Payer Coverage Policies of Tumor Biomarker and Pharmacogenomic Testing

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Conducted By: ADVI

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Overview of ADVI's Research Approach

Through secondary research efforts, ADVI evaluated payer policies and collated our findings to identify trends and opportunities for patient access to appropriate oncology biomarker testing in pharmacogenomic testing (e.g., TPMT, NUDT15, UGT1A1, DPYD, CYP2D6) and selected tumor types, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer, and prostate cancer.

ADVI evaluated payer policies to understand adoption and coverage of liquid biopsy (cell-free plasma-based/circulating tumor DNA) assays, single gene testing, targeted next-generation sequencing (NGS) panels, comprehensive genomic profiling (CGP), and immunohistochemistry (IHC) tests. ADVI considered how the type of test and clinical guidelines impacted payer policies.

ADVI focused on national commercial payers, a sampling of regional commercial payers (that have high incidence of the tumor types of interest in their populations), and Medicare Administrative Contractors. A complementary analysis examined State Medicaid FFS policies and Medicaid Managed Care Organizations in 15 states, including California, Colorado, Florida, Georgia, Kentucky, Maine, Maryland, Massachusetts, Minnesota, New Mexico, New York, Ohio, Pennsylvania, Texas, and Washington.

ADVI conducted similar analyses in 2018 and 2020, and this report reflects updates as of December 2022.

The below table reflects the payers assessed in this report. Total health plan enrollment numbers may not accurately represent the number of individuals impacted by policies included in this report, as they may vary across employer and exchange-based plans.

Payer	Total Commercial Covered Lives (Source: Policy Reporter)
National Commercial	
Aetna (CVS Health Corp.)	16,683,199
Anthem (Elevance Health)	21,509,438
Cigna	14,618,018
Humana	1,042,826
UnitedHealthcare	23,425,247
Regional Commercial	
Blue Shield of California	2,977,311
Blue Cross Blue Shield of Massachusetts	1,720,712
Centene Corporation	2,198,277
Excellus Health	485,599
Florida Blue	2,947,667
Paramount Health Plan	64,968
Regence Blue Cross Blue Shield	1,050,000

Executive Summary

For oncology biomarkers, coverage of single gene tests and IHC tests is widespread and considered standard of care, particularly if the biomarker is included in NCCN guidelines and/or there is a companion diagnostic paradigm; however**, coverage for all NCCN recommended biomarkers is not universal.**

Payers are increasingly focused on test performance, particularly absent FDA review and/or New York State Department of Health approval. Biomarkers are only safe and effective if they are accurate, and their use is guided by a foundational understanding of inherent limitations. Inadequate documentation of laboratory/test performance can lead to exclusion from payer networks and/or claim denials. The MolDX program critically reviews the analytical validity and clinical validity data supporting a test before providing coverage. Commercial payers, typically through laboratory benefit managers, are conducting similarly robust reviews before providing coverage.

Payer coverage of targeted multi-gene panels in solid tumors is expanding, likely as a result of the increasing number of FDA-approved therapies with an associated genomic marker. Broad coverage of targeted panels (< 50 genes) as the most expeditious and potentially most cost-effective approach is appealing to payers. Particularly in NSCLC, payers recognize that sequential testing of individual biomarkers is not practical, particularly when patients have limited tissue available, and the results of these tests are used to inform urgent treatment decisions.

Coverage of large multi-gene panels and comprehensive genomic profiling (CGP) remains limited. There is more positive coverage policy by the regional commercial payers compared to the national commercial payers. CGP tests typically consists of > 50 genes, include pan-tumor signatures (e.g., TMB, MSI,), eliminate the need for sequential testing, and may expedite time to appropriate treatment. Despite five FDA-approved tumor-agnostic therapies, many payers do not perceive there to be any proven advantage of CGP over small targeted panels or sequential single gene testing. Payers do not explicitly recognize the use of multi-gene panels to identify patients for clinical trials in medical policy.

The lack of uniformity with respect to tumor mutational burden (TMB) testing is creating coverage challenges. Friends of Cancer Research, in concert with other organizations, is working to develop testing standards via the TMB Harmonization Project to ensure a statistically robust calculation of TMB. Payers are concerned with the lack of harmonization in panel-based TMB quantification, adequate methods to convert TMB estimates across different panels and robust predictive cutoffs. As such, payer policies restrict coverage of TMB.

The maturation of the evidence base for liquid biopsy coupled with challenges of tissue stewardship has resulted in some payer coverage, particularly for CDx indications in NSCLC and breast cancer. Some payers are receptive to coverage of liquid biopsy tests when patients are medically unfit for invasive tissue sampling or if following pathologic confirmation of a diagnosis there is insufficient material for molecular analysis. Challenges with having adequate tissue to allow sequential biomarker testing in lung cancer (as recognized in the NCCN guidelines) has clearly impacted coverage policy for NGS panels in NSCLC. It is reasonable to expect the same logic to facilitate broader coverage of liquid biopsy in other tumor types.

Payers do not cover concurrent liquid biopsy and solid tumor tissue testing. Despite recent stakeholder efforts to expand coverage, there is no literature support showing net health outcome improvements by performing simultaneous plasma-based testing along with tissue testing. As such, payers are explicitly non-covering concurrent testing in medical policy.

Since our review in 2020, coverage of both individual biomarkers as well as multi-gene panels has expanded most in breast cancer. A select number of payers provide coverage for TMB and MSI testing with restrictive coverage criteria. Policy language for both biomarkers state that the patient must have unresectable or metastatic breast cancer that has progressed following standard treatment and have no alternative treatment option, consistent with NCCN guidelines.

The companion diagnostic paradigms in prostate cancer have resulted in expanded coverage for solid tumor testing. BRCA testing, including BRACAnalysis CDx and FoundationOne CDx, is widely covered for metastatic castration-resistant prostate cancer (mCRPC) patients who may benefit from treatment with Lynparza. Similarly, the companion diagnostic paradigm for homologous recombination repair (HRR) gene alterations in prostate cancer has resulted in widespread, consistent coverage across payers.

Inconsistent coverage of biomarkers for pharmacogenomic (PGx) testing in oncology across payers. PGx testing evaluates genetic variants to better understand drug metabolism and differential therapeutic effects prior to prescribing therapy for a patient. A potential lack of clarity regarding the evidence threshold needed for clinical application of PGx testing may be resulting in coverage inconsistencies across payers. The most well-established coverage is for TPMT testing when performed prior to the initiation of thiopurine medication therapy. There are a number of state Medicaid programs that provide coverage for tumor diagnostics and PGx, although the extent of this coverage differs from state to state. In compared to Medicare and other non-Medicare commercial payer policies, the coverage provided under the state's Medicaid program is not as comprehensive.

Non-Small Cell Lung Cancer

Key Takeaways

The number of covered biomarkers continues to grow based on inclusion in NCCN guidelines and/or on the availability of an FDA-approved targeted therapy or immunotherapy. Over 2/3 of payers examined cover Category 1, 2A, and 2B NCCN-recommended biomarkers, including EGFR, ALK, ROS1, BRAF, NTRK, RET, MET, PD-L1, KRAS (G12C mutation), and ERBB2 (HER2).

Since our review in 2020, coverage of targeted tissue-based multi-gene panels in NSCLC continues to expand. Payers recognize that sequential testing of individual biomarkers is not practical, particularly when patients have limited tissue available, and the results of these tests are used to inform urgent treatment decisions. The increasing number of individual actionable biomarkers in NSCLC is leading to a consideration of coverage for targeted panels (< 50 genes) as the most expeditious and potentially most cost-effective approach.

Coverage for comprehensive genomic profiling (CGP) remains limited – less than 1/3 of payers examined provide coverage for CGP tests. These tests typically consist of > 50 genes and include pan-tumor signatures (e.g., TMB, MSI). As the rationale for non-coverage, payers have cited that there is no proven advantage of CGP over single gene testing or small targeted panels.

Payers recognize the value of liquid biopsies in NSCLC in some clinical scenarios but are not receptive to simultaneous (concurrent) liquid biopsy and solid tumor tissue testing. Payers are receptive to coverage of liquid biopsy tests when patients are medically unfit for invasive tissue sampling of a metastatic focus or if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis. However, there is no literature support showing net health outcome improvements by doing simultaneous plasma-based testing along with tissue testing (in the hope of getting results a week sooner with plasma but having tissue as a backup).

Clinical Guidelines

NCCN Guidelines (Version 6.2022)[1] currently support biomarker testing of ALK rearrangements, BRAF p.V600E point mutations, EGFR mutations, ERBB2 (HER2) mutations, KRAS mutations, METex14 skipping mutations, NTRK1/2/3 gene fusions, RET rearrangements, and ROS1 rearrangements. Emerging predictive molecular biomarkers include high-level MET amplifications. NCCN strongly advises broad molecular profiling to identify these and other rare driver mutations for which effective therapy may be available.

The guidelines explicitly state that liquid biopsy should not be used to diagnose NSCLC. Generally, studies have shown liquid biopsy testing has high specificity but low sensitivity, with up to 30% false negative rate. Additionally, standards for analytical performance characteristics of liquid biopsy have not been established and there are no guideline recommendations regarding performance characteristics. Liquid biopsy testing can be used if 1) the patient is not medically fit for invasive tissue sampling; or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified.

[1] https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

The NCCN guidelines do not recommend measurement of TMB levels before deciding whether to use combination immuno-oncology therapy or other immune checkpoint inhibitors. Clinical trial data have not demonstrated utility, there is lack of agreement on the definition of a cut off for calling TMB high, and there is a lack of standardization of TMB measurements across laboratories. The guidelines recognize that PD-L1 expression level is a more useful immune biomarker compared to TMB when used to inform immunotherapy decisions – results are obtained more quickly, less tissue is required for testing, and data demonstrate relative reproducibility across platforms/labs. With respect to PGx, the guidelines do not include mention or recommendation for testing (e.g., DPYD).

Gene	NCCN Category	Change Since 2020
ALK	Category 1	
EGFR	Category 1	
ROS1	Category 2A	
KRAS	Category 2A	
BRAF	Category 2A	
NTRK 1/2/3	Category 2A	
MET	Category 2A	
RET	Category 2A	
TMB	Category 2A	
ERBB2	Category 2A	Added
HER2	Category 2B	

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors[2] represents a 2018 evaluation by the College for American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP). This joint guideline recommends multiplexed genetic sequencing panels (e.g., NGS testing) over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1. When NGS is performed, several other genes are also recommended – BRAF, ERBB2, MET, RET, and KRAS.

ASCO Guideline (2018). Molecular Testing Guideline for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors[3] supports testing for EGFR, ALK, BRAF, and ROS1. New for 2018 are recommendations for stand-alone ROS1 testing with additional confirmation testing in all patients with advanced lung adenocarcinoma, and RET, ERBB2 (HER2), KRAS, and MET testing as part of larger panels. ASCO also recommends stand-alone BRAF testing in patients with advanced lung adenocarcinoma. The guideline also preferentially supports multiplexed genetic sequencing panels, where available, over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, BRAF, and ROS1. The guideline recognizes IHC as an appropriate testing methodology for ALK and ROS1.

