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EGFR Testing Patterns and Detection of *EGFR* Exon 20 Insertions in the United States

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ABSTRACT

Introduction: *EGFR* exon 20 insertions (*EGFRex20ins*) are a diverse set of mutations in NSCLC that are refractory to tyrosine kinase inhibitors. We describe real-world *EGFRex20ins* detection patterns in patients with advanced NSCLC in the United States.

Methods: Data from 2011 to 2020 were extracted from the Flatiron Health electronic health record-derived deidentified database.

Results: Among 67,281 patients with advanced NSCLC and at least two clinic visits, 66.8% were tested for *EGFR* mutations, of whom 13.9% tested positive. Of these, 4.9% had *EGFRex20ins*. The median time from NSCLC diagnosis to the first positive *EGFRex20ins* test result was 23 days, including 9 days of laboratory testing time. The *EGFRex20ins* were reported in 0.6% to 1.0% of all patients with advanced NSCLC and account for 3.9% to 5.3% of all *EGFR* mutations. During the study period, reverse transcription–polymerase chain reaction testing rates decreased whereas next-generation sequencing rates increased both in overall and among patients with tumors positive for *EGFRex20ins*. Tissue was the most common sample type used for *EGFR* and *EGFRexon20ins* detection (81.1% and 84.9%, respectively), whereas blood sampling for *EGFRexon20ins* detection increased from 0% (2011) to 37.2% (2020). For 23.7% of patients with *EGFRex20ins*, treatment was initiated before receiving the first positive *EGFRex20ins* test result, with therapies including immuno-oncology agents as the most common treatment type from 2017 to 2020.

Conclusions: *EGFR* testing and detection of *EGFRex20ins* in patients with NSCLC have increased slightly over time with the increasing use of next-generation sequencing. The current late-stage development of *EGFRex20ins*-targeted therapy is driving a need for more efficient testing.

Introduction

NSCLC accounts for 84% of all lung cancer and has an incidence of 38.05 per 100,000 person-years.[1,2] Approximately 54% of patients with NSCLC present with advanced-stage disease and have a 5-year survival rate of only 6.9%.[2] EGFR-mutant NSCLC represents a distinct molecular subset of lung cancer. Most *EGFR* mutations in NSCLC consist of exon 19 deletions and exon 21 *L858R* point mutations.[3,4] *EGFR* exon 20 insertions (*ex20ins*) comprise an uncommon subset of

EGFR activating mutations, of which more than 60 unique variants have been identified.[4] *EGFRex20ins* represent an estimated 1% to 12% of all *EGFR* mutations in NSCLC and 0.1% to 4.0% of all mutations in NSCLC.[5]

EGFRex20ins are generally associated with a lack of responsiveness to first- and second-generation tyrosine kinase inhibitors (TKIs),[4] and poor results with third-generation TKIs.[6,7] Amivantamab, a bispecific antibody directed against EGFR and MET, was the first agent approved for the treatment of adult patients with NSCLC whose tumors have *EGFRex20ins*.[8,9] Mobocertinib was granted accelerated approval by the U.S. Food and Drug Administration in September 2021 for the treatment of adult patients with locally advanced or metastatic NSCLC with *EGFRex20ins* mutations, as detected by a test approved by the U.S. Food and Drug Administration, whose disease has progressed on or after platinum-based chemotherapy.[7,10] Several other agents are in clinical development, including TAS6417 and Compound 1A.[11]

With the diverse genomic spectrum of *EGFRex20ins* and the rapidly evolving therapies targeting NSCLC with *EGFRex20ins,* a real-world study was conducted to describe the testing and detection of *EGFRex20ins* in patients with advanced NSCLC in the United States.

Materials and Methods

Data Source

This retrospective observational study used Flatiron Health's nationwide longitudinal, demographically, and geographically diverse deidentified database. Electronic health record data are derived from over 280 cancer clinics (~800 sites of care) and 2.4 million U.S. patients with cancer.[12] The deidentified patient-level data in the electronic health records include structured data (e.g., laboratory values and prescribed drugs) in addition to unstructured data collected by means of technology-enabled chart abstraction from physicians' notes and other unstructured documents (e.g., biomarker reports). Data provided to third parties are deidentified, and provisions are in place to prevent re-identification and protect patients' confidentiality. This study included data from January 1, 2011 through December 31, 2020.

