ORIGINAL ARTICLE

# The Genomics of Young Lung Cancer: Comprehensive Tissue Genomic Analysis in Patients Under 40 With Lung Cancer

Barbara J. Gitlitz, MD,[a,^,*] Silvia Novello, MD, PhD,[b] Tiziana Vavalà, MD,[c] Marisa Bittoni, PhD,[d] Alicia Sable-Hunt, RN, MBA,[e,†] Dean Pavlick, BS,[f] Robert Hsu, MD,[g] S. Lani Park, PhD, MPH,[h,‡] Ruthia Chen, BA,[i,§] Matthew Cooke, BA,[f] Amy Moore, PhD,[j,‖] Alexa B. Schrock, PhD,[k] Joan H. Schiller, MD,[l,¶] Bonnie J. Addario,[e,j] Geoffrey R. Oxnard, MD[m,#]

[a]*Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California*
[b]*Department of Oncology, AOU San Luigi-Orbassano, University of Turin, Turin, Italy*
[c]*Screening Center of Oncology, Saluzzo Hospital, Saluzzo, Italy*
[d]*The Ohio State University, Comprehensive Cancer Center, Columbus, Ohio*
[e]*Addario Lung Cancer Medical Institute, San Carlos, California*
[f]*Foundation Medicine, Inc., Cambridge, Massachusetts*
[g]*Department of Oncology, Keck School of Medicine, University of Southern California, Los Angeles, California*
[h]*Keck School of Medicine, University of Southern California, Los Angeles, California*
[i]*Department of Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[j]*GO2 Foundation for Lung Cancer, San Carlos, California*
[k]*Clinical Development, Foundation Medicine, Inc., Cambridge, Massachusetts*
[l]*Inova Schar Cancer Institute, Fairfax, Virginia*
[m]*Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*

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## ABSTRACT

**Introduction:** Lung adenocarcinomas in young patients (<40 y) are more likely to harbor targetable genomic alterations. This study aimed to determine whether the prevalence of targetable alterations is greater in young adults with lung carcinoma than in the overall lung cancer

*Corresponding author.

[^]Affiliated with the Keck School of Medicine, University of Southern California, Los Angeles, California, at the time of this study and currently an employee of Genentech, Inc.

[†]Affiliated with the Addario Lung Cancer Medical Institute at the time of the study and currently president of Edwards-Hunt.

[‡]Affiliated with the Keck School of Medicine, University of Southern California, Los Angeles, California, at the time of this study and currently an employee of University of Hawaii Cancer Center.

[§]Affiliated with the Dana-Farber Cancer Institute at the time of this study and currently a medical student at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo.

[‖]Affiliated with $GO_2$ Foundation for Lung Cancer at the time of this study and currently an employee of LUNGevity.

[¶]Affiliated with the Inova Schar Cancer Institute at the time of this study and currently an adjunct professor at the University of Virginia Medical School.

[#]Affiliated with the Dana-Farber Cancer Institute at the time of this study and currently an employee of Foundation Medicine Inc.

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Address for correspondence: Barbara J. Gitlitz, MD, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080. E-mail: gitlitz.barbara@gene.com

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population. To reach this rare patient population, a web-based platform was used to recruit and enroll patients remotely.

**Methods:** In this prospective study, patients less than 40 years old at the time of primary lung cancer diagnosis with confirmed lung carcinoma were recruited from four global sites and remotely by means of a website. Genotyping data were collected, if available, or obtained by means of next-generation sequencing using the FoundationOne platform. The prevalence of targetable alterations was quantified across patients with advanced adenocarcinoma.

**Results:** Overall, 133 patients across five continents were included, 41% of whom enrolled online. The mean (SD) age at diagnosis was 34 (5.2) years; 79% had stage IV disease at diagnosis. Among patients with adenocarcinoma (n = 115), 112 entered the study with previous genomic testing results and 86 (77%) had targetable alterations in *EGFR*, *ALK*, *ROS1*, *MET*, *ERBB2*, or *RET*. Among those without targetable alterations, 14 received further testing and a targetable alteration was identified in eight (57%).

**Conclusions:** This study revealed the feasibility of using a web-based platform to recruit young patients with lung cancer and revealed that 94 of 112 (84%) with adenocarcinoma at any stage had targetable genomic alterations. Among patients with stage IV adenocarcinoma, 85% had a targetable alteration, which is higher than historical expectations for the general population.



*Keywords:* Lung adenocarcinoma; Mutation; Genotyping; Young; Targeted

## Introduction

Lung cancer is the second most common cancer but remains the most common cause of cancer death, accounting for approximately 24% of cancer deaths in the United States.[1] The median age at diagnosis is 70 years, with most cases diagnosed in patients older than 65 years.[1] Fewer than 2% of all cases are found in patients aged younger than 45 years.[2] Regardless of patient age, most lung cancer cases are diagnosed at an advanced, incurable stage.[3]

No longer considered a single disease entity, lung cancer is increasingly subdivided into distinct molecular genotypes that are treated with targeted therapies against oncogenic drivers.[4-6] The identification of genomic alterations sensitive to targeted therapies has transformed the management and survival of NSCLC.[7] The discovery of new molecular targets, mechanisms of resistance, and rare NSCLC genotypes will likely continue, thereby spurring drug development and broadening therapeutic possibilities.

