Genomic Profiling of Advanced Non–Small Cell Lung Cancer in Community Settings: Gaps and Opportunities

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Abstract

The US and European guidelines have recommended testing of advanced non–small cell lung cancer (NSCLC) patients for multiple targetable genomic alterations. We found that roughly one third of 814 nonsquamous NSCLC patients in a large oncology practice had not been tested for *EGFR* or *ALK*, with more marked under genotyping of additional genomic targets. The challenges and potential solutions are discussed.

Background: National guidelines have advocated broad molecular profiling as a part of the standard diagnostic evaluation for advanced non–small cell lung cancer (NSCLC), with the goal of identifying driver mutations for which effective therapies or clinical trials are available. However, adherence to genomic testing guidelines could present challenges to community oncologists. **Patients and Methods:** We performed a retrospective review of genomic testing patterns in patients with nonsquamous NSCLC treated by 89 oncologists at 15 sites throughout New Jersey and Maryland from January 2013 to December 2015. **Results:** A total of 814 patients (89% with stage IV; 11% with stage IIIB) were identified in the COTA Inc database. Of the 814 patients, 479 (59%) met the guideline recommendations for *EGFR* (epidermal growth factor receptor) and *ALK* (anaplastic lymphoma kinase) biomarker testing; 63 (8%) underwent comprehensive genomic profiling for all 4 major types of alterations (point mutations, indels, fusions, and copy number amplifications). Gender, age, race, site of care (referral vs. community center), and practice size did not influence comprehensive genomic profiling frequency. Active smokers and patients who died within 30 days were tested less frequently ($P < .05$). Among those not tested for *EGFR* and *ALK*, 52% received chemotherapy without documented reasons for no testing, 32% did not receive antineoplastic therapy, and 13% had insufficient tissue for genotyping. **Conclusion:** Genomic testing presents multiple logistical challenges for the community-based oncologist, including coordination of sample handling, long turnaround times, test reimbursement, access to targeted therapies, insufficient tissue, and patient harm from the repeat biopsies necessary if the tissue sample is insufficient. Opportunities exist for improvement in guideline adherence, possibly through new technologies such as "liquid biopsies," which obviates the need tissue biopsy samples in select settings.

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Introduction

Lung cancer is the leading cause of cancer death in the United States, with a projected 222,500 new patients diagnosed in 2017, resulting in 155,870 deaths.[1] Non–small cell lung cancer (NSCLC) accounts for approximately 85% to 90% of cases, with 60% of patients presenting with advanced-stage disease.[1,2] Small

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improvements in survival have been realized with the introduction of multiagent cytotoxic chemotherapy.[3] However, recent advances in our understanding of the biology of NSCLC, including both the genomic alterations that drive malignancy and the mechanisms of tumor immunologic escape, have led to new therapeutic approaches.[4-6]

The identification of oncogenic activation of tyrosine kinases in NSCLC, such as mutations in the *EGFR* (epidermal growth factor receptor) or rearrangements of the *ALK* (anaplastic lymphoma kinase) gene has enabled targeted molecular treatments. Notably, > 75% of patients with activating *EGFR* alterations experience major regression with gefitinib, erlotinib, or afatinib and prolongation of overall survival.[7-10] NSCLC patients whose tumors harbor rearrangements in *ALK* or *ROS1* have also benefited from targeted therapies, including crizotinib and alectinib.[11-13] Targeting of the *BRAF* V600E variant, *MET* gene amplification and exon 14 skipping, *RET* fusions, and *ERBB2* (HER2) mutations have also produced dramatic responses.[14-17] These oncogenic driver mutations account for more than one quarter of lung adenocarcinoma cases and are targetable with approved drugs. Ongoing sequencing studies have identified three quarters of the known drivers in this cancer, all generally mutually exclusive, although many driver mutations might not be amenable to medication management.[18]

Genomic testing for *EGFR* and *ALK* alterations as a part of the standard diagnostic evaluation for all patients with NSCLC whose tumors contain an element of adenocarcinoma, regardless of the clinical characteristics of the patient, has been recommended by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (CAP/IASLC/AMP) and has been endorsed by the American Society of Oncology.[19,20] In 2014, the National Comprehensive Cancer Network (NCCN) extended the recommendations for metastatic NSCLC to include "broad molecular profiling," consisting of not only *EGFR* and *ALK*, but also *BRAF*, *ERBB2* (HER2), *MET*, *RET*, and *ROS1*.[21] These 5 additional alterations are under consideration for inclusion in the upcoming revised lung cancer biomarker guidelines by the CAP/IASLC/AMP and are included in the European Society for Medical Oncology guidelines.[22,23] The clinical importance of broad genomic testing has been bolstered by multiple studies finding objective responses from targeted therapies in NSCLC to be 2 to 3 times better than cytotoxic chemotherapy.[7-9,11-17,24]

