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Retrospective database study of druggable mutation detection among patients with non-small cell lung cancer in Japan

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Generally, non-small cell lung cancer (NSCLC) accounts for 90% of lung cancer cases in Japan. The detection of druggable mutations is necessary for selecting the appropriate systemic therapy for patients with NSCLC. This study explored the proportion, characteristics, and treatments of patients with druggable mutations detected following standard therapy using cancer gene panel (CGP) testing. Adult NSCLC cases who had not been previously confirmed to have druggable mutations before CGP testing were extracted from the national database. A total of 1,425 cases were included and analyzed using descriptive statistics. Among the patients with NSCLC who underwent CGP testing, 44.6% exhibited druggable mutations ($n = 635$; mean age, 63.9 ± 10.7 years; 439 men [69.1%]). The most common types of mutations among those with druggable mutations were *EGFR* and *NTRK*, whereas the most common cancer subtypes were lung adenocarcinoma and lung squamous cell carcinoma. The median number of days from primary treatment initiation to druggable mutation detection was 701. As the first treatment after the CGP testing, 23.0% of the patients received molecularly targeted agents. Our findings emphasize the clinical importance of reducing barriers that hinder upfront multigene testing for driver gene mutations in ensuring patients receive appropriate treatment.

Keywords Non-small cell lung cancer, Driver mutations, Cancer gene panel testing, Next-generation sequencing, Targeted therapy

Abbreviations

CGP	Cancer gene panel
NSCLC	Non-small cell lung cancer
TKI	Tyrosine kinase inhibitors

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer that generally has a serious disease course considering that > 60% of patients present with advanced disease (stage III or IV) and have a very poor prognosis[1,2]. In fact, 126,548 people had been diagnosed with lung cancer in Japan in 2019[3], with NSCLC generally accounting for approximately 90% of the cases[4].

Although NSCLC has traditionally been histologically classified, a better understanding of the disease biology and the identification of oncogenic driver mutations have dramatically altered the therapeutic landscape. Consequently, the new NSCLC classification paradigm is further characterized by molecularly defined subsets actionable using targeted therapies, thereby increasing the complexity of the treatment landscape[5]. Epidermal growth factor receptor (*EGFR*) is a commonly observed mutation in Japanese patients with NSCLC, and a meta-analysis of 107 studies in Japan revealed that its prevalence is 36.6%[6]. Patients with an activating mutation of *EGFR* are highly sensitive to epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs)[7].

For many years, cytotoxic chemotherapeutic agents were mainly utilized in drug therapy for stage IV NSCLC. Since the 2000s, novel therapies including molecularly targeted therapeutics have become available and have been effective compared with cytotoxic chemotherapeutic agents[8]. To use molecularly targeted agents, companion diagnostics are needed.

To determine the most appropriate treatment option for individual patients with shorter time until treatment initiation, simultaneous testing of several biomarkers is critical. Traditionally, multigene diagnostic tests have

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been conducted using a series of single-gene assays. However, this approach can lead to considerable waste of specimens as well as increased costs and turnaround time. Moreover, single-gene tests for companion diagnostics of certain driver mutations, such as B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) and ret proto-oncogene (*RET*), are not available under Japanese regulatory approval[8]. Therefore, multigene assays are strongly recommended for advanced or relapsed non-small cell lung cancer before the initiation of first-line therapy[9]. In fact, it has been reported that individual testing of each mutation takes longer time until treatment initiation, when the number of testing instances are increased[10]. Considering that novel molecularly targeted agents have been introduced in Japan, the clinical importance of multiplex gene testing has been increased. The Japanese Lung Cancer Society Guidelines recommend the conduct of multiplex molecular testing and programmed cell death-ligand 1 (PD-L1) testing simultaneously without prioritization before starting systemic therapy to shorten the time until the treatment initiation and avoid missing the opportunity for optimal drug administration[8]. Upon the detection of druggable mutations, therapies targeting specific NSCLC driver genes have been recommended as the standard of care, based on the evidence that targeted therapy for each mutation improves objective response rate and progression-free survival in cases with driver gene mutations and good physical condition[8]. Tyrosine kinase inhibitors (TKIs) have been used as the primary therapy for several driver gene mutations, such as *EGFR*, anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*), *MET* exon 14 skipping, and neurotrophic tropomyosin receptor kinase (*NTRK*)[8]. However, previous studies have demonstrated that multiplex genetic testing has some limitations, such as the requirement for large quantities of high-quality specimen for a successful testing[11,12], which could hinder clinical processes, such as the conduct of tests before first-line treatment initiation. Sakamoto et al. reported that among those diagnosed with advanced or recurrent NSCLC from July 2020 to June 2021 in Japan, only 47.7% underwent multiplex genetic testing[13], indicating the challenges in the clinical settings. Although some studies have highlighted the importance of multiplex molecular testing before the initiation of first-line treatment[14,15], it has been suggested that upfront testing is not currently standard in real-world clinical practice. A retrospective study of real-world biomarker testing rates in the United States reported that only 46% of patients with metastatic NSCLC underwent all five major biomarker tests (*ALK*, *BRAF*, *EGFR*, *ROS1*, and PD-L1) and that 23% of them underwent the tests during or after first-line treatment[16]. Furthermore, the characteristics of patients with NSCLC who did not have opportunities for appropriate upfront testing in Japan remain to be elucidated.