Patient Population

Inclusion criteria included the following: (1) aged 18 years or older; (2) International Classification of Diseases (ICD) diagnosis of lung cancer (ICD-Ninth Revision 162.x or ICD-Tenth Revision C34.x, C39.9) and confirmed diagnosis of advanced NSCLC, including patients with stage IIIB or IV NSCLC at diagnosis or those who presented with earlier-stage NSCLC but subsequently developed advanced disease; and (3) two or more clinic encounters (as defined by records of vital signs,
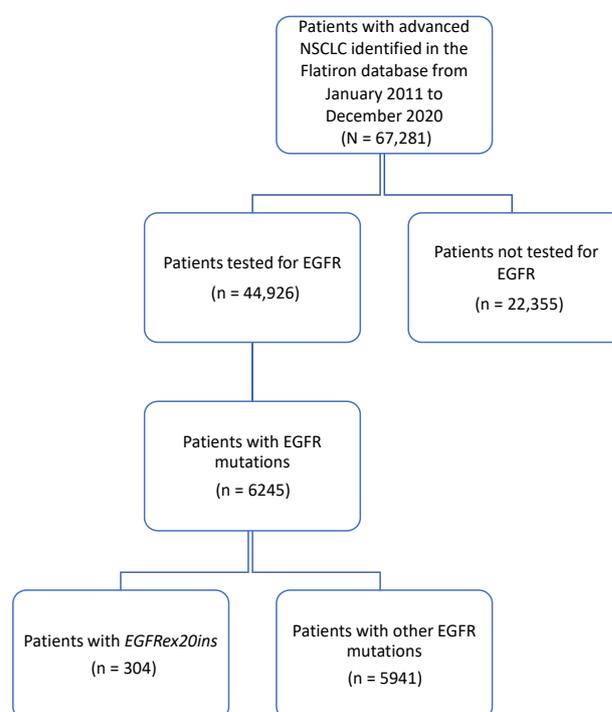
Figure 1. Patient attrition. *ex20ins*, exon 20 insertions.

treatment administration, or laboratory tests) occurring on or after January 1, 2011, consistent with previous analyses in the Flatiron database.[12]

Study Measures

Baseline demographic and clinical characteristics included age, sex, race, smoking history, histological subtype, line of therapy received, number of tests received, and practice type (i.e., community, academic). Other variables included the following: (1) dates of treatment initiation, specimen collection, specimen received in the laboratory, and date of result; (2) the result of the biomarker test (i.e., positive, negative for mutation); (3) type of mutation (i.e., *EGFR*, *EGFRex20ins*); (4) sample type (i.e., tissue, blood, or urine); and (5) type of test performed (i.e., polymerase chain reaction [PCR], next-generation sequencing [NGS], immunohistochemistry [IHC], fluorescence in situ hybridization [FISH], other). Turnaround times were calculated for tissue, blood, and all sample types from advanced diagnosis to first *EGFRex20ins* result and from receipt of the sample by the laboratory to first *EGFRex20ins* test result. Treatments were categorized as VEGF agents (bevacizumab and/or ramucirumab), immuno-oncology (IO) agents (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and/or durvalumab), chemotherapy (cisplatin, vinorelbine, etoposide, gemcitabine, docetaxel, pemetrexed, carboplatin, paclitaxel, and/or thiotepa), EGFR TKI (afatinib, erlotinib, gefitinib, osimertinib, and/or necitumumab), ALK TKI

Table 1. Baseline Demographics and Clinical Characteristics

Characteristics	Patients With NSCLC Tested for *EGFR* Mutations (n = 44,926)	Patients With NSCLC Not Tested for *EGFR* Mutations (n = 22,355)	Patients With *EGFRex20ins* (n = 304)	Patients With Other *EGFR* Mutations (n = 5941)
Age (y), mean ± SD	68.2 ± 9.8	69.1 ± 9.0	65.3 ± 11.5	68.0 ± 10.5
Age categories, n (%)				
<65 y	15,256 (34.0)	6430 (28.8)	134 (44.1)	2097 (35.3)
65-74 y	15,646 (34.8)	8199 (36.7)	91 (29.9)	1891 (31.8)
≥75 y	14,024 (31.2)	7726 (34.6)	79 (26.0)	1953 (32.9)
Sex, n (%)				
Female	22,839 (50.8)	9256 (41.4)	177 (58.2)	3940 (66.3)
Male	22,083 (49.2)	13,096 (58.6)	127 (41.8)	2001 (33.7)
Race, n (%)				
White	30,512 (67.9)	15,286 (68.4)	180 (59.2)	3410 (57.4)
Black or African American	3728 (8.3)	1970 (8.8)	22 (7.2)	429 (7.2)
Asian	1461 (3.3)	274 (1.2)	25 (8.2)	711 (12.0)
Hispanic or Latino	50 (0.1)	34 (0.2)	0 (0)	10 (0.2)
Other	4514 (10.0)	2001 (9.0)	33 (10.9)	709 (11.9)
Smoking history, n (%)				
Yes	37,728 (84.0)	20,672 (92.5)	151 (49.7)	3024 (50.9)
Histological subtype, n (%)				
Nonsquamous	36,657 (81.6)	9732 (43.5)	288 (94.7)	5650 (95.1)
Squamous	6301 (14.0)	11,031 (49.3)	8 (2.6)	155 (2.6)
NSCLC histological subtype NOS	1968 (4.4)	1592 (7.1)	8 (2.6)	136 (2.3)
Total lines of therapy received, n (%)				
0	9689 (21.6)	8702 (38.9)	59 (19.4)	686 (11.5)
1	18,705 (41.6)	8978 (40.2)	109 (35.9)	2470 (41.6)
2	9039 (20.1)	3056 (13.7)	61 (20.1)	1352 (22.8)
3	4167 (9.3)	1080 (4.8)	29 (9.5)	702 (11.8)
≥4	3326 (7.4)	539 (2.4)	46 (15.1)	731 (12.3)
Practice type, n (%)				
Community	40,685 (90.6)	20,095 (89.9)	265 (87.2)	5119 (86.2)
Academic	4241 (9.4)	2260 (10.1)	39 (12.8)	822 (13.8)

ex20ins, exon 20 insertions; NOS, not otherwise specified.

