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Next-Generation Sequencing Trends among Adult Patients with Select Advanced Tumor Types

A Real-World Evidence Evaluation

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There are limited data on the prevalence of next-generation sequencing (NGS) in the United States, especially in light of the increasing importance of identifying actionable oncogenic variants due to molecular biomarker–based therapy approvals. This retrospective study of adult patients with select metastatic solid tumors and central nervous system tumors from the Optum Clinformatics Data Mart US health care claims database (January 1, 2014, to June 30, 2021; $N = 63{,}209$) examined NGS use trends over time. A modest increase in NGS was observed across tumor types from 2015 (0.0% to 1.5%) to 2021 (2.1% to 17.4%). A similar increase in NGS rates was also observed across key periods; however, rates in the final key period remained <10% for patients with breast, colorectal, head and neck, soft tissue sarcoma, and thyroid cancers, as well as central nervous system tumors. The median time to NGS from diagnosis was shortest among patients with non–small-cell lung cancer and longest for patients with breast cancer. Predictors of NGS varied by tumor type; test rates for minorities in select tumor types appeared comparable to the White population. Despite improving payer policies to expand coverage of NGS and molecular biomarker–based therapy approvals, NGS rates remained low across tumor types. Given the potential for improved patient outcomes with molecular biomarker–based therapy, further efforts to improve NGS rates are warranted. *(J Mol Diagn 2024, 26: 292–303; https://doi.org/10.1016/j.jmoldx.2024.01.005)*

Precision cancer medicine is based on discovering specific targetable genomic variants.[1–3] Although historically cancer treatment followed a one-size-fits-all approach of categorizing cancers by histology alone, targetable genomic variants resulted in a shift in oncology practice with a focus on specific oncogenic variants.[1–3] Numerous genomic variants have been reported across a wide range of solid tumor histologies, many of which are observed with an overall low frequency but may serve as the primary oncogenic variant of the tumor.[4,5] There are currently numerous therapies that target oncogenic variants within specific tumor histologies [eg, *ALK*, *ROS1*, and *EGFR* in non–small-cell lung cancer (NSCLC)].[6–8] In addition, there are now six tumor-agnostic therapies or regimens that are approved to target specific oncogenic variants (ie, *NTRK*, *RET*, and *BRAF*), regardless of tumor histology.[9] One of the first US Food and Drug Administration–approved tumor-agnostic targeted therapies was larotrectinib (Vitrakvi prescribing information. Bayer Healthcare Pharmaceuticals, Inc., Whippany, NJ), which was approved in November 2018 (*http://cancer.org/treatment/treatments-and-side-effects/treatment-types/tumor-agnostic-drugs.html*, last accessed October 3, 2022). The approval of molecular biomarker–based targeted therapies has led to substantial clinical benefits for patients with advanced or metastatic cancer in recent years.[10–20]

Because of the rapidly evolving landscape of molecular biomarker–based targeted therapies and their integration into clinical practice, molecular biomarker testing has become increasingly important. Furthermore, with the approval of tumor-agnostic therapies that target genomic

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variants that occur at low frequencies across many solid tumors, it is imperative to have a testing strategy to identify these genomic variants to improve patient outcomes.[21] Currently, numerous testing methods are available to identify genomic variants, which include traditional sequencing methods (eg, Sanger sequencing), targeted molecular biomarker assessments, and next-generation sequencing (NGS); targeted molecular biomarker assessments include hybridization-based arrays, fluorescence *in situ* hybridization, qualitative real-time PCR, PCR coupled with fragment analysis platforms, and immunohistochemistry.[22] Many of these testing methods, including fluorescence *in situ* hybridization, PCR, and immunohistochemistry, only test for a single gene or a limited number of genomic variants (ie, hot spot testing). Using these tests would potentially require running multiple sequential tests to gain access to all actionable genomic variants, which may require multiple tissue samples and is time-consuming, potentially resulting in a delay in treatment decisions.[23] Compared with single-gene or hot spot testing methods, NGS requires low input of DNA/RNA. Furthermore, NGS technologies are a high-throughput method that allows for sequencing of multiple targeted genomic regions in a single sample, thus allowing for simultaneous screening of a variety of genomic variants (ie, single-/multiple-nucleotide variants, small and large insertions and deletions, copy number variations, structural variants, and fusion transcripts) with high accuracy and sensitivity.[24] Therefore, NGS enables the identification of actionable genomic variants, even those occurring at a low overall frequency across the population, simultaneously and efficiently while minimizing the amount of tissue sample required.[25] In addition, a recent analysis reported that NGS provides a less costly alternative (versus single-gene testing) to correctly identify clinically actionable genomic variants in most cancer types.[26] Clinical guideline recommendations also support NGS in multiple solid tumors.[7,8,27–29] In addition to tumor-specific guidelines that recommend NGS, the American Society of Clinical Oncology Provisional Clinical Opinion states that for any patient with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing (defined as NGS with at least 50 genes) is preferred whenever patients are eligible for a genomic biomarker-linked therapy that a regulatory agency has approved.[7,8,27–29] With six tumor-agnostic therapies/regimens approved in the United States, and others currently undergoing evaluation, this American Society of Clinical Oncology Provisional Clinical Opinion means that all patients with metastatic solid tumors should have NGS at some point in their treatment plan.[9,27]

Despite the functionality of detecting oncogenic variants and guideline recommendations associated with NGS, barriers to widespread adoption in clinical practice may still exist because of concerns regarding financial reimbursement, lack of knowledge regarding clinical validation and operational management of NGS assays, difficulty with interpretation of results, perceived lack of clinical utility, and logistical barriers (eg, turnaround time).[1,30–32] Coverage of NGS varies by multiple factors, including payer type. However, there has been modest progress in the last few years, as two major payers expanded coverage of NGS. The United Healthcare medical policy for molecular oncology testing expanded coverage in August 2016 (*https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/molecular-oncology-testing-for-cancer.pdf*, last accessed August 30, 2022), and the Centers for Medicare & Medicaid Services National Coverage Determination (NCD) for NGS was issued in March 2018 (*https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=290*, last accessed August 30, 2022).