Meanwhile, the Japanese government had established the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), which has been consolidating, storing, and using sequence and medical information obtained from the genome analyses of Japanese patients since June 2018. The C-CAT has established a "Cancer Genome Information Repository" based on cancer gene panel (CGP) testing data (sequence information) and the medical information of patients[17]. CGP testing is conducted to comprehensively examine gene mutations known to be associated with cancer, with or without approved drugs, whereas multiplex gene testing is generally used as a companion diagnosis to the drugs used in standard therapy. In Japan, CGP testing is covered by national insurance for patients with solid tumor that does not have standard therapy or patients with locally advanced or metastatic solid tumor who completed or are expected to complete standard therapy[18]. Moreover, CGP testing is available at designated core hospitals and designated hospitals, which are selected for cancer genomic medicine by the Ministry of Health, Labour and Welfare, and their cooperative hospitals[19].

By using the database established by the C-CAT, which covers the genomic information of patients with NSCLC nationwide, the current study aimed to elucidate the proportion, characteristics, and treatments of patients who have missed the opportunity to receive therapies targeting driver genes because druggable mutations were not detected before CGP testing. We hope that our findings will help accelerate upfront molecular testing for a broad range of NSCLC driver genes by highlighting the circumstances currently faced by these patients.

Materials and methods

Database

This retrospective observational study used data from the C-CAT database accessed through the C-CAT Research-Use Portal site after obtaining approval from the C-CAT Data Utilization Review Board (approval number: CDN2022-022E02).

As of December 24, 2023, the C-CAT database contained information of 67,630 patients who underwent CGP testing at each institution (designated core/designated/cooperative hospital) and agreed to their registration since June 1, 2019[19,20]. As of February 2023, the types of CGP tests covered by national insurance included FoundationOne CDx (since June 2019), OncoGuide NCC Oncopanel System (since June 2019), and FoundationOne Liquid CDx (since August 2021)[9]. Among the patients in the database, 99.7% agreed to the secondary use of their information for academic research and drug development[20]. Once the patients agree to their registration in the database, C-CAT reports containing the clinical interpretation of their genomic alterations and clinical study information will be created. Their treating physicians will subsequently decide the treatment strategy based on the C-CAT reports and opinions from the expert panel, where experts discuss the individual treatment strategies, including optimal drug selection, referring to their test results and C-CAT reports.

Study population

This study included patients with NSCLC who received standard therapy without any druggable mutations detected. As CGP tests can be reimbursed only for patients who have completed or were expected to complete the standard therapy, the end of standard therapy is determined based on the reimbursable treatment options and the physician's opinion. The eligible cases were selected from patients with NSCLC registered in the C-CAT database from June 1, 2019, to February 28, 2023, according to the following criteria: (1) adult patients (aged ≥ 15 years) with histologically or cytologically confirmed NSCLC, (2) patients who had never been confirmed to have

a druggable mutation by the end of the standard therapy, and (3) patients who had never received therapies targeting driver genes by the end of the standard therapy. Technically, these criteria were defined using the following variables from the C-CAT database: (1) was defined as the age (on the day the C-CAT report was created for the patient) of 15 years or older, registration of "lung" and "NSCLC" for the first and second levels of the registered cancer type, respectively. Subsequently, the cases with any gene mutations recorded in the following "cancer type" columns were excluded for (2): "*EGFR*," "*EGFR*-T790M after *EGFR*-TKI resistance," "*ALK* fusion," "*ROS1*," or "*BRAF* (V600)." Similarly, cases with records of any of the following regimens used before the expert panel were excluded for (3): gefitinib, erlotinib, afatinib, osimertinib, or dacomitinib for *EGFR*; alectinib, brigatinib, lorlatinib, ceritinib, or crizotinib for *ALK*; crizotinib or entrectinib for *ROS1*; dabrafenib + trametinib for *BRAF* V600E; capmatinib or tepotinib for *MET* exon 14 skipping; serpelukatinib for *RET*; entrectinib or larotrectinib for NTRK; or sotorasib for *KRAS* G12C. As of February 2023, 1,774 NSCLC cases were retrieved from the C-CAT database, of whom 349 were excluded due to the following reasons: age < 15 years ($n = 2$), detection of druggable mutations by the end of the standard therapy ($n = 318$), and receiving therapy targeting driver genes during their standard therapy ($n = 29$). Finally, 1,425 cases were included in our analyses (Fig. 1).