Multiple retrospective studies have found that genotype prevalence differs by age group and that the likelihood of harboring a targetable alteration in genes, such as *EGFR*, *ALK*, or *ROS1*, is increased in patients diagnosed at a young age.[4,8] We hypothesized that lung cancer in young patients—defined as patients younger than 40 years—would be enriched for targetable genomic alterations. We launched the multicenter Genomics of Young Lung Cancer study, the first study to prospectively characterize the clinical characteristics of and somatic genomic alterations in young patients with lung cancer. To best reach this rare population, we adopted a novel approach for consent and enrollment by including patients who enrolled online.

## Materials and Methods

### *Study Design and Patient Population*

Given the rarity of lung cancer in young patients, a website was created by the Addario Lung Cancer Medical Institute to provide study information and study personnel contact information and to prospectively recruit patients from a remote global population.[9] Informed consent was obtained from all patients. Remote patients were invited to enroll online by means of a secure portal, OpenMedNet, developed by the Open Medicine Institute[10] (Mountain View, CA), where they electronically signed an informed consent form. The University of Southern California Institutional Review Board was the governing ethics committee for remote patients and those who enrolled in person at the Norris Comprehensive Cancer Center at the University of Southern California. Local institutional review boards oversaw the following three other physical sites enrolling patients: Dana-Farber Cancer Institute (Boston, MA), Northside Hospital (Atlanta, GA), and University of Turin (Turin, Italy). This study was carried out in accordance with the Declaration of Helsinki.

Patients eligible for the study were less than 40 years old at the time of primary lung cancer diagnosis and had pathologically confirmed bronchogenic lung carcinoma (SCLC or NSCLC) at any stage and treatment time point. Patients with metastatic nonsquamous NSCLC were required to have *EGFR* and *ALK* genotyping by a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory at the time of enrollment. No genotyping was required before enrollment for patients with early stage NSCLC (stages I–III) or those with SCLC or squamous

NSCLC. Patients were excluded if use of their tissue sample for research would compromise the diagnosis or staging of their lung cancer.

### Sample Collection and Clinical Genomics

Any existing available results from genomic testing performed by a CLIA-certified laboratory were requested from enrolled patients. All patients were required to provide previously collected tumor samples consisting of 16 unstained slides or an adequate formalin-fixed, paraffin-embedded tumor block from a clinically indicated interventional procedure. All eligible participants were asked to complete a questionnaire to obtain demographics, basic lung cancer history, medical and social history, work and environmental exposure history, and family cancer history. A separate questionnaire regarding the patient's lung cancer diagnosis, staging, and treatment history was completed by the local investigator or mailed to patients to give to their treating physician for completion.

To investigate additional driver alterations that might guide potential targeted treatment options and to more comprehensively study the genomics of lung cancer in young patients, patients with metastatic nonsquamous NSCLC whose tissue samples had negative results for or had not been tested for all seven protocol-specified mutations or rearrangements (*EGFR*, *KRAS*, *ERBB2*, *BRAF*, *ROS1*, *ALK*, and *RET*) were offered next-generation sequencing (NGS) by means of the FoundationOne (F1) platform (Foundation Medicine Inc., Cambridge, MA).[11] F1 testing was also performed on samples from patients with SCLC or metastatic squamous NSCLC as an exploratory cohort.

For patients eligible for F1 testing, Foundation Medicine was notified, and a kit was shipped directly to the patient for CLIA testing. Remote participants were also mailed a kit containing the case report forms for completion by their treating physician and tubes for blood collection for exploratory genotyping.

### Study Objective and Statistical Analysis

The primary objective of this study was to determine whether the prevalence of targetable alterations is greater in young adults (<40 y old) with lung carcinoma than in the overall lung cancer population. Patients with stage IV adenocarcinoma were also compared with the historical experience of the Lung Cancer Mutation Consortium. Patients with SCLC or metastatic squamous NSCLC were included as an exploratory cohort.

A targetable alteration was defined as any alteration in a driver oncogene for which a U.S. Food and Drug Administration–approved therapy existed at the time of study enrolment (e.g., crizotinib for *ALK* rearrangement)[12] or for which an off-label therapy existed at the time of enrollment (e.g., crizotinib for *MET* amplification).[7] Alterations that exclude certain targeted therapies (e.g., erlotinib for *KRAS* mutations)[7] or mutations in tumor-suppressor genes (e.g., *PTEN*)[13] were not considered targetable.

The Lung Cancer Mutation Consortium[5] was formed to enable a collaborative multi-institutional analysis of potential oncogenic driver alterations in patients of any age with advanced lung adenocarcinoma. In the Lung Cancer Mutation Consortium experience, the prevalence of alterations in *EGFR*, *ALK*, *BRAF*, *ERBB2*, *ROS1*, or *MET* was 35% (36% if *ROS1* rearrangements were included). With a one-sided 0.07-level exact binomial test, 60 patients were needed to provide 82% power to detect a difference in the rate of targetable genotypes from the historical rate of 35% to 50% among young patients with lung adenocarcinoma. This is equivalent to observing greater than or equal to 27 patients with a targetable alteration among the cohort of 60 patients.

