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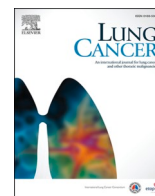
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Genomic testing among patients with newly diagnosed advanced non-small cell lung cancer in the United States: A contemporary clinical practice patterns study

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ABSTRACT

Objectives: According to 2018 United States and international lung cancer and pathology guidelines, testing of *EGFR*, *ALK*, *ROS1* and *BRAF* genes is a minimum requirement to identify targeted therapy options in patients with advanced non-small cell lung cancer (aNSCLC). We describe real-world use and clinical features of next-generation sequencing (NGS) and other non-NGS testing technologies in these patients.

Materials and methods: Patients were from the Flatiron Health electronic health record-derived de-identified database and were newly diagnosed with non-squamous aNSCLC between 1 January 2018 and 30 June 2019. We describe occurrence and patterns of NGS- (including comprehensive genomic profiling [CGP]) and non-NGS-based genomic testing before the start of first-line therapy, unsuccessful genotyping (<4 genes tested) and incidence of potentially missed targeted therapy options (<4 genes tested with no positive results).

Results: Among 3050 patients, 2356 received any type of genomic testing (NGS: 1406 [59.7%]). Unsuccessful genotyping occurred in 13.2% and 52.2% of NGS- and non-NGS-tested patients, respectively. Among NGS-tested patients, 10.0% had a potentially missed targeted therapy option (CGP: 2.9%), compared with 40.2% in the non-NGS tested group. While all four guideline-recommended genes were tested in ≥ 92% of patients who had NGS testing, when only non-NGS testing was used, although *EGFR* and *ALK* had similarly high testing proportions, *BRAF* and *ROS1* (56.1% and 83.7%, respectively) were examined less often.

Conclusions: Our findings suggest that in aNSCLC clinical practice, NGS testing may help to avoid potentially missed targeted therapy options and improve testing uptake for recently approved biomarkers. Results therefore support the use of guideline-recommended broad-panel NGS testing in clinical practice.

1. Introduction

Recent years have witnessed an unprecedented expansion in the

availability of molecularly guided therapies for patients with advanced non-small cell lung cancer (aNSCLC) [1–9]. For many of these therapies, treatment decisions rely on upfront verification of the presence of

Abbreviations: aNSCLC, advanced non-small cell lung cancer; CGP, comprehensive genomic profiling; FDA, Food and Drug Administration; FMI, Foundation Medicine, Inc.; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; US, United States.

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genomic alterations in the tumour by molecular testing. From 2018, according to guidelines from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology [10], the testing of *EGFR*, *ALK*, *ROS1* and *BRAF* genes have been considered to be a minimum requirement [11], given that these genes have all had targeted therapy options in newly diagnosed patients with non-squamous aNSCLC approved by the United States (US) Food and Drug Administration (FDA) [9,10]. Along with *NTRK* and programmed death-ligand 1 (PD-L1), such biomarker testing recommendations have also been seen in the latest European Society for Medical Oncology Clinical Practice Guidelines for metastatic NSCLC [12].

NSCLC guidelines discuss the option of broad next-generation sequencing (NGS) [10], but little is known about the contemporary patterns of use and clinical features of NGS and other non-NGS testing technologies in the real world [13]. In this study, we examine contemporary use of genomic testing among patients with newly diagnosed aNSCLC who were overwhelmingly cared for in the US community oncology setting.

Both clinically, and from the point of view of the patient, the desired outcome of genomic testing for targetable oncogenic drivers is the identification of a targeted therapy option or the clarification that no option for targeted therapy exists, within either standard of care or clinical development programmes. Accordingly, biomarker testing may be considered suboptimal if a patient does not have a positive test result that opens the way for targeted treatment options and targetable genes remain untested.

2. Materials and methods

2.1. Data and patients

The Flatiron Health electronic health record-derived database is a longitudinal, demographically and geographically diverse de-identified database. It is sourced from over 280 cancer clinics (~800 sites of care) representing more than 2.4 million US patients with cancer and available data for analysis. Disease-specific data are curated from patient-

level structured and unstructured electronic health records via technology-enabled abstraction.