Variables

The following variables were extracted from each case for analysis: age (years), sex (male/female), family history (yes/no/unknown/NA), smoking (yes/no/unknown/NA), cancer subtypes, mutation types (*EGFR*, *ALK*, *ROS1*, *BRAF* V600E, *MET* exon 14 skipping, *KRAS* G12C, *RET*, *NTRK* 1/2/3), number of Pharmaceuticals and Medical Devices Agency (PMDA)-approved drugs, date of expert panel (year/month/day), date of initiation

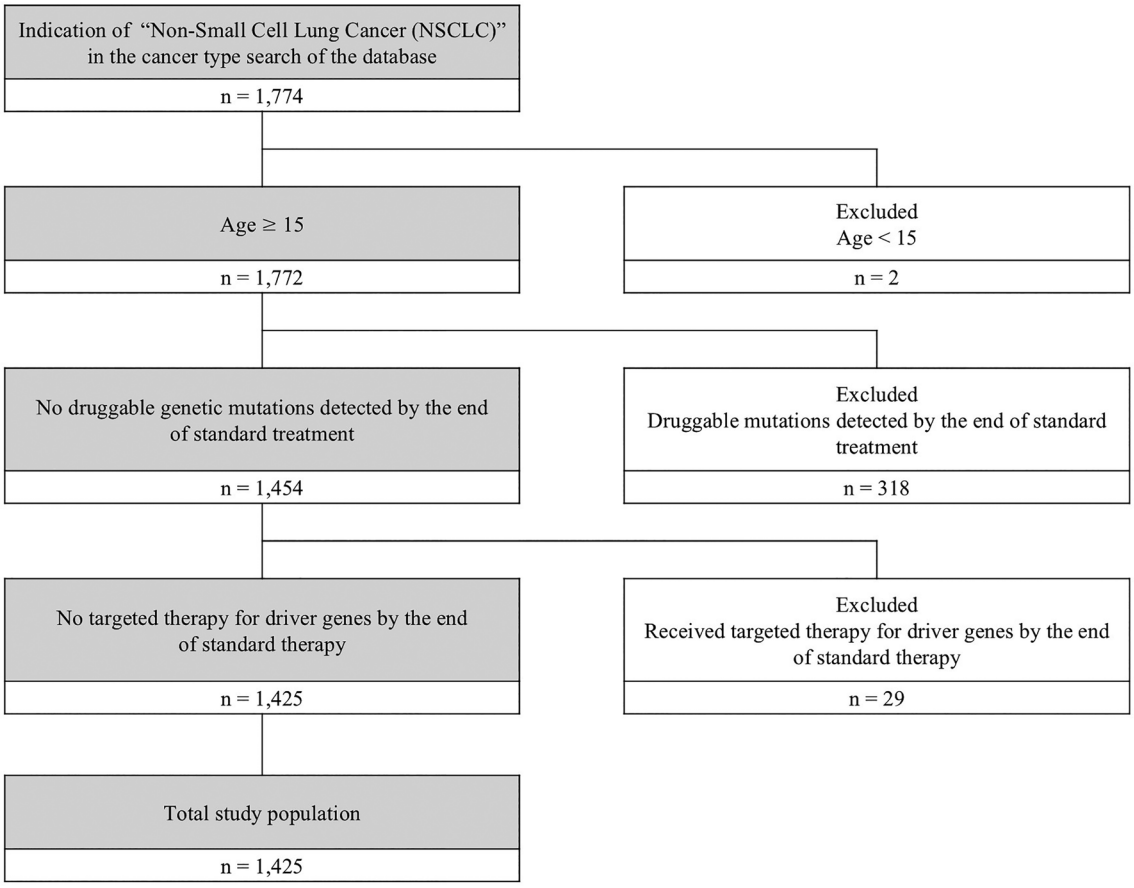

Fig. 1. Study population. Among 1,774 NSCLC cases retrieved from the C-CAT database, 1,425 eligible ones were included in the analysis based on the following criteria: age, detection of druggable gene mutation, and experience of targeted therapy for driver genes. Patients were excluded if at least one of the following options under "Cancer type information" was positive ("Druggable mutations detected by the end of standard treatment"), Lung-*EGFR*, Lung-*EGFR*-T790M after *EGFR*-TKI resistance, Lung-*ALK* fusion, Lungs-*ROS1*, or Lungs-*BRAF* (V600), or if at least one of the following therapies targeting driver genes was included in the "Pre-EP regimen information" ("Received targeted therapy for driver genes by the end of standard therapy"): (1) *EGFR* (gefitinib, erlotinib, afatinib, osimertinib, and dacomitinib), (2) *ALK* (alectinib, brigatinib, lorlatinib, ceritinib, and crizotinib), (3) *ROS1* (crizotinib and entrectinib), (4) *BRAF* V600E (dabrafenib + trametinib), (5) *MET* exon 14 skipping (capmatinib and tepotinib), (6) *RET* (serpelukatinib), (7) *NTRK* (entrectinib and larotrectinib), or (8) *KRAS* G12C (sotorasib). C-CAT, Center for Cancer Genomics and Advanced Therapeutics; NSCLC, non-small cell lung cancer.

and termination of each treatment (year/month/day), and drug names (free format). Cases confirmed to have druggable mutations via CGP testing were defined as those who met both of the following two criteria: (1) number of PMDA-approved drugs > 0 and (2) record of at least one of the eight aforementioned mutation types. The cancer subtypes were classified into 18 categories based on the "OncoTree" provided by the Memorial Sloan Kettering Cancer Center[21]. As the date of CGP testing was not available for the analysis, the date of the expert panel was utilized to define the date of mutation detection.

In addition, the number of beds and type of management of medical facilities, which was not included in the C-CAT database, was incorporated into the analytical dataset using the list of medical facilities obtained from the Regional Bureau of Health and Welfare[22].

Statistical analysis