Despite these advances, genomic evaluation of NSCLC poses major challenges in community settings. Difficulties include procuring adequate tissue samples by coordination among multiple medical specialists, selecting which biomarkers should be assayed, patient factors (including surgical and treatment candidacy), financial issues (including the Medicare 14-day rule for reimbursement), and accurate interpretation of test results.[25-27] These challenges can lead to under genotyping, with a recent series reporting as much as 40% and 60% of patients without guideline-recommended *EGFR* and *ALK* testing, respectively, and 19% receiving cytotoxic chemotherapy before test result review.[28] These factors also lead to under referral to clinical trials of molecularly targeted agents.[25] In the present report, we sought to determine the genomic testing patterns for patients with advanced NSCLC diagnosed in a large multisite community-based US oncology practice and to examine the potential barriers to adherence with published biomarker guidelines.

Patients and Methods

A retrospective medical record review of patients with pathologically confirmed stage IIIB and IV NSCLC, with nonsquamous histologic findings, diagnosed between January 1, 2013 and December 31, 2015, and treated within the Regional Cancer Care Associates network was performed. The Regional Cancer Care Associates network consists of 15 community oncology sites throughout New Jersey and Maryland. Cases were identified using the COTA Inc database, which extracts and organizes relevant demographic, diagnostic, treatment, and quality data from the electronic health records at all the clinical sites under business associate agreements. Trained COTA Inc abstractors reviewed and confirmed the medical record-derived data and the dates of testing. For the purposes of the present study, any laboratory or pathology report mentioning testing for a driver mutation was counted as "tested," regardless of method, vendor, or test completeness. The data were then merged with the study population using blinded patient identifiers for subsequent analysis. The overall proportion of eligible patients receiving genomic testing in each calendar year was calculated. The overall rate of genomic testing was determined by the number of patients tested at any point between diagnosis and the end of the follow-up period, divided by the total study sample. Demographic information, disease characteristics, and clinical history at the first diagnosis were compared between the tested and nontested patients using χ^2 tests for equality of proportions to test for differences in percentages (eg, testing rates), and the Wilcoxon rank sum test was used to test for differences in the median number of days. All statistical analyses were performed using the R statistical language.[29]

Results

Patient Demographics

A total of 814 patients with nonsquamous NSCLC diagnosed between January 1, 2013 and December 31, 2015 were identified in the COTA database (295, 226, and 293 patients received a diagnosis in 2013, 2014, and 2015 respectively; Table 1). Of these patients, 11% had stage IIIB and 89% stage IV disease. Adenocarcinoma was the most predominant pathologic subtype (89%), followed by NSCLC, not otherwise specified (6%), large cell (2%), and other subtypes (3%). The median age of the patient population was 67 years, with 57% ≥ 65 years old and 28% ≥ 75 years old; 53% of the patients were women and 72% were white, 4% were African-American, 3% were Asian, and the remainder was other or undeclared. The Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis was 0 in 4%, 1 to 2 in 32%, 2 in 8%, ≥ 3 in 2%, and not recorded in 54%. Of the 814 patients, 19% reported active tobacco use, 63% reported former use, and 17% denied smoking. The patients were treated by 89 oncologists at 15 centers in New Jersey and Maryland. Of the 814 patients, 251 (31%) were treated by physicians caring for < 10 NSCLC patients during the 3-year period; 75% were treated in community cancer centers and 25% in a referral center containing a dedicated lung cancer program.