Patients included in this study were newly diagnosed with non-squamous aNSCLC between 1 January 2018 and 30 June 2019 and had commenced first-line therapy ≤ 90 days after diagnosis. Exclusion criteria included missing biomarker testing date information (Supplementary Fig. 1 and Supplementary Table S1), a biomarker test date > 30 days before the date of advanced disease diagnosis, an unknown type of biomarker test or an unknown test result and histology other than non-squamous cell carcinoma (Fig. 1).

Patients were grouped according to the type of biomarker test(s) received between 30 days before the date of advanced diagnosis and the start of systemic first-line therapy. Testing groups were NGS, including a subgroup of patients who received comprehensive genomic profiling from Foundation Medicine Inc. (FMI CGP; Cambridge, MA, US), non-NGS (all methods that are used in practice and are not NGS-based) and no genomic testing. FMI CGP is based on massively parallel DNA sequencing of routine formalin-fixed and paraffin-embedded clinical specimens, to characterise mutations and other types of genomic changes across > 300 cancer-related genes [14,15]. A blood-based test that used a smaller number of genes was also available during the study [16]. Both types of tests covered all four genes specifically examined in this study (*ALK* and *ROS1* rearrangements, and *EGFR* and *BRAF* mutations [any and *BRAF*^{V600E}, respectively]). Grouping of tests was performed hierarchically, whereby patients who received any NGS test were assigned to the NGS group regardless of whether they received additional non-NGS testing (Supplementary Fig. 2). Similarly, patients with an FMI CGP test were assigned to that group regardless of whether they received other NGS or non-NGS tests (Supplementary Fig. 2).

2.2. Analysis

We defined successful biomarker testing as at least one successful test for each of the four examined genes, *ALK*, *BRAF*, *EGFR* and *ROS1* (Supplementary Fig. 3). We describe the following aspects of genomic testing: occurrence of testing, patterns of use of testing technologies (including side-by-side use), occurrence of successful biomarker testing,

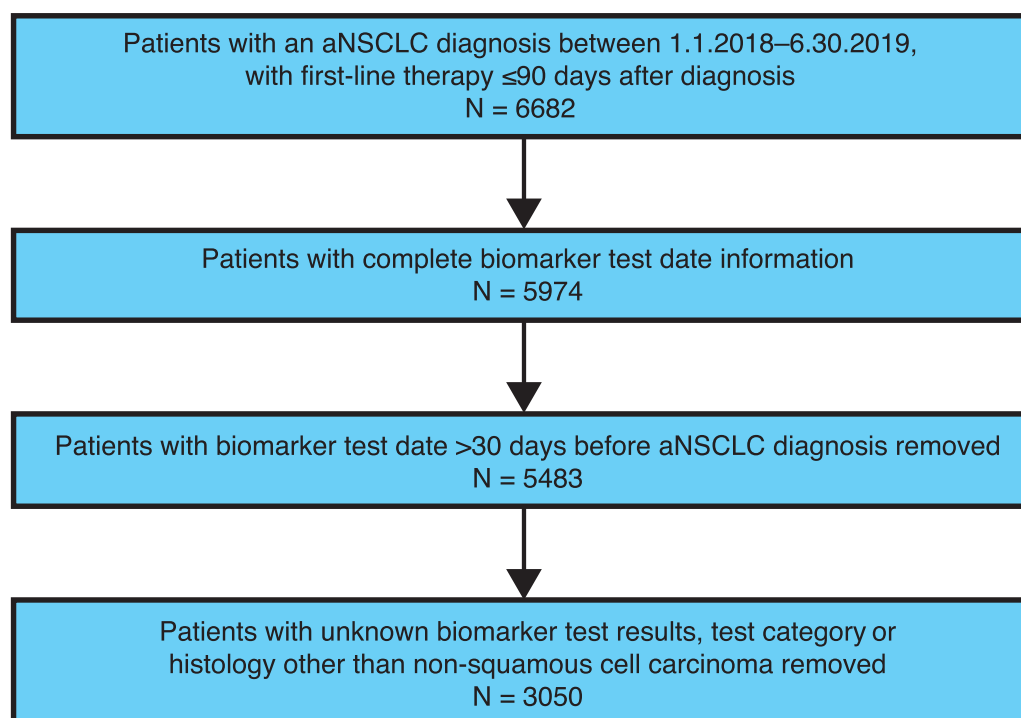


Fig. 1. Patient attrition chart (N = 3050 remaining patients). aNSCLC: advanced non-small cell lung cancer.

unsuccessful genotyping (defined as at least one of four genes with missing test order and/or a test failure and no result) and percentage of patients with a potentially missed targeted therapy option. The latter measure was defined as patients without a positive biomarker test result who did not receive successful tests for all four of the specified genes. All analyses were descriptive.