[2] https://www.amp.org/clinical-practice/practice-guidelines/updated-molecular-testing-guideline-for-the-selection-of-lung-cancer-patients-for-treatment-with-targeted-tyrosine-kinase-inhibitors/
[3] http://ascopubs.org/doi/full/10.1200/JCO.2017.76.7293

National Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers (link)	Covers most NCCN-recommended Category I, 2A, 2B biomarkers, except for MET, RET, and TMB: • ALK • BRAF V600 mutation • EGFR mutation testing for predicting response to Tarceva, Iressa, Gilotrif, Tagrisso • HER2 ERBB2 evaluation • KRAS • Liquid biopsy (up to 50 genes) • NTRK • ROS-1 to predict response to crizotinib (Xalkori) • Targeted solid organ genomic sequencing panel (5-50 genes)	8/1/2022	81401 81210 81235 81275, 81276 81194 81445
	Pharmacogenetic and Pharmacodynamic Testing (link)	Covers all NCCN-recommended biomarkers (Category I, 2A, 2B): • ALK • BRAF gene (V600E or V600K) mutation testing • EGFR T790 mutation testing for persons being considered Tagrisso • EGFR L858R substitution mutations for persons being considered Tagrisso, Tarceva, Vizimpro, Iressa or Gilotrif • EGFR exon 20 insertion mutations for being considered Rybrevant • EGFR exon deletions and L858R mutations for persons being considered for Yervoy or Opdivo • ERBB2 (HER2) amplification testing for persons being considered for Herceptin, Kadcyla, or Perjeta • KRAS G12C mutation testing for persons being considered for Lumakras • NTRK gene fusion for persons being considered for Vitrakvi • MET exon 14 skipping mutation for persons being considered for Tabrecta • PD-L1 expression for persons who are being considered for Tecentriq or Keytruda • RET fusion testing for persons being considered for Gavreto	7/21/2022	81210 81235 81275, 81276 0037U 88360, 88361

	• TMB for persons who may be appropriate for Keytruda	
	Non-covers:	
	• Guardant360 CDx for assessing candidacy of persons for treatment with Tagrisso – no proven advantage over targeted EGFR mutation testing or small targeted panels	0242U
	• Guardant360 CDx for assessing candidacy of persons for Rybrevant – no proven advantage over targeted EGFR mutation testing or small targeted panels	
	• FoundationOne Liquid CDx for assessing candidacy of persons for treatment with Tagrisso, Tarceva or Iressa – no proven advantage over targeted EGFR mutation testing or small targeted panels	0239U
	• FoundationOne CDx for NTRK gene fusion for persons being considered for treatment with Vitrakvi – no proven advantage over targeted NTRK testing	0037U
	• FoundationOne CDx for MSI-H/dMMR testing for persons with solid tumors being considered for treatment with Keytruda – no proven over targeted MSI-H/dMMR testing or small targeted panels	
	• Genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors)	
	• Dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase genetic polymorphisms to predict 5-fluorouracil toxicity	
	• UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer)	
	• Multi-gene pharmacogenetic panels (i.e., diagnostic tests to identify specific genetic variations that may be linked to	

		reduced/enhanced metabolism and/or severe side effects of multiple classes of drugs)		

Anthem	Gene Mutation Testing for Cancer Susceptibility and Management (link)	Covers:
		• Individual biomarker testing to guide targeted cancer therapy (NCCN-recommend Category 1 and a select number of 2A biomarkers) – ALK, BRAF, EGFR, KRAS, MET, ROS1
		• ctDNA test for EGFR to guide targeted cancer therapies in individuals with solid tumors when the following criteria are met:
		  • FFPE tissue is inadequate or is unavailable for testing
		  • The individual is a candidate for targeted therapy and the mutation status of a specific gene is required prior to initiating treatment
		  • A specific mutation, or set of mutations, has been established in the scientific literature to identify those most likely to respond to a targeted therapy
			2/17/2022	81401, 81210, 81235, 81275
				
				81235

	Circulating Tumor DNA Panel Testing (Liquid Biopsy) (link)	Non-covers use of a circulating tumor DNA panel test	11/11/2021	Non-covers: 0179U 0239U 0242U 0326U
	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling (link)	Covers testing for advanced NSCLC gene panels (containing 5-50 genes) prior to initiating first-line therapy when the panel contains, at minimum, the following Category 1 and select Category 2A NCCN-recommended biomarkers: ALK, BRAF, EGFR, ERBB2 (HER2), KRAS, MET, NTRK, RET, and ROS1. The test should be performed using tumor tissue (not liquid biopsy). Covers molecular profiling for unresectable or metastatic solid tumors when all of the criteria below are met: • The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy • Individual has progressed following prior treatment • Individual has no satisfactory alternative treatment options	2/17/2022	81479, 81445, 81455

Cigna	Molecular Diagnostic Testing for Hematology and Oncology Indications (link)	A tissue-based molecular tumor biomarker or broad molecular profile panel is considered medically necessary when ALL of the following criteria are met: • the individual is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site • results of testing will directly impact clinical decision making • the testing method is considered to be scientifically valid and proven to have clinical utility based on prospective evidence • no other tumor biomarker or broad molecular profile panel has been performed on this tumor sample for the same indication • ANY of the following: o identification of the specific biomarker has been validated by the NCCN Guidelines as a category 1, 2A or 2B recommendation for the individual's tumor type of disease o identification of the specific biomarker has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition being addressed o biomarker confirmation is required by an FDA-approved or cleared test prior to initiating therapy o broad molecular profile panel testing for advanced, metastatic solid tumors Covers targeted molecular testing for NTRK fusions (NTRK 1/2/3 fusions) Covers liquid biopsy when tissue testing is not available or contraindicated for EITHER of the following: a) advanced or metastatic solid tumors b) biomarker confirmation is required by an FDA-approved or cleared test prior to initiating therapy	8/15/2022	81210, 81235, 81275, 81276, 81455, 88360, 88361, 0022U, 0179U, 81538, 0037U, 0326U, 81191, 81192, 81193, 81194
Humana	Pharmacogenomics and Companion Diagnostics (link)	Covers nearly all NCCN-recommended Category I, 2A, 2B biomarkers, except for HER2 /ERBB2: • ALK - prior to initiation of Alecensa, Alunbrig, Lorbrena, Xalkori or Zykadia	8/25/2022	81445

		• MET - prior to initiation of Tabrecta Tepmetko • NTRK – prior to initiation of Vitrakvi or Rozlytrek • PD-L1 - prior to initiation Tecentriq, Libtayo, Keytruda, Yervoy • RAS (KRAS and NRAS) - prior to initiation of Lumakras • RET - prior to the initiation of Gavreto or Retevmo • ROS1 - prior to initiation Xalkori, Rozlytrek or Lorbrena • TMB - prior to initiation of Keytruda (with FDA-approved test and for individuals diagnosed with metastatic or unresectable solid tumor that has progressed on prior therapy with no alternatives) Non-covers: • Multigene panels unless ALL genes in the panel meet disease- or gene-specific criteria • Dihydropyrimidine dehydrogenase (DPYD) testing, TYMS genes) (eg, TheraGuide 5-FU) to predict or monitor response to florouracil (Adrucil) or capecitabine (Xeloda) chemotherapy • UGT1A1 molecular assay to predict dosing of Camptosar (irinotecan) in the treatment of colorectal and lung cancers		81191, 81192, 81193, 81194 81275, 81276, 81445 81445 0037U 81455 81232, 81346 81350
	Liquid Biopsy (link)	Non-covers liquid biopsy (eg, cfDNA, ctDNA, CTC tests)	1/27/2022	
	Comprehensive Molecular Profiling for Hematologic Malignancies and Solid Tumors (link)	Covers comprehensive molecular profiling consisting of 50 or fewer genes Non-covers comprehensive molecular profiling consisting of 51 or greater genes	6/23/2022	81479, 81445, 0022U 81455
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions (link)	Covers: • FDA-approved FoundationOne Liquid Biopsy CDx is medically necessary for advanced or metastatic breast cancer, non-small cell lung cancer, mCRPC, or recurrent ovarian, fallopian tube, or primary peritoneal cancer when no CGP has been done for this primary tumor type, the person is not medically fit for an invasive biopsy, or tumor tissue testing is not possible, and treatment with an FDA-approved drug for this cancer is being considered. • FDA-approved Guardant360 CDx is medically necessary for recurrent, relapsed, refractory, metastatic, or advanced NCSLC that did not originate from the central nervous system	4/1/2023	0037U, 0239U, 0242U

	and NSCLC has been pathologically established, no CGP has been conducted for this primary tumor type, the patient is not physically suitable for invasive biopsy or tumor tissue testing, and an FDA-approved cancer medication is being evaluated. • FDA-approved FoundationOne CDx is medically necessary for unresectable or metastatic primary solid tumor, or immune checkpoint inhibitor therapy is being considered for treatment, there has been progression of disease and there are no satisfactory alternative treatment options, and CGP has been performed previously for this primary tumor type.	

Regional Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Blue Shield of California	Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer (link)	Covers: • Molecular analysis (individual genes) for advanced or metastatic NSCLC, large cell, squamous cell, and NSCLC not otherwise specified or if a targeted therapy dependent on genetic testing is being considered • Small panel testing may be considered as an alternative to individual testing when there is limited tissue available • Plasma tests for oncogenic driver variants when tissue is insufficient Covers most NCCN-recommended Category I, 2A, 2B biomarkers, except for HER2/ERBB2 and TMB: • EGFR (exons 18-21) to predict response to an EGFR TKI; EGFR T790M variant for targeted therapy with osimertinib • ALK rearrangements to predict response to ALK inhibitor therapy • BRAF V600E to predict response to BRAF or MEK inhibitor therapy • ROS1 rearrangements to predict response to ALK inhibitor therapy • KRAS testing to predict response to Lumakras • NTRK fusions to predict response to Rozlytrek or Vitrakvi • RET rearrangements to predict response to Gavreto or Retevmo • MET exon 14 skipping to predict response to Tabrecta • PD-L1 to predict response to Tecentriq, Opdivo in combination with Yervoy, or Keytruda Non-covers: • HER2 unless included in a panel approved for other indications • TMB	9/1/2022	81235, 88342, 88365 81210 81275, 81276 81191, 81192, 81193, 81194 81404, 81405, 81406
	Comprehensive Genomic Profiling for Selecting Targeted	Non-covers CGP • The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered investigational.	8/1/2022	0037U 0211U 0239U 0242U

	Cancer Therapies (link)	• The use of concurrent (simultaneous) solid tumor tissue and plasma based (circulating or cell free tumor DNA or liquid biopsy) testing is considered investigational.		0244U 0250U 0297U 0298U 0299U 0300U 0329U 0334U
Blue Cross Blue Shield of Massachusetts	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) (link)	Covers: Plasma-based CGP testing using Guardant360® for patients with Stage IIIB/IV NSCLC) when the following criteria have been met: <u>Diagnosis:</u> • When tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated), AND • When prior results for ALL of the following tests are not available: ○ EGFR single nucleotide variants and insertions and deletions (indels) ○ ALK and ROS1 rearrangements ○ PDL1 expression. <u>Progression:</u> • Patients progressing on or after chemotherapy or immunotherapy who have never been tested for EGFR SNVs and indels, and ALK and ROS1 rearrangements, and for whom tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP), OR • For patients progressing on EGFR tyrosine kinase inhibitors (TKIs). Non-covers: other plasma-based CGP tests	6/1/2020	0242U
	Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies (link)	Covers: • NGS cancer mutation panel including analyses of the genes for solid tumors for selecting targeted cancer treatment in Stage IIIB, IV or recurrent NSCLC • NGS cancer mutation panel to exclude the use of ineffective targeted therapies, to select alternative	10/1/2021	81445 81455 0037U

			treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.		
Centene Corporation (and health plan affiliates)	Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies (link)	Covers: • Comprehensive molecular profiling panels for solid tumors when meeting all of the following: A. The member/enrollee has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy), C. One of the following: 1. The member/enrollee has not had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis, 2. The member/enrollee HAS had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis and has a new primary cancer diagnosis for which this testing is being ordered. • Lung cancer focused molecular profiling panels when meeting all of the following: A. The member/enrollee has a diagnosis of any of the following: 1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, 2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, 3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, 4. Advanced (stage IIIb or higher) or metastatic NSCLC not otherwise specified, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy), C. One of the following:	2/1/2022	0037U, 0048U, 0211U, 81445, 81455 0022U 81445

	1. The member/enrollee has not had previous somatic testing via a multigene cancer panel for the same primary lung cancer diagnosis, 2. The member/enrollee HAS had previous somatic testing via a multigene cancer panel for a primary lung cancer diagnosis, and has a new primary lung cancer diagnosis for which this testing is being ordered. • Covers individual gene testing for select NCCN-recommended biomarkers: • Somatic BRAF variant analysis in solid tumors when the member/enrollee has a diagnosis of advanced or metastatic NSCLC • Somatic EGFR variant analysis in solid when the member/enrollee has a diagnosis of any of the following: 1. Advanced or metastatic lung adenocarcinoma, 2. Advanced or metastatic large cell lung carcinoma, 3. Advanced or metastatic squamous cell lung carcinoma, 4. Advanced or metastatic NSCLC not otherwise specified • Somatic KRAS variant analysis in solid tumors when the member/enrollee is undergoing workup for metastasis NSCLC	81210 81235 81275, 81276
	Covers: • Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) when meeting all of the following: A. The member/enrollee has a diagnosis of one of the following: 1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, 2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, 3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma,	0239U 0242U 81455