Table 1 Study Population and Genomic Testing Patterns

Variable	Total	Both *EGFR* and *ALK* Mutations		All 7 NCCN Mutations	
		Not Tested	Tested	Not Tested	Tested
Patients (n)	814 (100)	335 (41)	479 (59)	751 (92)	63 (8)
Median interval from diagnosis to result (d)	22	NA	23	NA	28
Year of diagnosis					
2013	295 (36)	142 (42)	153 (32)	289 (38)	6 (10)
2014	226 (28)	73 (22)	153 (32)	207 (28)	19 (30)
2015	293 (36)	120 (36)	173 (36)	255 (34)	38 (60)
Clinic type					
Referral	204 (25)	78 (23)	126 (26)	197 (26)	7 (11)
Community	610 (75)	257 (77)	353 (74)	554 (74)	56 (89)
Died <30 days after diagnosis	31 (4)	22 (7)	9 (2)	30 (4)	1 (2)
Gender					
Female	430 (53)	174 (52)	256 (53)	395 (53)	35 (56)
Male	384 (47)	161 (48)	223 (47)	356 (47)	28 (44)
Median age at diagnosis (y)	67	67	67	67	64
Age group					
<65 y	350 (43)	143 (43)	207 (43)	318 (42)	32 (51)
≥65 y	464 (57)	192 (57)	272 (57)	433 (58)	31 (49)
Race					
Asian or Pacific Islander	26 (3)	8 (2)	18 (4)	25 (3)	1 (2)
Black	34 (4)	16 (5)	18 (4)	30 (4)	4 (6)
Other	46 (6)	20 (6)	26 (5)	43 (6)	3 (5)
Unknown	101 (12)	43 (13)	58 (12)	87 (12)	14 (22)
White	587 (72)	241 (72)	346 (72)	547 (73)	40 (63)
Missing	20 (2)	7 (2)	13 (3)	19 (3)	1 (2)
Hispanic status					
Hispanic	31 (4)	10 (3)	21 (4)	30 (4)	1 (2)
Non-Hispanic	529 (65)	232 (69)	297 (62)	492 (66)	37 (59)
Unknown	174 (21)	72 (21)	102 (21)	150 (20)	24 (38)
Missing	80 (10)	21 (6)	59 (12)	79 (11)	1 (2)
Smoking status					
Former smoker	516 (63)	204 (61)	312 (65)	474 (63)	42 (67)
Never smoker	136 (17)	49 (15)	87 (18)	122 (16)	14 (22)
Passive smoker	4 (0)	1 (0)	3 (1)	4 (1)	0 (0)
Smoker	151 (19)	76 (23)	75 (16)	144 (19)	7 (11)
Missing	7 (1)	5 (1)	2 (0)	7 (1)	0 (0)
Histologic type					
Adenocarcinoma and related	722 (89)	273 (81)	449 (94)	665 (89)	57 (90)
Large cell neuroendocrine carcinoma	15 (2)	14 (4)	1 (0)	14 (2)	1 (2)
Non–small cell, NOS	56 (7)	38 (11)	18 (4)	54 (7)	2 (3)
Other NSCLC	21 (3)	10 (3)	11 (2)	18 (2)	3 (5)
Stage					
IIIB	93 (11)	48 (14)	45 (9)	87 (12)	6 (10)
IV	721 (89)	287 (86)	434 (91)	664 (88)	57 (90)

Data presented as n (%).
Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; NA = not applicable; NCCN = National Comprehensive Cancer Network; NOS = not otherwise specified; NSCLC = non–small cell lung cancer.

EGFR *and* ALK *Biomarker Testing*

The joint CAP/IASLC/AMP recommendations require *EGFR* and *ALK* genomic testing in all patients with NSCLC whose tumors contain components of adenocarcinoma, regardless of the patient clinical characteristics. Of the 814 patients with data in the database, only 479 (59%) met the guidelines for testing for both

Table 2 Guideline Adherence for Genomic Testing

Variable	n (%)
Total patients	814 (100)
Tested for *EGFR*/*ALK*	479 (59)
Tested for all 7 NCCN recommended mutations	63 (8)
Patients aged ≥65 y	464 (100)
Tested for *EGFR*/*ALK*	272 (59)
Tested for all 7 NCCN recommended mutations	31 (7)

Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; NCCN = National Comprehensive Cancer Network.

biomarkers (Table 2). The testing rates remained fairly constant throughout the 3-year observation period (Table 3). The physicians at a tertiary referral center and those with ≥ 10 patients tested at the same frequency as physicians at community centers or those with < 10 patients. Gender and race did not influence testing frequency. Age (including Medicare age eligibility) did not influence testing frequency. However, active smokers were tested less frequently than never or former smokers ($P < .01$). Patients with stage IIIB disease were tested less frequently than those with stage IV disease ($P < .05$). Patients who died within 30 days of their cancer diagnosis ($P < .001$) were tested less frequently. ECOG performance status did not correlate with the testing rates, although a proportion of patients did not have their ECOG status documented (including the 217 patients who did not receive any drug-based therapy). During the 3-year study, 387 patients developed progression and received second-line therapy. The medical records of 331 of these patients were reviewed, and < 10% had undergone genomic profiling at that time (Table 4).