(alectinib, brigatinib, ceritinib, crizotinib and/or lorlatinib), and other (any other agents not specifically listed). A treatment line categorized as "IO included" may have been IO monotherapy or an IO agent as part of combination therapy. Chemotherapy used in combination with IO therapy or an EGFR TKI was categorized as IO therapy or EGFR TKI, respectively.

Statistical Analysis

Baseline patient demographics and clinical characteristics were summarized using standard descriptive statistics.

Results

Baseline Demographic and Clinical Characteristics

Patient flow is presented in Figure 1 and baseline demographics and clinical characteristics are described in Table 1. A total of 67,281 patients with advanced

NSCLC included in the database met the inclusion criteria. Of these, 44,926 (patients 66.8%) were tested for *EGFR* mutations, of whom 34.0% were less than 65 years, 50.8% were women, and 67.9% were White. A total of 6245 patients (13.9%) had tumors that were positive for *EGFR* mutations, of whom 304 (4.9%) had tumors harboring *EGFRex20ins*, representing 0.7% of the analysis population. The remaining 22,355 patients (33.2%) were not tested for *EGFR* mutations, of whom 28.8% were less than 65 years, 41.4% were women, and 68.4% were White.

EGFR Testing Patterns and Changes Over Time

Patterns of *EGFR* testing within specific patient characteristic subgroups are summarized over the 10-year analysis period in Figure 2. Testing patterns revealed that a higher percentage of women were tested for *EGFR* mutations (71.1% versus 62.8%) (Fig. 2A).
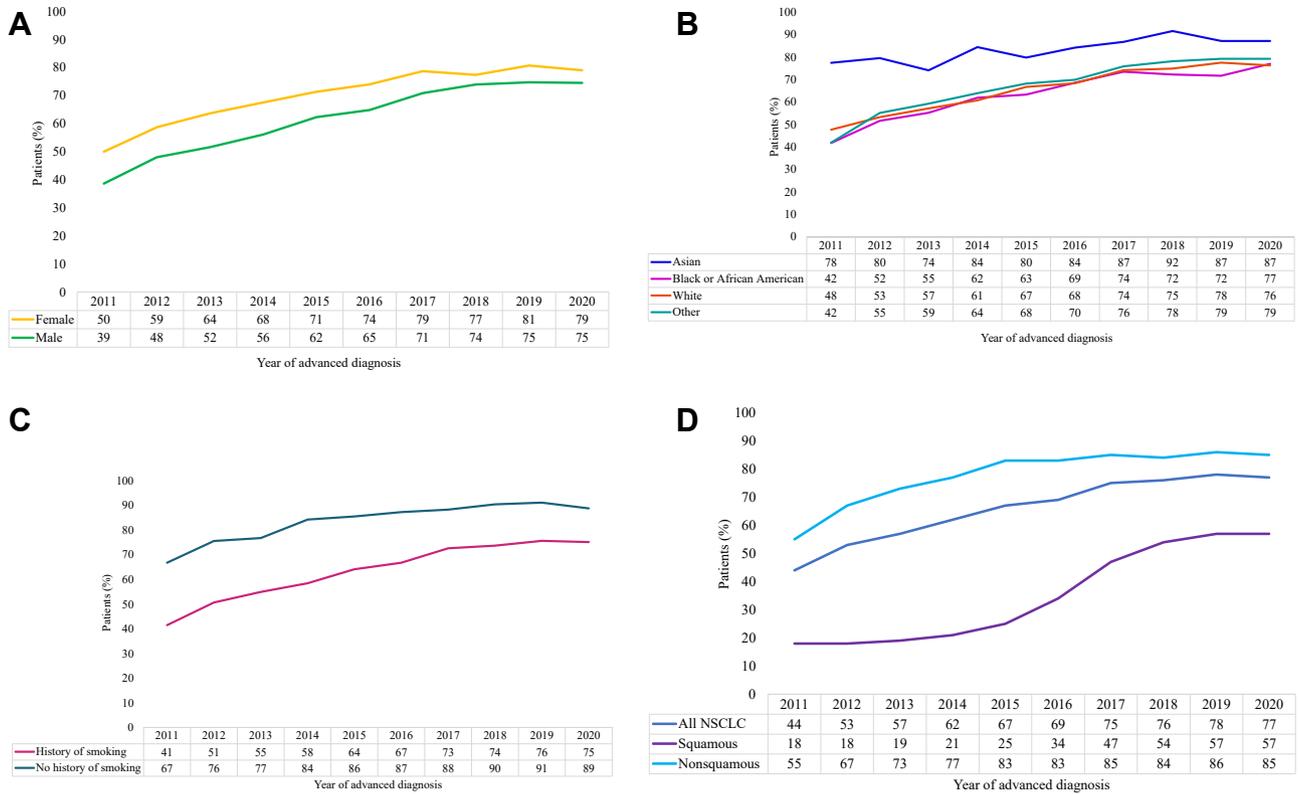
A