	4. Advanced (stage IIIb or higher) or metastatic NSCLC not otherwise specified, B. The member/enrollee is a candidate for an anti-cancer therapy, C. At least one of the following: 1. The member/enrollee is medically unfit for invasive tissue sampling (biopsy), 2. The member/enrollee does not have a biopsy-amenable lesion.	
•	Lung cancer focused panel tests via circulating tumor DNA when meeting all of the following: A. The member/enrollee has a diagnosis of any of the following: 1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, 2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, 3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, 4. Advanced (stage IIIb or higher) or metastatic NSCLC not otherwise specified NOS, B. The member/enrollee is a candidate for an anti-cancer therapy, C. At least one of the following: 1. The member/enrollee is medically unfit for invasive tissue sampling (biopsy), 2. The member/enrollee does not have a biopsy-amenable lesion.	0179U 81210 81235 81276
•	EGFR variant analysis via cell-free circulating tumor DNA when meeting all of the following: A. The member/enrollee has a diagnosis of any of the following: 1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, 2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, 3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma,	81235

		4. Advanced (stage IIIb or higher) or metastatic NSCLC not otherwise specified NOS, B. The testing is being done at time of diagnosis or at the time of progression, C. Treatment with an EGFR tyrosine kinase inhibitor therapy is being considered, D. At least one of the following: 1. The member/enrollee is medically unfit for invasive tissue sampling (biopsy), 2. The member/enrollee does not have a biopsy-amenable lesion.		
Excellus Blue Cross Blue Shield	Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers (link)	Covers gene mutational analysis of tumor tissue, to predict response to targeted therapies and to direct targeted therapy for individuals: A. Who have previous biopsy-confirmed, newly diagnosed advanced stage III or IV or metastatic NSCLC including adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified; or B. Who have advanced stage III or IV or metastatic NSCLC that is progressing on or after chemotherapy or immunotherapy, and who have never been tested for molecular and biomarker analysis; AND C. The results will be used to guide management of the patient For the following gene mutations (inclusive of all NCCN-recommended I, 2A, and 2B biomarkers except for TMB): • EGFR TKI-sensitizing variants (exon 19 deletion or a point mutation in exon 21 (L858R), (exon 20 or T790M) • ALK rearrangement • KRAS G12C • NTRK 1/2/3 gene fusion • ROS-1 gene rearrangement • BRAFV600E • MET ex 14 skipping • High-level MET amplification • RET rearrangements • ERBB2 (HER2)	12/16/2021	81235 81275 81191-81193 81210
	Circulating Tumor DNA for	Covers FDA-approved liquid biopsy assays (e.g., FoundationOne Liquid CDx, Guardant360 CDx) for advanced or metastatic NSCLC	11/18/2021	0239U, 0242U, 0326U

	Management of Cancer (Liquid Biopsy) (link)	patients (newly diagnosed and those progressing on or after chemotherapy or immunotherapy) who have never been tested for molecular and biomarker analysis.		
Paramount Health Plan	Liquid Biopsy (link)	Covers all NCCN-recommended biomarkers (Category I, 2A, 2B except TMB) 1. EGFR TKI-sensitizing variants (exon 19 deletion or a point mutation in exon 21 (L858R) 2. EGFR TKI-sensitizing variants (exon 20 or T790M) 3. anaplastic lymphoma kinase (ALK) rearrangement 4. KRAS G12C 5. NTRK 1/2/3 gene fusion 6. ROS-1 gene rearrangement 7. BRAFV600E 8. MET ex 14 skipping 9. High-level MET amplification 10. RET rearrangements 11. ERBBS (HER2) Covers liquid biopsies (PA required) for: • Initial Biomarker Determination - FDA approved companion diagnostic tests (i.e., cobas EGFR Mutation Test v2, FoundationOne Liquid CDx, or Guardant360 CDx) or a targeted multi-gene panel when tissue-based testing cannot be performed • At time of progression on an EGFR TKI therapy - Targeted cell-free testing (i.e., cobas EGFR Mutation Test v2) - Targeted cell-free testing is not medically necessary when progression is on Osimertinib	12/9/2021	81235 81275 81191-81193 81210
	Molecular Profiling (Somatic Testing) Panels for Solid Cancer Tumors and Hematologic Malignancies (link)	Covers genomic profiling of a solid tumor for advanced cancer pursuant to NGS NCD 90.2 (PA required)	11/8/2021	81445, 81455

Regence Blue Cross Blue Shield of Oregon	Targeted Genetic Testing for Selection of Therapy NSCLC (link)	Covers most NCCN-recommended Category I, 2A, and 2B biomarkers (except ERBB2/HER and TMB): • Testing for NTRK and RET gene fusions and ALK, KRAS, MET, PD-L1, and ROS1 variants for selection of therapy. • Testing for EGFR gene variants (in either tumor tissue or blood) to select patients with stage III or IV NSCLC for treatment with FDA approved TKIs • Tumor testing for the BRAF variants to select patients with stage III or IV NSCLC for treatment with BRAF- or MEK-inhibitor therapy. • The Oncomine™ Dx Target test to select patients with stage III or IV NSCLC for treatment with Iressa, Xalcori, or a combination of Tafinlar and Mekinist. Non-covers: • Testing for EGFR or BRAF variants for patients with NSCLC stage I or II and testing for purposes other than treatment selection.	3/1/2022	81191-81194, 81275, 81276, 81404, 81405 81235 81210 0022U

Medicare Administrative Contractor Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
All MACs	Next Generation Sequencing (link)	Covers NGS for somatic (acquired) cancer when: • Patient has: ○ either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and ○ not been previously tested with the same test using NGS for the same cancer genetic content, and ○ decided to seek further cancer treatment (e.g., therapeutic chemotherapy) • The diagnostic laboratory test using NGS must have: ○ FDA approval or clearance as a companion in vitro diagnostic; and, ○ an FDA-approved or -cleared indication for use in that patient's cancer; and, ○ results provided to the treating physician for management of the patient using a report template to specify treatment options	01/27/2020	0022U 0037U 0111U 0239U 0242U
MolDX	Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer (link)	Covers InvisionFirst® - Lung for patients with advanced NSCLC: 1) At diagnosis • When results for EGFR single nucleotide variants and insertions and deletions; rearrangements in ALK and ROS1; and SNVs for BRAF are not available AND when tissue-based CGP is infeasible [i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated], or 2) At progression • For patients progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR SNVs and indels; rearrangements in ALK and ROS1; and SNVs for BRAFs, and for whom tissue-based CGP is infeasible; or • For patients progressing on EGFR TKIs	6/16/2022	81479
	Plasma-Based Genomic Profiling in Solid Tumors (link)	Covers Guardant360® when certain criteria are met, notably when tissue-based CGP is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) or specifically in NSLC Tissue-based CGP has shown no actionable mutations. Covers other liquid biopsies for the same indications if they display similar performance in their intended used applications to Guardant360	10/13/2022	81479
NGS	Genomic Sequence Analysis Panels in	Covers genomic sequential analysis panel for the following:	4/1/2022	81445 0048U

	the Treatment of Solid Organ Neoplasms (link)	• Newly diagnosed patients with advanced (stage IIIB or IV) NSCLC, who are not treatable by resection or radiation with curative intent, and who are suitable candidates for therapy at the time of testing. • Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have not responded to at least one systemic therapy, or who have progressed following resection. The patient must be a candidate for treatment at the time of the testing. • Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have been resistant to at least one targeted therapy, are able to undergo tumor tissue biopsy for testing, and who are suitable candidates for additional treatment at the time of testing.		
	Molecular Pathology Procedures (link)	Covers most NCCN-recommended biomarkers, except for RET, HER2/ERBB2, and NTRK: • BRAF • EGFR for individuals undergoing treatment with EGFR TKI therapy (i.e, Tarceva, Iressa, or Gilotrif). • KRAS • MET • ROS1 • Targeted genomic sequence analysis panel, 5-50 genes • EML4-ALK with limitations as a tier 2 covered gene Non-covers RET	7/1/2020	81210 81235 81275,81276 81445,81450 81401 81404, 81405, 81406
Novitas	Biomarkers for Oncology (link)	Covers: • EGFR - PRED of anti-EGFR response • KRAS (12/13) - PRED of anti-EGFR resistance • KRAS codon 61 - PRED of anti-EGFR resistance • KRAS codon 146 - PRED of anti-EGFR resistance • BRAF - PROG + PRED for anti-RAF inhibitor • ThermoFisher Oncomine DX Target Test	12/13/2020	81235 81275 81276 81276 81210 0022U

Colorectal Cancer

Key Takeaways

All payers cover tissue-based testing of some NCCN-recommended biomarkers in CRC, however there is variation among payers. Over 2/3 of payers examined cover NRAS, KRAS, BRAF and NTRK. Fewer payers also cover HER2 (some restrict coverage to IHC testing) and MSI. Coverage for liquid biopsy is extremely limited as is coverage for TMB. Coverage has not changed significantly since our review in 2020.

Since our review in 2020, more payers provide coverage for targeted tissue-based multi-gene panels in CRC, though coverage remains limited. Less than 1/3 of payers examined cover targeted/small (< 50 genes) multi-gene panels. Expanded coverage is likely the result of the increase in the number of biomarkers with therapeutic associations (that are also supported by guidelines).

Extremely limited coverage (by one payer) of CGP in CRC. FoundationOne CDx has limited coverage (restricted to its FDA-approved indication for TMB by one national payer)**.** No other payers cover CGP assays in CRC.

Clinical Guidelines

NCCN Guidelines (Version 2.2022)[4] support biomarker testing of KRAS, NRAS, and BRAF mutations as well as HER2 amplifications in patients with metastatic CRC. Microsatellite instability (MSI) or mismatch repair (MMR) testing is also supported if not previously performed. The guidelines do not recommend a specific methodology but acknowledge that NGS panels have the advantage of being able to detect rare and actionable genetic alterations, like NTRK fusions. If the recommended biomarkers are tested individually, HER2 testing is not required for patients whose tumor is already known to have a KRAS/NRAS or BRAF mutation. The guidelines also limit testing for NTRK fusions to those patients with wild-type KRAS, NRAS, and BRAF. Based on the limited data in colorectal cancer patients, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial. With respect to PGx, the guidelines do not currently support universal pretreatment DPYD genotyping. For UGT1A1, the guidelines acknowledge the potential use case for testing vis-à-vis patients receiving Irinotecan. However, UGT1A1 is not currently supported given that guidelines for use of this test in clinical practice have not been established.

Gene	NCCN Category	Change Since 2020
KRAS/NRAS	2A	
BRAF V600E	2A	
MSI	2A	
HER2	2A	
NTRK 1/2/3	2A	
MLH1, MSH2, MSH6, PMS2 (MMR genes)	2A	Added

[4] https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

European Society for Medical Oncology (ESMO)[5] (2022) support biomarker testing of RAS, BRAF, and MSI in patients with metastatic CRC.

> RAS testing should be carried out on all patients at the time of diagnosis of mCRC. RAS testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab. RAS analysis should include at least KRAS exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and NRAS exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
>
> Tumor BRAF mutation status should be assessed alongside the assessment of tumor RAS mutational status for prognostic assessment (and/or potential selection for clinical trials).
>
> MSI testing in the metastatic disease setting can assist clinicians in genetic counselling. MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC.

Testing of other biomarkers including ALK and ROS1 gene fusions, mutations of PIK3CA and HER2 activating mutations is not currently recommended outside clinical trials.

Combined guideline from the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO (Version 2017)[6]

1. Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)

   Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate.