Because of the evolving landscape of molecular biomarker–based targeted therapy options associated with improved patient outcomes in solid tumors and the associated need for molecular biomarker testing, it is imperative to understand molecular biomarker testing patterns.[1,14–20,25,33,34] Although there are numerous publications related to molecular biomarker testing in general across solid tumors, there are limited published data that describe the current prevalence of NGS in the United States following expanded coverage of NGS and tumor-agnostic therapeutic approvals.[25] In addition, although NGS use has reportedly increased over the last decade, health inequities related to patient demographics may

Key Points

- Next-generation sequencing (NGS) is an increasingly important component of cancer care to enable identification of actionable genomic variants; however, there are limited data on the current prevalence of NGS in the United States, especially in light of the increasing importance of identifying actionable oncogenic variants due to molecular biomarker–based therapy approvals.
- This study demonstrated an increase in NGS across a variety of tumor types from 2015 (0.0% to 1.5%) to 2021 (2.1% to 17.4%); metastatic non–small-cell lung cancer and metastatic breast cancer had the highest and lowest NGS rates in 2021, respectively. One potential reason for the differences in NGS rates between tumor types may be the variation seen in guideline recommendations for NGS.
- NGS rates in the final key time period evaluated in this study (post-larotrectinib approval; November 26, 2018, to June 30, 2021) remained <10% for patients with metastatic breast cancer, central nervous system tumors, metastatic colorectal cancer, metastatic head and neck cancer, metastatic soft tissue sarcoma, and radioactive iodine-refractory metastatic thyroid carcinoma.
- Despite improved coverage determinations and tumor-agnostic therapeutic approvals, NGS rates remained low overall in this study, and further efforts to improve NGS rates are indicated, especially given the potential for improved patient outcomes with molecular biomarker–based therapy.

still exist as NGS rates appear to have increased at a slower rate for African American and Hispanic/Latino patients compared with White patients.[35] Evaluation of trends in NGS use by patient sociodemographic and clinical characteristics and across additional solid tumor disease states may provide a better understanding of populations who do not have equitable access to NGS. Therefore, this study aimed to provide additional insight into the prevalence of NGS and explore patient sociodemographic and clinical characteristics associated with NGS among adult patients with specific tumor types.

Materials and Methods

Study Design

A retrospective analysis was conducted using the Optum Clinformatics Data Mart US health care claims database from January 1, 2014, to June 30, 2021. The patient identification period was from January 1, 2015, to March 31, 2021. US adult patients (aged ≥18 years) with seven select metastatic cancers [NSCLC, soft tissue sarcoma, melanoma, head and neck cancer (H&N), radioactive iodine (RAI)–refractory thyroid carcinoma, colorectal cancer (CRC), and nonsecretory breast cancer], as well as primary central nervous system (CNS) tumors, were included. These cancers were selected to comprise frequently encountered solid tumors with approved targeted therapies and guideline recommendations for molecular diagnostic testing.[27] Patients were included in the study if they had: medical claims with diagnosis codes for NSCLC, soft tissue sarcoma, melanoma, H&N, RAI-refractory thyroid carcinoma, CRC, nonsecretory breast cancer, or primary CNS tumors on two different dates within the identification period; and one medical claim with diagnosis codes for metastasis (patients with non-primary CNS tumor only) between January 1, 2015, and March 31, 2021.

The index date was defined as the date of the first observed claim with a metastasis diagnosis in the study period for patients with non-primary CNS tumor; the index date must have occurred during the patient identification period (January 1, 2015, to March 31, 2021). The date of the earliest observed diagnosis for a primary CNS tumor served as the index date for the primary CNS tumor population (Figure 1). Patients were required to have enrollment for the full calendar year to be included. Diagnoses were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), or *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), codes. H&N included cancers of the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, and salivary glands; cancers of the brain, esophagus, eye, parathyroid, or thyroid were excluded from the H&N population. Eligible patients were also required to be continually enrolled in the database system for ≥12 months in the pre-index period and ≥3 months in the postindex period.

For the main analysis, two cohorts of patients were defined on the basis of tumor diagnosis: select metastatic cancers study population [defined as metastatic NSCLC (mNSCLC), metastatic soft tissue sarcoma (mSTS), metastatic melanoma (mM), metastatic H&N (mH&N), RAI-refractory metastatic thyroid carcinoma (mTC), metastatic CRC (mCRC), and nonsecretory metastatic breast cancer (mBC)]; or primary CNS tumor study population (defined as primary CNS cancer). In addition, a subanalysis of NGS trends by race/ethnicity was conducted.

Outcomes and Definitions

NGS was identified using Current Procedural Terminology (CPT) and procedures codes, and the proportion of patients who received NGS for each calendar year in the identification period (2015 to 2021) was calculated (Supplemental Table S1 provides a full list of CPT codes used in this study). Both the NGS test and diagnosis of metastatic disease must have fallen within the calendar year of interest, and NGS could have taken place before or after the index metastatic diagnosis. Patients could have fallen into more than one prevalence calendar window if they met all of the inclusion criteria in that year.