For individual biomarkers, all rearrangements in *ALK* and *ROS1*, *BRAF*^{V600E} mutations, as well as all *EGFR* mutations, were assumed to be treatable with targeted therapy.

3. Results

3.1. Patient demographics and use of genomic testing

Overall, 3050 patients with newly diagnosed, non-squamous aNSCLC were included in the study. The mean patient age at advanced disease diagnosis was 68 years old and the sex ratio was balanced (male: 50.2%; female: 49.8%); the majority of patients had a history of smoking ($n = 2589/3050$; 84.9%), were diagnosed with stage IV disease ($n = 2389/3050$ [78.3%]; of the rest, the majority were stage III [396/3050; 13.0%]) and were cared for in a community oncology setting ($n = 2822/3050$; 92.5%) (Table 1). Among the 3050 patients included in the analysis, 694 (22.8%; of whom 436/694 [62.8%] were stage IV) had no genomic testing performed on their tumour for any of the four guideline-recommended genes prior to first-line treatment. Among the other 2356 (77.2%) patients whose tumour had a genomic test, 1406 (59.7%) were tested with an NGS test (FMI CGP: $n = 443$ [18.8%]) and 950 (40.3%) with a non-NGS test only (Table 1). Non-NGS techniques used included polymerase chain reaction, immunohistochemistry, fluorescent in situ hybridisation, mass spectrometry, amongst others. The proportion of patients with a history of smoking was higher among those not tested versus those who were tested (93.2% versus 81.8% to 83.5%) (Table 1).

Among patients tested by NGS technologies, parallel use of other testing technologies did occur, but with considerable differences (Fig. 2 and Supplementary Table S2). Among patients tested by FMI CGP ($n = 443$), 93 (21.0%) received an additional test using another NGS or non-NGS method; however, in the subgroup of patients tested by another NGS test ($n = 963$), the majority (70.3%; Fig. 2 and Supplementary Table S2) received additional testing with a non-NGS method.

3.2. Features of biomarker testing

Among the 1406 patients who received an NGS test prior to first-line treatment, the majority were successfully genotyped for all four examined genes ($n = 1220/1406$; 86.8%; Fig. 3A and Supplementary Table S2). Successful genotyping was numerically more frequent for patients who received FMI CGP compared with those who received another type of NGS test (95.3% versus 82.9%; Fig. 3B). Unsuccessful genotyping occurred in 13.2% ($n = 186/1406$) of patients who received an NGS test, mainly due to a missing test order ($n = 128/186$; 68.8%; Fig. 3A and Supplementary Table S2), although the frequency of test failures was numerically greater in those who received an NGS test other than FMI CGP ($n = 42/963$ [4.4%] versus $n = 1/443$ [0.2%]; Fig. 3B and Supplementary Table S2). Among the 950 patients who received a non-NGS test prior to first-line treatment, unsuccessful genotyping occurred in 496 patients (52.2%; Fig. 3A and Supplementary Table S2). This was mainly due to a missing order ($n = 430/496$; 86.7%). In addition, test failures played a minor role ($n = 28/496$; 5.7%; Fig. 3A and Supplementary Table S2).

3.3. Potentially missed targeted therapy options

Of the 1406 patients who received an NGS test prior to first-line treatment, a positive genomic finding was identified in 28.3%, whereas targeted therapy was ruled out following negative results in all

Table 1
Patient demographics and disease characteristics by testing group.