Broad Molecular Testing

The 2014 NCCN guidelines extended the recommended genomic biomarkers to include *EGFR* mutations, *ALK* fusions, *ROS1* rearrangements, *BRAF* mutations, *MET* amplifications and mutations, *RET* rearrangements, and *ERBB2* (HER2) mutations.[21] Of the 814 patients, only 63 (8%) met these extended guidelines. After *EGFR* and *ALK* testing rates of 69% and 65%, respectively, testing for additional targetable alterations decreased precipitously for *BRAF* V600E (18%), *ROS1* fusion (25%), *MET* exon 14 skipping or amplification (15%), *RET* fusion (14%), and *ERBB2* (HER2) mutation (12%; Figure 1). Comprehensive tissue-based genotyping rates increased throughout the 3-year observation period, from 2% in 2013 to 16% in 2015 (Table 3). Physicians at community centers were more likely to test for all biomarkers (9% vs. 3%; $P < .01$), but physicians with > 10 patients tested at the same frequency as physicians with < 10 patients. Gender, age, and race did not influence testing frequency. Active smokers showed a trend toward less frequent testing than never and former smokers ($P = .07$). Stage did not correlate with testing frequency. Patients who died within 30 days of their cancer diagnosis were tested less frequently ($P < .02$).

Response Time for Biomarker Testing Results

The joint CAP/IASLC/AMP recommendations require *EGFR* and *ALK* results to be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory.[19] Laboratories with longer response times are encouraged to establish protocols for more rapid testing in matters of clinical urgency. Of the 479 patients successfully tested for both *EGFR* and *ALK* in the present series, the median response time (from the date of diagnosis to the test result received) was 23 days. Additionally, of the 63 patients successfully tested for all 7 NCCN recommended targets (57 using extensive and comprehensive next-generation sequencing (NGS) panels and 6 using limited-panel polymerase chain reaction), the response time for 54 patients (85%) exceeded the recommendations (these 54 patients received test results > 14 days after the diagnosis and 37 received test results > 30 days after diagnosis). Of these 54 patients, only 4 (7%) underwent duplicate rapid *EGFR* testing.

Limitations Affecting Testing

Of the 814 patients, 53 had insufficient tissue for testing of *EGFR*/*ALK* on the initial biopsy specimen (10% of the initial diagnostic samples sent for analysis). Of these 53 patients, 23 underwent a second diagnostic biopsy (of whom 16 were ultimately successfully tested for both *EGFR* and *ALK*). Thus, 30 of these patients did not have testing after failure of the first sample, and 7 patients underwent repeat biopsy but still with no documentation of test results. Of the 335 patients who did not undergo the guideline-recommended combined *EGFR*/*ALK* biomarker testing, 22 (7% of 335) died within 30 days of the diagnosis. In contrast, 9 tested patients (2% of 479) died within 30 days of the diagnosis ($P < .001$). Testing was also not performed in 93 patients who did not receive any antineoplastic drug-based therapy for NSCLC.

Table 3 Genomic Profiling Rates Before First-line Therapy

Variable	Patients	PCR/FISH Testing Attempted	NGS Attempted	Successfully Tested for Both *EGFR* + *ALK*	Successfully Tested for All 7 NCCN Mutations
Total patients, all years	814 (100)	471 (58)	73 (9)	479 (59)	63 (8)
Year of diagnosis					
2013	295 (36)	172 (58)	7 (2)	153 (52)	6 (2)
2014	226 (28)	145 (64)	19 (8)	153 (68)	19 (8)
2015	293 (36)	154 (53)	47 (16)	173 (59)	38 (13)

Data presented as n (%).
Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; NCCN = National Comprehensive Cancer Network; PCR = polymerase chain reaction.

Table 4 Genomic Profiling Rates at First Disease Progression

Variable	Patients	PCR/FISH Testing Attempted	NGS Attempted	Successfully Tested for Both *EGFR* + *ALK*	Successfully Tested for All 7 NCCN Mutations
Total patients, all years	331 (100)	24 (7)	19 (6)	29 (9)	15 (5)
Year of progression					
2013	48 (15)	2 (4)	1 (2)	1 (2)	1 (2)
2014	122 (37)	10 (8)	6 (5)	13 (11)	6 (5)
2015	132 (40)	12 (9)	9 (7)	12 (9)	6 (5)
2016	29 (9)	0 (0)	3 (10)	3 (10)	2 (7)

Data presented as n (%).
Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; NCCN = National Comprehensive Cancer Network; PCR = polymerase chain reaction.

Of the 335 patients who did not undergo *EGFR* and *ALK* testing, 45 had insufficient tissue samples available, 5 had other documented reasons, 24 had rapidly died, and 86 received no antineoplastic therapy. However, 175 patients with no documented reason for not performing testing received antineoplastic therapy (21% of the entire population; Table 5). Of these 175 patients, 94 (54%) received first-line therapy with pemetrexed, 40 (23%) received bevacizumab, and 32 (18%) received combination biologic therapy.