2a. BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification

   Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

2b. BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome

   Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

3. Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification

   Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

[5] https://www.annalsofoncology.org/article/S0923-7534(22)04192-8/fulltext
[6] http://ascopubs.org/doi/full/10.1200/JCO.2016.71.9807

National Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers (link)	Covers all NCCN-recommended biomarkers (Category 2A): • KRAS mutation analysis, with BRAF reflex testing, to predict non-response • NRAS • BRAF V600 mutation • Mismatch repair (MSI/dMMR) (MLH1, MSH2, MSH6) tumor testing • HER2 • NTRK for all solid tumors • Targeted solid organ genomic sequencing panel (5-50 genes) (includes KRAS, NRAS, BRAF) Non-covers: • NRAS mutation for selecting persons with metastatic colorectal cancer who may benefit from anti-VEGF antibody bevacizumab; to predict disease prognosis and select persons with melanoma who may benefit from tyrosine kinase inhibitor therapies, and other indications (experimental and investigational) • Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes	9/16/2022	81275, 81276 81311 81210 81292-81301 81194 81445 81455
	Pharmacogenetic and Pharmacodynamic Testing (link)	Covers all NCCN-recommended biomarkers (Category 2A): • BRAF and NRAS mutations (e.g., cobas KRAS Mutation Test; therascreen KRAS RGQ PCR Kit, Praxis Extended RAS Panel) • Praxis Extended RAS Panel • Microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) • ERBB2 (HER2) amplification testing • TMB (including FoundationOne CDx) for persons with solid tumors (TMB greater than or equal to 10 mutations per megabase) who may be appropriate for treatment with Keytruda Non-covers:	07/20/2020	81210, 81311, 81275, 81276 81301, 88341, 88342 0037U

		• Genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) • Dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase genetic polymorphisms to predict 5-fluorouracil toxicity • UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer) • Multi-gene pharmacogenetic panels (i.e., diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced metabolism and/or severe side effects of multiple classes of drugs)		
Anthem	Gene Mutation Testing for Cancer Susceptibility and Management (link)	Gene mutation testing to identify individuals who may benefit from the use of a targeted cancer therapy (associated therapeutic product [ATP]) is covered when all of the following criteria are met: • The individual is a candidate for targeted therapy using an ATP (for example, pharmaceutical or biologic treatment) and the mutation status of a specific gene is required prior to initiating treatment with the ATP; and • A specific mutation, or set of mutations, has been established in the scientific literature to identify those most likely to respond to a targeted therapy or ATP. Covers some, but not all, 2A NCCN-recommended biomarkers: • KRAS • NRAS • BRAF V600E • NTRK1, NTRK2, NTRK3	2/17/2022	81275 81311 81210 81191, 81192, 81193, 81194

	Circulating Tumor DNA Testing for Cancer (Liquid Biopsy) (link)	Non-covers the use of a circulating tumor DNA panel test for all indications.	11/11/2021	81479
	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling (link)	Covers molecular profiling for unresectable or metastatic solid tumors when all of the criteria below are met: • The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy • Individual has progressed following prior treatment • Individual has no satisfactory alternative treatment options	2/17/2022	0037U 0211U 0244U 0250U 0334U
Cigna	Molecular Diagnostic Testing for Hematology and Oncology Indications (link)	A tissue-based molecular tumor biomarker or broad molecular profile panel is considered medically necessary when ALL of the following criteria are met: • the individual is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site • results of testing will directly impact clinical decision making • the testing method is considered to be scientifically valid and proven to have clinical utility based on prospective evidence • no other tumor biomarker or broad molecular profile panel has been performed on this tumor sample for the same indication • ANY of the following: ○ identification of the specific biomarker has been validated by the NCCN Guidelines as a category 1, 2A or 2B recommendation for the individual's tumor type of disease ○ identification of the specific biomarker has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition being addressed ○ biomarker confirmation is required by an FDA-approved or cleared test prior to initiating therapy	8/15/2022	81275, 81276, 81311, 81210

		○ broad molecular profile panel testing for advanced, metastatic solid tumors Liquid biopsy is considered medically necessary when tissue testing is not available or contraindicated for EITHER of the following: • advanced or metastatic solid tumors • biomarker confirmation is required by an FDA-approved or cleared test prior to initiating therapy Targeted molecular testing for NTRK fusions (NTRK1/2/3 fusions) is considered medically necessary when the individual has a solid tumor known to respond to treatment with an FDA approved drug therapy targeting NTRK gene fusions.		81479 81191, 81192, 81193, 81194
Humana	Genetic Testing for Diagnosis and Monitoring of Cancer (link)	Covers: HER2/neu (ERBB2) testing when the following criteria are met: • HER2 testing performed by IHC; AND • Colorectal cancer that is metastatic disease Non-covers: • Targeted genomic sequence analysis panel (includes KRAS, NRAS, BRAF) • HER2-neu (ERBB2) testing performed by any method other than IHC, ISH or FISH	5/26/2022	88360, 88361
	Pharmacogenomics and Companion Diagnostics (link)	Covers RAS (KRAS and NRAS) mutation assay (eg, cobas KRAS mutation test) when the following criteria are met: • Individual diagnosed with CRC and testing performed prior to the initiation of anti-EGFR antibody therapies Erbitux or Vectibix Covers NTRK1, NTRK2 and NTRK3 gene testing when the following criteria are met: • Individual is diagnosed with advanced or metastatic solid tumor and testing performed prior to initiation of treatment with Vitrakvi; OR	8/25/2022	81191, 81192, 81193, 81194

		• Individual is diagnosed with metastatic solid tumor; at least 12 years of age or older; and testing performed prior to initiation of treatment with Rozlytrek		81445
		Non-covers: • Targeted genomic sequence analysis panel (includes KRAS, BRAF, NRAS) • Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes • Dihydropyrimidine dehydrogenase (DPYD) testing, TYMS genes) (eg, TheraGuide 5-FU) to predict or monitor response to florouracil (Adrucil) or capecitabine (Xeloda) chemotherapy • UGT1A1 molecular assay to predict dosing of Camptosar (irinotecan) in the treatment of colorectal and lung cancers		81455 81232, 81346 81350
	Liquid Biopsy (link)	Non-covers the use of a circulating tumor DNA panel test for all indications.	9/22/2022	
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions (link)	Covers: • FDA-approved FoundationOne Liquid Biopsy CDx is medically necessary for advanced or metastatic breast cancer, non-small cell lung cancer, mCRPC, or recurrent ovarian, fallopian tube, or primary peritoneal cancer when no CGP has been done for this primary tumor type, the person is not medically fit for an invasive biopsy, or tumor tissue testing is not possible, and treatment with an FDA-approved drug for this cancer is being considered. • FDA-approved Guardant360 CDx is medically necessary for recurrent, relapsed, refractory, metastatic, or advanced NCSLC that did not originate from the central nervous system and NSCLC has been pathologically established, no CGP has been conducted for this primary tumor type, the patient is not physically suitable for invasive biopsy or tumor tissue testing, and an FDA-approved cancer medication is being evaluated.	4/1/2023	0037U, 0239U, 0242U

	• FDA-approved FoundationOne CDx is medically necessary for unresectable or metastatic primary solid tumor, or immune checkpoint inhibitor therapy is being considered for treatment, there has been progression of disease and there are no satisfactory alternative treatment options, and CGP has been performed previously for this primary tumor type.	

Regional Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Blue Cross Blue Shield of Massachusetts	Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies (link)	Covers: • NGS cancer mutation panel including analyses of the genes for solid tumors for selecting targeted cancer treatment in Stage IV or recurrent or unresectable CRC • NGS cancer mutation panel to exclude the use of ineffective targeted therapies, to select alternative treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.	10/1/2021	81445 81455 0037U
Centene Corporation (and health plan affiliates)	Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies (link)	Covers: • Comprehensive molecular profiling panels for solid tumors when meeting all of the following: A. The member/enrollee has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy), C. One of the following: 1. The member/enrollee has not had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis, 2. The member/enrollee HAS had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis, and has a new primary cancer diagnosis for which this testing is being ordered. • Colorectal cancer focused molecular profiling panels in solid tumors when meeting all of the following: A. The member/enrollee has suspected or proven metastatic, synchronous or metachronous colorectal cancer, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy, C. One of the following:	2/1/2022	0037U, 0048U, 0211U, 81445, 81455 0111U 81301 81445

		1. The member/enrollee has not had previous somatic testing via a multigene cancer panel for the same primary diagnosis of colorectal cancer, 2. The member/enrollee HAS had previous somatic testing via a multigene cancer panel for a primary colorectal cancer diagnosis and has a new primary colorectal cancer diagnosis for which this testing is being ordered. • Somatic MSI analysis in colorectal cancer patients • Somatic NRAS variant analysis when the member/enrollee has suspected or proven metastatic, synchronous or metachronous colorectal cancer • Somatic MLH1 promoter methylation when meeting both of the following: o The member/enrollee has a diagnosis of colorectal cancer o Previous tumor testing showed loss of MLH1 on immunohistochemistry analysis. • Somatic KRAS variant analysis when the member/enrollee has suspected or proven metastatic, synchronous or metachronous colorectal cancer • Somatic BRAF variant when the member/enrollee has a diagnosis of suspected or proven metastatic, synchronous or metachronous colorectal cancer		81301 81311 81288 81275, 81276 81210
Excellus Blue Cross Blue Shield	Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers (link)	Covers gene mutational analysis of tumor tissue, to predict response to targeted therapies and to direct targeted therapy for individuals: A. In the treatment of metastatic Stage IV colorectal cancer; AND B. The results will be used to guide management of the patient For the following gene mutations (inclusive of some, but not all NCCN-recommended biomarkers. Notably MMR genes and MSI are non-covered): • KRAS • NRAS	12/16/2021	81275 81311 81210

		• BRAF • HER2 amplification • NTRK gene fusions		81191-81193
Florida Blue	KRAS, NRAS, and BRAF Variant Analysis (Including Liquid Biopsy & MicroRNA Expression Testing) in Metastatic Colorectal Cancer (link)	Covers: • KRAS to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumamab • NRAS to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab • BRAF for members with metastatic colorectal cancer who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions Non-covers: • Circulating tumor DNA testing (liquid biopsy)	7/1/2022	81275, 81276 81311 81210
Regence BlueCross BlueShield of Oregon	KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer (link)	Covers: KRAS, NRAS, and BRAF variant analysis for treatment selection in patients with metastatic, unresectable, or advanced colorectal cancer.	1/1/2022	81275, 81276, 81311, 81210
	Expanded Molecular Testing of Cancers to Select Targeted Therapies (link)	Covers tumor tissue testing using molecular panels, including expanded cancer panels, for selecting targeted cancer treatment for patients with advanced or metastatic (stage III or IV) non-squamous cell-type NSCLC	12/1/2022	

Medicare Administrative Contractor Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
All MACs	NCD: Next Generation Sequencing (NGS) (link)	Covers NGS for somatic (acquired) cancer when: • Patient has: ○ either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and ○ not been previously tested with the same test using NGS for the same cancer genetic content, and ○ decided to seek further cancer treatment (e.g., therapeutic chemotherapy) • The diagnostic laboratory test using NGS must have: ○ FDA approval or clearance as a companion in vitro diagnostic; and, ○ an FDA-approved or -cleared indication for use in that patient's cancer; and, results provided to the treating physician for management of the patient using a report template to specify treatment options	11/13/2020	0022U 0037U 0111U 0239U 0242U
MolDX	FDA-Approved KRAS Tests (link)	Covers: • KRAS, codon 12 and 13	3/3/2022	81275
	NRAS Genetic Testing (link)	Covers: • NRAS testing for metastatic colorectal cancer, per NCCN guidelines Non-covers: • All other NRAS testing	8/11/2022	81311
NGS	Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasm (link)	Covers genomic sequential analysis panel when the test is performed in a CLIA-certified laboratory qualified to perform high complexity testing, ordered by a treating physician, and the patient has: • metastatic CRC; and • is a candidate for intensive chemotherapy with an anti-EGFR biologic agent; and • has not had prior RAS/BRAF testing (except after initiation of anti-EGFR therapy with evidence of acquired resistance).	4/1/2022	81445
	Molecular Pathology Procedures (link)	Covers: • KRAS gene analysis, variants in codons 12 and 13 • KRAS gene analysis; additional variant(s) (e.g., codon 61, codon 146) • NRAS gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61) • BRAF gene analysis	7/1/2020	81275 81276 81311 81210
Novitas	Biomarkers for Oncology (link)	Covers: • KRAS (12/13)	12/13/2020	81275

	• KRAS codon 61	81276
	• KRAS codon 146	81276
	• NRAS	81311
	• BRAF	81210
	• MSI by PCR	81301

Breast Cancer

Key Takeaways

Established breast cancer biomarkers, including ER, PR, HER2 and PD-L1 remain widely covered. Immunohistochemistry (IHC) and/or in situ hybridization (ISH) are primarily used for these types of analyses.