Characteristic, no. (%)	All N = 3050	CGP (+other) n = 443 (18.8)	Other NGS (+non-NGS) n = 963 (40.9)	Non-NGS n = 950 (40.3)	No Test n = 694 (22.8)
Mean age, years (standard deviation)	68.3 (9.9)	68.1 (10.6)	68.5 (9.5)	68.3 (10.2)	68.4 (9.3)
Age group					
20–34	5 (0.2)	0	2 (0.2)	2 (0.2)	1 (0.1)
35–44	28 (0.9)	8 (1.8)	5 (0.5)	12 (1.3)	3 (0.4)
45–54	219 (7.2)	38 (8.6)	68 (7.1)	67 (7.1)	46 (6.6)
55–64	834 (27.3)	124 (28.0)	250 (26.0)	269 (28.3)	191 (27.5)
65–74	1052 (34.5)	126 (28.4)	359 (37.3)	312 (32.8)	255 (36.7)
75–84	853 (28.0)	134 (30.2)	256 (26.6)	273 (28.7)	190 (27.4)
≥85	59 (1.9)	13 (2.9)	23 (2.4)	15 (1.6)	8 (1.2)
Sex					
Female	1518 (49.8)	234 (52.8)	507 (52.6)	476 (50.1)	301 (43.4)
Male	1532 (50.2)	209 (47.2)	456 (47.4)	474 (49.9)	393 (56.6)
Race					
White	2012 (66.0)	324 (73.1)	651 (67.6)	573 (60.3)	464 (66.9)
Asian	106 (3.5)	10 (2.3)	40 (4.2)	48 (5.1)	8 (1.2)
Black or African-American	263 (8.6)	25 (5.6)	70 (7.3)	95 (10.0)	73 (10.5)
Hispanic or Latino	4 (0.1)	0	1 (0.1)	2 (0.2)	1 (0.1)
Other	284 (9.3)	38 (8.6)	82 (8.5)	104 (10.9)	60 (8.7)
Missing	381 (12.5)	46 (10.4)	119 (12.4)	128 (13.5)	88 (12.7)
Ethnicity					
Hispanic or Latino	78 (2.6)	9 (2.0)	17 (1.8)	34 (3.6)	18 (2.6)
Missing	2972 (97.4)	434 (98.0)	946 (98.2)	916 (96.4)	676 (97.4)
Stage at initial diagnosis					
Not reported	19 (0.6)	3 (0.7)	4 (0.4)	1 (0.1)	11 (1.6)
Stage I	143 (4.7)	21 (4.7)	32 (3.3)	34 (3.6)	56 (8.1)
Stage II	73 (2.4)	13 (2.9)	21 (2.2)	18 (1.9)	21 (3.0)
Stage III	396 (13.0)	44 (9.9)	99 (10.3)	94 (9.9)	159 (22.9)
Stage IIIC	30 (1.0)	5 (1.1)	9 (0.9)	5 (0.5)	11 (1.6)
Stage IV	2389 (78.3)	357 (80.6)	798 (82.9)	798 (84.0)	436 (62.8)
Practice type					
Academic	228 (7.5)	11 (2.5)	139 (14.4)	32 (3.4)	46 (6.6)
Community	2822 (92.5)	432 (97.5)	824 (85.6)	918 (96.6)	648 (93.4)
Smoking status					
History of smoking	2589 (84.9)	370 (83.5)	788 (81.8)	784 (82.5)	647 (93.2)
No history of smoking	459 (15.0)	73 (16.5)	175 (18.2)	165 (17.4)	46 (6.6)

(continued on next page)

Table 1 (continued)

Characteristic, no. (%)	All N = 3050	CGP (+other) n = 443 (18.8)	Other NGS (+non-NGS) n = 963 (40.9)	Non-NGS n = 950 (40.3)	No Test n = 694 (22.8)
Unknown/not documented	2 (0.1)	0	0	1 (0.1)	1 (0.1)
ECOG status at advanced disease diagnosis					
0/1	705 (23.1)	117 (26.4)	187 (19.4)	239 (25.2)	162 (23.3)
2	119 (3.9)	21 (4.7)	25 (2.6)	41 (4.3)	32 (4.6)
3/4	17 (0.6)	3 (0.7)	4 (0.4)	5 (0.5)	5 (0.7)
Missing	2209 (72.4)	302 (68.2)	747 (77.6)	665 (70.0)	495 (71.3)

CGP: comprehensive genomic profiling; ECOG: Eastern Cooperative Oncology Group; NGS: next-generation sequencing.