Implications of Testing on Treatment and Survival

Of the 479 patients tested for *EGFR* and *ALK*, 128 were noted to harbor mutations involving *EGFR* or *ALK* (13% had *EGFR* mutations and 3% had *ALK* fusions). Of these patients, 73% received first-line matched targeted therapies. Also, 12 patients harbored other NCCN-recommended mutations, and 2 (17%) received "off-label" matched therapies.

Overall survival data were available for 805 patients. For the 131 patients who received a targeted therapy at some time during their treatment, the median overall survival was 31.8 months. In contrast, of the 482 patients who received cytotoxic chemotherapy, the median overall survival was 12.7 months and was 5.1 months for the 192 patients who received only supportive care ($P < .001$; Figure 2). Seventeen patients with *EGFR* or *ALK* mutations did not receive targeted therapy but instead received chemotherapy; their overall survival was 15.5 months.

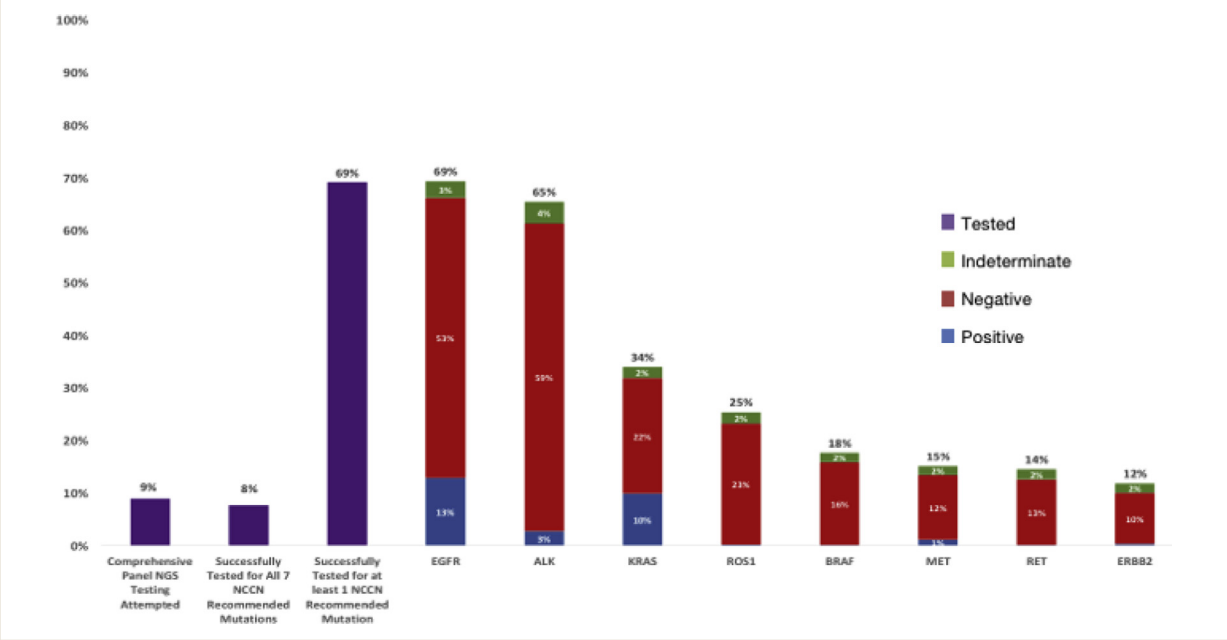
Discussion

The present retrospective review from 15 community oncology centers noted significant underusage of genomic testing among patients with advanced-stage NSCLC. Although the CAP/IASLC/AMP guidelines have recommended routine *EGFR* and *ALK* biomarker testing, only 69% and 65%, respectively, underwent testing in the present series. Only 12% underwent broad molecular profiling for the 5 additional mutations recommended by the 2014 NCCN guidelines. Despite the guidelines specifically recommending testing without regard to the clinical characteristics, the physicians appeared to withhold testing for active tobacco users. Smokers as a group have a lower frequency of *EGFR* and *ALK* genomic alterations, but *BRAF* and *MET* mutations occur more frequently in smokers.[14,30] The testing frequency was also lower for those rapidly approaching death.