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Female	50	59	64	68	71	74	79	77	81	79
Male	39	48	52	56	62	65	71	74	75	75

B

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Asian	78	80	74	84	80	84	87	92	87	87
Black or African American	42	52	55	62	63	69	74	72	72	77
White	48	53	57	61	67	68	74	75	78	76
Other	42	55	59	64	68	70	76	78	79	79

C

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
History of smoking	41	51	55	58	64	67	73	74	76	75
No history of smoking	67	76	77	84	86	87	88	90	91	89

D

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
All NSCLC	44	53	57	62	67	69	75	76	78	77
Squamous	18	18	19	21	25	34	47	54	57	57
Nonsquamous	55	67	73	77	83	83	85	84	86	85

Figure 2. *EGFR* testing rates by year on the basis of (*A*) sex, (*B*) race, (*C*) smoking history, and (*D*) histological subtype.

Asian patients had the highest rate of *EGFR* testing (84.2%), compared with White (66.6%), Black (65.4%), and Hispanic (59.5%) patients (Fig. 2*B*). A smaller proportion of smokers (64.6%) were tested for *EGFR* mutations compared with never-smokers (81.0%) (Fig. 2*C*). This disparity in testing rates by smoking status may have influenced the differences in testing rates observed by sex and racial groups (Supplementary Fig. 1).

Testing was more common among patients with nonsquamous histological subtype than squamous histological subtype (79.0% versus 36.4%) (Fig. 2*D*). On the basis of treatment history, the *EGFR* testing rate was lowest among patients with no previous therapy (52.7%) and increased for each subsequent treatment line that occurred before testing. Specifically, the rates of *EGFR* testing after one, two, three, or at least four previous lines of therapy were 67.6%, 74.7%, 79.4%, and 86.1%, respectively. *EGFR* testing rates were not notably different between community (66.9%) and academic (65.2%) settings (Supplementary Fig. 2).

Among all patients diagnosed with advanced NSCLC, *EGFR* testing rates by year of advanced diagnosis increased from 44% in 2011 to 77% in 2020 (Fig. 2*D*). Despite this improvement, 15% of patients with nonsquamous histological subtype and 43% with squamous histological subtype were not tested for *EGFR* mutations in 2020.

The most common assays used for *EGFR* testing were PCR and NGS. These assays revealed opposing trends over time, as the use of PCR decreased from 71.7% in 2011 to 8.3% in 2020, whereas the use of NGS increased from less than 1% in 2011 to 70.8% in 2020. The use of other sequencing assays for *EGFR* testing (including RNA sequencing, whole transcriptome shotgun sequencing, Sanger sequencing, and direct sequencing) also increased during the study period, from 8.2% in 2011 to 13.7% in 2020. The use of other assays (proteomics and mass spectrometry) for *EGFR* testing declined from 1.9% in 2011 to 0.3% in 2020. The use of IHC and FISH for *EGFR* testing was low during the study period (Fig. 3*A*).

During the study period, the most frequently used sample to test for *EGFR* mutations was tissue (81.1%), followed by blood (17.3%) (Supplementary Table 1). Over time, the use of tissue samples decreased whereas blood samples increased. Urine samples were used for less than 0.1% of all tests during the study period (Supplementary Fig. 3).

EGFRex20ins Detection Patterns

The proportion of patients with *EGFRex20ins* as a proportion of all NSCLC cases increased from 0.6% in 2011 to 1.0% in 2019, followed by a decrease to 0.7% in 2020. Among patients with EGFR-mutant NSCLC, the rate
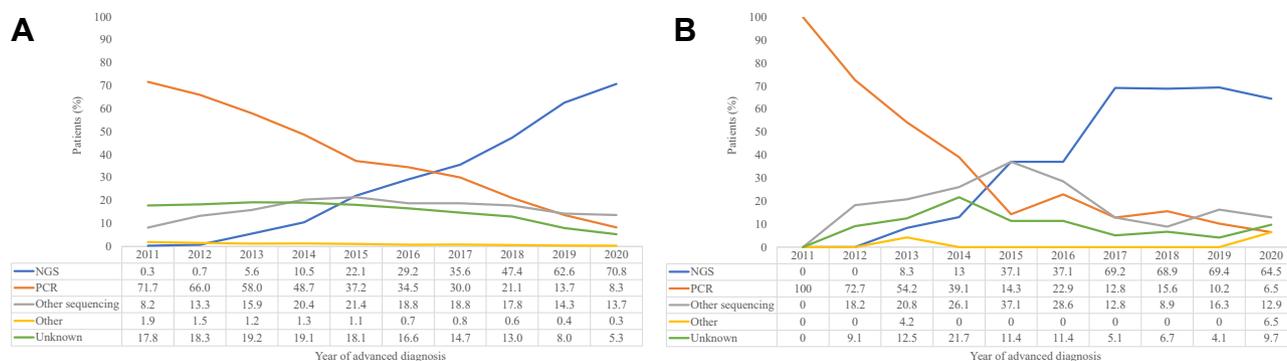
A