The prevalence of NGS in key time windows by tumor type was also assessed. Key periods were designated as the

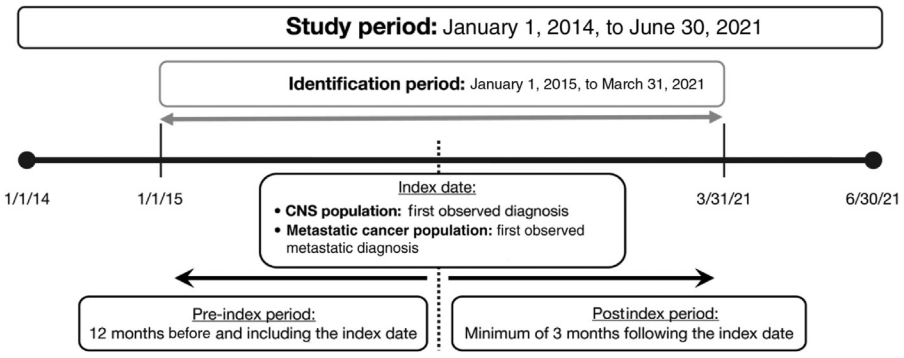


Figure 1 Overview of the study design, including study period, identification period, index date, and pre-index and postindex periods. CNS, central nervous system.

baseline period (January 1, 2015, to August 31, 2016), post−United Healthcare policy determination period (September 1, 2016, to March 30, 2018), post−Centers for Medicare & Medicaid Services policy determination period (April 1, 2018, to November 25, 2018), and post-larotrectinib approval period (November 26, 2018, to June 30, 2021). For this analysis, both an NGS test and diagnosis of metastatic disease (not required to be the index claim) must have fallen within the period of interest. Patients could also fall into more than one prevalence time window if they met all of the inclusion criteria in that period of interest.

Additional outcomes were time to NGS by tumor type in adult patients [calculated as the time between the earliest metastasis diagnosis (or earliest CNS cancer diagnosis for CNS patients) and the date of NGS test occurring closest to the metastasis or CNS tumor diagnosis in the measurement period; this outcome measure included all patients with a given metastatic cancer who eventually had NGS]; sociodemographic and clinical characteristics of patients stratified by tumor type; and NGS use trends by race/ethnicity.

Statistical Analysis

Covariates [age, sex, race, region, payer type, plan type, primary tumor type, Charlson Comorbidity Index (CCI) score, NGS status, site of care, and provider specialty/subspecialty] were analyzed descriptively between NGS status groups using *t*-tests and χ^2 tests to analyze unadjusted differences between the study groups.

Cox proportional hazard models were developed to estimate the hazard ratios between NGS status and patient/provider variables measured during the pre-index period while controlling for other covariates, including age, sex, race, region, payer, and CCI score.

All statistical tests were based on a two-sided hypothesis of no difference between cohorts at a significance level of 0.05. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Population Demographics

In total, 63,209 patients met the study inclusion criteria across the selected tumor types (Table 1); nonsecretory mBC (26,086 patients), mNSCLC (14,620 patients), and mCRC (9538 patients) were the most highly represented tumor types. The mean patient age ranged from 52.1 years (RAI-refractory mTC) to 71.4 years (mNSCLC), and the mean CCI score ranged from 0.0 (nonsecretory mBC) to 2.7 (mNSCLC). In line with Surveillance, Epidemiology, and End Results incidence rates by sex and tumor type, the mH&N population was predominantly male (74.7%).[36] In comparison, the RAI-refractory mTC and nonsecretory mBC patient populations included a lower percentage of male patients (36.2% and 0.8%, respectively). The payer mix was similar for most tumor types aside from mNSCLC and mCRC, which had higher Medicare populations (81.0% and 64.6%, respectively), and RAI-refractory mTC, which had a higher commercial payer population (69.9%).

Annual Prevalence of NGS

Across all tumor types, an increase in NGS prevalence was observed during the study period (2015 to 2021) (Figure 2). The most substantial increases in NGS rates were observed among patients with mNSCLC (1.5% to 17.4%) and mM (0.4% to 16.3%). By the end of the study period (2021), NGS rates remained <5% among patients with nonsecretory mBC (2.1%), mH&N (3.5%), mSTS (4%), and RAI-refractory mTC (3.9%).

Trends in NGS by Key Periods

An increase in NGS rates was observed across the key periods for all tumor types. During the initial time period (baseline period; January 1, 2015, to August 31, 2016), NGS rates ranged from 0.0% for patients with mSTS and mH&N to 3.3% for patients with mNSCLC (Figure 3). During the final key period (post-larotrectinib approval; November 26, 2018, to June 30, 2021), NGS rates increased to 18.2% for patients with mNSCLC and 12.3% for patients with mM. However, NGS rates during this period remained <10% for all other tumor types and remained particularly low for patients with nonsecretory mBC (2.1%) and mH&N (2.0%).

Time from Diagnosis to NGS During Key Periods

The median time from metastatic diagnosis (or primary CNS tumor diagnosis for CNS patients) to NGS was shortest among patients with mNSCLC (median, 1.3 months) and longest among patients with nonsecretory mBC (median, 6.5 months) (Supplemental Tables S2 and S3). From the earliest key period (baseline period; January 1, 2015, to August 31, 20161) to the most recent key period (post-larotrectinib approval; November 26, 2018, to June 30, 2021), most tumor types showed a trend of decreasing median time to NGS from metastatic diagnosis (or primary CNS tumor diagnosis for CNS patients) (Figure 4). The median time from metastatic diagnosis (or primary CNS tumor diagnosis for CNS patients) to NGS among all tumor types was <3 months in the most recent key period (post-larotrectinib approval; November 26, 2018, to June 30, 2021).

