

Expanded Molecular Testing of Cancers to Select Targeted Therapies

Effective: September 1, 2019

Next Review: April 2020

Last Review: August 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A growing number of cancer therapies target specific genetic variants in tumors. Expanded molecular panel tests are used to test tumor tissue for a large number of gene variants, and they are generally not tailored to a specific type of cancer. Tumor profiling with such panels is proposed to aid in treatment selection and to help patients find appropriate clinical trials for experimental therapy.

MEDICAL POLICY CRITERIA

Note: This policy does not address targeted variant testing, gene expression testing, or testing of circulating (cell-free) tumor DNA or circulating tumor cells (see Cross References section).

- I. Tumor tissue testing using molecular panels, including expanded cancer panels, for selecting targeted cancer treatment may be considered **medically necessary** for patients with advanced or metastatic (stage III or IV) non-squamous cell-type non-small cell lung cancer (NSCLC).

- II. The use of expanded cancer molecular panels for selecting targeted cancer treatment is considered **investigational** for all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Providers should be aware of the possibility of false positive and false negative results from tumor profiling tests. False positives may lead to a patient receiving an ineffective therapy with the risk of drug-related adverse events. Tests that include normal germline tissue testing for comparison may have a lower incidence of false positives compared with tumor-only tests. It is highly recommended that providers review the test's performance characteristics and discuss this information with patients prior to requesting.

EXAMPLES OF EXPANDED TUMOR PANEL TESTS

Expanded tumor panel tests that may be considered medically necessary when policy criteria are met include but are not limited to:

- Caris Molecular Intelligence Profile Panel
- FoundationOne® CDx
- GeneTrails® Comprehensive Solid Tumor Panel
- Illumina TruSeq™
- Ion AmpliSeq™
- MSK-IMPACT™
- NeoTYPE® Lung Tumor Profile
- OnkoMatch™
- Oncomine Comprehensive Assay
- Tempus xT
- UW-OncoPlex-Cancer Gene Panel

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
 - History and physical exam
 - Conventional testing and outcomes
 - Conservative treatment provided, if any

CROSS REFERENCES

1. [KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer](#), Genetic Testing, Policy No. 13
2. [PathFinderTG® Molecular Testing](#), Genetic Testing, Policy No. 16
3. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
4. [BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy](#), Genetic Testing, Policy No. 41
5. [Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer \(NSCLC\)](#), Genetic Testing, Policy No. 56
6. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
7. [Analysis of Proteomic and Metabolomic Patterns for Early Detection or Assessing Risk of Cancer](#), Laboratory, Policy No. 41
8. [Circulating Tumor DNA and Circulating Tumor Cells for Management \(Liquid Biopsy\) of Solid Tumor Cancers](#), Laboratory, Policy No. 46
9. [Laboratory and Genetic Testing for Use of 5-Fluorouracil \(5-FU\) in Patients with Cancer](#), Laboratory, Policy No. 64
10. [Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance](#), Laboratory, Policy No. 72

BACKGROUND

TRADITIONAL THERAPEUTIC APPROACHES TO CANCER

Tumor location, grade, stage, and the patient's underlying physical condition have traditionally been used in clinical oncology to determine the therapeutic approach to a specific cancer, which could include surgical resection, ionizing radiation, systemic chemotherapy, or combinations thereof. Currently, some 100 different types are broadly categorized according to the tissue, organ, or body compartment in which they arise. Most treatment approaches in clinical care were developed and evaluated in studies that recruited subjects and categorized results based on this traditional classification scheme.

This traditional approach to cancer treatment does not reflect the wide diversity of cancer at the molecular level. While treatment by organ type, stage, and grade may demonstrate statistically significant therapeutic efficacy overall, only a subgroup of patients may derive clinically significant benefit. It is unusual for a cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al analyzed the efficacy of major drugs used to treat several important diseases.^[1] They reported heterogeneity of therapeutic responses, noting a low rate of 25% for cancer chemotherapeutics, with response rates for most drugs falling in the range of 50% to 75%. The low rate for cancer treatments is indicative of the need for better identification of characteristics associated with treatment response and better targeting of treatment to have higher rates of therapeutic responses.