Descriptive statistics were used for all analyses. For categorial variables, the number of cases, relative frequency (%), and 95% confidence interval were calculated. Continuous variables were expressed as mean, standard deviation, minimum, maximum, median, and interquartile range.

Moreover, subgroup analysis was conducted according to facility size (< 200 beds, 200 to 399 beds, 400 to 599 beds, ≥ 600 beds, and unknown) and type of facility management (national or public hospitals, university hospitals, and other). Considering the descriptive nature of the study purpose, no statistical tests were conducted to compare the differences between the groups.

An analytical dataset was generated using R (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria) with the tidyverse package. All descriptive analyses were conducted using Hideyoshi Dplus and BellCurve for Excel (both developed by Social Survey Research Information Co., Ltd., Tokyo, Japan).

Ethical considerations

Our study protocol was approved by the Ethics Review Board of the Medical Corporation TOUKEIKAI Kitamachi Clinic (May 24, 2023, No. BGQ09464) and complied with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (March 10, 2022) issued by the Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; Ministry of Economy, Trade and Industry in Japan; and the tenets of the 2013 revision of the Declaration of Helsinki. The patients were clearly and fully informed of the purpose and scope of the registered data and agreed to the secondary use of their data upon registration to the C-CAT database. Based on this agreement, the need for informed consent to participate was waived by the Ethics Review Board of the Medical Corporation TOUKEIKAI Kitamachi Clinic. Before registration in the database, the patient's test data and medical information were converted into a form that does not directly identify them.

Results

Among the 1,425 cases with NSCLC in whom no druggable mutations were detected before CGP testing, 635 (44.6%) were confirmed to have druggable mutations via CGP testing. The most common types of mutations were *EGFR* and *NTRK* ($n = 219/1,425$, prevalence: 15.4%, for each), which corresponds to 34.5% each among 635 cases with detected mutations, followed by *ROS1* ($n = 160/1,425$, prevalence: 11.2%) and *ALK* ($n = 107/1,425$, prevalence: 7.5%) (Table 1). The percentages of these mutations stratified according to year are summarized in Table 1. Among patients who underwent CGP testing each year, 1 (100.0%) in 2019, 36 (59.0%) in 2020, 182 (40.8%) in 2021, 228 (42.6%) in 2022, and 6 (50.0%) in 2023 were confirmed to have druggable mutations. In the other 370 cases, the years were unknown, with 182 cases having druggable mutations.