The prevalence of targetable alterations was quantified across all patients with adenocarcinoma, and alterations in *EGFR*, *ALK*, *ROS1*, and others (*RET*, *ERBB2*, and *MET*) were summarized across all patients. For patients with adenocarcinoma, chi-square tests were used to determine the overall association of targetable alterations in *EGFR*, *ALK*, *ROS1*, and others (*KRAS*, *ERBB2*, and *RET*) by smoking history, marijuana use, race, and family history of lung cancer. A chi-square test was also used to determine the significance of stage by adenocarcinoma and association between cigarette smoking and marijuana use. Unique cases of clinical interest are highlighted in the patient spotlights section.

## Results

### Demographics

This study enrolled 133 young patients with lung cancer across 5 continents, including North America, South America, Europe, Asia, and Australia, between July 2014 and July 2017. The mean (SD) age at diagnosis was 34 (5.2) years with a range of 16 to 39 years; 57% were female and 73% were white (Table 1). Overall, 79% of patients had stage IV disease at diagnosis, and 86% had adenocarcinoma. Of the 121 patients with documented smoking status, 33 patients (27%) were or had been smokers and 88 patients (73%) were nonsmokers; among nonsmokers, 79 (90%) had adenocarcinoma. Overall, 62% reported no known exposure to secondhand smoke.

A total of 54 patients (41%) enrolled online. Their mean (SD) age was 34 years (5.2) (range: 17–39 y); 54% were female and 46% were male; 78% were white and 22% were minorities (Asian, n = 5; black, n = 1;

**Table 1.** Demographics and Mutations by Sex and Tumor Type

| Characteristic | Adenocarcinoma (n = 115) | | | Nonadenocarcinoma (n = 18) | | | Both (N = 133) |
|---|---|---|---|---|---|---|---|
| | Female (n = 68) | Male (n = 47) | Total (n = 115) | Female (n = 8) | Male (n = 10) | Total (n = 18) | Total (N = 133) |
| Age, mean (SD), y | 34 (5.0) | 34 (5.5) | 34 (5.2) | 33 (4.3) | 34 (4.9) | 34 (4.6) | 34 (5.2) |
| Range, y | 17–39 | 16–39 | 16–39 | 24–38 | 25–39 | 24–39 | 16–39 |
| Race, n (%)[a] | | | | | | | |
| White | 49 (72.1) | 36 (74.4) | 85 (73.9) | 6 (75.0) | 6 (60.0) | 12 (66.7) | 97 (72.9) |
| Asian | 13 (19.1) | 4 (8.5) | 17 (14.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (12.8) |
| Other[b] | 6 (8.8) | 7 (17.1) | 13 (11.3) | 2 (25.0) | 4 (40.0) | 6 (33.3) | 19 (14.3) |
| Stage, n (%)[c] | | | | | | | |
| N | 67 | 47 | 114 | 7 | 9 | 16 | 130 |
| I–III | 15 (22.4) | 3 (6.4) | 18 (15.8) | 4 (57.1) | 5 (55.6) | 9 (56.3) | 27 (20.8) |
| IV | 52 (77.6) | 44 (93.6) | 96 (84.2) | 3 (42.9) | 4 (44.4) | 7 (43.8) | 103 (79.2) |
| Mutations, n (%) | | | | | | | |
| N | 65 | 47 | 112[d] | 7 | 9 | 16[e] | 128 |
| *ALK* | 21 (32.3) | 20 (42.6) | 41 (36.6) | 0 (0.0) | 1 (11.1) | 1 (6.3) | 42 (32.8) |
| *EGFR* | 23 (35.4) | 13 (27.7) | 36 (32.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 36 (28.1) |
| *ROS1* | 7 (10.8) | 1 (2.1) | 8 (7.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (6.3) |
| Other | 14 (21.5) | 13 (27.7) | 27 (24.1)[f] | 7 (100.0) | 8 (88.9) | 15 (93.8)[g] | 42 (32.8) |
| Family history of lung cancer, n (%) | | | | | | | |
| N | 60 | 42 | 102 | 7 | 10 | 17 | 119 |
| Yes | 18 (30.0) | 6 (14.3) | 24 (23.5) | 1 (14.3) | 3 (30.0) | 4 (23.5) | 28 (23.5) |
| No | 42 (70.0) | 36 (85.7) | 78 (76.5) | 6 (85.7) | 7 (70.0) | 13 (76.5) | 91 (76.5) |
| Ever smoked, n (%) | | | | | | | |
| N | 61 | 43 | 104 | 7 | 10 | 17 | 121 |
| Yes | 14 (23.0) | 11 (25.6) | 25 (24.0) | 2 (28.6) | 6 (60.0) | 8 (47.1) | 33 (27.3) |
| No | 47 (77.0) | 32 (74.4) | 79 (76.0) | 5 (71.4) | 4 (40.0) | 9 (52.9) | 88 (72.7) |
| Ever used marijuana, n (%) | | | | | | | |
| N | 60 | 43 | 103 | 7 | 10 | 17 | 120 |
| Yes | 14 (23.3) | 13 (30.2) | 27 (26.2) | 2 (28.6) | 6 (60.0) | 8 (47.1) | 35 (29.2) |
| No | 46 (76.7) | 30 (69.8) | 76 (73.8) | 5 (71.4) | 4 (40.0) | 9 (52.9) | 85 (70.8) |
| Exposure to secondhand smoke, n (%) | | | | | | | |
| N | 60 | 43 | 103 | 7 | 10 | 17 | 120 |
| Yes | 24 (40.0) | 13 (30.2) | 37 (35.9) | 3 (42.9) | 6 (60.0) | 9 (52.9) | 46 (38.3) |
| No | 36 (60.0) | 30 (69.8) | 66 (64.1) | 4 (57.1) | 4 (40.0) | 8 (47.1) | 74 (61.7) |