Broad and consistent coverage across payers for tissue-based testing of NCCN-recommended biomarkers (all Category 1 and some Category 2A), including BRCA1, BRCA2, NTRK, and PIK3CA. Consistent with companion diagnostic paradigms, leveraging the association of these biomarkers with FDA-approved therapies to inform treatment decisions.

Since our review in 2020, coverage of tissue-based testing of individual biomarkers has increased, likely resulting from the preponderance of FDA-approved therapies with an associated genomic marker. Coverage of multi-gene panels remains limited with more positive coverage policy by the regional commercial payers compared to the national commercial payers.

Approximately 1/2 of payers examined provide coverage for TMB or MSI testing with restrictive coverage criteria. Policy language for both biomarkers state that the patient must have unresectable or metastatic breast cancer that has progressed following standard treatment and have no alternative treatment option. This language is consistent with NCCN guidelines.

Clinical Guidelines

NCCN Guidelines (Version 4.2022)[7] support biomarker testing of ER, PR, and HER2. The guidelines state that PIK3CA mutation testing (for HR-positive/HER2-negative patients) can be done on tumor tissue or liquid biopsy. Testing for NTRK fusions (by FISH, NGS, or PCR) and mismatch repair (by IHC or PCR), or TMB-H (by NGS) is recommended in certain circumstances (i.e., the patient has no satisfactory alternative treatment options and/or have progressed following prior treatment). With respect to PGx, the guidelines recommend against CYP2D6 testing for patients being considered for tamoxifen therapy based on limited evidence.

2020 Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update[8]

A multidisciplinary international Expert Panel updated the 2010 clinical practice guideline recommendations based on a systematic review of the medical literature. The guideline is aimed at improving the analytic performance and diagnostic accuracy of estrogen receptor (ER) and progesterone receptor (PgR) testing and their clinical utility as biomarkers for the management of women with primary breast cancer. The guideline focuses entirely on immunohistochemical testing.

[7] https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
[8] https://ascopubs.org/doi/full/10.1200/JCO.19.02309

2019 Update of the ASCO Endorsement of the Cancer Care Ontario Guideline Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer[9]

No biomarkers except for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were found to guide choices of specific treatment regimens. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

2018 HER2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update Summary[10]

The HER2 Testing Expert Panel updated the 2013 clinical practice guideline recommendations based on a systematic review of the medical literature. The guideline is intended to set standards to improve the performance and clinical utility of testing for HER2 as a predictive biomarker for potential responsiveness to therapies targeting the HER2 protein. HER2 gene amplification assessed by ISH and protein overexpression assessed by IHC remain the primary predictors of responsiveness to HER2-targeted therapies in breast cancer.

2009 ASCO Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction[11]Updates the 2002 ASCO guideline on pharmacologic interventions for breast cancer risk reduction. An expert panel reviewed the literature (randomized trials published since 2002) and developed updated consensus guidelines. Given the limited evidence, CYP2D6 testing is not recommended. Larger studies are needed to provide confirmation of the results in smaller studies.

[9] http://ascopubs.org/doi/full/10.1200/JCO.19.00948
[10] https://ascopubs.org/doi/full/10.1200/JOP.18.00206
[11] https://ascopubs.org/doi/10.1200/JCO.2008.20.5179?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

National Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers (link)	Covers all NCCN-recommended biomarkers (Category I, 2A, and 2B, except for TMB): • ER, PR • Mismatch repair (MSI/dMMR) (MLH1, MSH2, MSH6, PMS2) tumor testing (somatic mutations) • PIK3CA for breast cancer • NTRK for all solid tumors • uPA and PAI-1 to assess necessity of adjuvant chemotherapy in females or males with recently diagnosed breast tumors, where all of the following criteria are met: ○ Breast cancer is nonmetastatic (node negative); and ○ Breast tumor is estrogen receptor positive; and ○ Breast tumor is HER2 receptor negative; and ○ Adjuvant chemotherapy is not precluded due to any other factor (e.g., advanced age and/or significant co-morbidities); and ○ Member and physician (prior to testing) have discussed the potential results of the test and agree to use the results to guide therapy Non-covers: • Liquid biopsy for breast cancer	9/16/2022	81301 81309 81191-81194
	Pharmacogenetic and Pharmacodynamic Testing (link)	Covers: • BRCA testing for women with HER2-negative breast cancer who are being considered for Lynparza • ERBB2 amplification testing • PD-L1 expression for triple-negative breast cancer being considered for treatment with Tecentriq • PIK3CA mutation testing for persons with breast cancer being considered for treatment with Piqray • NTRK for solid tumors being treated with Larotrectinib	7/21/2022	81162, 81165, 81212, 81215, 81216, 81217 81309 81191-81194

		• MSI-H/dMMR for unresectable or metastatic solid tumors being considered for treatment with Keytruda Non-covers: • FoundationOne CDx for assessing candidacy of persons with breast cancer for treatment with Piqray • BRCA1 and BRCA2 full duplication/deletion analysis for breast cancer and PIK3CA for other indications • Genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) • Dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase genetic polymorphisms to predict 5-fluorouracil toxicity • UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer) • Multi-gene pharmacogenetic panels (i.e., diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced metabolism and/or severe side effects of multiple classes of drugs)		81301 0037U 81164 81232 81350
Anthem	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling (link)	Covers molecular profiling for unresectable or metastatic solid tumors when all of the criteria below are met: 1. The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy 2. Individual has progressed following prior treatment 3. Individual has no satisfactory alternative treatment options	9/28/2022	81445 0037U 0211U 0244U 0250U 0334U

	Circulating Tumor DNA Testing for Cancer (Liquid Biopsy) (link)	Non-covers circulating tumor DNA panel tests for all indications	9/28/2022	
	Gene Mutation Testing for Cancer Susceptibility and Management (link)	Covers gene mutation testing to guide targeted therapy for BRCA, PIK3CA, and NTRK if the following criteria are met: 1) Individual is a candidate for targeted therapy using an associated therapeutic product 2) A specific mutation, or set of mutations, has been established in the scientific literature to identify those most likely to respond to a targeted therapy or associated therapeutic product Covers liquid biopsy to test for PIK3CA when Piqray is being considered for targeted cancer therapy if criteria 1-2 above are met and when FFPE tissue is inadequate Non-covers: • Liquid biopsy to detect the recurrence of a solid tumor and for solid tumor cancer susceptibility	6/29/2022	81307, 81308, 81309, 81408, 0155U, 0177U, 81191, 81192, 81193, 81194
Cigna	Molecular Diagnostic Testing for Hematology and Oncology Indications (link)	Covers: • NTRK testing if the individual has a solid tumor known to respond to treatment with an FDA-approved drug • Liquid biopsy if tissue testing is not available Covers somatic testing for PIK3CA if the following criteria are met: 1) Post-menopausal female or male with advanced or metastatic, ER/PR positive and HER2 negative breast cancer 2) Patient has progressed on endocrine therapy Non-covers: • HER2 by FISH	8/15/2022	81191, 81192, 81193, 81194
Humana	Pharmacogenomics and Companion Diagnostics (link)	Covers all NCCN-recommended biomarkers (Category I, 2A, and 2B): • BRCA companion diagnostic test for individuals diagnosed with locally advanced or metastatic HER2-negative breast cancer and one of the following applies:	8/25/2022	0037U

		1) Testing is performed prior to initiation of treatment with Talzenna 2) Treated with prior chemotherapy and/or endocrine therapy AND testing is performed prior to initiation of treatment with Lynparza		81191, 81192, 81193, 81194
		• NTRK test (NTRK1, NTRK2, NTRK3 genes) for individuals diagnosed with advanced or metastatic solid tumor and one of the following applies: 1) Testing is performed prior to initiation of treatment with Vitrakvi 2) For adults 12+, testing is performed prior to initiation of treatment with Rozlytrek		
		• PD-L1 testing covered for individuals diagnosed with triple negative breast cancer and testing is performed prior to treatment with Keytruda		81309, 0155U
		• PIK3CA for individuals diagnosed with metastatic breast cancer or breast cancer that has advanced on an endocrine therapy AND testing is performed prior to treatment with Piqray and Faslodex		
		• TMB testing for individuals diagnosed with metastatic or unresectable solid tumor that has progressed on prior therapy with no alternatives AND testing performed prior to treatment with Keytruda		81455
		Non-covers:		
		• Multigene panels unless ALL genes in the panel meet disease- or gene-specific criteria		81232, 81346
		• Dihydropyrimidine dehydrogenase (DPYD) testing, TYMS genes) (eg, TheraGuide 5-FU) to predict or monitor response to florouracil (Adrucil) or capecitabine (Xeloda) chemotherapy		81350
		• UGT1A1 molecular assay to predict dosing of Camptosar (irinotecan) in the treatment of colorectal and lung cancers		
	Genetic Testing for Diagnosis and	Covers:	6/23/2022	
		• HER2/neu (ERBB2) testing if performed by IHC and for breast cancer that is newly diagnosed, nonmetastatic		88360, 88361, 0009U

	Monitoring of Cancer (link)	invasive or metastatic disease Non-covers: • Her2/neu (ERBB2) testing performed by any other method than IHC, ISH, or FISH		
	Liquid Biopsy (link)	Non-covers liquid biopsy for all indications	9/22/2022	
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions (link)	Covers: • FDA-approved FoundationOne Liquid Biopsy CDx is medically necessary for advanced or metastatic breast cancer, non-small cell lung cancer, mCRPC, or recurrent ovarian, fallopian tube, or primary peritoneal cancer when no CGP has been done for this primary tumor type, the person is not medically fit for an invasive biopsy, or tumor tissue testing is not possible, and treatment with an FDA-approved drug for this cancer is being considered. • FDA-approved Guardant360 CDx is medically necessary for recurrent, relapsed, refractory, metastatic, or advanced NCSLC that did not originate from the central nervous system and NSCLC has been pathologically established, no CGP has been conducted for this primary tumor type, the patient is not physically suitable for invasive biopsy or tumor tissue testing, and an FDA-approved cancer medication is being evaluated. • FDA-approved FoundationOne CDx is medically necessary for unresectable or metastatic primary solid tumor, or immune checkpoint inhibitor therapy is being considered for treatment, there has been progression of disease and there are no satisfactory alternative treatment options, and CGP has been performed previously for this primary tumor type.	4/1/2023	0037U, 0239U, 0242U

Regional Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Blue Shield of California	Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer (link)	Covers all NCCN-recommended biomarkers (Category I, 2A, 2B): • PIK3CA testing to predict treatment response to Piqray in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer • FoundationOne Liquid CDx to predict treatment response to Piqray in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer when there is insufficient tissue to be tested and an additional invasive procedure would be required otherwise • NTRK gene fusions to predict treatment response to Rozlytrek or Vitrakvi in patients with locally advanced or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option • PD-L1 testing to predict treatment response to Keytruda in patients with hormone receptor-negative/HER2-negative (triple negative) recurrent or metastatic breast cancer • MSI-H/dMMR testing to predict treatment response to Keytruda in patients with unresectable or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option • TMB to predict immunotherapy response in breast cancer patients may be medically necessary when all conventional therapies have failed and pembrolizumab testing is underway (Keytruda). Analysis of circulating tumor cells to select treatment	3/1/2023	81309 0037U 81191 81192 81193 81194 81301
Blue Cross Blue Shield of Massachusetts	Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies (link)	Covers: • NGS cancer mutation panel including analyses of the genes for solid tumors for selecting targeted cancer treatment in Stage IV or refractory or recurrent breast cancer	10/1/2021	81445 81455 0037U