TARGETED CANCER THERAPY

Much of the variability in clinical response may result from genetic variations. Within each broad type of cancer, there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. The use of genetic markers allows cancers to be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann (2013) categorized these findings into three classes,^[2] which are listed following: (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, and (3) genetic markers of uncertain importance.

A smaller number of individual genetic markers fall into the first category (i.e., have established utility for a specific cancer type). The utility of these markers has been demonstrated by randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. Testing for individual variants with established utility is not covered in this evidence review. In some cases, limited panels may be offered that are specific to one type of cancer (e.g., a panel of several markers for non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least one potentially pathogenic variant.^[3-5] The number of variants varies widely by types of cancers, different variants included in testing, and different testing methods among the available studies. In a 2015 study, 439 patients with diverse cancers were tested with a 236-gene panel.^[5] A total of 1,813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least one molecular alteration. The median number of alterations per patient was three, and 85% of patients (372/439) had two or more alterations. The most common alterations were in the genes *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%).

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs.^[2,6,7] There are several examples of variant-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) variants has been successful in non-small cell lung cancer (NSCLC) but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. “Basket” studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published by Hyman (2015).^[8] In this study, 122 patients with BRAF V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be antitumor activity for some but not all cancers, with the most promising results seen for NSCLC, Erdheim-Chester disease, and Langerhans cell histiocytosis.

EXPANDED CANCER MOLECULAR PANELS

Table 1 provides a select list of some commercially available expanded cancer molecular panels.

Table 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Tissue Testing

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
FoundationOne® CDx test (Foundation Medicine, Cambridge, MA) ^[9]	Solid	324 cancer-related genes and select rearrangements in 36 genes	NGS
OnkoMatch™ (GenPath Diagnostics, Elmwood Park, NJ) ^[10]	Solid	68 variants in 14 oncogenes and tumor suppressor genes	Multiplex PCR
GeneTrails® Comprehensive Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR) ^[11]	Solid	225 genes	NGS

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences, Irving, TX) ^[12]	Solid	Up to 592 tumor-associated genes	NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis
SmartGenomics™ (PathGroup, Nashville, TN) ^[13]	Solid and hematologic	160 genes and 126 gene fusions	NGS, cytogenomic array, other technologies
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY) ^[14]	Solid	341 cancer-associated genes	NGS
TruSeq® Amplicon Panel (Illumina, San Diego, CA) ^[15]	Solid	48 cancer-related genes	NGS
OncoPrint™ Comprehensive Assay v3 (Thermo Fisher Scientific, Waltham, MA) ^[16]	Solid	161 genes	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA) ^[17]	Solid	409 genes	NGS

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[18] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The evaluation of a genetic test focuses on three main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). This evidence review focuses on clinical validity and utility.

EXPANDED MOLECULAR PANEL TESTING FOR CANCER

Clinical Validity

The evidence on the clinical validity of expanded panels is incomplete. Because of the large number of variants contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole. While some variants have a strong association with one or a small number of specific malignancies, none has demonstrated high clinical validity across a wide variety of cancers. Some have reported that, after filtering variants by comparison with matched normal tissue and cancer variants databases, most identified variants are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each variant and each type of cancer individually.

Clinical Utility

The most direct way to demonstrate clinical utility is through controlled trials that compare a strategy of cancer variant testing followed by targeted treatment with a standard treatment strategy without variant testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for variant testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. Overall survival (OS) is most important; cancer-related survival and/or progression-free survival (PFS) may be acceptable surrogates. A quality-of-life measurement may also be important if study designs allow for treatments with different toxicities in the experimental and control groups.

Systematic Reviews

Schwaederle (2015) published a meta-analysis of studies comparing personalized treatment with nonpersonalized treatment.^[19] Their definition of personalized treatment was driven by a biomarker, which could be genetic or nongenetic. Therefore, this analysis not only included studies of matched vs unmatched treatment based on genetic markers, but also included studies that personalized treatment based on nongenetic markers. A total of 111 arms of identified trials received personalized treatment, and they were compared with 529 arms that received nonpersonalized treatment. On random-effects meta-analysis, the personalized treatment group had a higher response rate (31% vs 10.5%, $p < 0.001$), and a longer PFS (5.9 months vs 2.7 months, $p < 0.001$) compared with the nonpersonalized treatment group. Another meta-analysis (2015) by this group compared outcomes from 44 Food and Drug Administration-regulated drug trials that used a personalized treatment approach to 68 trials that used a nonpersonalized approach to cancer treatment.^[20] Response rates were significantly higher in the personalized treatment trials (48%) than in the nonpersonalized approach (23%; $p < 0.001$). PFS was 8.3 months in the personalized treatment trials compared with 5.5 months in the nonpersonalized approach ($p < 0.001$). For trials that used a personalized treatment strategy, OS was significantly longer (19.3 months) than in trials that did not (13.5 months, $p = 0.01$). Personalized treatment in these studies was based on various biomarkers, both genetic and nongenetic.