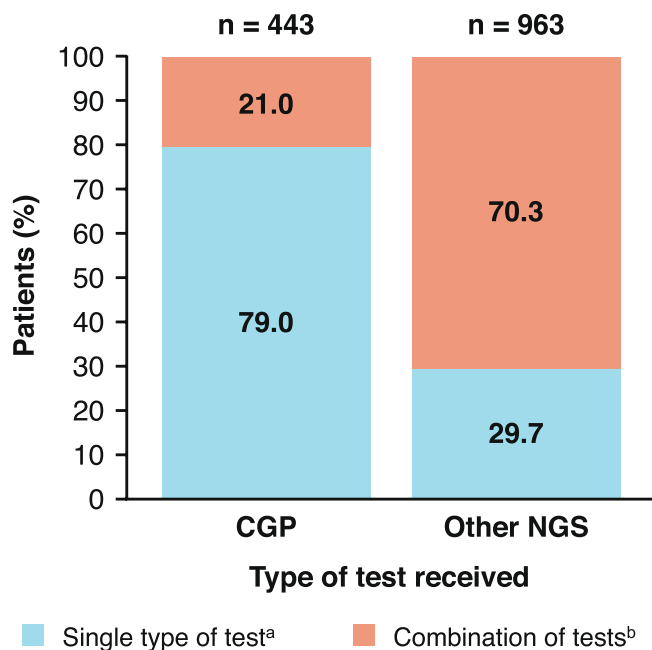


Fig. 2. Use of testing technologies in newly diagnosed patients with aNSCLC. aNSCLC: advanced non-small cell lung cancer; CGP: comprehensive genomic profiling; NGS: next-generation sequencing. ^a Includes CGP only or other NGS testing methods only. ^b For CGP, includes other NGS and/or non-NGS testing methods; for other NGS, other non-NGS testing methods were included.

four biomarkers in 61.7% (Table 2). Among NGS-tested patients, 10.0% were found to have a potentially missed targeted therapy option, which was numerically less pronounced in those receiving FMI CGP compared with those receiving another type of NGS test (2.9% versus 13.2%; Table 2). Among the 950 patients who received a non-NGS test only, a potential targeted therapy was identified in 20.7% and a potentially missed targeted therapy option was found in 40.2% (Table 2). When adjusting for the detection of a non-*BRAF*^{V600E} mutation (as these were not treatable, they were considered negative findings), 23.5% of patients with NGS testing had a result that indicated a treatable targeted therapy option, compared with 20.4% among those who received non-NGS testing only. At the same time, in patients tested with NGS, targeted therapy was ruled out in 66.4%, compared with 39.4% among those who received non-NGS tests only.

3.4. Testing of individual biomarkers

Regardless of the technology used, *EGFR* and *ALK* testing was performed in $\geq 95\%$ of patients (Table 3). However, while *BRAF* and *ROS1* were also tested in a high proportion of patients who received an NGS test ($\geq 92\%$), corresponding proportions were numerically lower when non-NGS tests only were used (56.1% and 83.7%, respectively; Table 3). Details of the *BRAF* and *EGFR* mutations detected are included in Supplementary Tables S3 and S4, respectively.

4. Discussion

We describe contemporary clinical patterns of genomic testing in patients with newly diagnosed non-squamous aNSCLC who were cared for within the Flatiron network, reflecting the community oncology care setting in the US. Overall, we found that not using genomic testing in aNSCLC remains a concern in recent clinical practice, with almost a quarter of patients not receiving any genomic testing before initiation of first-line therapy. Our results show that NGS tests are used in 60% of patients and that not using NGS testing may more often lead to a potentially missed targeted therapy option (compared with cases where NGS testing was used). We also found that when only non-NGS tests were used, testing for recently approved biomarkers such as *ROS1* and *BRAF* was lower. Furthermore, we found a slightly lower probability of finding an actionable *BRAF* mutation with non-NGS testing. There were no differences in testing between age groups, although there was a greater proportion of non-testing among smokers versus non-smokers and a greater use of CGP in a community versus academic setting; these findings are in line with previous research [17–19]. Unsuccessful genotyping, regardless of testing technique, occurred mainly due to a missing test order, with test failures playing a minimal role.

Previous studies suggest that while genomic testing has increased in recent years [17,20], there remains room for improvement. Previous research has indicated that potential reasons for the lack of biomarker testing include waiting time for results, insufficient tissue samples from biopsies for biomarker analysis, requirement for re-biopsies that may be challenging from a risk, cost and patient perspective [20] and insufficient payer coverage of testing [21]. However, in 2018, the US Centers for Medicare and Medicaid Services approved a national coverage decision for FDA-approved NGS testing in patients with aNSCLC [22]. Combined with the past and more recent FDA approval of NGS-based platforms for genomic testing in patients with aNSCLC [15,23,24], this should, based on the reduced overall costs and enhanced molecular sensitivity of these platforms [14,25,26], help to increase the proportion of patients who undergo testing both when tissue samples are available and when only a blood sample can be analysed.

