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

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Received 16 September 2021; revised 4 January 2022; accepted 15 January 2022
Available online - 25 January 2022

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.
EGFR activating mutations, of which more than 60 unique variants have been identified.\(^4\) EGFRexo20ins represent an estimated 1% to 12% of all EGFR mutations in NSCLC and 0.1% to 4.0% of all mutations in NSCLC.\(^5\)

EGFRexo20ins 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 EGFRexo20ins.\(^8,9\) 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 EGFRexo20ins 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 EGFRexo20ins and the rapidly evolving therapies targeting NSCLC with EGFRexo20ins, a real-world study was conducted to describe the testing and detection of EGFRexo20ins 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, 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, EGFRexo20ins); (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 EGFRexo20ins result and from receipt of the sample by the laboratory to first EGFRexo20ins 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

![Figure 1. Patient attrition. ex20ins, exon 20 insertions.](image-url)
(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 EGF
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 EGF
mutations, of whom 304 (4.9%) had tumors harboring EGF
ex20ins, representing 0.7% of the analysis population. The remaining 22,355 patients (33.2%) were not tested for EGF
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 EGF 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 EGF
mutations (71.1% versus 62.8%) (Fig. 2A).
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. 2B). A smaller proportion of smokers (64.6%) were tested for EGFR mutations compared with never-smokers (81.0%) (Fig. 2C). 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. 2D). 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. 2D). 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. 3A).

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
EGFR Exon 20 Insertion Testing Patterns

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
respective counterparts. 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.

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. 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. 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. 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. 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. 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

| Test | All (N=299) | 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) |

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

Figure 4. Treatments initiated before confirmation of first positive EGFRex20ins result, by year. Chemo, chemotherapy; ex20ins, exon 20 insertions; IO, immuno-oncology.
amivantamab. Tissue- and blood-based genomic profiling tests for use with mobocertinib are currently in development.

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 10 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 10 agents, respectively, both before and after a positive EGFRex20ins test result. Carboplatin is a standard chemotherapy treatment given as first-line in NSCLC. 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 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.

Acknowledgments

The authors wish to thank Eileen Curran, PhD of Takeda Development Center Americas, Inc. for substantive
contributes to the development of this manuscript. The authors acknowledge Jane Kondejewski, PhD and Joanna Dembowny, PhD of SNELL Medical Communication Inc., Montreal, QC, Canada, for providing medical writing support funded by Takeda Pharmaceuticals.

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.

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