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
NGS	0.3	0.7	5.6	10.5	22.1	29.2	35.6	47.4	62.6	70.8
PCR	71.7	66.0	58.0	48.7	37.2	34.5	30.0	21.1	13.7	8.3
Other sequencing	8.2	13.3	15.9	20.4	21.4	18.8	18.8	17.8	14.3	13.7
Other	1.9	1.5	1.2	1.3	1.1	0.7	0.8	0.6	0.4	0.3
Unknown	17.8	18.3	19.2	19.1	18.1	16.6	14.7	13.0	8.0	5.3

Year of advanced diagnosis

B

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
NGS	0	0	8.3	13	37.1	37.1	69.2	68.9	69.4	64.5
PCR	100	72.7	54.2	39.1	14.3	22.9	12.8	15.6	10.2	6.5
Other sequencing	0	18.2	20.8	26.1	37.1	28.6	12.8	8.9	16.3	12.9
Other	0	0	4.2	0	0	0	0	0	0	6.5
Unknown	0	9.1	12.5	21.7	11.4	11.4	5.1	6.7	4.1	9.7

Year of advanced diagnosis

Figure 3. Assays used for *EGFR* testing, by year in (*A*) patients with a diagnosis of advanced NSCLC, and (*B*) patients with a positive *EGFRex20ins* result. Other sequencing refers to sequencing methods other than NGS, including RNA sequencing, whole transcriptome shotgun sequencing, Sanger sequencing, direct sequencing, and others, or if a sequencing test was performed just to test one gene, as opposed to a large panel of genes. Other refers to proteomics and mass spectrometry. The use of IHC and FISH was none to very low. *ex20ins*, exon 20 insertions; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

of *EGFRex20ins* increased from 3.9% in 2011 to 6.8% in 2019, followed by a decrease to 5.3% in 2020 (Supplementary Fig. 4).

The most common assays used to detect *EGFRex20ins* by the year of first test result were PCR and NGS. These assays revealed opposing trends during the study period, as the use of PCR decreased from 100% in 2011 to 6.5% in 2020, whereas the use of NGS increased from 0% in 2011 to 64.5% in 2020. The use of other sequencing assays to detect *EGFRex20ins* fluctuated during the study period, reaching a peak of 37.1% in 2015 followed by a decrease to 12.9% in 2020. The use of other assays to detect *EGFRex20ins* was 0% in 2011, 2012, 2014 to 2019, 4.2% in 2013, and 6.5% in 2020. IHC and FISH were not used to detect *EGFRex20ins* during the study period (Fig. 3*B*).

Although tissue was the most common sample type used to test for *EGFRex20ins* during the study period, the use of tissue decreased with successive testing, having been used in 84.9% of first tests, 71.0% of second tests, and 63.6% of third tests (Supplementary Table 1). Blood samples represented 17.7% of all samples used for *EGFRex20ins* testing during the study period. The use of blood increased with successive tests, from 14.4% of first tests to 29.0% of second tests, and 36.4% of third tests (Supplementary Table 1).

Across all assays used for *EGFR* testing, the overall median time from advanced diagnosis to first *EGFRex20ins* result was 23 days (interquartile range [IQR]: 13–41), which included a median laboratory turnaround time of 9 days (Table 2). In addition, the median time from receipt of the sample by the laboratory to the first *EGFRex20ins* result was 10 days (IQR: 6–14) for tissue samples and 8 days (IQR: 6–10) for blood samples. When stratified by assay type, the median (IQR) time from advanced diagnosis to first *EGFRex20ins* result

was 28 (20–63) days for NGS and 12 (11–39) days for PCR (Supplementary Table 2). The median (IQR) time from receipt of the sample by the laboratory to first *EGFRex20ins* result was 11 (8–14) days for NGS and 8 (5–13) days for PCR (Supplementary Table 2). There was no evidence of time from diagnosis to *EGFRex20ins* result either increasing or decreasing over the course of the study period, although the sample size per year was small (data not provided).

A total of 23.7% of patients initiated treatment before the confirmation of the first positive *EGFRex20ins* test result. Chemotherapy was the most common treatment type initiated; however, therapies including IO agents were the most common treatment type from 2017 to 2020, coinciding with a steady decline in chemotherapy use (Fig. 4). The most common chemotherapeutic agent used before the first positive *EGFRex20ins* test result was carboplatin (31 of 39 patients), and the most common IO agent was pembrolizumab (16 of 25). Similarly, for patients who initiated treatment after the first positive *EGFRex20ins* test result, the most common chemotherapeutic agent was carboplatin (99 of 115) and the most common IO agent was pembrolizumab (52 of 101) followed by nivolumab (45 of 101).