Predictors of NGS by Tumor Type

In adjusted models, potential predictors of NGS varied by tumor type (Supplemental Table S4). Commercial insurance was associated with a greater likelihood of NGS compared

Table 1 Total Number of Patients and Patient Demographics in the Select Metastatic Cancers and the Primary CNS Tumor Study Populations

Variable	mBC*	mNSCLC	mCRC	mTC (RAIR)	mH&N	mM	mSTS	CNS
Total, *N*	26,086	14,620	9538	2751	2360	1740	279	5835
Age, mean (SD), years	65.7 (13.4)	71.4 (9.2)	67.9 (13.0)	52.1 (17.7)	64.3 (11.4)	63.7 (15.6)	63.7 (16.4)	58.8 (17.2)
Male sex, %	0.8	45.8	51.8	36.2	74.7	57.0	51.6	49.5
Race, %								
Asian	3.5	3.3	3.7	7.3	3.5	1.1	3.9	3.6
Black	13.5	12.3	11.8	5.6	7.8	4.4	14.0	8.4
Hispanic	10.1	7.1	11.3	15.8	8.2	4.5	9.3	10.8
White	68.4	71.5	68.1	66.7	76.2	85.6	69.9	71.8
Missing	4.6	5.8	5.1	4.5	4.3	4.3	2.9	5.4
Region, %								
Mid-Atlantic	9.6	9.8	9.7	11.1	9.9	9.3	10.8	10.8
Midwest	21.8	22.7	22.7	20.9	23.3	23.7	19.4	21.3
Northeast	3.4	5.0	3.3	3.0	4.1	3.8	3.6	4.2
South	31.1	33.8	29.6	24.4	31.1	27.8	28.0	28.7
Southwest	15.1	12.9	16.5	18.2	13.8	14.7	18.3	15.2
West	18.6	15.6	17.8	21.7	17.4	20.6	18.3	19.3
Other/missing	0.4	0.3	0.3	0.7	0.4	0.2	1.8	0.4
Payer, %†								
Commercial	40.8	19.0	35.4	69.9	47.8	47.5	46.2	50.0
Medicare	59.2	81.0	64.4	30.1	52.2	52.5	53.8	50.0
CCI, mean (SD)	0.0 (0.4)	2.7 (2.2)	2.0 (2.2)	0.9 (1.6)	1.4 (1.9)	1.3 (1.9)	1.8 (2.2)	1.5 (2.0)
Duration of postindex period, months								
Mean	26.5	15.4	21.3	26.3	22.9	22.5	18.7	22.7
Median	21.2	10.2	15.3	20.6	16.1	16.5	13.3	15.1

*Nonsecretory mBC.

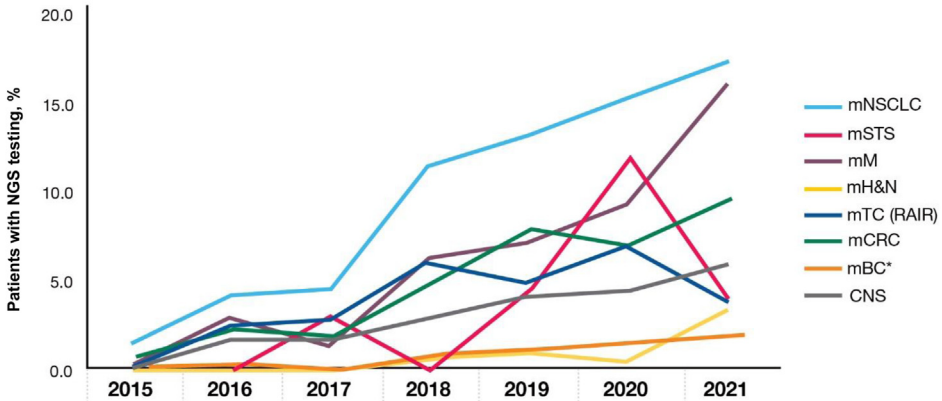
†Data set included patients with managed care plans [eg, private plans (captured under commercial payer type) and Medicare Part C (captured under Medicare payer type)].

CCI, Charlson Comorbidity Index; CNS, central nervous system; mBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; mH&N, metastatic head and neck cancer; mM, metastatic melanoma; mNSCLC, metastatic non—small-cell lung cancer; mSTS, metastatic soft tissue sarcoma; mTC, metastatic thyroid carcinoma; RAIR, radioactive iodine refractory.

with having Medicare for patients with CNS tumors ($P = 0.0018$). In contrast, Medicare payer type was associated with a greater likelihood of NGS among patients with mCRC ($P = 0.0002$) and mNSCLC ($P = 0.0167$). Compared with patients of the same tumor type from the Western region of the United States, patients with mNSCLC and nonsecretory mBC located in the Mid-Atlantic region and patients with mCRC and CNS tumors located in the Mid-Atlantic and South regions were more likely to undergo NGS (all, $P < 0.05$). Patients with mNSCLC and nonsecretory mBC located in the Southwest region were less likely to undergo NGS compared with patients with the respective tumor types located in the Western region of the United States (all, $P < 0.05$). No differences were observed by region for the other tumor types. By tumor type, other factors that were potential predictors of NGS included younger age and lower CCI score (mNSCLC); male sex and Black race (mSTS); higher CCI score (mM); older age (RAI-refractory mTC); younger age (mCRC); and older age, male sex, and lower CCI score (CNS tumors) (all, $P < 0.05$). None of the other covariates analyzed influenced NGS for patients with mH&N or nonsecretory mBC.

Racial and Ethnic Trends in NGS Use

In total, 57,819 patients met the inclusion criteria for the racial and ethnic trends subanalysis across five of the selected tumor types (mNSCLC, mCRC, nonsecretory mBC, mM, and CNS). Among the total patient population for the subanalysis, 70.0% were White, 12.1% were Black, 9.4% were Hispanic, and 3.4% were Asian. The findings stratified by racial/ethnic subgroups were similar to the findings for the overall study population. Median time to NGS from diagnosis across tumors ranged from 1.1 to 1.8 months for Asian patients, from 1.4 to 5.6 months for Black patients, from 1.4 to 5.1 months for Hispanic patients, and from 1.2 to 7.2 months for White patients. Furthermore, NGS use generally improved over key periods and the overall study period within each specific racial/ethnic subgroup (Figure 5 and Supplemental Table S5).