Year	CGP tested	Detected via CGP testing								
		Any druggable mutation [b]	EGFR	ALK	ROS1	BRAF V600E	MET exon 14 skipping [c]	KRAS G12C	RET	NTRK1/2/3
Total	$n = 1,425$	44.6% ($n = 635$) [42.0–47.1]	15.4% ($n = 219$) [13.5–17.2]	7.5% ($n = 107$) [6.1–8.9]	11.2% ($n = 160$) [9.6–12.9]	0.8% ($n = 12$) [0.4–1.3]	-	2.8% ($n = 40$) [1.9–3.7]	7.0% ($n = 100$) [5.7–8.3]	15.4% ($n = 219$) [13.5–17.2]
2019	$n = 1$	100.0% ($n = 1$) [-]	100% ($n = 1$) [-]	-	-	-	-	-	-	-
2020	$n = 61$	59.0% ($n = 36$) [46.7–71.4]	18.0% ($n = 11$) [8.4–27.7]	14.8% ($n = 9$) [5.9–23.7]	8.2% ($n = 5$) [1.3–15.1]	-	-	4.9% ($n = 3$) [0.0–10.3]	11.5% ($n = 7$) [3.5–19.5]	19.7% ($n = 12$) [9.7–29.6]
2021	$n = 446$	40.8% ($n = 182$) [36.2–45.4]	14.1% ($n = 63$) [10.9–17.4]	7.0% ($n = 31$) [4.6–9.3]	10.5% ($n = 47$) [7.7–13.4]	1.6% ($n = 7$) [0.4–2.7]	-	2.9% ($n = 13$) [1.4–4.5]	5.4% ($n = 24$) [3.3–7.5]	13.7% ($n = 61$) [10.5–16.9]
2022	$n = 535$	42.6% ($n = 228$) [38.4–46.8]	15.0% ($n = 80$) [11.9–18.0]	6.7% ($n = 36$) [4.6–8.9]	12.7% ($n = 68$) [9.9–15.5]	0.4% ($n = 2$) [0.0–0.9]	-	2.2% ($n = 12$) [1.0–3.5]	7.1% ($n = 38$) [4.9–9.3]	14.6% ($n = 78$) [11.6–17.6]
2023 [a]	$n = 12$	50.0% ($n = 6$) [21.7–78.3]	16.7% ($n = 2$) [0.0–37.8]	-	8.3% ($n = 1$) [0.0–24.0]	8.3% ($n = 1$) [0.0–24.0]	-	-	-	33.3% ($n = 4$) [6.7–60.0]
Unknown	$n = 370$	49.2% ($n = 182$) [44.1–54.3]	16.8% ($n = 62$) [13.0–20.6]	8.4% ($n = 31$) [5.6–11.2]	10.5% ($n = 39$) [7.4–13.7]	0.5% ($n = 2$) [0.0–1.3]	-	3.2% ($n = 12$) [1.4–5.0]	8.4% ($n = 31$) [5.6–11.2]	17.3% ($n = 64$) [13.4–21.2]

Table 1. Annual prevalence of druggable mutations detected via CGP testing. 95% confidence interval of each percentage is shown in brackets. CGP, cancer gene panel. [a]Analyzed data were limited to those registered and available by February 28, 2023. [b]There were some cases with records of more than one mutation type. [c]No record of *MET* exon 14 skipping was identified.

Table 2 presents the characteristics of patients with NSCLC confirmed to have druggable mutations. The mean (± standard deviation [SD]) age of the 635 patients was 63.9 (± 10.7) years, and 439 (69.1%) were men. Furthermore, 405 patients (63.8%) had a family history of cancer, whereas 463 (72.9%) had a history of smoking. The most common cancer subtypes were lung adenocarcinoma ($n = 470$, 74.0%) and lung squamous cell carcinoma ($n = 74$, 11.7%).

The duration from primary treatment initiation to druggable mutation detection was calculated to determine the extent to which druggable mutation detection was delayed. The median (interquartile range) duration from primary treatment initiation to druggable mutation detection ($n = 409$) was 701 (407, 1173) days, with a mean (± SD) of 928.3 (± 747.2) days.

The treatment patterns of patients confirmed to have druggable mutations via CGP testing are shown in Table 3. Although approximately 30% of cases did not have information on treatment, chemotherapy was the most commonly used for most treatment lines before CGP testing (27.7%, 36.6%, and 40.1% in the first-, third-, and fourth-line treatments and 40.8% in the fifth-line treatment or later, respectively), except the second-line treatment, where a combination of chemotherapy and molecularly targeted agents accounted for the highest percentage (22.8%). For the first treatment after the CGP testing, 28 (23.0%) of 122 patients received molecularly targeted agents. The list of drugs used is presented in Supplementary Table S1 online. Among the 122 cases, the commonly used drugs for the first treatment after CGP testing were osimertinib ($n = 7$, 5.7%), dabrafenib + trametinib ($n = 5$, 4.1%), atezolizumab ($n = 4$, 3.3%), afatinib ($n = 4$, 3.3%), and docetaxel + ramucirumab ($n = 4$, 3.3%). The lengths of the treatments (mean ± SD) before CGP testing were as follows: 173.4 ± 221.0 days ($n = 465$) for the first-line, 188.5 ± 216.1 days ($n = 364$) for the second-line, and 150.2 ± 197.5 days ($n = 241$) for the third-line treatments. Conversely, the length of the first treatment after CGP testing (mean ± SD) was 78.2 ± 98.9 days ($n = 38$).