It is worth noting that EGFR TKIs were used as any line of therapy, including first (52 patients), second (22 patients), and third or later line (20 patients).

Discussion

This retrospective real-world study of patients with advanced NSCLC revealed that *EGFR* testing rates increased from 2011 to 2020, reaching greater than 75% in more recent years. *EGFR* testing rates increased among all patient groups regardless of sex, race, smoking history, and histological subtype. As expected, testing was higher for Asians, never-smokers, women, and patients with adenocarcinoma compared with their

Table 2. Time to *EGFRex20ins* Test Result During the Study Period (2011–2020)

Test	From Advanced Diagnosis to First *EGFRex20ins* Test Result			From Receipt of Sample by the Laboratory to First *EGFRex20ins* Test Result		
	All (N=299)[a]	Tissue (n=254)	Blood (n=43)	All (N=294)	Tissue (n=251)	Blood (n=43)
Median, d (IQR)	23 (13–41)	23 (12–41)	25 (15–225)	9 (6–14)	10 (6–14)	8 (6–10)
Mean, d (SD)	48.9 (292.8)	33.5 (293.8)	141.2 (279.4)	20.4 (84.6)	22.4 (91.4)	9.0 (3.1)

[a]Unknown test result: n=2. *ex20ins*, exon 20 insertions; IQR, interquartile range.

respective counterparts.[13,14] These findings suggest that more patients with *EGFR* mutations may be identified if *EGFR* testing rates were to increase in men, smokers, and non-Asians. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) specify that clinicopathologic features such as smoking status, ethnicity, and tumor histology should not be used in selecting patients for EGFR biomarker testing.[15]

The present analysis found that the frequency of *EGFRex20ins* was 0.7% of all NSCLC cases and 5.3% of all EGFR-mutated NSCLC in 2020. This is consistent with frequencies of *EGFRex20ins* reported in multiple studies in various geographic and ethnic settings, in which *EGFRex20ins* ranged from 0.1% to 4.0% of all NSCLC and from 1% to 12% of all *EGFR*-mutated NSCLC. The highest frequencies of *EGFRex20ins* were reported in single-center Asian or U.S.-based studies, and the most frequently used assays for *EGFRex20ins* detection were PCR, Sanger sequencing, NGS, and mass spectroscopy.[5] The expanded use of NGS found in the present study may have resulted in the increase in the incidence of *EGFRex20ins* observed between 2011 and 2020, as NGS has an improved ability to identify rare *EGFR* variants,

including *EGFRex20ins*.[16–18] In a study comparing *EGFR* detection rates using comprehensive genomic profiling (CGP), an NGS approach, and PCR in 103 cases with confirmed previous *EGFR* test results, CGP identified 22 patients (21%) with sensitizing *EGFR* point mutations that were not detected by PCR, including four of seven patients (57%) with *EGFR exon 20* mutations.[18] A real-world study using genomic databases to analyze the ability of PCR and NGS to comprehensively identify *EGFRex20ins* revealed that PCR methods are projected to miss 50% or more of *EGFRex20ins*, whereas NGS is more likely to detect the full range of *EGFRex20ins* variants.[17] The limited ability of targeted PCR assays to comprehensively cover the molecular heterogeneity of *EGFRex20ins*, together with the availability of newer treatment options specifically targeting *EGFRex20ins*, emphasize the need for increased NGS testing.[19,20] The recent approval of targeted therapies and their associated companion diagnostics for the treatment of *EGFRex20ins* is likely to contribute to higher *EGFRex20ins* detection rates. Guardant360 (Guardant, California, CA) is an NGS-based device that uses cell-free DNA from plasma to identify patients with NSCLC who may benefit from treatment with osimertinib and now
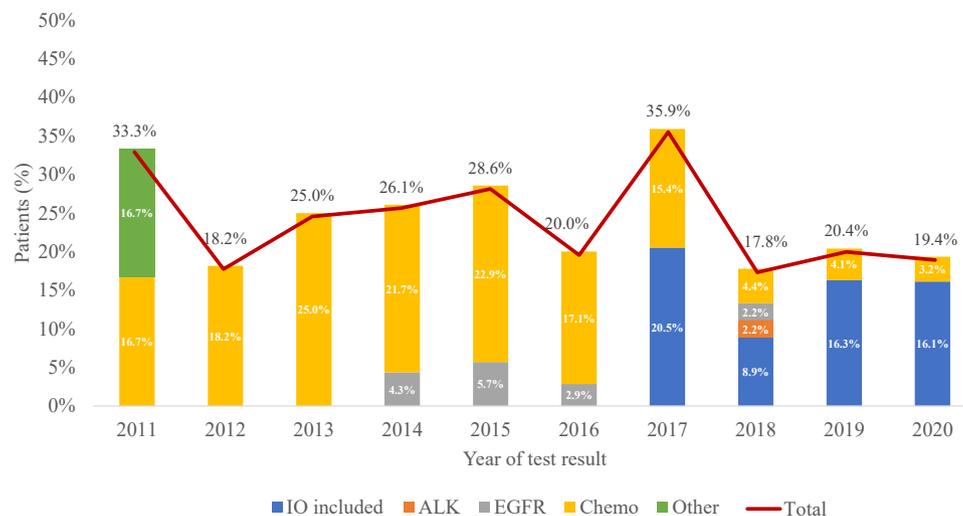