Randomized Controlled Trials

SHIVA was a randomized controlled trial of treatment directed by cancer variant testing vs standard care, with the first results published in 2015 (see Table 2).^[21,22] In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from eight academic centers in France. Variant testing included comprehensive analysis of three molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted next-generation sequencing, analysis of copy number variations, and hormone expression by immunohistochemistry. Based on the pattern of

abnormalities found, nine different regimens of established cancer treatments were assigned to the experimental treatment arm. The primary outcome was PFS analyzed by intention to treat. Baseline clinical characteristics and tumor types were similar between groups.

Table 2. Treatment Algorithm for Experimental Arm, From the SHIVA Trial^[21]

Molecular Abnormalities	Molecularly Targeted Agent
<i>KIT, ABL, RET</i>	Imatinib
<i>AKT, mTORC1/2, PTEN, PI3K</i>	Everolimus
<i>BRAF V600E</i>	Vemurafenib
<i>PDGFRA, PDGFRB, FLT-3</i>	Sorafenib
<i>EGFR</i>	Erlotinib
<i>HER2</i>	Lapatinib and trastuzumab
<i>SRC, EPHA2, LCK, YES</i>	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

Ninety-nine patients were randomized to the targeted treatment group, and 96 to standard care. Baseline clinical characteristics and tumor types were similar between groups. Molecular alterations affecting the hormonal pathway were found in 82 (42%) of 195 patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) of 195 patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) of 195 patients. After a median follow-up of 11.3 months, the median PFS was 2.3 months (95% confidence interval [CI] 1.7 to 3.8 months) in the targeted treatment group vs 2.0 months (95% CI 1.7 to 2.7 months) in the standard care group (hazard ratio, 0.88; 95% CI 0.65 to 1.19, p=0.41). Objective responses were reported for four (4.1%) of 98 assessable patients in the targeted treatment group vs three (3.4%) of 89 assessable patients in the standard care group. In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

A 2017 crossover analysis of the SHIVA trial evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agents (MTA) therapy to treatment at physician's choice (TPC) or vice versa.^[23] The PFS ratio was defined as the PFS on MTA (PFSMTA) to PFS on TPC (PFSTPC) in patients who crossed over. Of the 95 patients who crossed over, 70 patients crossed over from the TPC to MTA arm while 25 patients crossed over from MTA to TPC arm. In the TPC to MTA crossover arm, 26 (37%) of patients and 15 (61%) of patients in the MTA to TPC arm had a PFSMTA/PFSTPC ratio greater than 1.3. The post hoc analysis of the SHIVA trial has limitations because it only evaluated a subset of patients from the original clinical trial but used each patient as his/her control by using the PFS ratio. The analysis would suggest that patients may have benefited from the treatment algorithm evaluated in the SHIVA trial.

Nonrandomized Controlled Trials

Numerous nonrandomized studies have been published that use some type of control. Some of these studies had a prospective, interventional design. Wheler (2016) reported a prospective comparative trial of patients who had failed standard treatment and had been referred to their tertiary center for admission into phase 1 trials.^[24] Comprehensive molecular profiling (FoundationOne tumor panel) was performed on 339 patients, of whom 122 went onto a phase 1 therapy that was matched to their genetic profile; based on physician evaluation of additional information, 66 patients went onto a phase 1 trial not matched to their genetic profile. There was a significant benefit for time to treatment failure and a trend for an increased percentage of patients with stable disease and median OS in patients matched to their genetic

profile. When exploratory analysis divided patients into groups that had high matching results or low matching results (number of molecular matches per patient divided by the number of molecular alterations per patient), the percentage of patients with stable disease and the median time to failure were significantly better in the high-match group. Median OS did not differ significantly between groups. Notably, those patients had failed multiple prior therapies (median four) and had a number (median five, range 1 to 14) of gene alterations in the tumors. For comparison, response rates in phase 1 trials with treatment-resistant tumors are typically 5% to 10%.