*Note:* Denominators changed for several of the variables owing to missing data. Percentages may not add up to 100% owing to rounding.
[a]Race was self-identified.
[b]Five patients were black, nine were Hispanic, four were South Asian, and one was North African.
[c]A chi-square test was used to determine significance of stage by adenocarcinoma ($p = 0.02$).
[d]There were 115 patients with adenocarcinoma, but only 112 received genomic testing.
[e]There were 18 patients with nonadenocarcinoma, but only 16 received genomic testing.
[f]Includes four patients with a *RET* rearrangement, three with *ERBB2* mutations, and two with *MET* amplification.
[g]Includes one patient with a *MET* amplification.

Hispanic, n = 3; South Asian, n = 3). Most (81%) had stage IV disease at diagnosis, and 83% had adenocarcinoma. In comparison, among patients who enrolled at the study centers, 60% were female and 30% were minorities.

## Genomic Results

**Adenocarcinoma.** Among the 115 patients with adenocarcinoma, 112 had previous genomic testing results on study entry. Three patients did not have previous genomic testing at study entry owing to early stage disease. Of the 112 patients entering the study with genomic testing results, tumor samples from 86 (77%) harbored a targetable driver alteration. Of the 26 patients without a targetable alteration, 14 received further on-protocol F1 testing. For the remaining 12 patients, the reasons for no further on-protocol testing were as follows: not eligible owing to early stage disease (n = 4), tissue not available or not submitted (n = 6), *KRAS*+ (n = 1), and previous negative F1 test results on trial entry (n = 1) (Supplementary Fig. 1).

Of the 14 patients with adenocarcinoma who underwent on-protocol F1 testing, a targetable driver alteration was identified in eight (57%), consisting two with a

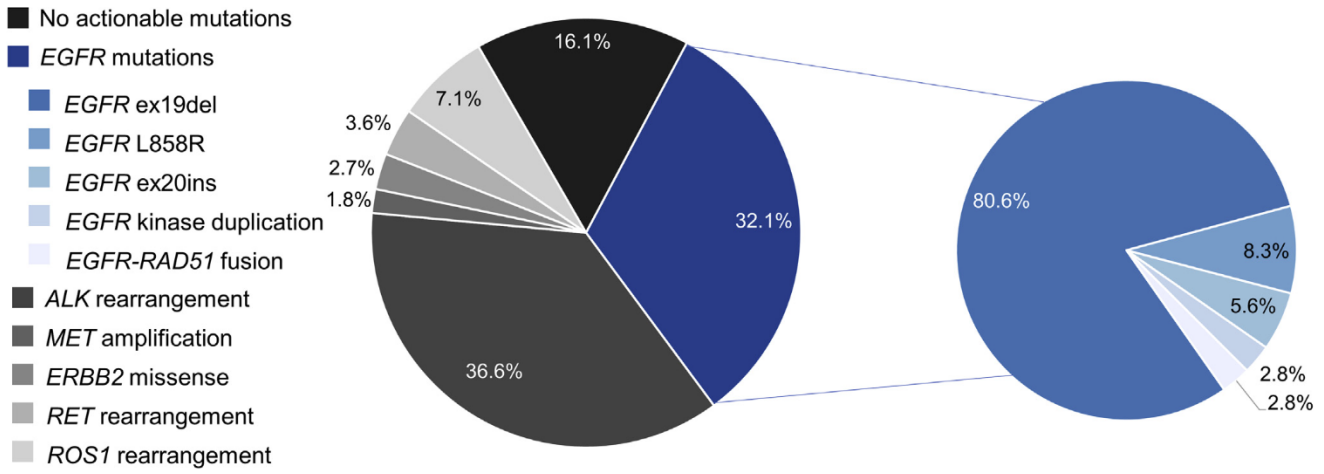


**Figure 1.** Targetable driver mutations in patients with lung adenocarcinoma. n = 112. ex19del, exon 19 deletion; ex20ins, exon 20 insertion.

*RET* rearrangement, two with *ERBB2* point mutations, two with *MET* amplification, one with an *ALK* rearrangement who had previous negative results from fluorescence in situ hybridization testing for *ALK,* and one with a novel *EGFR-RAD51* fusion[6] who had previous negative hotspot testing results for *EGFR* mutation.

