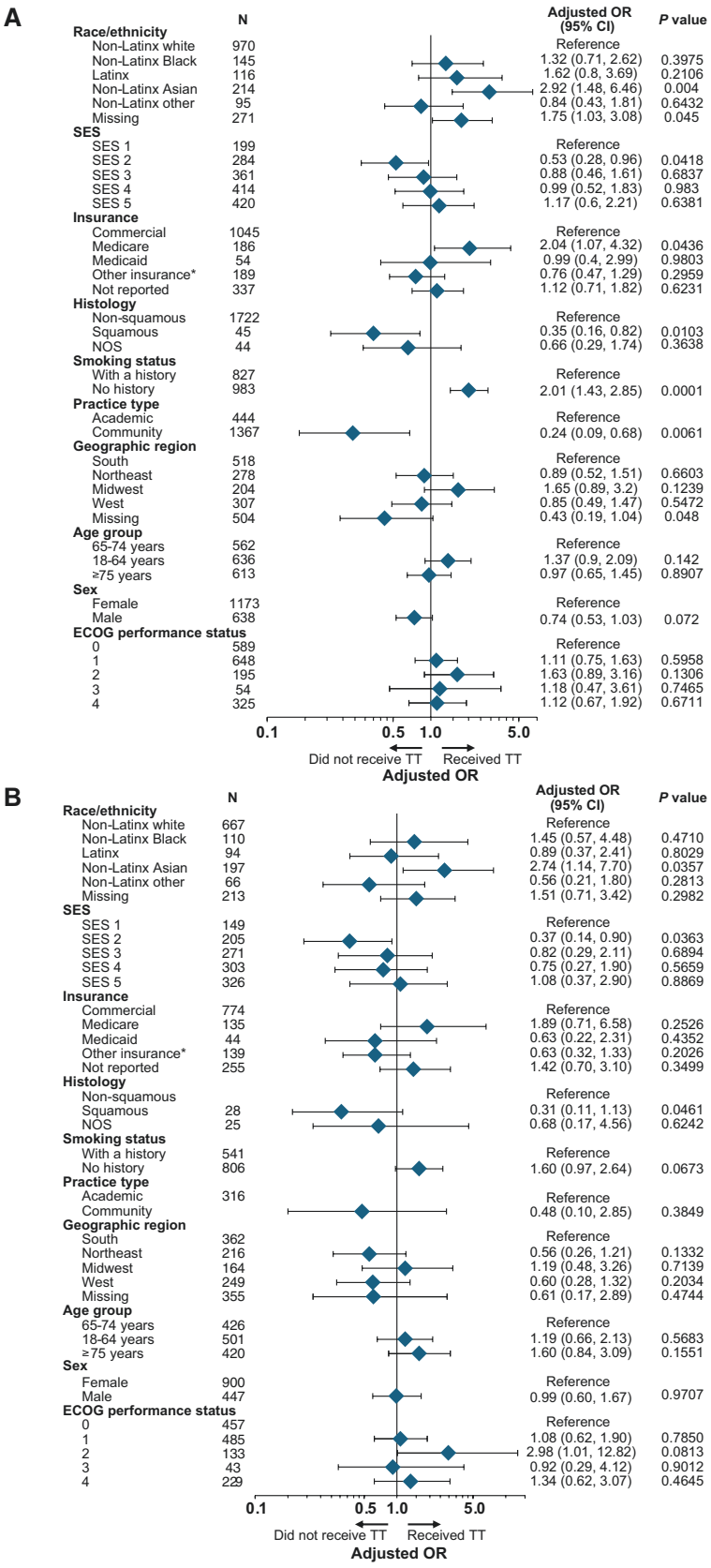

Figure 4. Odds of receiving targeted therapy among **(A)** patients with mNSCLC who received NGS testing and harbored ≥1 ADO (ie, ALK, BRAF, EGFR, MET, NTRK, RET, and/or ROS-1) and **(B)** a subcohort of patients with mNSCLC who received NGS testing and harbored EGFR, ALK, or ROS-1. ADO, actionable driver oncogene; ECOG, Eastern Cooperative Oncology Group; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; NOS, not otherwise specified; OR, odds ratio; SES, socioeconomic status; TT, targeted therapy. * Included 164 patients with other insurance and 25 with other government insurance. Other insurance and other government insurance categories were combined to preserve sample size. Other insurance programs included other payer type unknown, patient assistance program, self-pay, and workers' compensation. Other government insurance included Indian Health Service/Tribal Health Service, city or county coverage, and jail or correctional facility coverage.

testing among patients with mNSCLC. In particular, patients receiving care in the community setting were less likely to receive NGS testing if enrolled in Medicaid as opposed to commercial insurance. We also observed the importance of addressing inequity in NGS testing. When all patients with mNSCLC received NGS testing, we observed the downstream positive benefit of achieving equity in these patients receiving biomarker-driven TT, with the exception of those with lower SES, which was potentially due to ineligibility for Medicaid. Future studies are warranted to better understand the effectiveness of state legislation on addressing inequities in biomarker testing and identify opportunities to further refine the statutes so that all patients have equal coverage, can afford out-of-pocket costs, and receive timely access to NGS testing and TT. This will ensure that an equitable, personalized cancer care journey can be a reality for all patients with mNSCLC.

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Author contributions

All authors contributed to study inception and design, analysis plan, results interpretation, and manuscript revision.

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Conflicts of interest

Victor T. G. Lin received research funding from AstraZeneca, Aveo, BeiGene, Genentech, GSK, Loxo/Lilly, Merck, and Pfizer and serves as the site principal investigator for a variety of clinical trials for Mary Bird Perkins Cancer Center. Esprit Ma is an employee of Genentech and owns stock in Roche. Zhiyu Xia is an employee of Genentech and owns stock in Roche. Danny Sheinson is an employee of Genentech and owns stock in Roche. Elaine Yu is an employee of Genentech and owns stock in Roche. Neha Jain has participated in a J&J scientific advisory board. Richard Lewis Martin reports no conflicts. Richard Zuniga has participated in Flatiron and Bristol-Myers Squibb scientific advisory boards and received honoraria and been lead author for ChemoMouthpiece. Davey Daniel has received research funding from AstraZeneca, Genentech, Guardant Health, Janssen, Bristol Myers Squibb, G1 Therapeutics, Merck, Novartis, AbbVie, ARMO, Immunomedics, Lilly, Merus NV, Daiichi Sankyo, Roche, Celgene, and Amgen. Richard S.P. Huang is an employee of Foundation Medicine and owns stock in Roche. Gregory Vidal has received consulting fees from Roche/Genentech, Novartis, Eli Lilly, Gilead, Puma, Pfizer, Stemline, and Biotheranostics; has received fees for non-CME services from Eli Lilly, Novartis, Puma, and Pfizer; has conducted contracted research for Roche/Genentech, Puma, Celcuity, Merck, BMS, Eli Lilly, GTx, AstraZeneca, Pfizer, Gilead, Tesaro, Halozyme, GSK, and Natera; and owns stock in Oncodisc. Thomas Stricker is an employee of Tennessee Oncology/One Oncology and has received honoraria from Illumina.

Data availability

The data that support the findings of this study were originated by and are the property of Flatiron Health, Inc., which has restrictions prohibiting the authors from making the data set publicly available. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to publicationsdataaccess@flatiron.com.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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