Few studies have examined the adherence to genomic testing guidelines in NSCLC in the community setting. A report from Montefiore Medical Center (Bronx, NY) also noted a sizable undergenotyped patient population. Of 1910 patients with NSCLC (874 with nonsquamous histologic types) from 2009 to 2013, the testing rates for *EGFR* and *ALK* were 62% and 23%, respectively, despite an institutional policy permitting pathology department-guided reflex testing (compared with only 26% and 7%, respectively, before the reflex policy).[31] In a separate online survey of 562 oncologists in 10 countries, *EGFR* testing was self-reported as requested for approximately 81% of patients with advanced NSCLC. Although 49% of oncologists responded that their treatment decisions were influenced by detected mutations, 23% stated that *EGFR* mutational status did not affect their first-line treatment decisions. Separate from the histologic type, the main reasons given for not testing were insufficient tissue, poor performance status, and long response times.[32]

Even at academic centers, genomic testing can be inconsistent. A survey of 55 National Cancer Institute-designated centers in 2012 found that all had stated policies for routine testing of NSCLC patients for *EGFR* and *ALK* biomarkers. However, at 43% of the institutions, the sequence of NSCLC biomarker testing relied on an oncologist's order; 34% performed testing for all biomarkers upfront for patients with a new diagnosis, and 22% used a sequential protocol.[33] The reliance on physician judgment decreases the likelihood of full adherence to testing guidelines. An estimate of adherence in academic centers can be inferred by reviewing the conduct of the Lung Cancer Mutation Consortium's prospective multi-institutional study of genomic profiling. A total of 1536 patients with adenocarcinoma and a good performance status were enrolled in the study; however, only 1102 were eligible for genomic testing. The primary reason for ineligibility was the lack of tumor tissue for genomic testing. Of the 1017 patients with confirmed adenocarcinoma, 1007 had tumors with $\geq$ 1 gene studied for genomic changes (99% of eligible patients but only 65% of enrolled patients), and 733 had tumors fully genotyped for all 7 NCCN recommended alterations (72%; but only 48% of enrolled patients).[34] Similarly, a tertiary academic center in Canada performing reflex testing of *EGFR* and *ALK* had rates of 58% and 40%, respectively.[28] The primary challenge was, again, insufficiency of tissue after histopathologic examination and staining. Only 13% of medical oncologists had biomarker test results available at the first

Figure 1 Genotyping Rates for National Comprehensive Cancer Network (NCCN) Genomic Targets in Non–Small Cell Lung Cancer (Stage IIIB/IV, Nonsquamous). Testing Rates for Epidermal Growth Factor Receptor (*EGFR*) Were 61% in 2013, 75% in 2014, and 66% in 2015 (Similar Pattern for Other Genomic Targets). After *EGFR* and *ALK* Testing, It Appears That Tissue Samples Might Be Exhausted. Adoption of Comprehensive Panel Next-generation Sequencing (NGS) Testing Increased From 2% of All Patients in 2013 to 16% of All Patients in 2015 (n = 814; 15 Community Oncology Sites Throughout New Jersey and Maryland, 2013-2015). Because of Rounding, Percentages Might Not Sum to 100%



visit. This led to missed opportunities for 19% of the patients, who started first-line chemotherapy before the biomarker results were available.[28] Thus, even at academic centers participating in prospective studies of genomic profiling, a sizable population of patients will not receive the guideline-recommended molecular analysis.

The increasing number of potential targetable alterations in NSCLC also presents additional clinical and logistic challenges to models of sequential gene-by-gene testing. To obtain all 7 NCCN targetable mutations testing requires multiple modalities, including immunohistochemistry, polymerase chain reaction-based tests, capillary sequencing, fluorescence in situ hybridization-based testing, and mass spectrometry-based sizing assays. Insufficient tissue to supply all these tests, therefore, becomes a recurring problem. In our series, 23 patients underwent a second biopsy to obtain additional material to test for *EGFR and ALK* mutations before first-line therapy, and in the Lung Cancer Mutation Consortium study, insufficient tissue was the leading cause of ineligibility.[34] The deployment of multiplex testing using NGS, which requires less tissue, has begun to address this issue. However, repeat biopsy might still be necessary, adding additional costs (mean Medicare cost of $14,634 but increasing to $37,745 if complicated) and the potential for complications.[35] Three recent series of NSCLC patients at academic centers where tissue-based NGS is standard practice each reported tissue insufficiency (quantity not sufficient) rates of ≥ 50%.[36-38]