	2015	2016	2017	2018	2019	2020	2021
mNSCLC	28/1820	58/1312	81/1700	240/2068	306/2313	343/2216	126/725
mSTS	0/39	0/20	1/33	0/34	2/46	7/59	1/25
mM	1/276	1/173	3/209	15/235	22/300	31/325	16/98
mH&N	0/403	0/273	0/272	2/301	3/334	2/411	6/173
mTC (RAIR)	1/495	9/348	11/383	25/411	21/424	30/421	5/129
mCRC	11/1557	25/1051	24/1194	63/1347	118/1479	103/1473	50/521
mBC*	5/4543	11/3128	4/3469	37/3910	53/4177	70/4228	27/1292
CNS	7/1503	10/547	12/663	24/741	31/718	31/679	11/183

Figure 2 Prevalence of next-generation sequencing (NGS) testing by year. The numbers indicate *n/N* (number of NGS tests per total number of patients per tumor type in each time period indicated). Note that the total numbers of patients included in each time period may not align to the total number of patients for each tumor type as described in Table 1 because of definitions used for the time periods in this analysis. *Nonsecretory metastatic breast cancer (mBC). CNS, central nervous system; mCRC, metastatic colorectal cancer; mH&N, metastatic head and neck cancer; mM, metastatic melanoma; mNSCLC, metastatic non–small-cell lung cancer; mSTS, metastatic soft tissue sarcoma; mTC, metastatic thyroid carcinoma; RAIR, radioactive iodine refractory.

Discussion

Although an increase in NGS was observed across a variety of tumor types (ranging from 0.0% to 1.5% in 2015 to 2.1% to 17.4% in 2021) in this retrospective, claims-based analysis, room for improvement was demonstrated as NGS rates across the tumor types and periods never exceeded 20%. Furthermore, despite evolving payer preference for NGS and tumor-agnostic therapeutic approvals, the analysis by key periods demonstrated that NGS rates in the final key period evaluated (post-larotrectinib approval; November 26, 2018, to June 30, 2021) remained particularly low (<10%) for patients with nonsecretory mBC, CNS tumors, mCRC, mH&N, mSTS, and RAI-refractory mTC. This finding is not aligned with many recent guideline recommendations and is concerning given the potential benefits of comprehensive genomic profiling

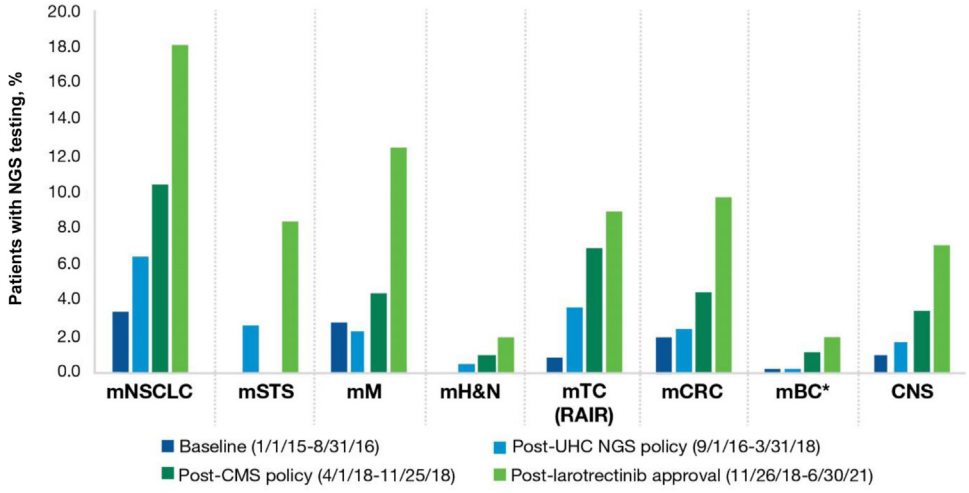


Figure 3 Next-generation sequencing (NGS) testing rates by key time period: baseline, post–United Healthcare (UHC) NGS policy, post–Centers for Medicare & Medicaid Services (CMS) policy, and post-larotrectinib approval. *Nonsecretory metastatic breast cancer (mBC). CNS, central nervous system; mCRC, metastatic colorectal cancer; mH&N, metastatic head and neck cancer; mM, metastatic melanoma; mNSCLC, metastatic non–small-cell lung cancer; mSTS, metastatic soft tissue sarcoma; mTC, metastatic thyroid carcinoma; RAIR, radioactive iodine refractory.