In the present study, use of NGS-based techniques in patients with non-squamous aNSCLC, particularly CGP, was found to increase the frequency of successful genotyping and reduce the likelihood of a potentially missed targeted therapy option, which is critical given the observed clinical benefit of such treatments, both in clinical trials and in the real world [6,7,27–32]. Analysis of individual biomarkers revealed that when only non-NGS techniques were used, testing was numerically lower for *BRAF* and *ROS1* genes than for *EGFR* or *ALK*. Slower adoption of these more recently approved biomarkers (i.e., from 2018) [10,11], technical difficulties, possibly including a lack of material for testing due to prior biomarker analysis, and patients being directed to immunotherapy without genomic testing because of high PD-L1 expression (not recommended by guidelines) [11], may explain these findings. Regarding the latter, clinical implementation of both PD-L1 testing and testing of molecular biomarkers recommended by NSCLC guidelines can be challenging, due to lack of adequate tissue quantity and quality. Indeed, a real-world, retrospective cohort study demonstrated an increase in PD-L1 testing among patients diagnosed with aNSCLC since 2016, and, concomitantly, an increase in first-line cancer immunotherapy, suggesting a high level of enthusiasm for use of PD-L1 testing

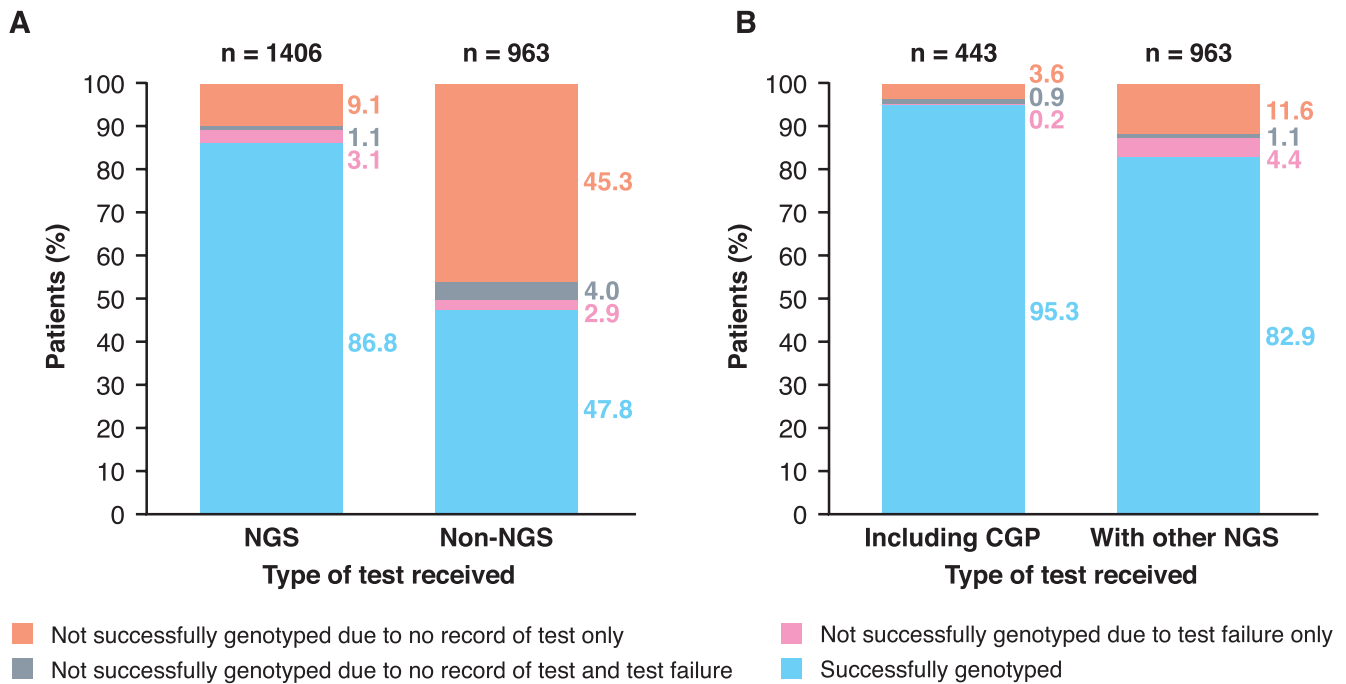


Fig. 3. Overall results of genotyping in patients by (A) NGS and non-NGS testing methods and (B) CGP and other NGS testing methods. CGP: comprehensive genomic profiling; NGS: next-generation sequencing.