In summary, of 112 patients with adenocarcinoma who had previous genomic testing, 86 patients had previously identified targetable driver alterations, whereas 14 patients received on-protocol F1 testing that identified targetable alterations in an additional eight patients. Overall, of these 112 patients, 94 (84%) had a targetable driver alteration, with 85 (76%) harboring an *ALK* (n = 41; 37%), *EGFR* (n = 36; 32%), or *ROS1* (n = 8; 7%) mutation or rearrangement (Fig. 1). Other drivers included *RET* rearrangement (n = 4; 4%), *ERBB2* mutations (n = 3; 3%), and *MET* amplification (n = 2; 2%). Of patients who enrolled online with adenocarcinoma, 36 (80%) had one of the following targetable driver alterations: *ALK* rearrangement (n = 14), *EGFR* mutation (n = 15), *ROS1* rearrangement (n = 4), *RET* rearrangement (n = 2), and *ERBB2* mutation (n = 1).

Of the 115 patients with adenocarcinoma, 84% had stage IV disease and were the focus of the comparison to historical expectations of the Lung Cancer Mutation Consortium (Table 1). In this study, 82 (85%) of these patients had tumors harboring a targetable driver alteration in *ALK* (n = 37), *EGFR* (n = 30), *ERBB2* (n = 4), *BRAF* (n = 1), *ROS1* (n = 6), or *RET* (n = 4). In comparison, the consortium found that the prevalence of *ALK*, *EGFR*, *ERBB2*, *BRAF*, *ROS1*, and *MET* alterations in patients with advanced lung adenocarcinoma was 35%.[5]

Among patients with adenocarcinoma, targetable alterations were analyzed by smoking status (n = 104), marijuana use (n = 103), race (n = 115), and family history of lung cancer (n = 102) (Fig. 2). Because of small cell counts, statistical significance could not be determined for these analyses. The analysis by smoking status included 79 nonsmokers and 25 smokers (Fig. 2*A*). Most patients with an alteration in a driver oncogene were nonsmokers versus smokers (*ALK* rearrangement, 77% versus 23%; *EGFR* mutation, 80% versus 20% versus genomic aberrations in other genes described in our study population [i.e., *KRAS*, *ERBB2*, *TP53*, *RET*, *NF1*], 64% versus 36%). None of the patients with *ROS1*+ were smokers. Cigarette smoking and marijuana use were significantly associated ($p < 0.0001$). Most marijuana users, approximately 70%, did not have targetable alterations. Alteration prevalence in *ALK*, *EGFR*, and other genes was similar among users (25%, 29%, and 31%, respectively) and among nonusers (75%, 71%, and 69%, respectively) (Fig. 2*B*). When analyzed by white (n = 85), Asian (n = 17), or other race (n = 13), most patients with alterations in *ALK*, *EGFR*, *ROS1*, and other were white (50%–80%). The *ROS1*+ group had the highest proportion of Asian patients (38%), followed by *EGFR* (22%) (Fig. 2*C*). Among patients with a family history of lung cancer (n = 24) versus without (n = 78), most patients with alterations did not have a family history of lung cancer. The *ROS1*+ and other groups had the highest proportion of patients with a family history of lung cancer (43% and 32%, respectively) (Fig. 2*D*).

**Nonadenocarcinoma.** The 18 patients with nonadenocarcinoma consisted of nine with squamous cell carcinoma, six with SCLC, one with pulmonary blastoma, and two not otherwise specified. Among these 18 patients, 13 entered the trial with previous genomic testing results; one patient with stage IV squamous cell

