Epidermal growth factor receptor (*EGFR*) testing and treatment patterns associated with diagnosis of non-small cell lung cancer (NSCLC) with *EGFR* exon 20 insertions (ex20ins) in the US

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Zofia Piotrowska[1], Huamao M Lin[2], Yu Yin[2], Eileen Curran[2], Victoria Crossland[2], Yanyu Wu[2], Sai-Hong Ou[3]

[1] Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [2] Takeda Development Center Americas, Inc., Lexington, MA, USA; [3] The University of California, Irvine School of Medicine, Orange, CA, USA

Background

- *EGFR* exon 20 insertion mutations (*EGFRex20ins*), which represent an uncommon subset of *EGFR* activating mutations in NSCLC, are associated with a limited response to treatment with first- and second-generation tyrosine kinase inhibitors (TKIs).[1]
- It is important to understand the real-world diagnosis, testing patterns, and treatment choices in patients with NSCLC with *EGFRex20ins*, as these mutations are associated with poor prognosis and require tailored treatment.[2]
  - Amivantamab and mobocertinib are new targeted therapies that have demonstrated efficacy in patients with NSCLC with *EGFRex20ins*.
  - In 2021, amivantamab and mobocertinib received Food and Drug Administration (FDA) approval under the accelerated approval pathway for adult patients with locally advanced or metastatic NSCLC with *EGFRex20ins*, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[2-4]
- The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V3.2022 recommend broad molecular profiling[5] to help identify rare driver mutations for which effective drugs may be available.
- A real-world study that described *EGFR* mutation testing patterns and rates of detection of *EGFRex20ins* in patients with advanced NSCLC in the US up to 2020, found that the *EGFRex20ins* detection rate has increased over a 10-year period.[6]

Objectives

- To update previously described[6] real-world *EGFR* mutation testing patterns and *EGFRex20ins* detection in patients with advanced NSCLC in the US (2011-2021).
- To add to the evidence base by describing real-world first-line (1L) treatments of patients with advanced NSCLC with *EGFRex20ins* in the last 5 years (2017-2021), stratified by whether they initiated treatment before or after their first positive exon 20 (*EGFRex20ins*[+]) test result.

Methods

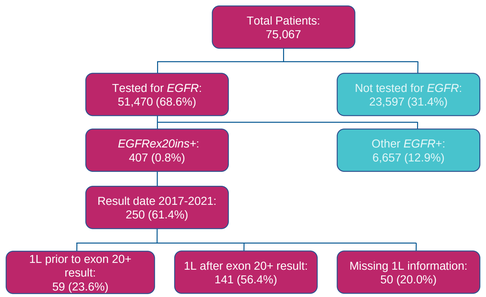
Data Source

- This retrospective observational study used the Flatiron Health electronic health record (EHR)-derived database, a nationwide longitudinal, demographically and geographically diverse deidentified database.
- Data were collected from January 1, 2011, to December 31, 2021.

Patient Population

- Patients aged ≥18 years with a confirmed diagnosis of advanced NSCLC (clinical stage IIIB or IV) and ≥2 visits within the Flatiron Network during the data collection period were identified (**Figure 1**).
- Diagnosed with advanced NSCLC 2011-2021 (for testing analysis); diagnosed with advanced NSCLC with *EGFRex20ins* mutation 2017-2021 (for treatment patterns analysis)

Figure 1. Patient Selection



EGFR, epidermal growth factor receptor gene; *EGFRex20ins*, *EGFR* exon 20 insertions; 1L, first-line.

Methods

Outcomes

- *EGFR* mutation testing rates and distribution of sequencing technology used were described for all patients.
- 1L treatments were described for patients stratified by initiation of 1L treatment before or after *EGFRex20ins*(+) testing results.

Statistical Analysis

- Patient demographic and clinical characteristics, and treatment patterns, were summarized using standard descriptive statistics.

Results

Patient Baseline Characteristics

- A total of 75,067 patients with NSCLC were identified (**Table 1**). Of these, 51,470 (69% of patients) were tested for *EGFR* mutations and 407 (0.5%) harbored an *EGFRex20ins.*
- Among those tested for *EGFR* mutations, there was a higher proportion of patients who were female (50.8% vs 41.4%), Asian (3.0% vs 1.1%), and with non-squamous histology (80.7% vs 43.6%).
- Demographics and clinical characteristics among the patients with *EGFRex20ins* were similar to those among patients with other *EGFR* mutations (i.e., exon 19 deletion, L858R, T790M, other).