Table 5 Reasons for Not Testing

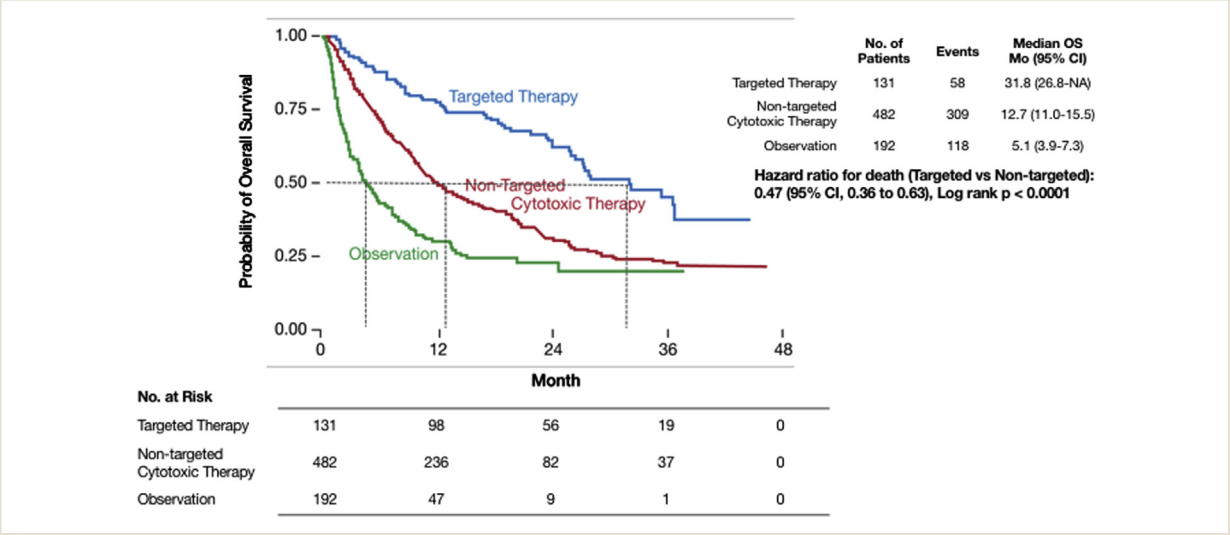
Reason for Not Testing for *EGFR/ALK*	n (%)
Total not tested	335 (100)
Reason not reported, antineoplastic therapy started	175 (52)
Reason not reported, not treated	86 (26)
Insufficient tissue sample	45 (13)
Rapid death	24 (7)
Other	5 (1)

Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor.

Of the 335 patients in our series who did not undergo genomic profiling, 22 (7%) died within 30 days of their lung cancer diagnosis. Frail patients might not be able to undergo biopsy or wait for extended periods for genomic test results. The median response time from diagnosis to the receipt of results was 23 days in our series. The delays in obtaining results can be exacerbated by the Medicare 14-day rule, which encourages delayed ordering of expensive testing until 2 weeks after hospital discharge.[32] The use of either liquid biopsy or performing sequential testing with inexpensive rapid immunohistochemistry/fluorescence in situ hybridization technology for *EGFR/ALK*, followed by comprehensive molecular profiling, can be considered to enable more rapid response times for the results. However, only 7% of the patients in our series who underwent comprehensive NGS testing, with its longer response time, underwent dual-level testing.

In the present "real world" series, patients with a targetable mutation who received the matched targeted therapy (principally for

Figure 2 Overall Survival Stratified by Therapy Type (n = 805). Log-rank *P* < .0001 (Targeted vs. Nontargeted). Hazard Ratio for Death 0.47 (95% Confidence Interval, 0.36-0.63). Overall Survival for 805 Patients With Non–Small Cell Lung Cancer Demonstrating That Treatment (Tx) With Matched Targeted Therapy Yields Superior Outcomes



EGFR mutations) experienced superior overall survival durations approaching 32 months compared with patients with or without mutations who received cytotoxic chemotherapy (median survival, 12-15 months). The clinical utility of genomic profiling justifies adherence to testing guidelines. In addition to the improved survival with targeted therapy among patients with alterations of *EGFR*, *ALK*, and *ROS1*, other studies have suggested benefits with targeted therapies against *BRAF*, *RET*, *MET*, and *ERBB2* (HER2). Large national trials are attempting to confirm the benefits of broad molecular profiling with comprehensive genotyping.[39-41] An Israeli review of 101 NSCLC patients tested by hybrid capture NGS, principally after negative *EGFR/ALK* test results, identified clinically actionable genomic alterations in 50% of patients and changed the treatment strategies for 43 patients. NGS also identified *EGFR* mutations in 15 patients identified as *EGFR* wild type using conventional testing. The overall response rate in these patients was 65% (complete response, 14.7%; partial response, 50%), supporting the use of NGS instead of 1-gene-at-a time testing.[42] Notably, in 19 of the 101 NSCLC patients, the tissue for NGS was insufficient, and comprehensive cell-free DNA testing of plasma found targetable alterations, which changed the treatment for 6 of the 19 patients (32%). Objective responses were obtained for plasma-detected genomic targets in 50% (including 2 patients with *EGFR* mutations missed using local quantitative polymerase chain reaction tissue testing) and stable disease in 33%.[42]