Figure 4. Treatments initiated before confirmation of first positive *EGFRex20ins* result, by year. Chemo, chemotherapy; *ex20ins*, exon 20 insertions; IO, immuno-oncology.

amivantamab.[21] Tissue- and blood-based genomic profiling tests for use with mobocertinib are currently in development.[22]

In the present study, the use of blood samples as an alternative to invasive tissue biopsies increased over time, especially for subsequent *EGFR* testing in individual patients. Notably, blood samples were used to obtain 11.1% of the first *EGFR* test results, which increased to 57.6% after the third test result and from 14.4% of first *EGFRex20ins* test results to 36.4% of third test results. These increases are in line with NCCN Guidelines recommendations, which strongly advise that if there is insufficient tissue to allow testing for *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, and *RET* mutations, repeat biopsy and/or plasma testing should be performed.[15]

Despite the increase in *EGFRex20ins* detection rates in patients with advanced NSCLC observed in this study, many patients initiated treatment before receiving confirmation of the first positive *EGFRex20ins* test result, which may lead to patients being prescribed a suboptimal therapy. This study found that only 52.7% of patients with NSCLC were tested for an *EGFR* mutation before any treatment, and among patients who tested positive for *EGFRex20ins*, 23.7% initiated treatment before receiving the first positive *EGFRex20ins* test result. Similar results were reported in a previous U.S.-based retrospective study of 814 patients with advanced NSCLC, which revealed that 59% of patients were tested for *EGFR* mutations and *ALK* rearrangements before treatment, whereas only 8% underwent CGP for alterations in guideline-recommended genes. Among patients who were not tested for *EGFR* and *ALK* genetic aberrations, 52% initiated chemotherapy.[23] There could be multiple drivers for initiating therapy before receiving *EGFR* test results, including patients who may be considered too ill to wait for results and physicians deciding to postpone testing until later lines of therapy. However, for many patients, treatment initiation before a confirmed *EGFR* test result negates the benefits of well-established, biomarker-driven therapies and may cause unnecessary exposure to ineffective treatments and associated adverse effects.[15]

In the present study, chemotherapy was the predominant treatment until 2017, with a small proportion of patients also receiving EGFR TKIs between 2014 and 2016. The use of IO therapy steadily increased since 2017 to become the dominant treatment between 2018 and 2020. Across the study period, carboplatin and pembrolizumab were the most frequently used chemotherapy and IO agents, respectively, both before and after a positive *EGFRex20ins* test result. Carboplatin is a standard chemotherapy treatment given as first-line in NSCLC.[15] A phase 2 study of pembrolizumab in patients whose tumors harbored *EGFR* mutations including *EGFRex20ins*, and were programmed death-ligand 1–positive (most of whom were treatment-naive) revealed pembrolizumab's lack of efficacy, suggesting it is not an appropriate therapeutic choice in this setting.[24] A previous real-world study describing treatment patterns and outcomes in U.S. patients with advanced NSCLC with *EGFRex20ins* revealed limited effectiveness of the most common treatments for this patient population including EGFR TKIs, which were associated with a confirmed real-world overall response rate of 2.7% in the first-line setting, 5.0% in second- or later-line therapy, and 10.0% in the second-line setting among patients previously treated with platinum-based chemotherapy.[25]

This study had limitations. Patients included in the study may have received multiple tests, and testing may have occurred during different time points throughout the diagnosis (e.g., before advanced diagnosis, after diagnosis but before first-line therapy). The study relied on the quantity and quality of data available in medical records and some data, especially dates, were frequently missing. Overall, findings should be interpreted with caution as the sample size was small. *EGFRex20ins* are numerous and heterogenous[6,17] and detailed information on variants was not available for this data source.

In conclusion, the detection rate of *EGFRex20ins* in patients with NSCLC increased over a 10-year period, coinciding with a shift in testing methods from PCR to NGS. Changes in treatment guideline recommendations, increased use of NGS-based genomic testing, and recent approvals of treatments for *EGFRex20ins*-mutant NSCLC and their companion diagnostics may have led to increased detection of *EGFRex20ins*. With the development of targeted therapies specific to patients with *EGFRex20ins* and considering the limitations associated with the use of targeted PCR assays, there is a need for early and broad biomarker testing with NGS to comprehensively cover the molecular heterogeneity of *EGFRex20ins*.

CRediT Authorship Contribution Statement

Huamao M. Lin: Conceptualization, Methodology, Writing - review & editing, Supervision.

Yu Yin: Methodology, Formal analysis, Writing - review & editing.