Moreover, when the facilities were stratified according to the number of beds, the highest percentage of druggable mutations detected via CGP testing was observed in those with 200 to 399 beds (32/55, 58.2%),

Patients with NSCLC with druggable gene mutations detected via CGP testing ($n = 635$)	
Age, mean (SD)	63.9 (10.7)
Male, n (%)	439 (69.1)
Family history, n (%)	
Yes	405 (63.8)
No	150 (23.6)
Unknown	28 (4.4)
NA	52 (8.2)
Ever-smoker, n (%)	
Yes	463 (72.9)
No	110 (17.3)
Unknown	10 (1.6)
NA	52 (8.2)
Cancer type classification (OncoTree code), n (%)	
Lung adenocarcinoma (LUAD)	470 (74.0)
Lung squamous cell carcinoma (LUSC)	74 (11.7)
Non-small cell lung cancer (NSCLC)	53 (8.3)
Poorly differentiated non-small cell lung cancer (NSCLCPD)	10 (1.6)
Pleomorphic carcinoma of the lung (LUPC)	9 (1.4)
Lung adenosquamous carcinoma (LUAS)	9 (1.4)
Large cell lung carcinoma (LCLC)	4 (0.6)
Adenoid cystic carcinoma of the lung (LUACC)	4 (0.6)
Spindle cell carcinoma of the lung (SPCC)	1 (0.2)
Mucoepidermoid carcinoma of the lung (LUMEC)	1 (0.2)
Ciliated muconodular papillary tumor of the lung (CMPT)	0 (0.0)
Basaloid large cell carcinoma of the lung (BLCLC)	0 (0.0)
Clear cell carcinoma of the lung (CCLC)	0 (0.0)
Giant cell carcinoma of the lung (GCLC)	0 (0.0)
Large cell lung carcinoma with rhabdoid phenotype (RLCLC)	0 (0.0)
Lymphoepithelioma-like carcinoma of the lung (LECLC)	0 (0.0)
NUT carcinoma of the lung (NUTCL)	0 (0.0)
Salivary gland-type tumor of the lung (SGTTL)	0 (0.0)

Table 2. Characteristics of non-small cell lung cancer patients with druggable mutations detected via CGP testing. CGP, cancer gene panel; NSCLC, non-small cell lung cancer.

Treatment line	Total	Chemotherapy	Immune checkpoint inhibitors	Molecularly targeted drugs	Chemotherapy + immune checkpoint inhibitors	Chemotherapy + molecularly targeted drugs	Immune checkpoint inhibitors + molecularly targeted drugs	Chemotherapy + immune checkpoint inhibitors + molecularly targeted drugs	Other	Treatment unknown
	n	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Before CGP testing										
First-line treatment	559	155 (27.7)	27 (4.8)	0 (0.0)	145 (25.9)	30 (5.4)	0 (0.0)	10 (1.8)	0 (0.0)	192 (34.3)
Second-line treatment	499	104 (20.8)	74 (14.8)	2 (0.4)	34 (6.8)	114 (22.8)	1 (0.2)	1 (0.2)	1 (0.2)	168 (33.7)
Third-line treatment	377	138 (36.6)	49 (13.0)	1 (0.3)	9 (2.4)	57 (15.1)	1 (0.3)	4 (1.1)	1 (0.3)	117 (31.0)
Fourth-line treatment	232	93 (40.1)	36 (15.5)	2 (0.9)	3 (1.3)	23 (9.9)	0 (0.0)	1 (0.4)	0 (0.0)	74 (31.9)
Fifth-line treatment or later (combined)	147	60 (40.8)	6 (4.1)	0 (0.0)	20 (13.6)	13 (8.8)	1 (0.7)	4 (2.7)	0 (0.0)	43 (29.3)
Unknown (treatment before CGP testing partly available) [a)]	5									
Unknown (treatment before CGP testing not available) [b)]	71									
After CGP testing										
First treatment	122	7 (5.7)	10 (8.2)	28 (23.0)	0 (0.0)	4 (3.3)	0 (0.0)	1 (0.8)	0 (0.0)	72 (59.0)
Second treatment	9	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
Third treatment	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fourth treatment	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fifth treatment or later (combined)	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown (treatment after CGP testing not available) [b)]	513									