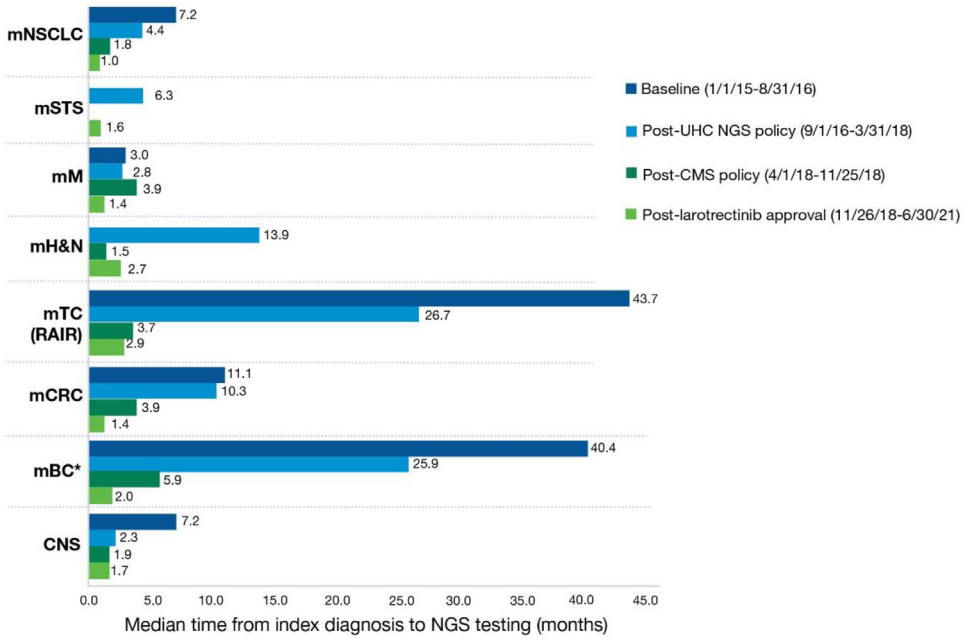


Figure 4 Median time from metastatic or primary central nervous system (CNS) diagnosis to next-generation sequencing (NGS) testing by key time period. For the median time from index diagnosis to NGS analysis, no data were available for the following tumor types and key time periods: metastatic soft tissue sarcoma (mSTS; January 1, 2015, to August 31, 2016; and April 1, 2018, to November 25, 2018) and metastatic head and neck cancer (mH&N; January 1, 2015, to August 31, 2016). *Nonsecretory metastatic breast cancer (mBC). CMS, Centers for Medicare & Medicaid Services; mCRC, metastatic colorectal cancer; mM, metastatic melanoma; mNSCLC, metastatic non—small-cell lung cancer; mTC, metastatic thyroid carcinoma; RAIR, radioactive iodine refractory; UHC, United Healthcare.

using NGS in assisting with treatment selection, guiding potential clinical trial enrollment, and improving patient outcomes.[7,8,27–29,37]

A previous study by Sheinson et al[25] reported an increase in NGS use across four tumor types (advanced NSCLC, mCRC, mBC, and advanced melanoma) following the Centers for Medicare & Medicaid Services NCD in 2018, from <1% in 2011 to approximately 40% in 2019 for both Medicare beneficiaries and commercially insured patients. Similar to the current study, NGS use increased after the implementation of the NCD, with the greatest increase observed for patients with advanced NSCLC. Use of NGS increased from <1% in 2011 across the four tumors combined to 48% in Medicare patients and 58% in commercially insured patients with advanced NSCLC in 2019. Increases to 30% in Medicare patients and 40% in commercially insured patients with mCRC in 2019 were also observed, but NGS rates remained <20% across payer types in mBC and advanced melanoma. Other US-based studies have also demonstrated an increase in NGS among patients specifically with advanced or metastatic NSCLC over time, including from 28% in 2015 to 68% in 2020 (Flatiron Health database),[38] from 25% in 2016 to 36% in 2019 (US Oncology Network),[39] from 33% in 2018 to 45% in 2020 (US Oncology Network),[40] and from 35% in 2015 to 59% in 2019 (Florida Cancer Specialists & Research Institute community-based oncology/hematology practice network electronic medical record data).[41] These studies collectively demonstrate higher overall rates of NGS for patients with advanced or metastatic NSCLC compared with the rates demonstrated in this study (1.5% in 2015 to 17.4% in 2021). The low rates in general in this analysis may be due to the nature of claims-based data, which is dependent on diagnostic and procedural codes; accordingly, the rate of NGS may have been underrepresented.

As noted in both this analysis and in previously published analyses,[25,38–41] there is considerable variation of NGS rates between tumor types. In the one analysis that reviewed multiple tumor types outside of this analysis, mNSCLC had the highest rates of NGS, whereas mBC had the lowest rates of NGS.[25] The variation in NGS across tumor types may be a result of differences in guideline recommendations for molecular testing and the availability of molecular biomarker—based targeted treatment. NSCLC has multiple clinical guidelines that recommend a broad, panel-based approach to testing, most commonly with NGS.[7,8] In addition, NSCLC also has nine genomic variants with US Food and Drug Administration—approved targeted therapies.[42] Also, health care provider preference may play a role in the variation in NGS across tumor types. Therefore, for tumor types with fewer targetable genomic variants and/or lacking clinical guideline recommendations specific to NGS, there may be a lower rate of NGS.

Although it is important to obtain NGS in patients with advanced cancer, it is also essential that NGS results are obtained promptly to ensure these results are available for