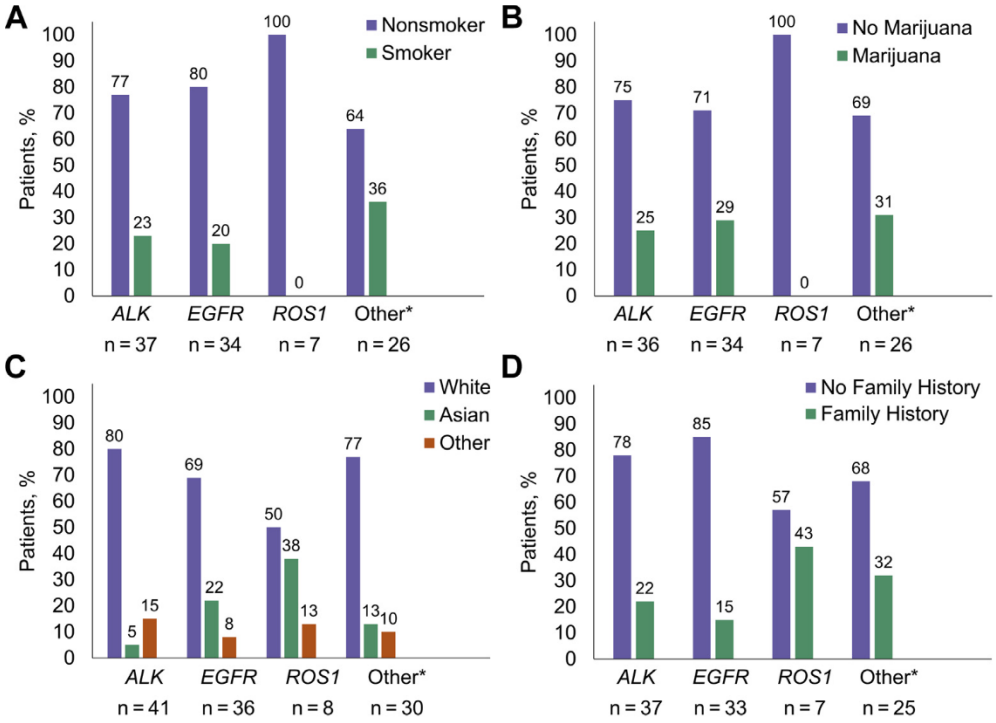


**Figure 2.** Genetic mutation by (*A*) cigarette smoking, (*B*) marijuana use, (*C*) race, and (*D*) family history of lung cancer. Because of small cell counts, statistical significance could not be determined for these analyses. *Other includes *KRAS*, *ERBB2*, *TP53*, *RET*, and *NF1*.

carcinoma harbored an *ALK* rearrangement. Four patients received further on-protocol F1 testing; one of these patients had a *MET* amplification. For the remaining patients, the reasons for no further on-protocol testing were previous negative F1 test results on trial entry (n = 4), no tissue (n = 3), and tissue not sent (n = 1) (Supplementary Fig. 1).

## *Patient Spotlights*

**Patient 1.** A 33-year-old white male patient with stage IV lung adenocarcinoma was tested on the F1 platform. He had never smoked and had no family history of lung cancer. F1 testing detected a 12-fold amplification of *EGFR* and *EGFR* kinase domain duplication of exons 18 to 25 (Supplementary Table 1). Similar to the more canonical L858R mutation or exon 19 deletions, this lesser-described, tandem, in-frame duplication of the *EGFR* tyrosine kinase is expected to be pathogenic, and the functional and therapeutic implications are being explored.[14-16] Of note, this patient and others have revealed response to EGFR tyrosine kinase inhibitors. Other alterations detected by F1 testing included amplifications of *GNAS* and *ZNF217* (Supplementary Table 1).

**Patient 2.** A 36-year-old black male patient with stage IV lung adenocarcinoma was tested only for *EGFR* and *ALK* at study entry, and both were negative. The patient had never smoked and had no family history of lung cancer. Per protocol, F1 testing was performed revealing two missense alterations in *ERBB2* (T862A and L869R), highlighting the importance of deeper genomic testing (Supplementary Table 1). Further analysis of NGS data revealed that both T862A and L869R, described as pathogenic mutations, were located in cis (Supplementary Table 1). Other alterations detected by F1 testing included amplification of *EMSY*, *NFKBIA*, and *NKX2-1* (Supplementary Table 1). Although both testing methodologies were *ERBB2*-amplification negative, activating base substitutions of *ERBB2* have been found to respond to anti–*ERBB2*-targeted therapies.[17]

**Patient 3.** A 27-year-old white female patient with stage IV lung adenocarcinoma was tested with both standard genomics and the F1 platform (per protocol). The patient was a 2-pack-year smoker and had no family history of lung cancer. Both testing methodologies detected a Y163C alteration in *TP53* (Supplementary Table 1). F1 testing further revealed a 36-fold amplification of *MET* (Supplementary Table 1). Other alterations detected by F1 testing include *MAP2K4* Q93* and amplifications in *CDK8*, *FLT3*, and *PIK3CG* (Supplementary Table 1). Response to MET inhibitors has been found with focal, high copy number amplifications, albeit more often with exon 14 skipping events.[18,19]