Table 3. Treatment pattern of patients with delayed detection of gene mutation before and after cancer gene panel testing. Classification was based on the combination of chemotherapeutic agents, immune checkpoint inhibitors, and molecularly targeted drugs. CGP, cancer gene panel. [a)]Cases that included regimens with no treatment line information and whose treatment line could not be identified. [b)]Cases with missing treatment information.

followed by those with 400 to 599 beds (205/429, 47.8%), ≥600 beds (395/929, 42.5%), and <200 beds (3/12, 25.0%). Furthermore, the percentage of druggable mutations detected via CGP testing was 49.2% in national or public hospitals ($n=512$), 39.6% in university hospitals ($n=694$), and 49.3% in other types of facilities ($n=219$).

Discussion

The present study demonstrated that among the Japanese patients with NSCLC who had no druggable mutations detected before CGP testing, who completed or were expected to complete the standard therapy, and who underwent CGP testing, 44.6% exhibited druggable mutations via CGP testing. This suggests that several patients might have had the opportunity to receive appropriate targeted therapies at an earlier treatment line had they been tested for multiple mutations before the completion of the standard therapy. Our results indicate that patients may not be provided with sufficient opportunities to undergo multiplex genetic testing before completing the standard therapy to allow them access to potential treatment options. By using the C-CAT database, which contains CGP testing results and clinical information of a large sample of patients nationwide, we were able to describe the circumstances of the patients with druggable mutations that were left undetected until the patients underwent CGP testing after the standard therapy.

A previous Japanese study using the C-CAT database reported that, in 986 patients with NSCLC who underwent CGP assays between August 2019 and March 2022, the proportion of newly detected driver oncogenes was 45.7%[23]. When limited to the 330 patients with undetected *EGFR*, *ALK*, *ROS1*, and *BRAF* V600E mutations at diagnosis, the proportion decreased to 24.5%[23]. Although they included human epidermal growth factor receptor type 2 (*HER2*) mutation in the newly detected driver oncogenes, our analysis results using the updated data showed a higher percentage (44.6%) in patients with no previously detected mutations. Moreover, our results indicated that the mutations most frequently detected via CGP testing were *EGFR* (15.4%), *NTRK* (15.4%), *ROS1* (11.2%), and *ALK* (7.5%) (Table 1). Previous studies have shown that *EGFR* and *ALK* mutations were present in approximately 50% and 5% of Japanese patients with lung adenocarcinoma, respectively[7]. Alternatively, the frequencies of *NTRK* gene fusion and *ROS1* fusion were reported to be 0.2–3.3%[24] and 2–3%[25] in lung adenocarcinoma, respectively. Our study did not include cases where major gene mutations, such as *EGFR* and *ALK*, were detected via singleplex tests (where each gene is individually examined) before CGP testing. This may have resulted in a relatively high proportion of rare gene mutations, such as *NTRK* and *ROS1*, which can currently be identified only by multiplex tests.

The mean (±SD) and median ages of the patients with NSCLC whose druggable mutations were detected via CGP testing were 63.9 (±10.7) and 65 years, respectively, and 69.1% of them were men. Looking at the epidemiology of lung cancer in Japan, 84,325 (66.6%) of the 126,548 patients with lung cancer diagnosed in 2019 were reported to be men[3]. According to data from the National Cancer Registry, 83–85% of patients with lung cancer were aged 65 years or older in each year from 2016 to 2019[26]. However, the median age of our study population with druggable mutations was 65 years, indicating that approximately half of them were below 65 years old. This gap could be attributed to the relatively favorable performance status of patients who undergo CGP testing and their desire to proceed with the next treatment or participate in clinical trials compared with those who did not undergo testing.

Our results indicated that adenocarcinoma was the most commonly observed subclassification among the cases with druggable mutations detected through CGP testing. However, squamous cell carcinoma was also detected in 13.3% of those cases. Although *EGFR*, *ALK*, *ROS1*, *BRAF V600E*, *RET*, and *KRAS G12C* mutations are rarely observed or typically absent in lung squamous cell carcinoma[27–31], the *MET* exon 14 skipping mutation has been detected relatively frequently in squamous cell lung cancer and pulmonary sarcomatoid carcinoma[32,33]. The Japanese guidelines recommend conducting genetic testing regardless of histological subtype, including those other than adenocarcinoma[8]. The present study reported that driver mutations can be detected even in squamous cell carcinoma, suggesting the importance of conducting genetic testing regardless of the histological type.