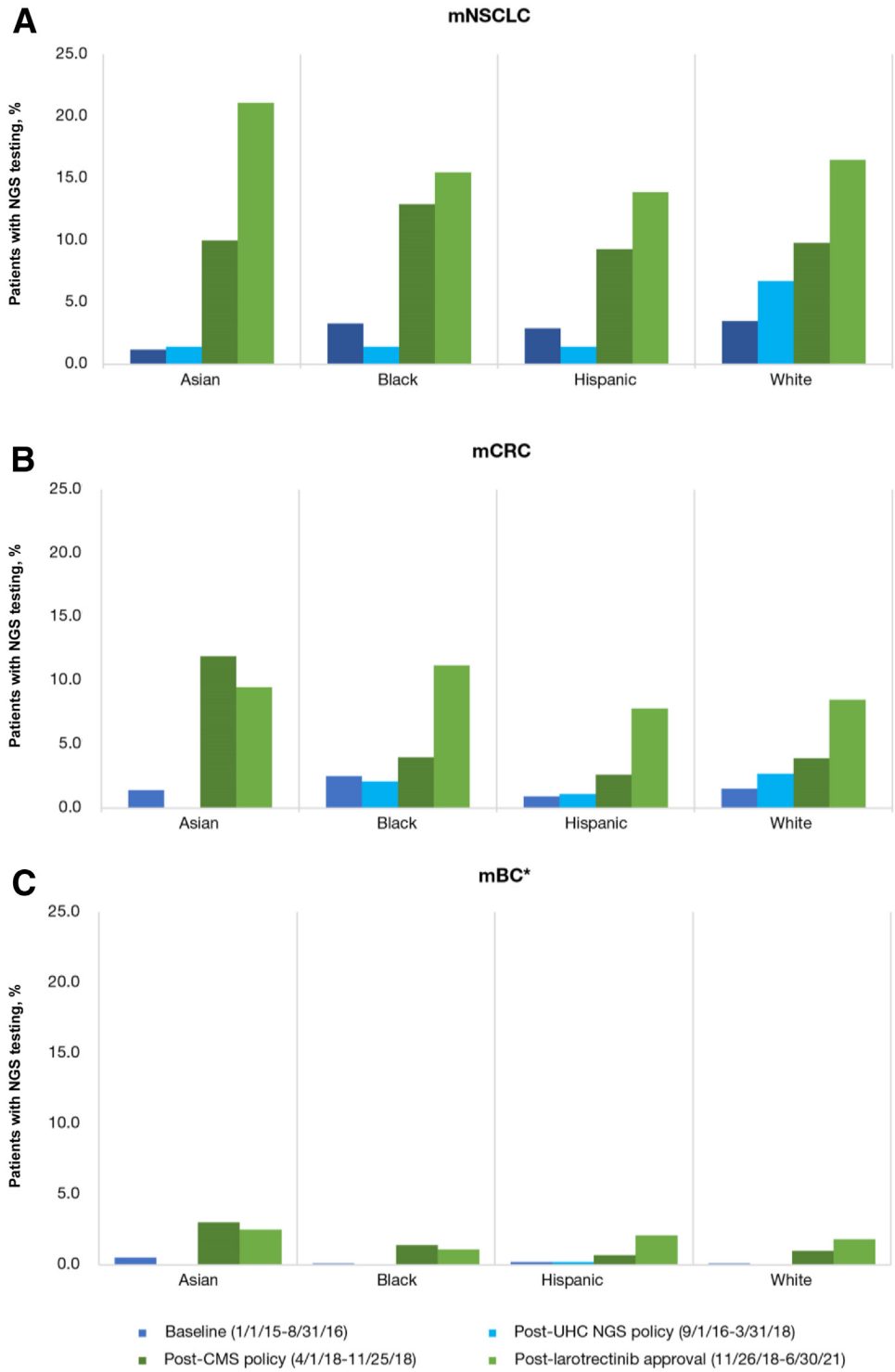


Figure 5 Next-generation sequencing (NGS) prevalence by race/ethnicity and key time frames for metastatic non–small-cell lung cancer (mNSCLC), metastatic colorectal cancer (mCRC), and metastatic breast cancer (mBC). The subanalysis was only conducted in five tumor types (mNSCLC, mCRC, mBC, metastatic melanoma, and primary central nervous system) as there were inadequate patient numbers in racial/ethnic subgroups in the other tumor types for inclusion. This figure reports the three tumor types with the largest patient populations: mNSCLC (**A**), mCRC (**B**), and mBC (**C**). The data for all five tumor types are reported in Supplemental Table S4. *Nonsecretory metastatic breast cancer. CMS, Centers for Medicare & Medicaid Services; UHC, United Healthcare.

treatment decisions. However, limited data describing the time from diagnosis to NGS are available.[43] Vanderwalde et al[43] evaluated time to NGS among patients with advanced NSCLC and mBC. Although their study evaluated a slightly different metric (time from diagnosis to NGS result rather than time from diagnosis to NGS order, as was done in the current study), the findings demonstrated that patients with advanced NSCLC had a shorter time from diagnosis to NGS

results than patients with mBC.[43] Similarly, in this study, the median time to NGS after index diagnosis was shortest among patients with mNSCLC and longest for patients with nonsecretory mBC. This finding may be due to the long-standing history of molecular biomarkers to inform clinical care in mNSCLC; accordingly, reflex testing protocols are now incorporated in certain practice settings.[44] An analysis by Hooper et al[45] reported that implementation of a pathology-driven molecular reflex pathway for non-squamous NSCLC was associated with increased identification of potentially targetable genomic variants and improved adherence to NSCLC molecular biomarker testing guidelines.

Given the substantial clinical benefits associated with NGS and the suboptimal NGS use trends that have been demonstrated, it is essential to gain a better understanding of populations who may not have equitable access to NGS. Sociodemographic and clinical factors associated with molecular biomarker testing in patients with advanced cancer have been reported in the literature, although few studies have reported factors explicitly associated with NGS. In these studies, factors associated with differences in molecular biomarker testing rates appeared to vary by tumor type. Norris et al[46] conducted a recent systemic literature review and meta-analysis that included 10 studies across four tumor types (breast, 4 studies; CRC, 3 studies; melanoma, 1 study; and NSCLC, 2 studies); results demonstrated that low socioeconomic status was associated with modestly lower predictive molecular biomarker test use (odds ratio, 0.86; 95% CI, 0.71−1.05). This pattern was consistent across tumor types, but the findings were only significant in CRC (odds ratio, 0.76; 95% CI, 0.65−0.88). In addition, in an analysis by Markt et al,[47] differences in NGS rates in patients with mCRC were observed based on age, race/ethnicity, payer type, and site of care (academic versus community setting). Previous studies have also indicated that molecular testing patterns in NSCLC vary based on factors such as location, sex, and age.[48,49] In the current study, potential predictors of NGS also varied by tumor type and included age (mNSCLC, RAI-refractory mTC, mCRC, and CNS tumors), sex (mSTS and CNS tumors), race (mSTS), region (mNSCLC, mCRC, nonsecretory mBC, and CNS tumors), payer type (mNSCLC, mCRC, and CNS tumors), and CCI score (mNSCLC, mM, and CNS tumors).