**Table 2.** Comparison With Retrospective Studies

| Parameter | GoYLC2020 | Galvez-Nino et al.[25] | Chen et al.[21] | Liu et al.[20] | Pan et al.[24] | Tanaka et al.[23] | Sacher et al.[4] | Wang et al.[22] |
|---|---|---|---|---|---|---|---|---|
| Patient age evaluated | <40 | <40 | <35 | <35 | <40 | <40[a] | <40[a] | <30 |
| Tumor type | | | | | | | | |
| N | 133 | 166 | 89 | 82 | 270 | 81 | 81 | 41 |
| Adenocarcinoma, n (%) | 115 (86.5) | 105 (63.3) | 89 (100) | 37 (45.1) | 194 (71.8) | 81 (100) | 68 (84.0) | 32 (78.0) |
| SCLC, n (%) | 6 (4.5) | – | – | 21 (25.9) | 18 (6.7) | – | – | 2 (4.9) |
| Squamous cell, n (%) | 9 (6.8) | 13 (7.8) | – | 9 (11.0) | 42 (15.6) | – | 3 (3.7) | 1 (2.4) |
| Stage | | | | | | | | |
| N | 130 | 137[b] | 89 | 63 | 252 | 81 | 81 | 39[b] |
| I-III, n (%) | 27 (20.8) | 10 (7.3) | 74 (83.1) | 32 (50.8) | 84 (33.3) | 23 (28.4) | 28 (34.6) | 19 (48.7) |
| IV, n (%) | 103 (79.2) | 116 (84.7) | 15 (16.9) | 31 (49.2) | 159 (63.1) | 58 (71.6) | 53 (65.4) | 20 (51.2) |
| Unknown/other, n (%) | – | 11 (8.1) | – | – | 9 (3.6) | – | – | – |
| Mutations | | | | | | | | |
| N | 128 | 0 | 89 | 18 | –[c,d] | 81 | –[d] | 22[c] |
| *EGFR*, n (%) | 36 (28.1) | – | 19 (21.4) | 10 (55.6) | 29 (39.7)[e] | 24 (29.6) | 25 (32.1)[f] | 5 (22.7) |
| *ALK*, n (%) | 42 (32.8) | – | 15 (16.9) | 5 (27.8) | 25 (33.8)[g] | 33 (40.7) | 13 (19.1)[h] | 6 (27.2) |
| Mutation negative, n (%) | 13 (10.2) | – | 29 (32.6) | 3 (16.7) | – | 22 (27.1) | – | 7 (31.8) |
| Smoking, n (%) | | | | | | | | |
| N | 121 | 137[b] | 89 | 81 | 252 | 81 | 81 | 41 |
| Smoking, n (%) | 33 (27.2) | 17 (14.4) | 9 (10.1) | 23 (28.4) | 48 (19.0) | 36 (44.4) | 27 (33.3) | 5 (12.2) |
| Nonsmoking, n (%) | 88 (72.8) | 101 (73.7) | 80 (89.9) | 58 (71.6) | 196 (77.8) | 45 (55.6) | 54 (66.7) | 36 (87.8) |
| Unknown/not registered, n (%) | – | 19 (13.9) | – | – | 8 (3.2) | – | – | |

[a]Patients less than 40 were a subgroup within the study.
[b]Patients with NSCLC only.
[c]Patients with adenocarcinoma only.
[d]Number of patients with data available for *EGFR* and *ALK* mutations differed between groups.
[e]n = 73.
[f]n = 78.
[g]n = 74.
[h]n = 68.

## Discussion

This study is the first prospective, multicenter, web-based investigation of the genomics of young patients with lung cancer. In our series, patients aged less than 40 years who were diagnosed with primary NSCLC tended to be never-smokers and have stage IV adenocarcinoma. Most adenocarcinomas occurred in female patients (59%), whereas most nonadenocarcinomas occurred in male patients (56%).

Notably, 94 of 112 patients (84%) with adenocarcinoma at any stage harbored a targetable driver alteration: 86 patients entered the study with evidence of targetable driver alterations, whereas 8 patients were found to have targetable alterations during further on-study testing. Among the patients with adenocarcinoma who underwent additional on-study comprehensive testing, more than half (8 of 14) were found to harbor an actionable alteration, including a *RET* rearrangement, a novel actionable *EGFR* fusion, and an *ALK* rearrangement. One of our patients with squamous NSCLC was found to harbor an *ALK* rearrangement on testing before study consent only after a second opinion consultation suggested testing owing to his young age and never-smoking status. This underscores the need for genomic testing with comprehensive panels that include *ROS1*, *RET*, and *ERBB2* alteration in young patients with adenocarcinoma or nonadenocarcinoma, particularly as the landscape of diverse targetable alterations and approved therapies continues to expand. Among patients with stage IV adenocarcinoma, 85% had a targetable alteration, which is higher than historical expectations on the basis of the Lung Cancer Mutation Consortium and warrants further investigation.

We observed differences and similarities between our prospective study and previous retrospective studies of young patients with lung cancer. These studies revealed a similar predominance of adenocarcinoma, but with variations in disease stages and specific targetable driver alterations (Table 2). One study had a subset of 81 patients who were younger than 40 years, with similar proportions of adenocarcinoma and female predominance.[4] Our prospective cohort had a slightly higher percentage of patients with stage IV disease (79% versus 65%) and a similar percentage of *EGFR* mutations in all patients (28% versus 32%) but a higher percentage of *ALK*

rearrangements (33% versus 19%). Compared with retrospective studies, our study reveals a similar percentage of never-smokers (73%; Table 2)[4,20-25]; however, we saw greater percentages of *EGFR* and *ALK* alterations in nonsmokers.