		• NGS cancer mutation panel to exclude the use of ineffective targeted therapies, to select alternative treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.		
Centene Corporation (and health plan affiliates)	Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies (link)	Covers: • Comprehensive molecular profiling panels for solid tumors when meeting all of the following: A. The member/enrollee has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy), C. One of the following: 1. The member/enrollee has not had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis, 2. The member/enrollee HAS had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis and has a new primary cancer diagnosis for which this testing is being ordered. • MSI analysis in unresectable or metastatic breast cancer patients • Somatic PIK3CA variant analysis when the member/enrollee has recurrent or stage IV, HR positive, HER2 negative invasive breast cancer	2/1/2022	0037U, 0048U, 0211U, 81445, 81455 81301 81309 0155U 0177U
	Oncology Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) (link)	Covers PIK3CA variant analysis via circulating tumor DNA when the member/enrollee has recurrent or stage IV hormone receptor-positive/HER2-negative breast cancer		0177U 81309
Excellus Blue Cross Blue Shield	Molecular Testing of Tumor Tissue to Identify Targeted	Covers gene mutational analysis of tumor tissue, to predict response to targeted therapies and to direct targeted therapy for individuals:	12/16/2021	

	Therapies for Cancers (link)	A. Who have previous biopsy-confirmed, newly diagnosed advanced stage III or IV or metastatic cancer; or B. Advanced stage III or IV or metastatic cancer that is progressing on or after chemotherapy or immunotherapy, and who have never been tested for molecular and biomarker analysis; And all of the following: C. Testing is recommended (2A or 1) by the current NCCN Guidelines for the cancer indication; D. Testing should include only the number of genes necessary for therapeutic decision making; and E. The results will be used to guide management of the patient.	
Paramount Health Plan	Liquid Biopsy (link)	General coverage criteria: Cell-free/circulating tumor DNA (ctDNA or liquid biopsy) (e.g., Guardant 360, Foundation One Liquid CDx, Cobas, Genestrat, OncoBEAM) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique, a companion diagnostic assays to direct targeted drug therapy for individuals: • When the 'liquid biopsy' is not used in lieu of a histological tissue diagnosis; and • The Member has a diagnosis of cancer; and • Treatment with a medication for which there is a liquid biopsy-based FDA-approved companion diagnostic is being considered, and • Note: not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of the test prior to prescribing. Testing would not be considered medically necessary when prescribed for indications that do not require the companion diagnostic. • Whom the result will be used to guide management of the member; and • The test has received FDA approval for the specific tumor type or disease site; and	12/9/2021

	• The Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration; and • Repeat invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis <u>Advanced or Metastatic Breast Cancer</u> • Coverage Criteria indicated above has been met; and FoundationOne Liquid CDx is medically necessary if tumor is unavailable in individuals with breast cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic OR • therascreen PIK3CA testing is medically necessary using liquid biopsy if tumor is unavailable for advanced or metastatic breast cancer when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic	0037U 0155U

Medicare Administrative Contractor Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes

All MACs	Next Generation Sequencing (NGS) (link)	Covers NGS for somatic (acquired) cancer when:
		• Patient has:
		  ○ either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
		  ○ not been previously tested with the same test using NGS for the same cancer genetic content, and
		  ○ decided to seek further cancer treatment (e.g., therapeutic chemotherapy)
		• The diagnostic laboratory test using NGS must have:
		  ○ FDA approval or clearance as a companion in vitro diagnostic; and,
		  ○ an FDA-approved or -cleared indication for use in that patient's cancer; and, results provided to the treating physician for management of the patient using a report template to specify treatment options
			01/27/2020	0037U

NGS	Molecular Pathology Procedures (link)	Covers: • BRCA1 and BRCA2 Non-covers: • Targeted genomic sequence analysis panels for 5-50 genes • MSI testing	07/01/2020	81162, 81163, 81164, 81165, 81166, 81167 81445 81301
Novitas	BRCA1 and BRCA2 Genetic Testing (link)	Covers: • BRCA1 and BRCA2 testing for individuals with a personal history of breast, ovarian, pancreatic, or prostate cancer Non-covers: Testing of minors, individuals with no personal history of the above cancer types, and repeat testing prior to Lynparza therapy if the patient has already been tested	12/10/2020	Covers: 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81432, 81433

Prostate Cancer

Key Takeaways

Inconsistent coverage of liquid biopsy, including assessment of AR-V7, across payers. Minimal payer coverage of AR-V7 in later lines of therapy, consistent with guidelines. Coverage of large liquid biopsy panels (> 50 genes) is even more limited.

Companion diagnostic paradigm for BRCA testing in prostate cancer has expanded coverage for tissue-based testing. Over 2/3 of payers examined provide coverage for BRCA testing when the individual is a candidate for a PARP inhibitor. BRACAnalysis CDx and FoundationOne CDx are indicated for metastatic castration-resistant prostate cancer (mCRPC) patients who may benefit from treatment with Lynparza. Coverage of liquid biopsy testing, including FoundationOne Liquid CDx, which is indicated for mCRPC patients who may benefit from treatment with Rubraca or Lynparza remains limited.

Similarly, the companion diagnostic paradigm for homologous recombination repair (HRR) gene alterations in prostate cancer has resulted in widespread, consistent coverage across payers. However, the FDA-approved companion diagnostic test (i.e., BRACAnalysis CDx, FoundationOne CDx, FoundationOne Liquid CDx) may not always be covered.

Clinical Guidelines

NCCN Guidelines (Version 1.2023)[12] recommend tumor testing for alterations in homologous recombination DNA repair genes, such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12 in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer. Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC and may be considered in patients with regional or castration-sensitive metastatic prostate cancer. If MSI is performed, testing using an NGS assay validated for prostate cancer is preferred. Multigene molecular testing can be considered for patients with low-, intermediate-, and high-risk prostate cancer and life expectancy ≥10 years.

The guidelines also specify that TMB testing may be considered for patients with mCRPC to inform possible use of Keytruda in later lines of therapy. AR-V7 testing in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide mCRPC setting.

The guidelines acknowledge that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. The guidelines explicitly state that tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making.

[12] https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Gene	NCCN Category	Change Since 2020
Somatic: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L	2A	
AR-V7	2A	
MLH1, MSH2, MSH6, PMS2	2A	
MSI	2A	
KLK3	2A	Added

ASCO Guideline (2021). Molecular Biomarkers in Localized Prostate Cancer[13] recognizes that Oncotype Dx Prostate, Prolaris, Decipher, and ProMark may improve risk stratification when added to standard clinical parameters. However, the guideline recommends their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision. These assays are not recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes.

[13] http://ascopubs.org/doi/full/10.1200/JCO.2017.76.7293

National Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers (link)	Covers: • AR-V7 in mCRPC after progression on abiraterone or enzalutamide • Mismatch repair (MSI/dMMR) (MLH1, MSH2, MSH6, PMS2) tumor testing (somatic mutations) for prostate cancer • Targeted solid organ genomic sequencing panel (5-50 genes) Non-covers: • Large liquid biopsy panels (> 50 genes) (e.g., FoundationOne Liquid CDx)	9/16/2022	81479 81301, 81292, 81295, 81298, 81317 81445 0239U
	Pharmacogenetic and Pharmacodynamic Testing (link)	Covers: • BRCA testing for men with advanced, recurrent or metastatic prostate cancer who have been treated with one of the following: -Androgen-receptor directed therapy and are being considered for treatment with Lynparza -Androgen-receptor directed therapy and a taxane-based chemotherapy and are being considered for treatment with rucaparib • MSI-H and mismatch repair deficiency for unresectable or metastatic solid tumors being considered for treatment with Keytruda Non-covers: • FoundationOne Liquid CDx for persons with prostate cancer being considered for treatment with rucaparib • Genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450	7/21/2022	81162, 81163, 81165, 81212, 81215, 81216, 81217 81301 0239U

		system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) • Dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase genetic polymorphisms to predict 5-fluorouracil toxicity • UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer) • Multi-gene pharmacogenetic panels (i.e., diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced metabolism and/or severe side effects of multiple classes of drugs)		81232 81350
	BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy (link)	Covers: • BRCA testing for men with mCRPC who have been treated with one of the following: -Androgen receptor-directed therapy and are considering initiation of olaparib -Androgen receptor-directed therapy and a taxane-based chemotherapy and are considering initiation of rucaparib Non-covers: • BRCA testing to assess the risk of prostate cancer in men without breast cancer or for surveillance • FoundationOne Liquid CDx to assess the candidacy of persons with prostate cancer being considered for treatment with recaparib	8/16/2022	81162,81163, 81164, 81165, 81166, 81167
Anthem	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling (link)	Covers: • Testing for prostate cancer using gene panels if the following criteria are met: 1. The panel evaluates homologous recombination repair (HRR) gene alterations; and	9/28/2022	81445, 81479

		2. The individual is a candidate for treatment using a PARP inhibitor. • Molecular profiling for unresectable or metastatic solid tumors when all of the criteria below are met: 1. The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy; and 2. Individual has progressed following prior treatment; and 3. Individual has no satisfactory alternative treatment options.		
	Circulating Tumor DNA Testing for Cancer (Liquid Biopsy) (link)	Non-covers circulating tumor DNA panel tests for all indications	9/28/2022	
	Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer (link)	Non-covers the use of protein biomarker tests, including AR-V7, for the screening, detection, and management of prostate cancer	4/13/2022	
	Gene Mutation Testing for Cancer Susceptibility and Management (link)	Covers gene mutation testing to guide targeted therapy for homologous recombination repair gene alterations (e.g., ATM, BARD1, BRIP1, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L) when the following criteria are met: 1. Individual is a candidate for targeted therapy using a PARP inhibitor 2. A specific mutation, or set of mutations, has been established in the scientific literature to identify those most likely to respond to a targeted therapy or a PARP inhibitor	2/17/2022	81479, 81307, 81408
	BRCA Genetic Testing (link)	Covers genetic testing to detect BRCA (BRCA1 and/or BRCA2) mutations: • for individuals who meet one or more BRCA1 or BRCA2 testing criteria established by the NCCN; OR • for individuals who are a candidate for a PARP inhibitor; AND	2/17/2022	81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81479

		• when genetic counseling, which encompasses all of the following components, has been performed:
		  • Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
		  • Education about inheritance, genetic testing, disease management, prevention and resources; and
		  • Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
		  • Counseling for the psychological aspects of genetic testing.		

Cigna	Molecular Diagnostic Testing for Hematology and Oncology Indications (link)	Covers AR-V7 testing from circulating tumor cells for a male with mCRPC considering second line therapy when BOTH of the following criteria are met: 1. Progression on androgen receptor–signaling inhibitor therapy (i.e., Xtandi, Zytiga) 2. Nuclear expression of AR-V7 will be assessed to guide subsequent therapeutic decision making	8/15/2022	81479

Humana	Genetic Testing and Liquid Biopsy for Prostate Cancer (link)	Covers HRR germline and/or somatic tumor testing single gene or multi-gene panel (< 50 genes) that includes: ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, PALB2, RAD51D when the following criteria are met:
		• Testing performed prior to initiation of treatment with Rubraca; AND
		  • Progression of disease despite prior treatment with Yonsa; Zytiga, Xtandi, Erleada or Nubeqa and a taxane-based chemotherapy (eg, Taxotere); OR
		• Testing performed prior to initiation of treatment with Lynparza; AND
		  • Progression of disease despite prior treatment with abiraterone or enzalutamide
		
		Covers somatic tumor testing for MSI and dMMR by IHC if the following criteria are met:
			10/27/2022	

		• Metastatic or unresectable prostate cancer; AND • Progression of disease despite prior treatment; AND • Testing performed prior to initiation of treatment with Keytruda Covers TMB testing when the following criteria are met: • Metastatic or unresectable prostate cancer; AND • Progression of disease despite prior treatment and no alternative treatments available; AND • Testing performed with FDA-approved assay (eg, FoundationOne CDx) prior to initiation of treatment with Keytruda Non-covers: • Liquid biopsy, including AR-V7 variant testing		0037U
	Pharmacogenomics and Companion Diagnostics (link)	Covers: • NTRK test (NTRK1, NTRK2, NTRK3 genes) for individuals diagnosed with advanced or metastatic solid tumor and one of the following applies: 1) Testing is performed prior to initiation of treatment with Vitrakvi 2) For adults 12+, testing is performed prior to initiation of treatment with Rozlytrek • TMB testing for individuals diagnosed with metastatic or unresectable solid tumor that has progressed on prior therapy with no alternatives AND testing performed prior to treatment with Keytruda Non-covers: • Multigene panels unless ALL genes in the panel meet disease- or gene-specific criteria • Dihydropyrimidine dehydrogenase (DPYD) testing, TYMS genes) (eg, TheraGuide 5-FU) to predict or monitor response to florouracil (Adrucil) or capecitabine (Xeloda) chemotherapy	8/25/2022	81191, 81192, 81193, 81194 81455 81232, 81346 81350