Research on the impact of race and ethnicity on NGS rates has been conflicting. A US-based, retrospective cohort analysis conducted by Sheinson et al[35] evaluated the impact of race and ethnicity on NGS patterns among patients with advanced NSCLC, mCRC, mBC, or advanced melanoma diagnosed from January 1, 2011, through March 31, 2020 [N = 92,687; White, 64.5%; African American, 9.3%; Hispanic/Latino, 4.8%; Asian, 2.4%; and other, 10.1% (American Indian or Alaska Native, Hawaiian or Pacific Islander, and race descriptions that fall into multiple race categories)]. Although NGS rates increased for all racial and ethnic groups following the Centers for Medicare & Medicaid Services NCD in 2018, results demonstrated that the increase in NGS use from the pre-NCD period to the post-NCD period was 14% lower (odds ratio, 0.86; 95% CI, 0.74−0.99; P = 0.04) among African American patients and 23% lower (odds ratio, 0.77; 95% CI, 0.62−0.96; P = 0.02) among Hispanic/Latino patients compared with non-Hispanic White patients. These findings suggest ongoing disparities in NGS. Conversely, Al-Ahmadi et al[10] conducted a large institutional database analysis of patients with mNSCLC who underwent broad-based NGS as part of routine care between August 2013 and December 2017 (N = 295; White, 73%; African American, 25.2%; Hispanic, 0.5%; and Asian, 1.4%) to evaluate the potential racial differences in NGS use. In this study, no difference in NGS use based on race was reported (P = 0.32). Similar to the findings from Sheinson et al,[35] findings from this analysis, which evaluated NGS rates within a similar payer system, also reported that NGS rates increased between 2015 and 2021 for racial and ethnic minorities in mNSCLC, mCRC, nonsecretory mBC, mM, and primary CNS tumors. However, findings from this analysis regarding differences by race appear to align with the results by Al-Ahmadi et al,[10] as NGS rates in racial and ethnic minorities in this study appeared comparable to the White population. These findings suggest that equitable access to health insurance in a commercially insured population can lead to equal access to NGS between races.

This study had several limitations. First, this analysis was conducted using health care claims data from a single national health plan and may not fully represent the United States as a whole. Furthermore, details of health care use outside of the health plan were unavailable. The database used for this analysis provided limited information regarding practice location; as such, practice location may be a confounding variable for NGS, and additional research on equitable access to genomic assays is needed to better understand this factor. Because of the nature of claims-based research, patient identification could have been affected by coding inaccuracies, and the rationale for molecular screening was not available for evaluation. In addition, NGS rates may have been underestimated among patients who underwent testing before study inclusion or among the approximately 20% of patients for whom laboratory orders were unavailable. NGS was identified through CPT codes; therefore, missing data could have also contributed to the underreporting of NGS. Because of implementation of NGS CPT codes in 2015, earlier years may be confounded by lower uptake of these codes. In addition, codes not specific to NGS (ie, CPT code 81479, unlisted molecular pathology procedure) were not used as these were considered too broad for inclusion in an NGS-focused study. Fewer than 5000 patients were included in the mH&N, mM, mSTS, and RAI-refractory mTC patient populations, with an especially low number of mSTS patients included (279 total). Therefore, the ability to draw firm conclusions on trends in NGS in those tumor types is

limited. Although this was a descriptive study and type 1 errors were less of a concern, no statistical adjustment for multiplicity was done in this analysis. Finally, the study period for this analysis included the coronavirus disease 2019 (COVID-19) global pandemic, which may have affected health care provider visits.

Conclusions

In conclusion, despite improving payer coverage determinations and both molecular biomarker–based tumor-specific and tumor-agnostic therapeutic approvals, NGS rates remained low overall in this real-world, solid tumor patient population from the Optum Clinformatics Data Mart US health care claims database. Differences in NGS rates were observed across tumor types and across time periods, with increased NGS as time periods progressed. More important, NGS rates for minorities in mNSCLC, mCRC, nonsecretory mBC, mM, and primary CNS tumors increased across key time periods and appeared comparable to the White population, suggesting equitable access to health insurance in a commercially insured population can lead to equal access to NGS regardless of race/ethnicity. However, the data for NGS rates across solid tumors remain limited, especially in light of the recent advances in therapeutics and payer coverage determinations. Therefore, further studies are needed to better understand these inequities and allow for increased targeted efforts to improve NGS rates so that patients may access optimal therapeutic strategies. The use of comprehensive genomic profiling using NGS has the potential to support molecular biomarker–based targeted therapy selection on a much larger scale with improvement in health outcomes while using health care resources more efficiently. As such, it is imperative to understand the barriers to use of NGS and work toward policy interventions that support broader access to NGS.

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Author Contributions

All authors conceptualized the study, developed the protocols, and wrote, reviewed, and edited the manuscript; and S.S. analyzed the data. All authors have read and agreed to the final version of the manuscript. G.K. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data as well as the accuracy of the data analysis.

Disclosure Statement

B.H., G.K., S.B., and S.A. are employees of Bayer HealthCare Pharmaceuticals, Inc. S.S. is a former employee of Bayer Healthcare Pharmaceuticals, Inc. A.F.-G. is a paid consultant of Bayer HealthCare Pharmaceuticals, Inc., and has received honoraria for presentations for Qiagen and Assuragen, Inc.

Supplemental Data

Supplemental material for this article can be found at *http://doi.org/10.1016/j.jmoldx.2024.01.005*.

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