Another type of study compares patients matched to targeted treatment with patients not matched. In this type of study, all patients undergo comprehensive genetic testing, but only a subset is matched to targeted therapy. Patients who are not matched continue to receive standard care.

An individual study of this type is Tsimberidou (2012).^[25] In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. Polymerase chain reaction–based targeted sequencing was used to assess variants in 10 cancer genes. Loss of *PTEN* was determined using immunohistochemistry, and anaplastic lymphoma kinase (*ALK*) translocation was assessed using fluorescence in situ hybridization. Of 1,144 patients, 460 had a molecular aberration based on this panel of tests. From this group of 460 patients, 211 were given “matched” treatment and 141 were given nonmatched treatment. The principal analysis presented was of a subgroup of the 460 patients who had only one molecular aberration (n=379). Patients were enrolled in one of 51 phase 1 clinical trials of experimental agents. It was not stated how patients were assigned to matched or unmatched therapy, or how a particular therapy was considered a match or not. In the list of trials in which patients were enrolled, it appears that many of the investigational agents were inhibitors of specific kinases, and thus a patient with a particular aberration of that kinase would probably be considered a match for that agent.^[25]

Among the 175 patients treated with matched therapy, the overall response rate was 27%. Among the 116 patients treated with nonmatched therapy, the response rate was 5% (p<0.001 for the difference in response rates). The median time to failure was 5.2 months for patients on matched therapy and 2.2 months for those on nonmatched therapy (p<0.001). At a median 15-month follow-up, survival was 13.4 months vs 9.0 months (p=0.017) in favor of matched therapy. Due to small numbers, individual molecular aberrations could not be analyzed, but some sensitivity analyses, excluding certain aberrations, demonstrated that the results were robust, with the exclusion of certain groups.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of recommendations for variant testing of common solid tumors are listed below:

- Colon cancer^[26]
 - *KRAS*, *NRAS*, and *BRAF* testing for patients with metastatic colon cancer.

- Non-small-cell lung cancer^[27]
 - Metastatic adenocarcinoma, large cell, or other nonsquamous cell carcinoma:
 - *EGFR*, *ALK*, *ROS1*, *BRAF* testing recommended
 - Testing should be conducted as part of broad molecular profiling
 - Metastatic squamous cell carcinoma:
 - Consider *EGFR* and *ALK* testing in never smokers, small biopsy specimens, or mixed histology
 - Consider *ROS1* and *BRAF* testing in small biopsy specimens or mixed histology
 - Testing should be conducted as part of broad molecular profiling
 - The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.
- Cutaneous melanoma^[28]
 - *BRAF* V600 testing for patients with metastatic disease
 - *KIT* variants for patients with metastatic disease
- Ovarian cancer^[29]
 - *BRCA1/2*, consider homologous recombination pathway genes
- Gastrointestinal stromal tumors^[30]
 - *KIT*, *PDGFRA*

SUMMARY

There is limited evidence that molecular profiling of tumor tissue can improve health outcomes for patients with cancer. However, for certain patients with advanced non-small cell lung cancer (NSCLC) this type of testing may help to identify targeted treatments or clinical trials for which a patient may be eligible. In addition, current clinical guidelines recommend broad molecular profiling for certain NSCLC patients. Therefore, tumor testing using molecular panels, including expanded cancer panels, may be considered medically necessary for patients with advanced or metastatic (stage III or IV) non-squamous cell-type NSCLC.

There is not enough evidence that tumor profiling can improve health outcomes for patients with cancers other than advanced non-small cell lung cancer. Clinical guidelines based on evidence do not currently recommend this strategy for other tumor types. Therefore, expanded panel testing is considered investigational for patients that do not meet the policy criteria.

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CODES

Codes	Number	Description
CPT	0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence

Codes	Number	Description
		variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
	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
	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)
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
	81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	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)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	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)
	81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81400	Molecular pathology procedure, Level 1

Codes	Number	Description
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81408	Molecular pathology procedure, Level 9
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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