		• UGT1A1 molecular assay to predict dosing of Camptosar (irinotecan) in the treatment of colorectal and lung cancers		
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions (link)	Covers: • FDA-approved FoundationOne Liquid Biopsy CDx is medically necessary for advanced or metastatic breast cancer, non-small cell lung cancer, mCRPC, or recurrent ovarian, fallopian tube, or primary peritoneal cancer when no CGP has been done for this primary tumor type, the person is not medically fit for an invasive biopsy, or tumor tissue testing is not possible, and treatment with an FDA-approved drug for this cancer is being considered. • FDA-approved Guardant360 CDx is medically necessary for recurrent, relapsed, refractory, metastatic, or advanced NCSLC that did not originate from the central nervous system and NSCLC has been pathologically established, no CGP has been conducted for this primary tumor type, the patient is not physically suitable for invasive biopsy or tumor tissue testing, and an FDA-approved cancer medication is being evaluated. • FDA-approved FoundationOne CDx is medically necessary for unresectable or metastatic primary solid tumor, or immune checkpoint inhibitor therapy is being considered for treatment, there has been progression of disease and there are no satisfactory alternative treatment options, and CGP has been performed previously for this primary tumor type.	4/1/2023	0037U, 0239U, 0242U

Regional Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Blue Shield of California	Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) (link)	Full sequence and duplication/deletion analysis genetic testing for BRCA1, BRCA2, and PALB2 gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered medically necessary under any of the following circumstances: • Diagnosed at any age with one or more of the following: a. One or more close blood relative with one or more of the following: i. Breast cancer diagnosed on or before 50 years of age ii. Ovarian carcinoma iii. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group prostate cancer iv. Pancreatic cancer • Personal history of one or more of the following at any age: 1. Male breast cancer 2. Epithelial ovarian carcinoma 3. Exocrine pancreatic cancer 4. Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer 5. Prostate cancer with one or more of the following: a. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer at age 50 years or younger b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age c. Ashkenazi Jewish ancestry 6. Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline.	12/1/2022	81432

Blue Cross Blue Shield of Massachusetts	Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies (link)	Covers: • NGS cancer mutation panel including analyses of the genes for solid tumors for selecting targeted cancer treatment in mCRPC • NGS cancer mutation panel to exclude the use of ineffective targeted therapies, to select alternative treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.	10/1/2021	81445 81455 0037U
Centene Corporation (and health plan affiliates)	Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies (link)	Covers: • Comprehensive molecular profiling panels for solid tumors when meeting all of the following: A. The member/enrollee has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, B. The member/enrollee is seeking further cancer treatment (e.g., therapeutic chemotherapy), C. One of the following: 1. The member/enrollee has not had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis, 2. The member/enrollee HAS had previous comprehensive solid tumor molecular profiling for the primary cancer diagnosis and has a new primary cancer diagnosis for which this testing is being ordered. • Somatic BRCA1 and BRCA2 variant analysis in metastatic prostate cancer	2/1/2022	0037U, 0048U, 0211U, 81445, 81455 81162, 81163, 81164, 81165, 81166, 81167, 81216
	Oncology Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) (link)	Covers: • Comprehensive molecular profiling panel tests via circulating tumor DNA (liquid biopsy) for patients diagnosed with metastatic prostate cancer • AR-V7 androgen receptor splice variant analysis in circulating tumor cells for patients with mCRPC		0239U, 0242U, 81455 81479

Excellus Blue Cross Blue Shield	Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers (link)	Covers gene mutational analysis of tumor tissue, to predict response to targeted therapies and to direct targeted therapy for individuals: A. Who have previous biopsy-confirmed, newly diagnosed advanced stage III or IV or metastatic cancer; or B. Advanced stage III or IV or metastatic cancer that is progressing on or after chemotherapy or immunotherapy, and who have never been tested for molecular and biomarker analysis; And all of the following: C. Testing is recommended (2A or 1) by the current NCCN Guidelines for the cancer indication; D. Testing should include only the number of genes necessary for therapeutic decision making; and E. The results will be used to guide management of the patient.	12/16/2021
Paramount Health Plan	Liquid Biopsy (link)	General coverage criteria: Cell-free/circulating tumor DNA (ctDNA or liquid biopsy) (e.g., Guardant 360, Foundation One Liquid CDx, Cobas, Genestrat, OncoBEAM) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique, a companion diagnostic assays to direct targeted drug therapy for individuals: • When the 'liquid biopsy' is not used in lieu of a histological tissue diagnosis; and • The Member has a diagnosis of cancer; and • Treatment with a medication for which there is a liquid biopsy-based FDA-approved companion diagnostic is being considered, and • Note: not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of the test prior to prescribing. Testing would not be considered medically necessary when prescribed for indications that do not require the companion diagnostic. • Whom the result will be used to guide management of the member; and	12/9/2021

	• The test has received FDA approval for the specific tumor type or disease site; and • The Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration; and • Repeat invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis <u>Metastatic Castrate-Resistant Prostate Cancer</u> • Coverage Criteria indicated above has been met; and FoundationOne Liquid CDx is medically necessary in men with mCRPC when the individual meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic	0037U

Medicare Administrative Contractor Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
All MACs	Next Generation Sequencing (NGS) (link)	Covers NGS for somatic (acquired) cancer when: • Patient has: ○ either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and ○ not been previously tested with the same test using NGS for the same cancer genetic content, and ○ decided to seek further cancer treatment (e.g., therapeutic chemotherapy) • The diagnostic laboratory test using NGS must have: ○ FDA approval or clearance as a companion in vitro diagnostic; and, ○ an FDA-approved or -cleared indication for use in that patient's cancer; and, results provided to the treating physician for management of the patient using a report template to specify treatment options	01/27/2020	0037U
MolDX	Phenotypic Biomarker Detection from Circulating Tumor Cells (link)	Covers Androgen Receptor Variant (AR-V7) Protein Test in CTCs if the following criteria are met: -Cancer with established biomarker testing, as recommended by society or national guidelines -Assay that detect biomarkers from CTCs met certain criteria	7/21/2022	81479
NGS	Molecular Pathology Procedures (link)	Covers: • BRCA1 and BRCA2 • PCA3 Non-covers: • Targeted genomic sequence analysis panels for 5-50 genes • MSI testing • MLH1	7/1/2020	81162, 81163, 81164, 81165, 81166, 81167 81313 81445 81301
Novitas	Biomarkers for Oncology (link)	Covers: • Progensa PCA3 Assay • PTEN – PROG and THER • RB1 – DX and PROG • TP53 - PROG	12/13/2020	 81313 81321, 81322, 81323 81479

				81351, 81352, 81353
	BRCA1 and BRCA2 Genetic Testing (link)	Covers: • BRCA1 and BRCA2 testing for individuals with a personal history of breast, ovarian, pancreatic, or prostate cancer Non-covers: • Testing of minors, individuals with no personal history of the above cancer types, and repeat testing prior to Lynparza therapy if the patient has already been tested	12/10/2020	81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81432, 81433

Pharmacogenomic Testing

Key Takeaways

Inconsistent coverage of oncology biomarkers for pharmacogenomic (PGx) testing across payers. A potential lack of clarity regarding the evidence threshold needed for clinical application of PGx testing may be resulting in coverage inconsistencies across payers. However, payers generally acknowledge the importance of the FDA Table of Pharmacogenetic Associations and CPIC guidelines for determining clinically actionable gene-drug interactions.

Extremely limited coverage of targeted multi-gene panels for pharmacogenomic genotyping. Payer coverage criteria varies significantly – some payers require that each included target on the panel must meet the criteria of actionable gene-drug interactions whereas other payers require only that more than a single gene meet the criteria of actionable gene-drug interactions.

Coverage of TPMT testing when performed prior to the initiation of thiopurine medication therapy is covered by approximately 1/2 of payers examined. Some payers further limit TPMT testing to when the results of phenotype testing is indeterminate. Approximately 1/3 of payers examined cover NUDT15 testing.

Only one payer of those examined covers DPYD variant analysis to determine drug metabolizer status for treatment with any 5-FU containing therapy.

Widespread non-coverage of CYP2D6 variant analysis to determine drug metabolizer status for managing treatment with tamoxifen for women at high risk for or with breast cancer. This is consistent with a recommendation against CYP2D6 testing in the breast cancer NCCN guidelines. The most well-established coverage is for CYP2C19 and CYP2D6. Notably, the coverage criteria are restricted to variant analysis to determine drug metabolizer status for Plavix (CYP2C19) and for treatment of Gaucher disease and Huntington's disease (CYP2D6)

Widespread non-coverage of UGT1A1 via molecular assay to predict dosing of irinotecan in the treatment of colorectal and lung cancers. This is consistent with language in the colon cancer NCCN guidelines.

Clinical Guidelines

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines[14]

CPIC maintains guidelines designed to assist clinicians with understanding how available PGx test results could be used to optimize drug therapy, rather than to provide guidance as to whether a genetic test should be ordered for a particular patient.

CPIC guidelines adhere to a standard format and include a standard system for grading levels of evidence linking genotypes to phenotypes, assigning phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and assigning strength to each prescribing recommendation.

[14] https://cpicpgx.org/guidelines/

Additionally, guidelines are given rankings or "Current CPIC Levels"[15], which are based upon prescribing actionability, severity of clinical consequences (i.e., adverse effects, lack of clinical response, etc.) without PGx testing, mention of genetic or PGx testing in drug labeling, and recommendations from specialty societies, among other criteria.

CPIC Level Definitions for Genes and Drugs

CPIC Level	Clinical Context	Level of Evidence	Strength of Recommendation
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended

FDA Table of Pharmacogenetic Associations (Last Updated 10/26/2022)[16]

For the pharmacogenetic associations listed in the table below, the FDA has evaluated and believes there is sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes (such as affected subgroup), are likely to have altered drug

[15] https://cpicpgx.org/prioritization-of-cpic-guidelines/
[16] https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events.

The table is not intended to make an assessment on the safe and effective use of, or regulatory requirements for, tests that detect variants in the referenced genes, or to provide comprehensive information on the described gene-drug interactions.

ADVI has only included information regarding specific genes of interest in oncology.

Gene	Generic Name	Trade Name(s)	Intended use for Drug(s)	Guidance
CYP2D6	gefitinib, tamoxifen	Iressa, Soltamox, Nolvadex	Antineoplastic	CPIC/FDA
DPYD	capecitabine, fluorouracil	Xeloda, Adrucil, Efudex, Fluoroplex, Tolak	Antineoplastic	CPIC/FDA
NUDT15	azathioprine, mercaptopurine, thioguanine	Azasan, Purixan, Tabloid	Antineoplastic	CPIC/FDA
TPMT	azathioprine, mercaptopurine, thioguanine	Azasan, Purixan, Tabloid	Antineoplastic	CPIC/FDA
UGT1A1	belinostat, irinotecan, nilotinib, pazopanib, Sacituzumab Govitecan - hziy	Beleodaq, Camptosar, Tasigna, Votrient, Trodelvy	Antineoplastic	FDA

Acute Lymphoblastic Leukemia NCCN Guidelines (Version 1.2022)[17] recommend consideration of testing for TPMT and NUDT15, especially for patients of East Asian origin. The guidelines also recommend consideration of testing for TPMT for patients receiving 6-mercaptopurine (6-MP), particularly those patients who develop severe neutropenia after starting 6-MP.

Breast Cancer NCCN Guidelines (Version 4.2022) recommend against CYP2D6 testing for patients being considered for tamoxifen therapy based on limited evidence.

Colon Cancer NCCN Guidelines (Version 2.2022) do not currently support universal pretreatment DPYD genotyping. For UGT1A1, the guidelines acknowledge the potential use case for testing vis-à-vis patients receiving Irinotecan. However, UGT1A1 is not currently supported given that guidelines for use of this test in clinical practice have not been established.

NSCLC NCCN Guidelines (Version 6.2022) do not include mention or recommendation for testing (e.g., DPYD).