The median duration from primary treatment initiation to druggable mutation detection in our sample was 701 days (approximately 1 year and 11 months). The most commonly used treatment before CGP testing among cases confirmed to have druggable mutations via CGP testing was chemotherapy. Meanwhile, molecular-targeted agents were utilized in 23.0% (first treatment after CGP testing) of such cases, with the primary drugs used after CGP testing being osimertinib, dabrafenib plus trametinib, atezolizumab, afatinib, and docetaxel + ramucirumab, in order of frequency. Although the guidelines recommend the conduct of genetic testing before the initiation of first-line treatment and the use of molecularly targeted agents accordingly after mutation detection[8], the results of this study suggest that patients whose druggable mutations were detected via CGP testing may have missed the opportunity to receive molecularly targeted agents for their gene mutation for over a period of 1 year and 11 months. Given the turnaround time of approximately 2 weeks or less for multiplex companion diagnostics[34,35], the observed delay of nearly 2 years indicates a substantial gap in time for patients to receive potentially more effective treatment associated with improved response rate and progression-free survival. The results also indicated that patients whose mutations were detected via CGP testing subsequently received appropriate molecularly targeted therapy. One of the major reasons for the gap of 1 year and 11 months may be that the patients did not receive comprehensive multigene testing. Although we cannot exclude the possibility that those mutations are newly detected owing to differences in characteristics between the initial testing and CGP or evaluation using different specimens (i.e., specimens collected from different areas) exhibiting different genetic characteristics from the ones used for the initial diagnosis due to tumor heterogeneity, the priority order and comprehensiveness of diagnostic testing at individual hospitals may hinder initial multigene testing[10]. It is necessary to ensure that healthcare providers are fully aware of the impact of test timing on patients and to develop systems that eliminate any disadvantages for healthcare institutions in conducting upfront multiplex testing.

The duration of each treatment line ranged from an average of approximately 150 to 188 days for the first- to third-line treatments before CGP testing and approximately 58 to 78 days for the first to second treatment after CGP testing. Given that our study population included patients who had completed or were expected to complete standard therapy and had already received several treatments, such as chemotherapy, before CGP testing, they had a poor disease condition or were expected to have a poor prognosis due to treatment burden. Consequently, the treatment duration after CGP testing was shorter than that before CGP testing, suggesting that the treatment effect was limited.

The present study has some limitations that need to be acknowledged. First, considering that the registration information from the C-CAT database was utilized as the data source for this study, data for patients who did not consent to the C-CAT registration or secondary use of information were unavailable. This may have resulted in limited representativeness. Second, since 2019, the status of companion diagnoses related to each multiplex genetic testing has been changing throughout Japan. Notably, the data analyzed in the current study represents a period of time during which the choice of tests at each medical institution was in a state of transition. Therefore, the results of the present study may not be directly generalized in future situations. However, as recent research and PMDA approvals have continuously added novel drugs that can be used for gene mutations in cancer, the importance of genetic testing for precision medicine is expected to increase. In this regard, our findings provide a reference point to evaluate the current situation. Given this rapidly evolving landscape surrounding genetic testing and novel treatment options, future research should continue to monitor the emerging trends and challenges. Third, only limited information before registration in the C-CAT database could be obtained. Thus, this study could not examine what testing platforms were used or their test results before the patients were registered. Finally, some variables from the C-CAT database had missing values, and some of the analyses did not include a sufficiently large sample size for result interpretation. In particular, information on treatment after CGP testing was available for only 122 cases, which resulted in a smaller sample size compared with the other analyses. Moreover, considering that data registration and updates are handled at each medical facility, there may be some differences in the regulations and procedures for data registration at each facility.

In conclusion, based on data obtained from the C-CAT database, our study found that gene mutations potentially leading to the use of approved drugs in Japan were identified in 44.6% of the patients who had not been detected with those mutations. Furthermore, it highlighted the landscape of druggable mutation detection among Japanese patients with NSCLC. Our results emphasized the gap between the recommended timeline and real-world practice in Japan, indicating that a considerable proportion of the Japanese patients were not detected with druggable mutations until they underwent CGP testing after the standard therapy. The current study adds to the extant literature detailed clinical profile of Japanese patients with NSCLC who underwent CGP testing after standard therapy, including the treatment strategies used after CGP testing. Reducing the barriers that prevent healthcare providers from upfront multigene testing for driver gene mutations is essential to promote precision medicine and improve the efficiency of NSCLC treatment by facilitating appropriate treatment after discussion with patients at an early stage.

Data availability

The data generated in this study are available from the corresponding author upon reasonable request.

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Author contributions

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Declarations

Competing interests

Yuya Yokochi is an employee of Novartis Pharma K.K. Moemi Miura and Masayuki Hamakawa are employees of Social Survey Research Information Co., Ltd.

Additional information

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