NGS of cell-free circulating solid tumor DNA, commonly known as "liquid biopsy," could help rescue patients who cannot receive genotype testing because of insufficient tissue or tissue sampling error related to tumor heterogeneity.[43-46] This method of massively parallel and deep sequencing, both enables assessment of a comprehensive genomic profile from a simple blood sample and reduces the need for repeat invasive tissue biopsies.[47] The response rates based on cell-free DNA-detected mutations might be similar to those reported by tissue biopsy-based studies.[37,38,42,48]

The higher costs associated with the genomic diagnostic testing (upward of $4000 per sample) might deter adherence to guideline evaluations. However, if a genomic driver is identified, not only might the outcomes be improved, but also the total cost of cancer care might be reduced. The treatment costs for matched therapies such as erlotinib for *EGFR* mutations have been associated with much lower total health care costs than chemotherapy plus biologic agents such as bevacizumab, for both first- and second-line therapy.[49] Ambulatory infusion, the high costs of biologic agents, and hospitalization related to neutropenia from chemotherapy were among the drivers of the greater costs with chemotherapy. Immunotherapy costs might be even greater, and consideration of tumor genomic status is important, because patients with NSCLC with *EGFR* mutations might have poor responses to immunotherapy.[6]

Current molecularly targeted therapies are not curative, and most patients will experience disease progression within 1 to 2 years. Newer targeted therapies designed to combat acquired mutations have been released, and the NCCN and European Society for Medical Oncology guidelines now recommend repeat genomic testing at progression to identify *EGFR*- and *ALK*-resistance targets.[21,23] In our series, which largely predated these agents, repeat biopsies at progression during matched therapy were uncommon. Liquid biopsy approaches to detect acquired mutations or for identification of targets missed during the initial evaluation could be useful in this secondary resistance setting.[50-52] In our series, 9 patients, including 6 patients receiving matched therapies for *EGFR* driver mutations, underwent liquid biopsy testing on progression. Targetable clonal *EGFR* T790M mutations were detected in 3 of the *EGFR* patients (50%), avoiding the need for repeat tissue biopsies. All 3 were treated with osimertinib, and 2 had a brief

response (2 months). The third patient, who had developed brain metastases, had stable disease for > 1 year.

Conclusion

The present retrospective "real world evidence" review has demonstrated that genomic testing presents multiple clinical and logistical challenges for community-based oncologists.[53] These challenges include insufficient tissue owing to sequential or parallel testing and unacceptably long response times. The lack of integration of biomarker testing into routine pathology practice and uncertainty about reimbursement create additional barriers. Solutions might include new technologies such as "liquid" biopsies (useful when the initial tissue biopsy is insufficient for genotyping or to detect acquired mutations at disease progression). Although gaps in genomic biomarker testing remain, opportunities for improvement in guideline adherence exist.

Clinical Practice Points

- Patients with advanced NSCLC (nonsquamous histologic types) might harbor genomic alterations that are amenable to matched targeted therapies.
- The CAP/IASLC/AMP guidelines have recommended routine testing for *EGFR* and *ALK* alterations, and the 2014 NCCN NSCLC guidelines added broad molecular profiling for 5 additional mutations.
- However, the demands for tissue specimens for histopathologic diagnosis and programmed cell death ligand 1 expression staining might leave little tissue remaining for genomic testing.
- In the present 3-year study (2013-2015) of a large community-based oncology network consisting of multiple sites, we measured the genotyping rates.
- More than one third of patients were not tested for *EGFR* and *ALK*, and the testing rate for all 7 genes was only 8%.
- Among those not tested for *EGFR* and *ALK*, 52% received chemotherapy without documented reasons for not testing, 32% did not receive antineoplastic therapy, and 13% had insufficient tissue.
- Under genotyping has significant implications because the overall survival rates were significantly improved with matched therapies compared with cytotoxic chemotherapy in the present real world series.
- Because the clinical outcomes are improved and the total cost of care might be lessened with targeted therapies, efforts to increase adherence with guideline recommended genomic profiling should be encouraged.
- New strategies, including tissue-based NGS, to improve efficient testing of multiple targets and plasma-based cell-free circulating tumor DNA NGS to obviate the need for repeat invasive tissue biopsies when the initial samples have been exhausted by pathologic examination or to avoid repeating biopsies at progression should be considered.

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Disclosure

Dr Lanman and Mr Skrzypczak are employees with stock ownership in Guardant Health, Inc. The remaining authors declare that they have no competing interests.

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