[17] https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

National Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Pharmacogenetic and Pharmacodynamic Testing (link)	Non-covers: • Genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, **tamoxifen**, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) • DPYD and TYMS genetic polymorphisms to predict 5-fluorouracil toxicity • UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer or other types of cancer (e.g., non-small-cell lung cancer) • Multi-gene pharmacogenetic panels (i.e., diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced metabolism and/or severe side effects of multiple classes of drugs)	7/21/2022	81232 81350
	Inflammatory Bowel Disease: Serologic Markers and Pharmacogenomic and Metabolic Assessment of Thiopurine Therapy (link)	Covers: • TPMT gene mutation or TPMT phenotypic assays (e.g., Prometheus TPMT Genetics, Prometheus TPMT Enzyme) prior to initiation of 6-mercaptopurine or azathioprine therapy. Only 1 genotypic or phenotypic assay of TPMT activity is necessary per member per lifetime. • NUDT15 gene analysis to identify member at risk of thiopurine-induced toxicity prior to initiation of thiopurine therapy (i.e. azathioprine, mercaptopurine, or thioguanine)	4/8/2022	81335, 0034U, 0169U
Anthem	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling (link)	Covers: • Genotype testing for individual genetic polymorphisms to determine TPMT genotype prior to the initiation of thiopurine medication when the results of phenotype testing is indeterminate	10/5/2022	81225

		Non-covers: • Genotype testing for individual genetic polymorphisms to determine drug-metabolizer status when criteria or circumstances detailed in the policy are not met		81226 81227 81335
	Genotype Testing for Individual Genetic Polymorphisms to Determine Drug-Metabolizer Status (link)	Covers: • Genotype testing for individual genetic polymorphisms to determine TPMT prior to the initiation of thiopurine medication when the results of phenotype testing is indeterminate Non-covers: • DPYD • UGT1A1	8/11/2022	81335

Cigna	Pharmacogenetic Testing for Non-Cancer Indications (link)	Covers pharmacogenetic testing (e. g., genotyping, mutation analysis) when ALL of the following criteria are met (this list may not be all inclusive):
		• The individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation
		• The results of the pharmacogenetic test will directly impact clinical decision-making
		• The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene mutation
		• EITHER of the following:
		  ○ Identification of the specific gene or biomarker for use with a specific drug target has been demonstrated to improve clinical outcomes for the individual's condition being addressed
		  ○ Identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with drug target as noted within the FDA-approved prescribing label
			1/15/2022	81226, 81247, 81400, 81401, 81405, 0070U, 81227

		Non-covers: • Pharmacogenetic screening in the general population		
Humana	Pharmacogenomics – Noncancer Indications (link)	Covers: • NUDT15 and/or TPMT testing when performed prior to the initiation of thiopurine medication therapy (eg, azathioprine, mercaptopurine)	4/28/2022	81306, 81335, 0034U, 0169U
	Pharmacogenomics and Companion Diagnostics (link)	Non-covers: • DPYD testing, TYMS genes (eg, TheraGuide 5-FU) to predict or monitor response to florouracil (Adrucil) or capecitabine (Xeloda) chemotherapy • UGT1A1 molecular assay to predict dosing of Camptosar (irinotecan) in the treatment of colorectal and lung cancers	8/25/2022	81232, 81346 81350
UHC	Pharmacogenetic Testing (link)	Covers: • Pharmacogenetic multi-gene panels to guide therapy decisions for antidepressant and antipsychotic medications when all the following criteria are met: - The individual has a diagnosis of major depressive disorder or generalized anxiety disorder; and - The individual has failed at least one prior medication to treat their condition - The multi-gene panel has no more than 15 relevant genes Non-covers: • Pharmacogenetic multi-gene panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.	10/1/2022	

Regional Commercial Payer Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Blue Shield of California	Cytochrome P450 Genotype-Guided Treatment Strategy (link)	Non-covers genetic testing panels that include multiple CYP450 variants	8/1/2022	
	Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer (link)	Non-covers testing for genetic variants in DPYD or TYMS genes to guide 5-fluorouracil dosing and/or treatment choice in patients with cancer	5/1/2022	81232 81346
	Genotype-Guided Tamoxifen Treatment (link)	Non-covers genotyping to determine CYP2D6 variants for the purpose of managing treatment with tamoxifen for individuals at high risk for or with breast cancer	10/1/2022	81226
Blue Cross Blue Shield of Massachusetts	AIM Clinical Appropriateness Guidelines for Pharmacogenomic Testing (link)	Pharmacogenetic testing of common variants associated with drug metabolism is medically necessary when the following criteria are met: • The individual is a candidate for a targeted drug therapy associated with a specific genotype • The results of the pharmacogenetic test will directly impact clinical decision-making and clinical outcome for the individual • Published, peer-reviewed studies have proven that identifying the specific genetic variant improves clinical outcomes • Identification of the genetic variant is required or recommended in a specific population prior to initiating therapy with the target drug as noted by the FDA-approved prescribing label Multi-gene pharmacogenomic genotyping assays in which each included target does not meet the above criteria are not covered (i.e., GeneSight)	3/6/2022	81225, 81226, 81227, 81231, 81306, 81335, 81350, 81355, 81404, 0030U, 0034U, 0070U, 0169U
Centene Corporation (and health plan affiliates)	Genetic Testing Pharmacogenetics (link)	Covers: • DPYD variant analysis to determine drug metabolizer status when the member/enrollee		81232

		being considered for treatment with any 5-FU containing therapy* (e.g., Fluorouracil®, Xeloda®). *Commonly prescribed for individuals diagnosed with colorectal, breast and aerodigestive tract tumors • TMPT and NUDT15 variant analysis to determine drug metabolizer status when meeting either of the following: A. The member/enrollee is beginning therapy with azathioprine* (e.g. Imuran and Azasan), mercaptopurine* (e.g. Purinethol® and Purixan®), or thioguanine* (e.g. Tabloid®), B. The member/enrollee is on thiopurine therapy and has had abnormal complete blood count results that do not respond to dose reduction. *Commonly prescribed for patients with autoimmune disorders (e.g. inflammatory bowel disease, Crohn's disease, rheumatoid arthritis) and for treatment of hematologic malignancies (e.g., leukemia and lymphoma) • UGT1A1 variant analysis to determine drug metabolizer status when meeting either of the following: A. The member/enrollee is beginning irinotecan therapy (e.g., Onivyde®, Camptosar®) for elevated serum bilirubin or Gilbert syndrome, B. The member/enrollee is beginning therapy with atazanavir (e.g. Reyataz®). Non-covers: • CYP2D6 variant analysis for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer	81306, 81335, 0034U, 0169U 81350
Excellus Blue Cross Blue Shield	Genotyping or Phenotyping for Thiopurine Methyltransferase (TPMT) for Patients	Covers genotyping or phenotyping for TPMT mutations prior to initiation of azathioprine (AZA) or 6-mercaptopurine (6-MP) therapy, or when standard dosing of AZA/6-MP fails to produce a therapeutic response	1/20/2022	

	Treated with Azathioprine (6-MP) (link)			

Paramount Health Plan	CYP2C19 & CYP2D6 Pharmacogenetic Testing (link)	Non-covers:
		• CYP2C19 and CYP2D6 genotyping for:
		  ○ General population screening
		  ○ Antidepressants other than those listed above
		  ○ Antipsychotics
		  ○ Antiepileptics
		  ○ Donepezil or Galantamine for Alzheimer's disease
		  ○ Tamoxifen
		  ○ Warfarin
			5/24/2018	

	Genetic Testing (link)	Covers pursuant to prior authorization: • NUDT15 gene analysis requires PA • TPMT gene analysis requires PA Non-covers: • DPYD genotyping • TPMT and NUDT15 panels	10/18/2022	81306 81335 81232 0034U, 0169U
	UGT1A1 Targeted Mutation Analysis for Irinotecan Response (link)	Non-covers UGT1A1 genotyping to determine genetic polymorphisms	7/26/2018	81350

Medicare Administrative Contractor Policies

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
MolDX	MolDX: Pharmacogenomics Testing (link)	The clinical record must clearly show the use of or intent to prescribe a drug that has known drug-gene interactions that require a PGx test to be ordered to define the safe use of that drug in that patient. In such cases, MolDX covers: • PGx testing in limited circumstances as an adjunctive personalized medical decision-making tool once a treating clinician has narrowed treatment possibilities to specific medications under consideration for use, or is already using a specified medication, based on other clinical considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgment, clinical science and basic science pertinent to the drug, and the patient's preferences and values. • A multi-gene panel when more than one single gene on that panel would be considered reasonable and necessary for safe use of the medication in question or if multiple drugs are being considered (each fulfilling the criteria of actionable gene-drug interactions identified above) that have different relevant genes. ○ If two or more single genes are tested, rather than a multi-gene panel, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered. Non-covers: • A multi-gene panel when only a single gene on the panel is considered reasonable and necessary. • Genes not identified as having actionable use are not considered reasonable and necessary.	08/17/2020	81220, 81225, 81226, 81227, 81231, 81232, 81247, 81283, 81306, 81328, 81335, 81350, 81355, 81406, 81479, 0029U, 0030U, 0034U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0286U, 0345U

		• The algorithms employed in combinatorial testing are also not currently considered reasonable and necessary components of multi-gene testing.		
Novitas/First Coast	Pharmacogenomics Testing (link)	Pharmacogenetics testing will be considered medically reasonable and necessary if: • The patient has a condition where clinical evaluation has determined the need for a medication that has a known gene-drug interaction(s) for which the test results would directly impact the drug management of the patient's condition; AND • The test meets evidence standards for genetic testing as evaluated by a scientific, transparent, peer-reviewed process and determined to demonstrate actionability in clinical decision making by CPIC guideline level A or B1; or is listed in the FDA table of known gene-drug interactions where data support therapeutic recommendations or a potential impact on safety or response or the FDA label	12/12/2021	81220, 81225, 81226, 81227, 81231, 81232, 81247, 81283, 81306, 81328, 81335, 81350, 81355, 81406, 81479, 0029U, 0030U, 0034U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0286U, 0345U

Appendix A: CPT Codes

CPT Code	Descriptor	2023 CLFS Payment Rate
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)	$1,824.88
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	$468.00
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)	$584.23
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	$282.88
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)	$301.35
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)	$282.88
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)	$175.40
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants	$440.00
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant	$375.25
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	$185.12
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant	$375.25
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)	$556.60
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)	$450.91
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)	$174.81
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)	$324.58
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)	$193.25

81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)	$193.25
81301	Microsatellite instability analysis (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed	$348.56
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)	$291.36
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence	$676.50
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)	$274.83
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)	$295.79
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)	$255.05
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)	$174.81
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)	$174.81
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (eg, *28, *36, *37)	$234.00
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) EML4/ALK (inv(2)) (eg, non-small cell lung cancer), translocation or inversion analysis	$137.00
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)	$274.83
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) - KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence - RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)	$301.35

81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) - BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence - RET (ret proto-oncogene) (eg, Hirschsprung disease), full gene sequence	$282.88
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) - ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia), full gene sequence	$2,000.00
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	$597.91
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis	$2,919.60
81479	Unlisted molecular pathology procedure	N/A
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure	$89.63
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure	$102.43
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual	$122.51
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology	$122.16
88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each multiplex probe stain procedure	$411.81
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider Oncomine Dx Target Test, Thermo Fisher Scientific	$1,950.00

0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Mayo Clinic	$466.17
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationOne CDx, Foundation Medicine, Inc.	$3,500.00
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) MSK-IMPACT, Memorial Sloan Kettering Cancer Center	$2,919.60
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis, utilizing formalin-fixed paraffin embedded tissue Praxis Extended RAS Panel, Illumina	$682.29
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status therascreen PIK3CA RGQ PCR Kit, QIAGEN	$274.83
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants NT (NUDT15 and TPMT) genotyping panel, RPRD Diagnostics	$466.17
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status therascreen PIK3CA RGQ PCR Kit, QIAGEN	$274.83
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s) Resolution ctDx Lung, Resolution Bioscience	$1,943.21
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association	$8,455.00

	MI Cancer Seek; Caris Life Sciences	
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations FoundationOne® Liquid CDx, Foundation Medicine Inc	$3,500.00
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements Guardant360® CDx, Guardant Health Inc	$5,000.00