Table 2

Overall outcomes of genomic testing strategies: Identification or exclusion of potential targeted therapy options, including adjusted values for non-*BRAF*^{V600E} mutations.

	NGS n = 1406			Non-NGS n = 950
	CGP (+other) n = 443	Other NGS (+non-NGS) n = 963	Overall	
Potential targeted therapy identified, % (adj.%)^a				
Mutation positive in at least 1 marker, 4 tested	28.0 (21.4)	23.7 (19.8)	25.0 (20.3)	8.7 (8.4)
Mutation positive in at least 1 marker, <4 tested	1.8 (1.8)	3.9 (3.8)	3.3 (3.2)	12.0 (12.0)
Total	29.8 (23.2)	27.6 (23.6)	28.3 (23.5)	20.7 (20.4)
Targeted therapy ruled out, % (adj.%)^a				
Mutation negative in 4 markers	67.3 (73.8)	59.2 (63.0)	61.7 (66.4)	39.1 (39.4)
Potentially missed targeted therapy, % (adj.%)^a				
Only negative tests in < 4 markers and at least 1 Untested or unsuccessfully tested marker	2.9 (2.9)	13.2 (13.3)	10.0 (10.0)	40.2 (40.2)

CGP: comprehensive genomic profiling; NGS: next-generation sequencing.

^a adj.%: Adjusted percentage values accounted for the finding of a non-*BRAF*^{V600E} mutation; as these were not treatable, they were considered negative findings for the adjusted values. Detailed information on *BRAF* mutation findings in the study are provided in [Supplementary Table S3](#).

and cancer immunotherapy that may supersede recommendations for biomarker testing [33]. Nevertheless, given the emergence and recent approval of new biomarkers (e.g., *KRAS*, *NTRK*, *MET*, *RET*, *HER2*) [10,11], our results support an increasing clinical need for broader NGS-based testing, which tends to be more cost- and time-effective than single-gene testing, in patients with aNSCLC [26]. This supports the application of standardised testing algorithms in pathology to ameliorate waiting for individual test results, i.e., *EGFR*, *BRAF*, *ALK*, *ROS1* and any other approved genomic biomarker should be tested by pathologists in every patient with stage IV non-squamous NSCLC by default.

A limitation of the current study is that the reasons why patients received genomic testing were not available; it is possible that for some patients, the lack of a solid tumour sample or insufficient tumour tissue, or other technical barriers [34,35], may have prevented any or some of the testing. In patients for whom a solid tumour sample was unavailable, both in the first-line setting [36] and otherwise [37,38], NGS-based liquid biopsies may be considered, which are minimally invasive, have

a shorter turnaround time for test results and may serve to reduce overall healthcare costs [39,40]. This technique has already shown high concordance with tumour tissue genotyping for detection of genomic alterations and subsequent clinical decision-making in aNSCLC [25,37,40–42], and a number of NGS-based liquid biopsy platforms have since been granted FDA approval [43,44]. Compared with tumour tissue genotyping, NGS liquid biopsies have also been demonstrated to enable enhanced detection of therapeutically relevant genomic alterations in aNSCLC and thus stratification to targeted therapy in cases of insufficient tissue availability, failed quality control, incomplete genotyping or a negative biomarker result from tissue testing [40,45,46].

Furthermore, some patients may have tested positive for rare genomic alterations that were not documented routinely in our data, e.g., *NTRK* fusions; however, given the rarity of these alterations in aNSCLC (~0.1%) [47], it seems unlikely that they would have had a major influence on the results.

Table 3

Proportion of patients tested for individual biomarkers who had a successful test and mutation positivity by test approach.