Our study revealed a predominance of *EGFR* exon 19 deletions in patients with *EGFR* mutations (81%; Fig. 1). Retrospective studies have revealed a similar majority of *EGFR* exon 19 deletions, with 66% reported by Pan et al.[24] and 75% reported by Tanaka et al.[23] Conversely, our study revealed a smaller proportion of *EGFR* L858R mutations (8%) compared with 31% reported by Pan et al.[24] and 17% reported by Tanaka et al.[23]

Subgroup analysis by race revealed variations within the driver alterations, with 38% of Asians having a *ROS1* rearrangement and 22% having an *EGFR* mutation (Fig. 2*C*). Multiple single-center retrospective studies have evaluated the molecular features of lung cancer in young patients (Table 2).[4,20-25] The predominant alterations in these studies are *EGFR* mutations and *ALK* rearrangements, although our study revealed fewer *ALK* rearrangements in the Asian population. Nevertheless, across all age groups, Asians have consistently been found to have higher *EGFR* mutation rates.[26]

A previous study by Sacher et al.[4] found a higher prevalence of driver alterations in young patients (<40 y of age) with lung cancer than in an older population (>70 y of age): *EGFR*, 32% versus 23%; *ALK*, 19% versus 1%; *ROS,* 6% versus 1%.[4] Similarly, Tanaka et al.[23] reported that patients less than 40 years of age had significant increases in *EGFR* exon 19 deletions (75% versus 43%; $p = 0.002$) and exon 20 insertions (8% versus 1%; $p = 0.002$) and a significant decrease in EGFR L858R mutations (17% versus 48%; $p = 0.002$), compared with patients more than 40 years of age. Tanaka et al.[23] also found that the percentage of *ALK* rearrangements increased in patients less than 40 years of age compared with all other age groups.

Given the rare incidence of lung cancer in young patients, we developed a website to expand our recruitment efforts. The 54 patients who enrolled by means of the website included patients from multiple states in the United States and multiple countries in Europe; a few patients were from the South Pacific, South America, and Afghanistan. This concept of "bringing the research to the patient" demonstrated in our study reveals the feasibility of using the internet to recruit patients internationally. We observed differences in enrollment demographics in the web-based population versus the study center, with slightly fewer female patients enrolling online than in study centers (54% versus 60%). The web-based population was also predominantly white (78%), with fewer minorities enrolling by means of the web compared with study centers (22% versus 30%), which may indicate unequal access to technology in some regions.

Approximately 30% of our patients learned of the trial from patient advocacy groups. This successful foray into web-based informed consent and remote collection of data and specimens has motivated additional partnerships with patient advocacy groups for individuals with rare oncogenes (the ROS1ders,[27] EGFR Resisters,[28] and ALK Positive[29]). These partnerships are supporting the creation of cancer models (ROS1ders and EGFR Resisters), informing surveys on adverse effects (ROS1ders and ALK Positive) and accelerating studies on resistance mechanisms (EGFR Resisters and ALK Positive).

Our study has several limitations. Not all patients received genomic testing from the same platform, as some genomic results were available from previous testing and some patients were given additional testing by means of the F1 platform; however, previous studies have revealed consistency of results for mutational profiling across diverse platforms.[5] At the time of protocol development, evaluating alteration status in early stage disease was not standard of care, and we did not require this testing at study entry for these patients; however, among the 27 patients with stages I to III disease, 22 entered with study with standard genomic testing. Since this study, additional biomarkers have been identified as actionable, several with associated approved targeted therapies (e.g., *NTRK*, *BRAF*, *MET*ex14, and tumor mutational burden).[30,31] Disparate access to technology in some countries may have resulted in a biased patient population for those who participated remotely. Even in the United States, access to NGS can be harder for younger patients with cancer owing to variable insurance coverage, whereas Medicare routinely covers Food and Drug Administration–approved NGS tests for older patients. Lastly, our study has limited generalizability: assessments of alteration prevalence depended on those who participated; 30% of patients were recruited by means of patient advocacy groups, although many of these groups were forming at the time of the study, and it was not necessarily established that patients had mutations in known oncogenes. Nevertheless, the alteration prevalence found in this study may not reflect a real-world population.

In summary, we adopted a unique, web-based, patient-engaged trial design, which enabled us to recruit and enroll more young patients with lung cancer, a rare subset. Genomic testing revealed that a high percentage of these patients (84%) harbored a targetable genomic alteration. The results of our study highlight the need to prioritize comprehensive genomic testing, as targeted treatment increases patient survival.[32,33] Genomics of Young Lung Cancer lays the groundwork for a planned future study,

Epidemiology of Young Lung Cancer, which will build on our unique web-based, patient-engaged trial design and seek to identify risk factors related to specific genomic alterations.

## CRediT Authorship Contribution Statement

**Barbara J. Gitlitz**: Conceptualization, Methodology, Supervision, Investigation, Writing—original draft preparation, Writing—reviewing and editing.

**Silvia Novello, Alicia Sable-Hunt, Tiziana Vavalà**: Investigation, Writing—reviewing and editing.

**Marisa Bittoni**: Investigation, Formal analysis, Visualization, Writing—original draft preparation, Writing—reviewing and editing.

**Dean Pavlick**: Investigation, Formal analysis, Writing—Reviewing and Editing

**Robert Hsu, S. Lani Park**: Investigation, Writing—original draft preparation, Writing—reviewing and editing.

**Ruthia Chen**, **Matthew Cooke**, **Amy Moore**, **Alexa B. Schrock**: Investigation, Writing—reviewing and editing.

**Joan H. Schiller**: Writing—reviewing and editing.

**Bonnie J Addario**, **Geoffrey R. Oxnard**: Funding acquisition, Supervision, Writing—reviewing and editing.

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## Data Sharing Statement

Data will be made available to researchers on request.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100194.

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