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Patients with NSCLC not tested for *EGFR* mutations (N=23,597)	Patients with NSCLC tested for *EGFR* mutations (N=51,470)	Patients with *EGFRex20ins* mutations (N=407)	Patients with other *EGFR* mutations (N=6,657)
Age in years, median (IQR)	71 (63,76)	69 (62,76)	67 (58,75)	69 (61,76)
Sex, n (%)[a]				
Female	9,768 (41.4)	26,149 (50.8)	238 (58.5)	4,456 (66.9)
Race, n (%)				
White	15,998 (67.8)	3,4801 (67.6)	239 (58.7)	3,848 (57.8)
Black or African American	2,185 (9.3)	4,390 (8.5)	33 (8.1)	482 (7.2)
Asian	256 (1.1)	1,555 (3.0)	28 (6.9)	740 (11.1)
Hispanic or Latino/other race/missing	5,158 (21.9)	10,724 (20.8)	107 (26.3)	1,587 (23.8)
Disease stage, n (%)				
Stage I	2,430 (10.3)	4,594 (8.9)	36 (8.8)	579 (8.7)
Stage II	1,361 (5.8)	2,661 (5.2)	20 (4.9)	293 (4.4)
Stage III	6,432 (27.3)	9,321 (18.1)	42 (10.3)	811 (12.2)
Stage IV	12,343 (52.3)	3,514 (65.1)	303 (74.4)	4,795 (72.0)
Not reported/others	1,028 (4.3)	1,377 (2.7)	6 (1.5)	178 (2.7)
History of smoking, n (%)[b]				
Yes	21,895 (92.8)	43,382 (84.3)	208 (51.1)	3,369 (50.6)
Histology, n (%)				
NSCLC histology NOS	1,626 (6.9)	2,214 (4.3)	9 (2.2)	141 (2.1)
Non-squamous cell carcinoma	10,297 (43.6)	41,532 (80.7)	385 (94.6)	6,339 (95.2)
Squamous cell carcinoma	11,674 (49.5)	7,724 (15.0)	13 (3.2)	177 (2.7)

[a]Patients with NSCLC not tested for *EGFR* mutations: Male, 13,826 (58.6%); Missing, 3 (0.0%); Patients with NSCLC tested for *EGFR* mutations: Male, 25,317 (49.2%); Missing, 4 (0.0%); Patients with *EGFRex20ins* mutations: Male, 169 (41.5%); Patients with other *EGFR* mutations: Male, 2,201 (33.1%).

[b]Patients with NSCLC not tested for *EGFR* mutations: No/missing, 1,702 (7.2%); Patients with NSCLC tested for *EGFR* mutations: No/missing, 8,088 (15.7%); Patients with *EGFRex20ins* mutations: No/missing, 199 (48.9%); Patients with other *EGFR* mutations: No/missing, 3,288 (49.4%).

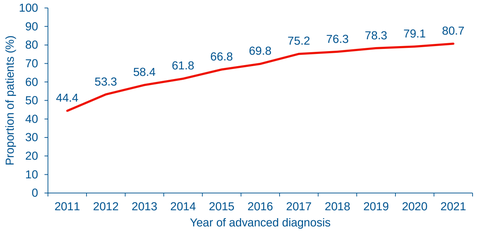
EGFR, epidermal growth factor receptor gene; *EGFRex20ins*, *EGFR* exon 20 insertions; IQR, interquartile range; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

Results

2011 - 2021: *EGFR* Mutation Testing Patterns Over Time

- The proportion of patients tested for *EGFR* mutations increased from 44.4% in 2011 to 80.7% in 2021 (**Figure 2**).

Figure 2. 2011-2021: Rate of testing for EGFR mutations (by year of diagnosis of advanced NSCLC)

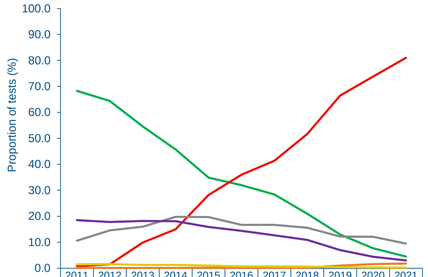


Note: Among patients who had year of advanced diagnosis recorded and who received at least one *EGFR* test at any time (n=38,990).

EGFR, epidermal growth factor receptor gene.

- The proportion of tests conducted using NGS increased from <0.1% in 2011 to 81.0% in 2021 (**Figure 3**). The corresponding proportion of tests conducted using PCR decreased from 68.3% in 2011 to 4.5% in 2021.

Figure 3. 2011-2021: Sequencing Technology Used for the Detection of any *EGFR* Mutation Over Time



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PCR	68.3	64.4	54.6	45.7	34.9	32	28.4	21	13	7.7	4.5
NGS	0.8	1.5	9.9	15	28.2	36	41.4	51.7	66.5	73.8	81
FISH	0.1	0.1	0	0	0	0.1	0	0	0	0	0
IHC	0.2	0	0.1	0.1	0.2	0.2	0.1	0.2	1	1.6	1.8
Other	1.5	1.6	1.3	1.3	1	0.7	0.7	0.6	0.4	0.3	0.2
Other sequencing	10.6	14.6	16	19.8	19.7	16.7	16.7	15.6	12.2	12.1	9.5
Unkown	18.5	17.8	18.2	18.1	15.9	14.4	12.7	10.9	7	4.4	3

Note: Data include all non-missing result date records.

EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

2017-2021: Treatment Patterns Before and After *EGFRex20ins*(+) Results

- Among patients with *EGFRex20ins*(+) results between 2017 and 2021 (n = 250), 59 (24%) patients started 1L treatment prior to their first *EGFRex20ins*(+) result and 141 (56%) patients started 1L treatment after their first *EGFRex20ins*(+) result (information missing, n = 50) (**Table 2**).
- Demographic and clinical characteristics were similar across groups.

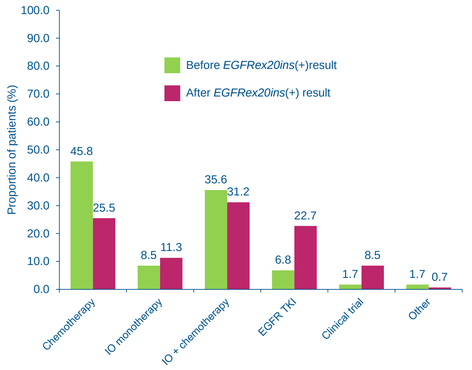
Table 2. 2017-2021: *EGFR* Mutation Testing and *EGFRex20ins* Detection Patterns

	Treated prior to *EGFRex20ins* result (n=59)	Treated after *EGFRex20ins* result (n=141)	1L information missing (n=50)
Age, median (IQR)	66 (56, 73)	66 (61, 74)	67 (54, 78)
Sex, n (%)			
Female	35 (59.3)	87 (61.7)	26 (52.0)
Male	24 (40.7)	54 (38.3)	24 (48.0)
Race, n (%)			
White	29 (49.2)	81 (57.4)	27 (54.0)
Black or African American	6 (10.2)	13 (9.2)	5 (10.0)
Asian	7 (11.9)	11 (7.8)	1 (2.0)
Hispanic or Latino/other race/missing	17 (28.8)	36 (25.5)	17 (34.0)
Disease stage, n (%)			
Stage I	4 (6.8)	13 (9.2)	3 (6.0)
Stage II	0	5 (3.5)	3 (6.0)
Stage III	9 (15.3)	7 (5.0)	6 (12.0)
Stage IV	45 (76.3)	115 (81.6)	36 (72.0)
Not reported/others	1 (1.7)	1(0.7)	2(4.0)
Smoking status, n (%)			
No/missing	27 (45.8)	69 (48.9)	26 (52.0)
Yes	32 (54.2)	72 (51.1)	24 (48.0)
Histology			
NSCLC histology NOS	2 (3.4)	3 (2.1)	1 (2.0)
Non-squamous cell carcinoma	52 (88.1)	133 (94.3)	49 (98.0)
Squamous cell carcinoma	5 (8.5)	5 (3.5)	0

EGFR, epidermal growth factor receptor gene; *EGFRex20ins*, *EGFR* exon 20 insertions; IQR, interquartile range; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; 1L, first-line.

- Among patients who initiated 1L treatment after their first *EGFRex20ins*(+) result, a higher proportion received *EGFR* TKIs or were enrolled in clinical trials, and a lower proportion received chemotherapy, compared to patients who started 1L treatment before their first *EGFRex20ins*(+) result (**Figure 4**).
- Similar proportions of patients were treated with immuno-oncology (IO) monotherapy or IO + chemotherapy regardless of when treatment was started (**Figure 4**).

Figure 4. 1L Treatments in Patients Before and After *EGFRex20ins*(+) Result 2017 – 2021



EGFR, epidermal growth factor receptor gene; *EGFRex20ins*, *EGFR* exon 20 insertions; IO, immuno-oncology; TKI, tyrosine kinase inhibitor.

Limitations

- Patients included in the study may have received multiple *EGFR* mutation tests, testing may have occurred at different time points during the patient treatment pathway, and test results may not have been fully captured.
- The study relied on the quantity and quality of data available in EHR, and data, especially dates, were frequently missing in the database.
- Due to small sample sizes in some study groups, findings should be interpreted with caution.

Discussion

- Between 2011 and 2021, *EGFR* testing rates and the proportion of tests conducted using NGS increased over time; however, 20% of patients remained untested in 2021. These data are an update of a previous analysis,[6] and confirm the previously reported increasing trend.
- Between 2017 and 2021, among patients with *EGFRex20ins*(+) results, 24% started 1L treatment before receiving their first *EGFRex20ins*(+) result.
- A high proportion of patients with *EGFRex20ins* started IO or *EGFR* TKIs after genetic testing despite limited effectiveness[1,7,8] of these treatments in this patient population.
- With the recent approval of therapies targeting *EGFRex20ins*, increased testing and awareness of treatment outcomes in this population are needed.
- This analysis illustrated two barriers to patients with EGFRex20ins receiving appropriate treatment:
  - Consistent with previous results, increased testing is still needed.
  - Patients who were tested did not receive optimal treatment, highlighting the need for increased awareness of treatment outcomes in this patient population.

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