Victoria Crossland, Yanyu Wu: Methodology, Visualization, Writing - review & editing.

Sai-Hong Ignatius Ou: Methodology, Writing - review & editing.

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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.2022.100285.

References

1. American Cancer Society. Cancer facts & figures 2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed November 24, 2021.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER cancer statistics review (CSR) 1975-2017. https://seer.cancer.gov/csr/1975_2017. Accessed November 24, 2021.
3. Arcila ME, Nafa K, Chaft JE, et al. EGFR Exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther*. 2013;12:220-229.
4. Riess JW, Gandara DR, Frampton GM, et al. Diverse EGFR exon 20 insertions and co-occurring molecular alteration identified by comprehensive genomic profiling of NSCLC. *J Thorac Oncol*. 2018;13:1560-1568.
5. Burnett H, Emich H, Carroll C, Stapleton N, Mahadevia P, Li T. Epidemiological and clinical burden of EGFR exon 20 insertion in advanced non-small cell lung cancer: a systematic literature review. *PLoS One*. 2021;16:e0247620.
6. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: a new history begins. *Cancer Treat Rev*. 2020;90:102105.
7. Vyse S, Huang PH. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther*. 2019;4:5.
8. Park K, John T, Kim SW, et al. Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2020;38(suppl 15):9512-9512.
9. Janssen Biotech, Inc. Rybrevant, prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s000lbl.pdf. Accessed November 24, 2021.
10. Takeda Pharmaceutical Company Limited. Announces U.S. FDA breakthrough therapy designation for Mobocertinib (TAK-788) for the treatment of NSCLC patients with EGFR exon 20 insertion mutations. https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-u.s.-fda-breakthrough-therapy-designation-for-mobocertinib-tak-788-for-the-treatment-of-nsclc-patients-with-egfr-exon-20-insertion-mutations. Accessed November 24, 2021.
11. Zhou C, Ramalingam SS, Kim TM, et al. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. *JAMA Oncol*. 2021;7:e214761.
12. Ma X, Long L, Moon S, Adamson BJS, Baxi SS. Comparison of population characteristics in real-world clinical oncology databases in the US: flatiron health, SEER, and NPCR. *MedRvix*. https://www.medrxiv.org/content/10.1101/2020.03.16.20037143v2. Accessed November 24, 2021.
13. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339-346.
14. Thi AM, Tin Tin S, McKeage M, Elwood JM. Utilisation and determinants of epidermal growth factor receptor mutation testing in patients with non-small cell lung cancer in routine clinical practice: a global systematic review. *Target Oncol*. 2020;15:279-299.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for non-small cell lung cancer, version 1.2022. NCCN.org. Accessed December 16, 2021.
16. Russo A, Franchina T, Ricciardi G, Battaglia A, Picciotto M, Adamo V. Heterogeneous responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with uncommon EGFR mutations: new insights and future perspectives in this complex clinical scenario. *Int J Mol Sci*. 2019;20:1431.
17. Bauml JM, Viteri S, Minchom A, et al. FP07. 12 Underdiagnosis of EGFR exon 20 insertion mutation variants: estimates from NGS-based real-world datasets. *J Thorac Oncol*. 2021;16:S208-S209.
18. Suh JH, Schrock AB, Johnson A, et al. Hybrid capture-based comprehensive genomic profiling identifies lung cancer patients with well-characterized sensitizing epidermal growth factor receptor point mutations that were not detected by standard of care testing. *Oncologist*. 2018;23:776-781.
19. Ou S, Hong J, Lin H, et al. MA14.01 distribution and detectability of *EGFR* exon 20 insertion variants in non-small cell lung cancer. *J Thorac Oncol*. 2021;16(suppl):S928-S929.
20. Feng Y, Feng G, Lu X, et al. Exploratory analysis of introducing next-generation sequencing-based method to treatment- naive lung cancer patients. *J Thorac Dis*. 2018;10:5904-5912.
21. Food and Drug Administration. FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-liquid-biopsy-ngs-companion-diagnostic-test-multiple-cancers-and-biomarkers. Accessed November 24, 2021.
22. Takeda Pharmaceutical Company Limited. Foundation medicine and Takeda announce collaboration to develop FoundationOne®CDx and FoundationOne®Liquid CDx as Companion Diagnostics for Takeda's Late-Stage Lung Cancer Portfolio. https://www.takedaoncology.com/media/news-media/news-releases/Foundation-Medicine-and-Takeda-Announce-Collaboration-To-Dev-11511/. Accessed November 24, 2021.

23. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. *Clin Lung Cancer*. 2017;18:651–659.

24. Metro G, Baglivo S, Bellezza G, et al. Sensitivity to immune checkpoint blockade in advanced non-small cell lung cancer patients with *EGFR* exon 20 insertion mutations. *Genes (Basel)*. 2021;12:679.

25. Ou SI, Lin HM, Hong JL, et al. Real-world response and outcomes in NSCLC patients with EGFR exon 20 insertion mutations. *J Clin Oncol*. 2021;39(suppl 15):9098–9098.