	NGS n = 1406		Non NGS n = 950
	CGP (+other) n = 443	Other NGS (+non-NGS) n = 963	
ALK, %			
Tested ^a	98.0	95.5	94.9
Successful ^b	99.5	97.9	96.0
Positive ^c	2.5	3.2	3.3
Negative ^c	97.5	96.8	96.7
BRAF, %			
Tested ^a	96.4	95.3	56.1
Successful ^b	99.8	97.8	97.9
Positive ^c	10.3	6.7	1.5
Negative ^c	89.7	93.3	98.5
EGFR, %			
Tested ^a	98.4	99.3	94.9
Successful ^b	99.3	97.6	98.6
Positive ^c	17.8	18.8	17.4
Negative ^c	82.2	81.2	82.6
ROS1, %			
Tested ^a	98.0	92.4	83.7
Successful ^b	99.8	96.2	95.6
Positive ^c	1.4	0.9	1.1
Negative ^c	98.6	99.1	98.9

CGP: comprehensive genomic profiling; NGS: next-generation sequencing.

^a % of patients overall.

^b % of patients tested.

^c % of successful tests (positive = rearrangement present for ALK or ROS1, or mutation positive for EGFR or BRAF).

5. Conclusions

The findings of this study suggest that among US patients with newly diagnosed non-squamous aNSCLC, a lack of NGS testing may increase the probability of a potentially missed targeted therapy option. The use of NGS, particularly CGP, may also help to avoid suboptimal biomarker testing, minimise test failures, improve uptake of testing for recently approved biomarkers and enable enhanced access to clinical trials of molecularly guided therapies and individualised, targeted therapy. Our results provide support for the use of guideline-recommended broad-panel NGS testing in clinical practice, which is also warranted by the ever increasing molecularly guided treatment options for aNSCLC.

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Data Sharing Statement: The data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

CRedit authorship contribution statement

Luis Paz-Ares: Conceptualization, Supervision, Validation, Investigation, Visualization, Writing – original draft, Project administration,

Writing – review & editing. **Adam Gondos:** Conceptualization, Data curation, Software, Formal analysis, Supervision, Validation, Investigation, Visualization, Methodology, Writing – original draft, Project administration, Writing – review & editing. **Diego Saldana:** Conceptualization, Data curation, Software, Formal analysis, Validation, Investigation, Visualization, Methodology, Project administration, Writing – review & editing. **Marlene Thomas:** Conceptualization, Supervision, Funding acquisition, Investigation, Visualization, Methodology, Project administration, Writing – review & editing. **Celine Mascaux:** Conceptualization, Validation, Investigation, Writing – review & editing. **Lukas Bubendorf:** Conceptualization, Validation, Investigation, Writing – review & editing. **Fabrice Barlesi:** Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **LPA:** has received a research grant from Bristol Myers Squibb, AstraZeneca and PharmaMar, and personal fees from MSD, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, AstraZeneca, Eli Lilly, Merck, Novartis, Amgen, Pfizer, Takeda, Blueprint, Bayer, PharmaMar, Ipsen, AbbVie, GSK, Janssen, Boehringer Ingelheim, Sanofi, Tesaro, Mirati, Altum sequencing and Genomica. **AG:** Employed by and has stocks or other ownership in F. Hoffmann-La Roche Ltd. **DS:** Employed by F. Hoffmann-La Roche Ltd (previously) and Novartis, has stocks or other ownership in Novartis and has received research funding (institution) from F. Hoffmann-La Roche Ltd and Novartis. **MT:** Employed by and has a leadership role in F. Hoffmann-La Roche Ltd, and has stocks or other ownership, and holds patents, royalties, other intellectual property (self) with F. Hoffmann-La Roche Ltd. **CM:** Has received personal fees for consulting or advisory boards from F. Hoffmann-La Roche Ltd, AstraZeneca, Kephren, Bristol Myers Squibb, MSD and Pfizer, and has received travel and accommodation expenses from F. Hoffmann-La Roche Ltd, AstraZeneca, Takeda and Boehringer Ingelheim. **LB:** has received a research grant from MSD and personal fees for advisory boards from AstraZeneca, AbbVie, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, MSD and Pfizer. **FB:** has received personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda. All authors received research support in the form of third-party medical writing assistance for this manuscript, provided by F. Hoffmann-La Roche Ltd.

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Appendix A. Supplementary data

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